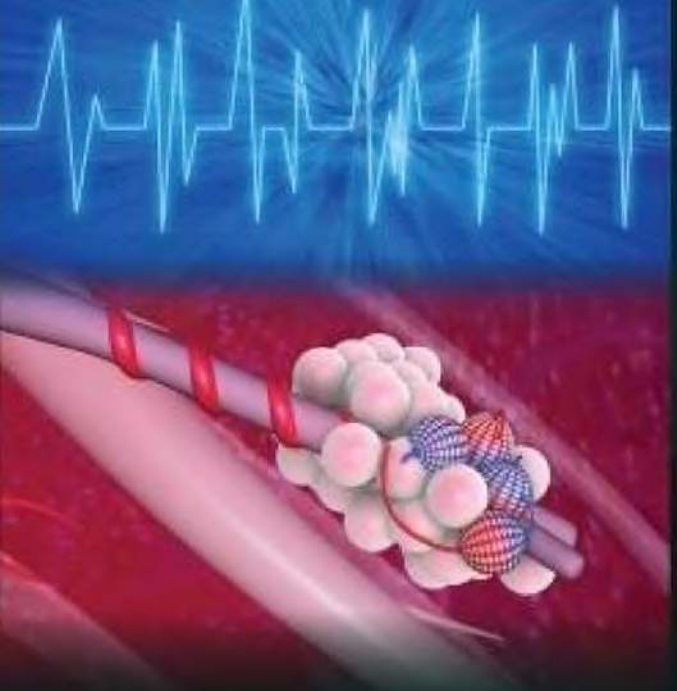

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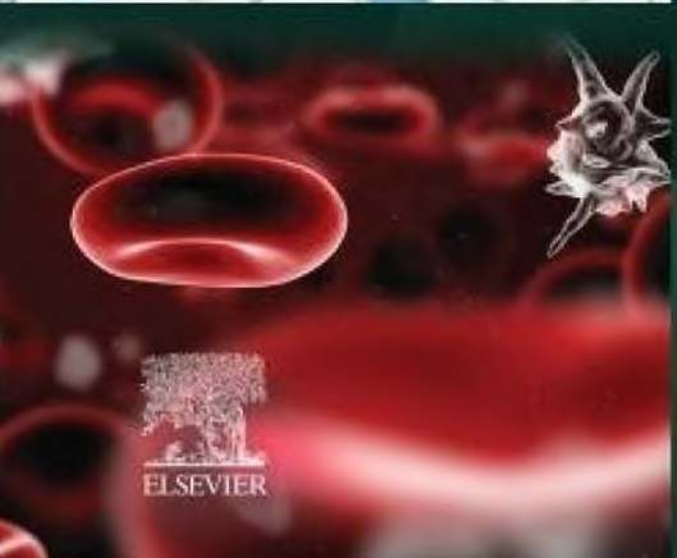

JEAN-LOUIS VINCENT
FREDERICK A. MOORE
RINALDO BELLOMO
JOHN J. MARINI

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8TH EDITION

Jean-Louis Vincent, MD, PhD
Professor of Intensive Care
Université libre de Bruxelles
Department of Intensive Care
Hôpital Erasme
Brussels, Belgium

Frederick A. Moore, MD, MCCM
Professor of Surgery
Co-Director, Sepsis and Critical Illness Research Center
University of Florida College of Medicine
Gainesville, FL, United States

Rinaldo Bellomo, MD, PhD, FRACP, FCICM
Department of Intensive Care Austin Health
Melbourne, VIC, Australia

John J. Marini, MD
Professor of Medicine
Pulmonary and Critical Care Medicine
University of Minnesota
Minneapolis/St. Paul, MN, United States

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PREFACE

The *Textbook of Critical Care* is an established and trusted source of information in the field of intensive care medicine, focused on presenting current understanding of core physiologic principles and the fundamentals for clinical, evidence-based, and practice-related decision making. A reference book that successfully bridges the gap between medical and surgical intensive care practice and covers topics relevant to adult and pediatric populations, the *Textbook of Critical Care* offers chapters that address common problems with concise, easily understood descriptions of the underlying pathophysiology, evidence-based interventions, and state-of-the-art chapters for diagnosis, monitoring, and management of commonly encountered organ dysfunctions. System-based chapters with tables, figures, images, algorithms, and key points organize complex information concerning specific topics in an easily understood format for quick reference. The accompanying e-book, included with the book purchase, provides ready access to procedural videos, a powerful search engine, hyperlinked references, and downloadable images. Importantly, it is optimized for convenient use on all devices, providing a real-time, point-of-care reference.

This eighth edition has been fully updated to take into account new developments in intensive care medicine since the last edition, with chapters authored by leading experts in critical care, anesthesia, surgery, pulmonary medicine, and pediatrics from around the world. There is a continued emphasis on the importance of a multidisciplinary approach to the care of critically ill patients, with special attention to rapidly evolving areas that include imaging and monitoring, advanced respiratory modalities, extracorporeal gas exchange, and renal replacement therapy. We are sure that all those with an interest in critical care medicine, from student to expert, will find this eighth edition of the *Textbook of Critical Care* a valuable source of information.

Jean-Louis Vincent, MD, PhD
Frederick A. Moore, MD, MCCM
Rinaldo Bellomo, MD, PhD, FRACP, FCICM
John J. Marini, MD

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1

Sudden Deterioration in Neurologic Status

Alexis Steinberg and Joseph M. Darby

Patients admitted to the intensive care unit (ICU) with critical illness or injury are at risk for neurologic complications.[1–5] A sudden or unexpected change in the neurologic condition of a critically ill patient often heralds a complication that may cause direct injury to the central nervous system (CNS). Alternatively, such changes may simply be neurologic manifestations of the underlying critical illness or treatment that necessitated ICU admission (e.g., sepsis). These complications can occur in patients admitted to the ICU without neurologic disease and in those admitted for management of primary CNS problems (e.g., stroke). Neurologic complications can also occur as a result of invasive procedures and therapeutic interventions. Commonly, recognition of neurologic complications is delayed or missed entirely because therapeutic interventions such as intubation and sedatives interfere with the physical examination or otherwise confound the clinical picture. In other cases, neurologic complications are not recognized because of a lack of sensitive methods to detect the problem (e.g., delirium). Morbidity and mortality are increased among patients who develop neurologic complications; therefore the intensivist must be vigilant in evaluating all critically ill patients for changes in neurologic status.

As the complexity of ICU care has increased over the course of time, so has the risk of neurologic complications. In studies of medical and surgical ICU patients, the incidence of neurologic complications has ranged from 12.3% to 54%[1,6] and is associated with increased morbidity, mortality, and ICU length of stay.

Sepsis is the most common clinical problem associated with development of neurologic complications (sepsis-associated encephalopathy). In addition to encephalopathy, other common neurologic complications include seizures and stroke. Neuromuscular disorders are now recognized as a major source of morbidity in severely ill patients.[7] Recognized neurologic complications occurring in selected medical, surgical, and neurologic ICU populations are shown in Table 1.1.[8–35]

IMPAIRMENT IN CONSCIOUSNESS

Global changes in CNS function, best described in terms of impairment in consciousness, are generally referred to as *encephalopathy* or *altered mental status*. An acute change in the level of consciousness, undoubtedly, is the most common neurologic complication that occurs after ICU admission. *Consciousness* is defined as a state of awareness (arousal or wakefulness) and the ability to respond appropriately to changes in environment.[36] For consciousness to be impaired, global hemispheric dysfunction or dysfunction of the brainstem reticular activating system must be present.[37] The degree of impairment in consciousness may range from a sleeplike state (coma) to states characterized primarily by confusion and agitation (delirium). States and descriptions of acutely altered consciousness are listed in Table 1.2.

When an acute change in consciousness is observed, the patient should be evaluated in the clinical context with consideration of the age, presence or absence of coexisting organ system dysfunction, metabolic status, medications, and presence or absence of infection. In patients with a primary CNS disorder, deterioration in the level of consciousness frequently represents the development of brain edema, increasing intracranial pressure, new or worsening intracranial hemorrhage, hydrocephalus, CNS infection, or cerebral vasospasm. In patients without a primary CNS diagnosis, an acute change in consciousness is often the result of the development of infectious complications (i.e., sepsis-associated encephalopathy), drug toxicities, or the development or exacerbation of organ system failure. Nonconvulsive status epilepticus (NCSE) is increasingly being recognized as a cause of impaired consciousness in critically ill patients (Box 1.1).[38–43]

Altered consciousness manifesting as impairment in wakefulness or arousal (i.e., coma and stupor) and their causes are well defined.[36–39] Substantial confusion remains, however, regarding the diagnosis and management of delirium. When dedicated instruments are used, delirium can be diagnosed in between 50% and 75% of critically ill patients, making this condition the most common neurologic complication of critical illness.[40–44] Difficulty in establishing the diagnosis of delirium stems primarily from prior beliefs that agitation and confusion in the critically ill are expected consequences of the unique environmental factors and sleep deprivation that characterize the ICU experience.

Currently accepted criteria for the diagnosis of delirium include impaired cognition that has a fluctuating course and is not explained by an underlying neurocognitive disorder.[45] Delirium is considered a direct physiologic consequence of another medical condition. Subtypes of delirium include hyperactive (agitated) delirium and the more common hypoactive or quiet delirium.[44] Impaired consciousness may be apparent as a reduction in awareness, psychomotor retardation, agitation, or impairment in attention (increased distractibility or vigilance). Cognitive impairment can include disorientation, impaired memory, and perceptual aberrations (hallucinations or illusions).[46] Autonomic hyperactivity and sleep disturbances may be features of delirium in some patients (e.g., those with drug withdrawal syndromes

TABLE 1.1 Neurologic Complications in Selected Specialty Populations

Medical	
Bone marrow transplantation[8,9]	CNS infection, stroke, subdural hematoma, brainstem ischemia, hyperammonemia, Wernicke encephalopathy
Cancer[10,11]	Stroke, intracranial hemorrhage, CNS infection, neurotoxicity from chimeric antigen receptor T-cell therapy (CAR T-cell)
Fulminant hepatic failure[12]	Encephalopathy, coma, brain edema, increased ICP
HIV/AIDS[13,14]	Opportunistic CNS infection, stroke, vasculitis, delirium, seizures, progressive multifocal leukoencephalopathy
Pregnancy[15,16]	Seizures, ischemic stroke, cerebral vasospasm, intracranial hemorrhage, cerebral venous thrombosis, hypertensive encephalopathy, pituitary apoplexy
Surgical	
Cardiac surgery[17,18]	Stroke, delirium, brachial plexus injury, phrenic nerve injury
Vascular surgery[19,20]	
Carotid	Stroke, cranial nerve injuries (recurrent laryngeal, glossopharyngeal, hypoglossal, facial), seizures
Aortic	Stroke, paraplegia
Peripheral	Delirium
Transplantation[12,21–23]	
Heart	Stroke
Liver	Encephalopathy, seizures, opportunistic CNS infection, intracranial hemorrhage, Guillain-Barré syndrome, central pontine myelinolysis
Renal	Stroke, opportunistic CNS infection, femoral neuropathy
Urologic surgery (TURP)[24]	Seizures and coma (hyponatremia)
Otolaryngologic surgery[25,26]	Recurrent laryngeal nerve injury, stroke, delirium
Orthopedic surgery[27]	
Spine	Myelopathy, radiculopathy, epidural abscess, meningitis
Knee and hip replacement	Delirium (fat embolism)
Long-bone fracture/nailing	Delirium (fat embolism)
Neurologic	
Stroke[28–30]	Stroke progression or extension, reocclusion after thrombolysis, bleeding, seizures, delirium, brain edema, herniation
Intracranial surgery[31]	Bleeding, edema, seizures, CNS infection
Subarachnoid hemorrhage[32,33]	Rebleeding, vasospasm, hydrocephalus, seizures
Traumatic brain injury[34]	Intracranial hypertension, bleeding, seizures, stroke (cerebrovascular injury), CNS infection
Cervical spinal cord injury[35]	Ascension of injury, stroke (vertebral artery injury)

CNS, Central nervous system; *HIV/AIDS,* human immunodeficiency virus/acquired immunodeficiency syndrome; *ICP,* intracranial pressure; *TURP,* transurethral prostatic resection.

TABLE 1.2 States of Acutely Altered Consciousness

State	Description
Coma	Closed eyes, sleeplike state with no response to external stimuli (pain)
Stupor	Responsive only to vigorous or painful stimuli
Lethargy	Drowsy, arouses easily and appropriately to stimuli
Delirium	Acute state of confusion with or without behavioral disturbance
Catatonia	Eyes open, unblinking, unresponsive

or delirium tremens). Delirium in critically ill patients is associated with increased morbidity, mortality, and ICU length of stay.[47–49] Both vulnerability factors (e.g., age, comorbidities) and precipitating hospital factors (e.g., acute illness and medications) are recognized risk factors for delirium.[50,51] Other major risk factors include psychoactive medications (benzodiazepines),[52,53] drug-induced coma, sleep alterations,[54] metabolic disturbances, and sepsis.

As has been noted, NCSE is increasingly recognized as an important cause of impaired consciousness in critically ill patients and is characterized by electrographic seizure activity without clear clinical convulsive activity.[55,56] Several electroencephalographic (EEG) criteria exist for classification of NCSE.[57] Nonconvulsive seizures make up around 90% of seizures detected in critically ill patients undergoing continuous EEG out of concern for subclinical seizures or unexplained altered mental status.[58,59] The frequency of NCSE in general ICU patients varies from between 8% and 20%.[58–61] Approximately 48% of patients remaining comatose after convulsive status epilepticus were found to be in NCSE.[62,63] Other predisposing factors for NCSE in the ICU include traumatic brain injury, subarachnoid hemorrhage, global brain ischemia or anoxia, stroke, sepsis, multiple organ failure, and medication intoxication or withdrawal. Substantial mortality and morbidity are associated with NCSE, with the underlying etiology affecting the outcome.[64] Early recognition of NCSE can prevent the development of refractory status epilepticus and allow for timely

BOX 1.1 General Causes of Acutely Impaired Consciousness in the Critically Ill

Infection
Sepsis encephalopathy
CNS infection

Drugs
Narcotics
Benzodiazepines
Anticholinergics
Anticonvulsants
Tricyclic antidepressants
Selective serotonin uptake inhibitors
Phenothiazines
Steroids
Immunosuppressants (cyclosporine, FK506, OKT3)
Anesthetics

Electrolyte and Acid-Base Disturbances
Hyponatremia
Hypernatremia
Hypercalcemia
Hypermagnesemia
Severe acidemia and alkalemia

Organ System Failure
Shock (if severe)
Renal failure
Hepatic failure
Pancreatitis
Respiratory failure (hypoxia, hypercapnia)

Endocrine Disorders
Hypoglycemia
Hyperglycemia
Hypothyroidism
Hyperthyroidism
Pituitary apoplexy

Drug Withdrawal
Alcohol
Opiates
Barbiturates
Benzodiazepines

Vascular Causes
Shock
Hypotension
Hypertensive encephalopathy
CNS vasculitis
Cerebral venous sinus thrombosis

CNS Disorders
Hemorrhage
Stroke
Brain edema
Hydrocephalus
Increased intracranial pressure
Meningitis
Ventriculitis
Brain abscess
Subdural empyema
Seizures
Vasculitis

Seizures
Convulsive and nonconvulsive status epilepticus

Miscellaneous
Fat embolism syndrome
Neuroleptic malignant syndrome
Thiamine deficiency (Wernicke encephalopathy)
Psychogenic unresponsiveness

CNS, Central nervous system.

treatment to be initiated. Currently, no clear guidelines exist for the management of NCSE.[65]

STROKE AND OTHER FOCAL NEUROLOGIC DEFICITS

The new onset of a major neurologic deficit that manifests as a focal impairment in motor or sensory function (e.g., hemiparesis) or one that results in focal seizures usually indicates a primary problem referable to the cerebrovascular circulation. In a study evaluating the value of computed tomography (CT) in medical ICU patients, ischemic stroke and intracranial bleeding were the most common abnormalities associated with the new onset of a neurologic deficit or seizures.[66] Even though the majority of strokes present through the emergency room, 7%–15% of all strokes occur in the hospital, with unique mechanisms including paradoxical embolism in immobile patients, cerebral hypoperfusion causing watershed infarcts, and extracorporeal membrane oxygenation.[67] In-hospital strokes can either be ischemic infarcts or intracerebral hemorrhage (ICH). Overall, the frequency of new-onset stroke is between 1% and 4% in medical ICU patients.[1,68] Among general surgical patients, the frequency of perioperative stroke ranges from 0.3% to 3.5%.[69] Patients undergoing cardiac or vascular surgery and surgical patients with underlying cerebrovascular disease can be expected to have an increased risk of perioperative stroke.[18] Around 7%–15% of patients requiring extracorporeal membrane oxygenation have neurologic complications, including ischemic and hemorrhage stroke and seizures.[70,71] In view of the preexisting complexity in critically ill patients, an in-hospital rapid-response stroke protocol can lead to significant reductions in time to evaluation and treatment of patients with new focal neurologic deficits.[72]

The frequency of new or worsening focal neurologic deficits in patients admitted with a primary neurologic or neurosurgical disorder is variable. Patients admitted with stroke can develop worsening or new symptoms as a result of stroke progression, bleeding, or reocclusion of vessels previously opened with interventional therapy. In patients who have undergone elective intracranial surgery, postsurgical bleeding or infectious complications are the main causes of new focal deficits. In trauma patients, unrecognized injuries to the cerebrovascular circulation can cause new deficits. Delayed cerebral ischemia related to vasospasm frequently occurs in patients presenting with aneurysmal subarachnoid hemorrhage. Patients presenting with traumatic spinal

cord injury and those who have undergone surgery of the spine or of the thoracic or abdominal aorta can develop new or worsening symptoms of spinal cord injury. Early deterioration of CNS function after spinal cord injury usually occurs as a consequence of medical interventions to stabilize the spine, whereas late deterioration is usually the result of hypotension and impaired cord perfusion. Occasionally, focal weakness or sensory symptoms in the extremities occur as a result of occult brachial plexus injury or compression neuropathy. New cranial nerve deficits in patients without primary neurologic problems can occur after neck surgery or carotid endarterectomy.

SEIZURES

New-onset seizures in general medical-surgical ICU patients are typically caused by narcotic withdrawal, hyponatremia, drug toxicities, or previously unrecognized structural abnormalities.[3,73] New stroke, intracranial bleeding, and CNS infection are other potential causes of seizures after ICU admission. The frequency of seizures is higher in patients admitted to the ICU with a primary neurologic problem such as traumatic brain injury, aneurysmal subarachnoid hemorrhage, stroke, or CNS infection.[74] Because NCSE is more common than was previously appreciated, NCSE should also be considered in the differential diagnosis of patients developing new, unexplained, or prolonged alterations in consciousness.

GENERALIZED WEAKNESS AND NEUROMUSCULAR DISORDERS

Generalized muscle weakness often becomes apparent in ICU patients as previous impairments in arousal are resolving or sedative and neuromuscular blocking agents are being discontinued or tapered. Polyneuropathy and myopathy associated with critical illness are now well recognized as the principal causes of new-onset generalized weakness among ICU patients being treated for nonneuromuscular disorders.[7,75–77] These disorders also may be responsible for prolonged ventilator dependency in some patients. Patients at increased risk for these complications include those with sepsis, systemic inflammatory response syndrome, and multiple organ dysfunction syndrome, in addition to those who require prolonged mechanical ventilation. Other risk factors include treatment with corticosteroids or neuromuscular blocking agents. In contrast to demyelinating neuropathies (e.g., Guillain-Barré syndrome), critical illness polyneuropathy is primarily a condition in which there is axonal degeneration. Critical illness polyneuropathy is diagnosed in a high percentage of patients undergoing careful evaluation for weakness acquired while in the ICU. Because primary myopathy coexists in a large number of patients with critical illness polyneuropathy, *ICU-acquired paresis*[77] or *ICU-acquired weakness*[7] may be better terms to describe this problem. Although acute Guillain-Barré syndrome and myasthenia gravis are rare complications of critical illness, these diagnoses should also be considered in patients who develop generalized weakness in the ICU.

NEUROLOGIC COMPLICATIONS OF PROCEDURES AND TREATMENTS

Routine procedures performed in the ICU or in association with evaluation and treatment of critical illness can result in neurologic complications.[78] The most obvious neurologic complications are those associated with intracranial bleeding secondary to the treatment of stroke and other disorders with thrombolytic agents or anticoagulants. Other notable complications are listed in Table 1.3.

EVALUATION OF SUDDEN NEUROLOGIC CHANGE

A new or sudden change in the neurologic condition of a critically ill patient necessitates a focused neurologic examination, review of the

TABLE 1.3 Neurologic Complications Associated With ICU Procedures and Treatments

Procedure	Complication
Angiography	Cerebral cholesterol emboli syndrome
Anticoagulants/antiplatelet agents	Intracranial bleeding
Arterial catheterization	Cerebral embolism
Bronchoscopy	Increased ICP
Central venous catheterization	Cerebral air embolism, carotid dissection, Horner syndrome, phrenic nerve injury, brachial plexus injury, cranial nerve injury
DC cardioversion	Embolic stroke, seizures
Dialysis	Seizures, increased ICP (dialysis disequilibrium syndrome)
Endovascular procedures (CNS)	Vessel rupture, thrombosis, reperfusion bleeding
Epidural catheter	Spinal epidural hematoma, epidural abscess
ICP monitoring	CNS infection (ventriculitis), hemorrhage
Intraaortic balloon pump	Lower extremity paralysis
Intubation	Spinal cord injury
Left ventricular assist devices	Stroke, seizures
Extracorporeal membrane oxygenation	Stroke, seizures
Lumbar puncture or drain	Meningitis, herniation
Mechanical ventilation	Cerebral air embolism, increased ICP (high PEEP and hypercapnia), seizures (hypocapnia)
Nasogastric intubation	Intracranial placement

CNS, Central nervous system; *DC,* direct current; *ICP,* intracranial pressure; *ICU,* intensive care unit; *PEEP,* positive end-expiratory pressure.

clinical course, medications, laboratory data, and appropriate imaging or neurophysiologic studies when indicated. The type and extent of the evaluation depend on the clinical context and the general category of neurologic change occurring. The history and physical examination should lead the clinician to the diagnostic approach best suited to the individual patient.

Essential elements of the neurologic examination include an assessment of the level and content of consciousness, pupillary size and reactivity, and motor function. Additional evaluation of the cranial nerves and peripheral reflexes and a sensory examination are conducted as indicated by the clinical circumstances. If the patient is comatose on initial evaluation, a more detailed coma examination should be performed to help differentiate structural from metabolic causes of coma.[37,38] When the evaluation reveals only a change in arousal without evidence of a localizing lesion in the CNS, a search for infection, discontinuation or modification of drug therapy, and a general metabolic evaluation may be indicated. Lumbar puncture to aid in the diagnosis of CNS infection may be warranted in selected neurosurgical patients and immunocompromised individuals. Lumbar puncture to rule out nosocomial meningitis in other patients is generally not rewarding.[79] EEG should be performed in patients with clear evidence of seizures and when the diagnosis of NCSE is being considered. Continuous EEG should be performed when the index of suspicion for NCSE remains high despite an unrevealing initial EEG examination.[58,80]

CT is indicated for nonneurologic patients with new focal deficits, seizures, or otherwise unexplained impairments in arousal.[66] In patients with primary neurologic disorders, CT is indicated if worsening brain edema, herniation, bleeding, and hydrocephalus are considerations when new deficits or worsening neurologic status occurs. In some cases, when the basis for a change in neurologic condition remains elusive, magnetic resonance imaging (MRI) may be helpful. In particular, the diffusion-weighted MRI technique can reveal structural abnormalities such as hypoxic brain injury, fat embolism, vasculitis, cerebral venous thrombosis, or multiple infarcts after cardiopulmonary bypass that are not apparent by standard CT.[81–86] MRI may be the imaging modality of choice in patients with human immunodeficiency virus (HIV) and new CNS complications.[81] For patients who develop signs and symptoms of spinal cord injury complicating critical illness, MRI can be used to further delineate the nature and severity of the injury. For patients who develop generalized muscle weakness or unexplained ventilator dependency, electromyography and nerve conduction studies can confirm the presence of critical illness polyneuropathy or myopathy.

MONITORING FOR NEUROLOGIC CHANGES

The common occurrence of neurologic changes in critically ill patients emphasizes the need for vigilant monitoring. A variety of clinical techniques such as the Glasgow Coma Scale, FOUR score,[87] National Institutes of Health (NIH) Stroke Scale, Ramsay Sedation Scale, Richmond Agitation-Sedation Scale, and Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) can be used to monitor clinical neurologic status.[40,41,43,88–90] For patients admitted to the ICU with a primary neurologic disorder, a variety of monitoring techniques, including measurements of intracranial pressure, brain tissue Po_2, cerebral metabolism, cerebral blood flow, cerebral perfusion pressure, autoregulation, and electrographic measurements, can be used.[91,92] Monitors can be invasive or noninvasive. More commonly used noninvasive measures are pupillometry,[93,94] near-infrared spectroscopy, bispectral index, transcranial Doppler, and EEG.

KEY POINTS

- An abrupt change in neurologic status is a common problem in critically ill patients that may be either a manifestation of the underlying critical illness and treatment or result from an acute unanticipated insult or injury to the nervous system. Neurologic changes in the critically ill are associated with increased morbidity and mortality.
- Impairment in consciousness manifesting as delirium is the most common neurologic complication occurring after ICU admission.
- NCSE is characterized by an alteration in consciousness or behavior associated with EEG changes without clear convulsive motor activity and is increasingly recognized as a cause for impaired consciousness in critically ill patients.
- Critical illness polyneuropathy and myopathy are now well recognized as the principal causes for the new onset of generalized weakness in critically ill patients and may contribute to prolonged ventilator dependency.
- An abrupt change in the neurologic condition of a critically ill patient necessitates a focused neurologic examination, review of medications, laboratory assessment and neuroimaging, and/or neurophysiologic studies when indicated.
- In-hospital stroke (ischemic or hemorrhagic) manifesting as a focal impairment in motor/sensory function or seizures is not uncommon and requires urgent workup and treatment.
- The Glasgow Coma Score, FOUR score, NIH Stroke Scale, Ramsay Sedation Scale, Richmond Agitation-Sedation Scale, and CAM-ICU are clinical assessment tools that are potentially useful in evaluating and monitoring neurologic status. A wide variety of invasive and noninvasive monitors exist for measuring specific brain physiology.

References for this chapter can be found at expertconsult.com.

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De Jonghe B, Sharshar T, Lefaucheur JP, Authier FJ, Durand-Zaleski I, Boussarsar M, et al. Paresis acquired in the intensive care unit: a prospective multicenter study. *JAMA*. 2002; 288(22):2859–2867.
This prospective multicenter study of critically ill patients was the first to assess the clinical incidence, risk factors, and outcomes of mechanically ventilated patients developing ICU-acquired weakness, emphasizing a central role for corticosteroid use in its genesis and prolonged mechanical ventilation as a relevant ICU outcome.

Ely EW, Shintani A, Truman B, Speroff T, Gordon SM, Harrell FE Jr, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA*. 2004;*291*(14):1753–1762.
This was a prospective cohort multicenter study of mechnically ventilated patients to determine if delirium was an independent predictor of outcome. Of 275 patients, delirium was found to be an independent predictor of 6-month mortality and ICU length of stay, even when covariates such as coma, sedatives, and analgesia were adjusted for.

Girard TD, Thompson JL, Pandharipande PP, Brummel NE, Jackson JC, Patel MB, et al. Clinical phenotypes of delirium during critical illness and severity of subsequent long-term cognitive impairment: a prospective cohort study. *Lancet. Respiratory Medicine*. 2018;6(3):213-222. doi:10.1016/S2213-2600(18)30062-6.
A multicenter, prospective cohort study of critically ill patients in medical and surgical ICUs with respiratory failure, shock, or both that assessed the prevelance of risk factors of delirium and their effects on long-term cognitive

outcomes. Sedative-associated, hypoxic, and septic delirium were common risk factors and frequently co-occurred. These are all indicators of acute brain injury and were identified as potential risk factors for long-term cognitive impairment, noting that some are not modifiable such as sedation.

Le Roux P, Menon DK, Citerio G, et al. Consensus summary statement of the International Multidisciplinary Consensus Conference on Multimodality Monitoring in Neurocritical Care: a statement for healthcare professionals from the Neurocritical Care Society and the European Society of Intensive Care Medicine. *Intensive Care Medicine*. 2014;40(9):1189-1209. doi:10.1007/s00134-014-3369-6.

A collaboration of multiple societies to address the evidence for multimodality monitoring, including invasive and noninvasive measures. A systematic literature review was done to develop specific recommendations about physiologic processes that may be important to the care of patients with neurologic complications.

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2

Agitation and Delirium

Christina Boncyk, E. Wesley Ely, and Arna Banerjee

Agitation and delirium are commonly encountered in the intensive care unit (ICU). Although frequently underrecognized, delirium is present in up to 80% of critically ill adults on mechanical ventilation when routinely assessed.[1] Delirium and agitation are more than just an inconvenience; these conditions can have deleterious effects on patient and staff safety and contribute to poor outcomes, including increased duration of mechanical ventilation, increased ICU length of stay, increased risk of death, physical disability, and long-term cognitive impairment.[2–5] It is therefore important for clinicians to be able to recognize agitation and delirium and to have an organized approach for its evaluation and management.

AGITATION

Agitation is a psychomotor disturbance characterized by excessive motor activity associated with a feeling of inner tension.[6,7] The activity is usually nonproductive and repetitious, consisting of behaviors such as pacing, fidgeting, wringing of hands, pulling of clothes, and an inability to sit still. Careful observation of the patient may reveal the underlying intent. In the ICU, agitation is frequently related to anxiety or delirium. Agitation may be caused by various factors: metabolic disorders (hyponatremia and hypernatremia), hyperthermia, hypoxia, hypotension, use of sedative drugs and/or analgesics, sepsis, alcohol withdrawal, and long-term psychoactive drug use, to name a few.[8,9] It can also be caused by external factors such as noise, discomfort, and pain.[10] Agitation is important to manage, as it is associated with a longer length of stay in the ICU and higher costs.[8] Symptoms can be mild, characterized by increased movements and an apparent inability to get comfortable, or severe. Severe agitation can be life threatening, leading to higher rates of self-extubation, self-removal of catheters and medical devices, nosocomial infections,[8] hypoxia, barotrauma, and/or hypotension because of patient/ventilator asynchrony. Indeed, recent studies have shown that agitation contributes to ventilator asynchrony, increased oxygen consumption, and increased production of carbon dioxide (CO_2) and lactic acid; these effects can lead to life-threatening respiratory and metabolic acidosis.[9]

DELIRIUM

Delirium can be defined as follows: (1) A disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention. (2) A change in cognition (e.g., memory deficit, disorientation, language disturbance) or development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia. (3) The disturbance develops over a short period (usually hours to days) and tends to fluctuate during the course of the day. (4) There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiologic consequence of a general medical condition, an intoxicating substance, medication use, or more than one cause (Fig. 2.1).[7] Delirium is commonly underdiagnosed in the ICU and has a reported prevalence of 20%–80%, depending on the severity of the illness and the need for mechanical ventilation.[2,4,11–13] Recent investigations have shown that the presence of delirium is a strong predictor of longer hospital stay, higher costs, and increased risk of death.[2,3,14] Each additional day with delirium increases a patient's risk of dying by 10%.[15] Longer periods of delirium are also associated with greater degrees of cognitive decline when patients are evaluated after 1 year.[3] Thus delirium can adversely affect the quality of life in survivors of critical illnesses and may serve as an intermediate recognizable step for targeting therapies to prevent poor outcomes in survivors of critical illness, including depression, posttraumatic stress disorder, and functional disability.[3,16]

Unfortunately, the true prevalence and magnitude of delirium have been poorly documented because myriad terms, including *acute confusional state, ICU psychosis, acute brain dysfunction,* and *encephalopathy,* have been used to describe this condition.[17] Delirium can be classified according to psychomotor behavior into hypoactive delirium, hyperactive delirium, or a mixed subtype. Hypoactive delirium, which is the most prevalent form of delirium, is characterized by decreased physical and mental activity and inattention. In contrast, hyperactive delirium is characterized by combativeness and agitation. Patients with both features have mixed delirium.[18,19] Hyperactive delirium puts both patients and caregivers at risk of serious injury but fortunately only occurs in a minority of critically ill patients.[18,19] Hypoactive delirium might actually be associated with a worse prognosis.[20,21] The Delirium Motor Subtype Scale may assist in making this diagnosis.[22]

Although healthcare professionals realize the importance of recognizing delirium, it frequently goes unrecognized in the ICU when not routinely screened for.[23–25] Even when ICU delirium is recognized, most clinicians consider it an expected event that is often iatrogenic and without consequence.[26] However, delirium needs to be viewed as a form of organic brain dysfunction that has consequences if left undiagnosed and untreated. Given the limited pharmacologic treatment options available, the most effective strategy for reducing its prevalence lies in prevention with nonpharmacologic treatment bundles, the cornerstone of which include routine patient assessments.[27,28]

Risk Factors for Delirium

The risk factors for agitation and delirium are many and overlap to a large extent (Table 2.1). Fortunately, several mnemonics can aid clinicians in recalling the list; three common ones are IWATCHDEATH, DELIRIUM, and THINK (Table 2.2). In practical terms, risk factors can be divided into three categories: the acute illness itself, patient factors, and iatrogenic or environmental factors. Importantly, a number of medications that are commonly used in the ICU are associated with the development of

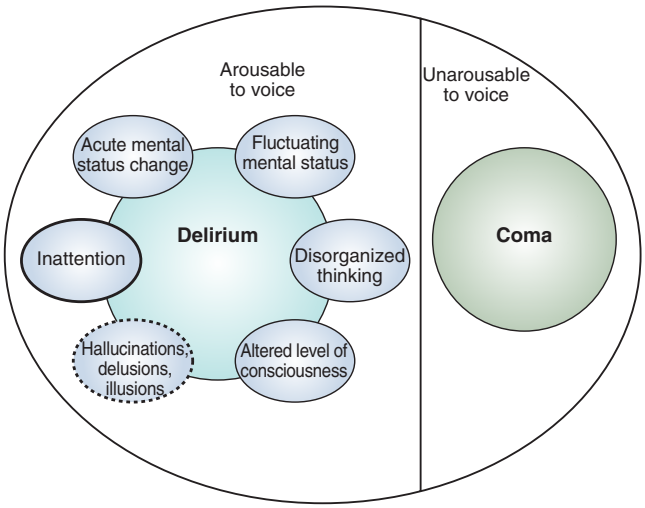


Fig. 2.1 Acute Brain Dysfunction. Patients who are unresponsive to voice are considered to be in a coma. Patients who respond to voice can be further evaluated for delirium using validated delirium monitoring instruments. Inattention is a cardinal feature of delirium. Other pivotal features include a change in mental status that fluctuates over hours to days, disorganized thinking, and altered levels of consciousness. Although hallucinations, delusions, and illusions may be part of the perceptual disturbances seen in delirium, they on their own are not synonymous with delirium, a diagnosis of which requires the presence of inattention and other pivotal features outlined earlier. (With permission from E. Wesley Ely and A. Morandi) (www.icudelirium.org).

TABLE 2.1 Risk Factors for Agitation and Delirium

Age >70 years	BUN/creatinine ratio ≥18
Transfer from a nursing home	Renal failure, creatinine >2.0 mg/dL
History of depression	Liver disease
History of dementia, stroke, or epilepsy	CHF
Alcohol abuse within past month	Cardiogenic or septic shock
Tobacco use	Myocardial infarction
Drug overdose or illicit drug use	Infection
HIV infection	CNS pathology
Psychoactive medications	Urinary retention or fecal impaction
Hyponatremia or hypernatremia	Tube feeding
Hypoglycemia or hyperglycemia	Rectal or bladder catheters
Hypothyroidism or hyperthyroidism	Physical restraints
Hypothermia or fever	Central line catheters
Hypertension	Malnutrition or vitamin deficiencies
Hypoxia	Procedural complications
Acidosis or alkalosis	Visual or hearing impairment
Pain	Sleep disruption
Fear and anxiety	

BUN, Blood urea nitrogen; *CHF,* congestive heart failure; *CNS,* central nervous system; *HIV,* human immunodeficiency virus.

agitation and delirium (Box 2.1). A thorough approach to the treatment and support of the acute illness (e.g., controlling sources of sepsis and giving appropriate antibiotics; correcting hypoxia, metabolic disturbances, dehydration, and hyperthermia; normalizing sleep/wake cycles), in addition to minimizing iatrogenic factors (e.g., excessive sedation), can

TABLE 2.2 Mnemonics for Risk Factors for Delirium and Agitation

IWATCHDEATH	DELIRIUM	THINK
Infection	**D**rugs	**T**oxic situations (CHF, shock, organ failure)
Withdrawal	**E**lectrolyte and physiologic abnormalities	**H**ypoxemia/**H**ypercarbia
Acute metabolic	**L**ack of drugs (withdrawal)	**I**nfection, **I**nflammation, **I**mmobility
Trauma/pain	**I**nfection	**N**onpharmacologic interventions
Central nervous system pathology	**R**educed sensory input (blindness, deafness)	**K**$^+$ or other electrolyte abnormalities
Hypoxia	**I**ntracranial problems (CVA, meningitis, seizure)	
Deficiencies (vitamin B_{12}, thiamine)	**U**rinary retention and fecal impaction	
Endocrinopathies (thyroid, adrenal)	**M**yocardial problems (MI, arrhythmia, CHF)	
Acute vascular (hypertension, shock)		
Toxins/drugs		
Heavy metals		

CHF, Congestive heart failure; *CVA,* cerebrovascular accident; *MI,* myocardial infarction.

BOX 2.1 Commonly Used Drugs Associated With Delirium and Agitation

Benzodiazepines	H_2 blockers
Opiates (especially meperidine)	Antibiotics
Anticholinergics	Corticosteroids
Antihistamines	Metoclopramide

reduce the incidence and/or severity of delirium and its attendant complications. A retrospective study conducted on postoperative delirium, specifically in patients undergoing cardiopulmonary bypass, has alluded to a decreased incidence of delirium in patients pretreated with statins.[29] Furthermore, ICU statins have been associated with decreased delirium, most significantly in the early stages of sepsis; in contrast to this, discontinuation of statins has been shown to be associated with increased delirium.[30] Randomized controlled trials, however, have yet to show a reduction in delirium outcomes with the use of statins versus no statins.[31,32]

PATHOPHYSIOLOGY

The pathophysiology of delirium is poorly understood, although there are a number of hypotheses.[33] It is likely that that the delirium is a result of the interaction of multiple pathophysiologic hypotheses rather than the result of one prevailing hypothesis. There are primary hypotheses:

- **Monoamine Axis Hypothesis.** Multiple neurotransmitters have been implicated, including dopamine (excess), acetylcholine (relative depletion), γ-aminobutyric acid (GABA), serotonin, endorphins, norepinephrine, and glutamate.[34–36] Elevated norepinephrine levels have been found in hyperactive delirium patients and,

when measured after traumatic brain injury, they are associated with poor neurologic status.[37]

- **Neuroinflammatory Hypothesis.** Inflammatory mediators, such as tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1), and other cytokines and chemokines, have been implicated in the pathogenesis of endothelial damage, thrombin formation, and microvascular dysfunction in the central nervous system (CNS), contributing to delirium.[36,38,39] Studies in the ICU have strengthened the evidence of a role for endothelial dysfunction in increasing the prevalence and duration of delirium.[40]
- **Cholinergic Deficiency Hypothesis.** Impaired oxygen metabolism contributes to cholinergic deficiency in the brain. According to this hypothesis, delirium is a result of cerebral insufficiency secondary to a global failure in oxidative metabolism.[41,42] In postoperative cardiac surgery patients, oxidative damage is associated with increased neuronal injury and postoperative delirium.[43]
- **Amino Acid Hypothesis.** Increased cerebral uptake of tryptophan and tyrosine can lead to elevated levels of serotonin, dopamine, and norepinephrine in the CNS. Altered availability of these amino acids is associated with increased risk of development of delirium.[44,45]

ASSESSMENT

The Society of Critical Care Medicine (SCCM) has recently updated guidelines for the use of sedatives and analgesics in the ICU.[46] The SCCM has recommended the routine monitoring of pain, anxiety, and delirium and the documentation of responses to therapy for these conditions.[46] These updated guidelines further include immobility and sleep disruption to emphasize the importance of mobility and adequate sleep hygiene in the acute care setting.

Many scales are available for the assessment of agitation and sedation, including the Ramsay Scale,[47] the Riker Sedation-Agitation Scale (SAS),[48] the Motor Activity Assessment Scale (MAAS),[49] the Richmond Agitation-Sedation Scale (RASS),[50] the Adaptation to Intensive Care Environment (ATICE)[51] scale, and the Minnesota Sedation Assessment Tool (MSAT).[51] Most of these scales have good reliability and validity among adult ICU patients and can be used to set targets for goal-directed sedative administration. The SAS, which scores agitation and sedation using a 7-point system, has excellent inter-rater reliability (kappa = 0.92) and is highly correlated (r^2 = 0.83–0.86) with other scales. The RASS (Table 2.3), however, is the only method shown to detect variations in the level of consciousness over time or in response to changes in sedative and analgesic drug use.[52] The 10-point RASS scale has discrete criteria to distinguish levels of agitation and sedation. The evaluation of patients consists of a three-step process. First, the patient is observed to determine whether he or she is alert, restless, or agitated (0 to +4). Second, if the patient is not alert and does not show positive motoric characteristics, the patient's name is called and his or her sedation level scored based on the duration of eye contact (−1 to −3). Third, if there is no eye opening on verbal stimulation, the patient's shoulder is shaken or pressure applied over the sternum by rubbing and the response noted (−4 or −5). This assessment takes less than 20 seconds in total and correlates well with other measures of sedation (e.g., Glasgow Coma Scale [GCS], bispectral electroencephalography, and neuropsychiatric ratings).[50]

Until recently, there was no valid and reliable way to assess delirium in critically ill patients, many of whom are nonverbal because of sedation or mechanical ventilation.[53,54] A number of tools have been developed to aid in the detection of delirium in the ICU. These tools have been validated for use in both intubated and nonintubated patients and measured against a "gold standard," the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) criteria. The tools are the Confusion Assessment Method for the ICU (CAM-ICU)[53,55–58] and the Intensive Care Delirium Screening Checklist (ICDSC).[11] Although there was initial hesitance about their ability to detect delirium in neurologically injured patients, delirium screening has shown to be possible, with delirious features remaining an important predictor for clinical outcomes.[59]

The CAM-ICU (Fig. 2.2) is a delirium measurement tool developed by a team of specialists in critical care, psychiatry, neurology,

TABLE 2.3 Richmond Agitation-Sedation Scale

+4	Combative	Combative, violent, immediate danger to staff
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive
+2	Agitated	Frequent nonpurposeful movement; fights ventilator
+1	Restless	Anxious, apprehensive, but movements not aggressive or vigorous
0	Alert and calm	
−1	Drowsy	Not fully alert but has sustained (>10 sec) awakening (eye opening/contact) to voice
−2	Light sedation	Drowsy; briefly (<10 sec) awakens to voice or physical stimulation
−3	Moderate sedation	Movement or eye opening (but no eye contact) to voice
−4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation
−5	Unarousable	No response to voice or physical stimulation

Procedure For Assessment

1. Observe patient. Is patient alert, restless, or agitated?	(Score 0 to +4)
2. If not alert, state patient's name and tell him or her to open eyes and look at speaker. Patient awakens, with sustained eye opening and eye contact.	(Score −1)
3. Patient awakens, with eye opening and eye contact, but not sustained.	(Score −2)
4. Patient does not awaken (no eye contact) but has eye opening or movement in response to voice.	(Score −3)
3. Physically stimulate patient by shaking shoulder and/or rubbing sternum. No response to voice, but response (movement) to physical stimulation.	(Score −4)
4. No response to voice or physical stimulation.	(Score −5)

From Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: Validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med* 2002;166(10):1338–1344.

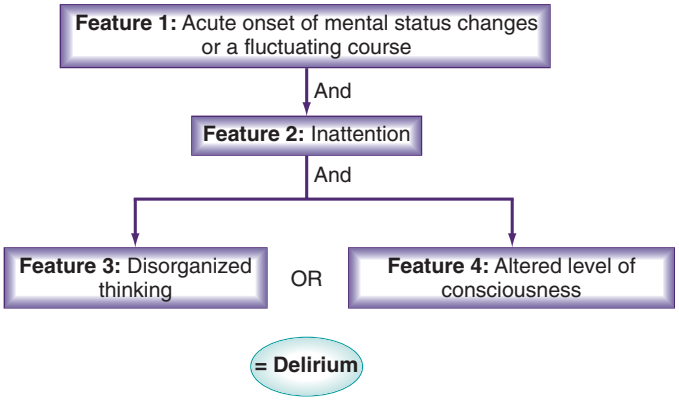


Fig. 2.2 Confusion Assessment Method for the Intensive Care Unit (CAM-ICU).

and geriatrics.[53,54] Administered by a nurse, the evaluation takes only 1–2 minutes to conduct and is 98% accurate in detecting delirium as compared with a full DSM-V assessment by a geriatric psychiatrist.[53,55] To perform the CAM-ICU, patients are first evaluated for level of consciousness; patients who respond to verbal commands (a RASS score of −3 or higher level of arousal) can then be assessed for delirium. The CAM-ICU comprises four features: (1) a change in mental status from baseline or a fluctuation in mental status, (2) inattention, (3) disorganized thinking, and (4) altered level of consciousness. Delirium is diagnosed if patients have features 1 and 2 and either feature 3 or 4 is positive (see Fig. 2.2).

The ICDSC[11] (Table 2.4) is a checklist-based assessment tool that evaluates inattention, disorientation, hallucination, delusion or psychosis, psychomotor agitation or retardation, inappropriate speech or mood, sleep/wake cycle disturbances, and fluctuations in these symptoms. Each of the eight items is scored as absent or present (0 or 1), respectively, and summed. A score of 4 or above indicates delirium, and 0 indicates no delirium. Patients with scores between 1 and 3 are considered to have subsyndromal delirium,[60] which has worse prognostic implications than the absence of delirium but a better prognosis than clearly present delirium.

Previous studies have called into question the usefulness of delirium evaluations for patients under sedation.[61,62] A small subset of patients (approximately 10%) were noted to have rapidly reversible sedation-related delirium, but unfortunately in this study the majority of patients continued to have persistent delirium even after interruption of sedation. Thus when feasible, delirium evaluation should be performed after interruption of sedation; however, delirium evaluations should not be forgone just because a patient is under sedation because the omission of the diagnosis would be far worse than overdiagnosing delirium in a handful of patients.

MANAGEMENT

The development of effective evidence-based strategies and protocols for prevention and treatment of delirium awaits data from ongoing randomized clinical trials of both nonpharmacologic and pharmacologic strategies. A brief overview is provided here.

When agitation or delirium develops in a previously comfortable patient, a search for the underlying cause should be undertaken before attempting pharmacologic intervention. A rapid assessment should be performed, including assessment of vital signs and physical examination to rule out life-threatening problems (e.g., hypoxia, self-extubation, pneumothorax, hypotension), or other acutely reversible physiologic causes (e.g., hypoglycemia, metabolic acidosis, stroke, seizure, pain). The previously mentioned IWATCHDEATH and DELIRIUM mnemonics can be particularly helpful in guiding this initial evaluation.

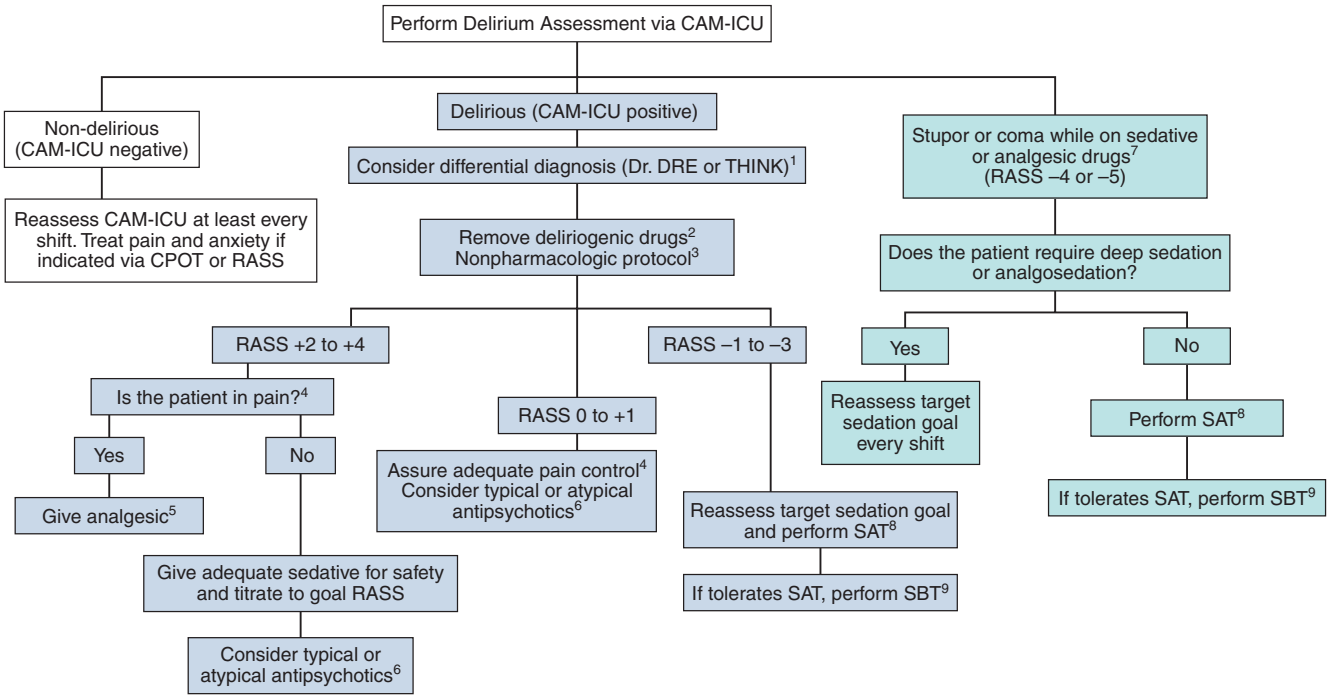
Once life-threatening causes are ruled out as possible etiologies, aspects of good patient care such as reorienting patients, improving sleep and hygiene, providing visual and hearing aids if previously used, removing medications that can provoke delirium, and decreasing the use of invasive devices if not required (e.g., bladder catheters, restraints), should be undertaken.

The use of the ABCDEF Bundle (**A**ssess, prevent, and manage pain; **B**oth spontaneous awakening and breathing trials; **C**hoice of appropriate sedation; **D**elirium monitoring and management; **E**arly mobility and exercise; and **F**amily engagement and empowerment) has been shown to decrease the incidence of delirium and improve patient outcome (Fig. 2.3).[27,28] This algorithm, building on the PADIS 2018 guidelines,[46] involves the following: (1) Routine *assessment* of agitation, depth and quality of sedation, and delirium using appropriate scales (RASS and SAS for agitation and sedation and CAM-ICU or ICDSC for delirium). They recommend using protocol target-based sedation and

TABLE 2.4 Intensive Care Delirium Screening Checklist

Patient Evaluation	
Altered level of consciousness	(A–E)*
Inattention	Difficulty in following a conversation or instructions. Easily distracted by external stimuli. Difficulty in shifting focus. Any of these scores 1 point.
Disorientation	Any obvious mistake in time, place, or person scores 1 point.
Hallucinations-delusions-psychosis	The unequivocal clinical manifestation of hallucination or behavior probably attributable to hallucination or delusion. Gross impairment in reality testing. Any of these scores 1 point.
Psychomotor agitation or retardation	Hyperactivity requiring the use of additional sedative drugs or restraints to control potential danger to self or others. Hypoactivity or clinically noticeable psychomotor slowing.
Inappropriate speech or mood	Inappropriate, disorganized, or incoherent speech. Inappropriate display of emotion related to events or situation. Any of these scores 1 point.
Sleep/wake cycle disturbance	Sleeping less than 4 h or waking frequently at night (do not consider wakefulness initiated by medical staff or loud environment). Sleeping during most of the day. Any of these scores 1 point.
Symptom fluctuation	Fluctuation of the manifestation of any item or symptom over 24 h scores 1 point.
Total Score (0–8)	

*Level of consciousness:
A—No response: score 0.
B—Response to intense and repeated stimulation (loud voice and pain): score 0.
C—Response to mild or moderate stimulation: score 1.
D—Normal wakefulness: score 0.
E—Exaggerated response to normal stimulation: score 1.
Available at: http://www.acgme.org/acgmeweb/tabid/445/GraduateMedicalEducation/SingleAccreditationSystemforAOA-ApprovedPrograms.aspx.



1. Dr. DRE:
   Diseases: Sepsis, CHF, COPD
   Drug **R**emoval: SATs and stopping benzodiazepines/narcotics
   Environment: Immobilization, sleep and day/night orientation, hearing aids, eye glasses, noise
   THINK:
   Toxic Situations – CHF, shock, dehydration – Deliriogenic meds (tight titration) – New organ failure (liver, kidney, etc.)
   Hypoxemia
   Infection/sepsis (nosocomial), immobilization
   Nonpharmacologic interventions[3]
   K$^+$ or electrolyte problems
2. Consider stoppinig or substituting deliriogenic medications such as benzodiazepines, anticholinergic medications (metoclopramide, H_2 blockers, promethazine, diphenhydramine), steroids, etc.
3. See nonpharmacologic protocol – see below.
4. If patient is nonverbal, assess via CPOT, or if patient is verbal assess via visual analog scale.
5. Analgesia – Adequate pain control may decrease delirium. Consider opiates, non-steroidals, acetaminophen, or gabapentin (neuropathic pain).
6. Typical or atypical antipsychotics. Discontinue if high fever, QTc prolongation, or drug-induced rigidity.
7. Consider non-benzodiazepine sedation strategies (propofol or dexmedetomidine)
8. Spontaneous Awakening Trial (SAT) – If meets safety criteria (no active seizures, no alcohol withdrawal, no agitation, no paralytics, no myocardial ischemia, normal intracranial pressure, $FiO_2 \leq 70\%$)
9. Spontaneous Breathing Trial (SBT) – If meets safety criteria (no agitation, no myocardial ischemia, $FiO_2 \leq 50\%$, adequate inspiratory efforts, O_2 saturation $\geq 88\%$, no vasopressor use, PEEP ≤ 7.5 cm)

Nonpharmacologic protocol[3]

Orientation
- Provide visual and hearing aids
- Encourage communication and reorient patient repetitively. Have familiar objects from patient's home in the room
- Attempt consistency in nursing staff
- Family engagement and empowerment

Environment
- Sleep hygiene: Lights off at night, on during day.
- Control excess noise (staff, equipment), earplugs
- Early mobilization and exercise
- Music

Clinical parameters
- Maintain systolic blood pressure > 90 mm Hg
- Maintain oxygen saturations >90%

Treat underlying metabolic derangements and infections

Fig. 2.3 Delirium protocol as a part of the ABCDEF Bundle.

targeting the lightest possible sedation, thus exposing the patient to lower cumulative doses of sedatives[63] and/or daily awakening trials[64] and spontaneous breathing trials[65] to reduce the total time spent on mechanical ventilation. Coordination of daily awakening and daily breathing was associated with shorter durations of mechanical ventilation, reduction in length of hospital stay, and no long-term neuropsychologic consequences of waking patients during critical illness.[66,67] (2) *Treatment* should start with treating analgesia first. Choosing the right sedative regimen in critically ill patients is important. Numerous studies have confirmed that benzodiazepines are associated with poor clinical outcomes.[68,69] The guidelines also recommend avoiding rivastigmine and antipsychotics if there is an increased risk of torsades de pointes. (3) *Prevention* also plays an important role. Risk factors for delirium need to be identified and eliminated, particularly with noise and immobility. Exercise and early mobility in ICU patients is associated with decreased length of both ICU and hospital polypharmacy.[70,71] Promoting day/night cycles within the ICU with minimization of noise and disturbance overnight to optimize sleep should be initiated.

Data from the Maximizing Efficacy of Targeted Sedation and Reducing Neurological Dysfunction (MENDS)[68] study and the Safety and Efficacy of Dexmedetomidine Compared with Midazolam (SEDCOM) trial[69] also support the view that dexmedetomidine can decrease the duration and prevalence of delirium when compared with lorazepam or midazolam. A recent large, randomized, multicentered, placebo-controlled trial failed to show benefit for use of haloperidol or ziprasidone in the treatment of delirium.[72] Routine use of antipsychotic medications for the treatment of delirium is not recommended.[46] Pharmacologic therapy should be attempted only after

correcting any contributing factors or underlying physiologic abnormalities. Although these agents are intended to improve cognition, they all have psychoactive effects that can further cloud the sensorium and promote a longer overall duration of cognitive impairment.

Benzodiazepines are not recommended for the management of delirium because they can paradoxically exacerbate delirium. These drugs can also promote oversedation and respiratory suppression. However, they remain the drugs of choice for the treatment of delirium tremens (and other withdrawal syndromes) and seizures.

At times, mechanical restraints may be needed to ensure the safety of patients and staff while waiting for medications to take effect. It is important to keep in mind, however, that restraints can increase agitation and delirium, and their use may have adverse consequences, including strangulation, nerve injury, skin breakdown, and other complications of immobilization.

SUMMARY

Agitation and delirium are very common in the ICU, where their occurrence puts patients at risk of self-injury and poor clinical outcomes. Available sedation and delirium monitoring instruments allow clinicians to recognize these forms of brain dysfunction. Through a systematic approach, life-threatening problems and other acutely reversible physiologic causes can be rapidly identified and remedied. A strategy that focuses on early liberation from mechanical ventilation and early mobilization can help reduce the burden of delirium. Use of antipsychotics should be reserved for patients who pose an imminent risk to themselves or staff.

KEY POINTS

- Delirium and agitation are prevalent within the ICU and unless routinely assessed are frequently overlooked.
- Clinicians should be aware of modifiable and nonmodifiable risk factors for delirium and agitation and work to decrease those risk factors when able.
- Once detected, investigation into the cause of agitation and delirium is necessary, as they may be a harbinger of metabolic, pharmacologic, or physical derangements (i.e., pain, sepsis, withdrawal, hypoxia).
- Several pathophysiologic hypotheses have been proposed to describe the etiology of delirium. It is likely that the presentation of delirium is a result of a combination of these mechanisms.
- Nonpharmacologic treatment bundles are successful in decreasing the incidence of delirium; however, once it occurs, there is limited evidence for the use of pharmacologic medications in decreasing delirium severity or duration.
- Identifying delirium and agitation within the ICU is important. Lack of identification can result in prolonged symptom duration, which is associated with worse survival and functional patient outcomes years after hospital discharge.

References for this chapter can be found at expertconsult.com.

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3

Management of Acute Pain in the Intensive Care Unit

Lauren Coleman, Jin Lee, and Christine Cocanour

INTRODUCTION

Pain management in the critically ill patient is complex. Each patient brings a unique set of sociodemographic, pharmacokinetic, and pharmacogenomic variables that are coupled with underlying psychosocial and medical comorbidities. These not only influence a patient's response to painful stimuli but also to treatment. We know that critically ill patients experience pain at rest, during routine intensive care unit (ICU) care, and during procedures.[1,2] Pain can originate from multiple sources, including somatic, visceral, and neuropathic. Pain may be acute, chronic, or acute on chronic in nature. Comorbidities such as depression and anxiety can exacerbate pain.[3,4] Patients that are younger, female, and of nonwhite ethnicity are more likely to experience more intense pain.[4–8] Aging patients experience many physiologic changes that may decrease their perception of pain and increase their vulnerability to the adverse effects of pain medications.[9–11]

It is imperative to adequately treat pain in the ICU patient. Pain during a procedure is not only influenced by the type of procedure (including routine care such as turning) but also by preprocedural pain intensity.[2,5,8,12,13] Adequate assessment of pain and preemptive analgesia are essential.[14] Inadequate pain control contributes to the development of delirium, and severe pain may lead to cardiac instability (tachycardia, bradycardia, hypertension, and/or hypotension), respiratory distress (desaturation, bradypnea, and/or ventilator distress), and immunosuppression.[14,15]

To optimize an analgesic regimen, it is important to obtain a thorough past medical history that includes a complete list of medications and whether alcohol, tobacco, or opioid dependence is present. Managing drug withdrawal in addition to achieving satisfactory analgesia requires a multimodal approach.

Multimodal analgesia combines two or more drug classes or techniques, employing different mechanisms of action that may target multiple pain pathways in order to achieve a synergistic or additive effect. This results in lower opioid consumption with the same or improved level of comfort.[16] Multimodal analgesia may include opioids, nonopioid analgesics such as nonsteroidal antiinflammatory drugs (NSAIDs) or gabapentinoids, regional or neuraxial blocks, and nonpharmacologic therapies. Each patient's medical history, allergies, age, injuries, and comorbidities will dictate the optimum regimen. Pain management protocols that mandate the use of validated pain and sedation scales consistently decrease the consumption of opioids and sedatives in ICU patients.[17,18]

ASSESSMENT

An assessment-driven and standardized pain management protocol improves ICU patient outcomes, but assessment of pain in the critically ill patient can be challenging. Many ICU patients are ventilated, cognitively impaired, and/or unable to self-report pain. Consequently, these patients are at risk for undertreatment of their pain. Valid assessment tools help guide analgesia while avoiding excess medication administration in those patients with adequate pain control.[16,19–22] A number of assessment tools are available for use in the ICU patient.[14]

For those patients able to self-report pain, the Numeric Rating Scale (NRS) in a visual format had the best sensitivity, negative predictive value, and accuracy in ICU patients.[14] More recently, the Defense and Veterans Pain Rating Scale (DVPRS) has become increasingly popular.[23] It combines a 1–10 pain scale with facial expressions and colors to express pain intensity. The DVPRS also includes supplementary questions to measure the degree to which pain interferes with a patient's usual activity, sleep, mood, and stress (Fig. 3.1).

The Behavioral Pain Scale (BPS) and the Critical Care Pain Observation Tool (CPOT) (Fig. 3.2) have the greatest validity and reliability for monitoring pain in those unable to self-report.[14] BPS is a three-domain assessment tool with four possible scores in each domain. Scores range from 3 to 12, with scores above 6 indicating an unacceptable level of pain.[14,24–26] CPOT is similar, with four domains and scores ranging from 0 to 2 in each domain. The possible score ranges from 0 to 8, with 3 or above indicating the presence of pain.[27–32]

Vital signs (heart rate, blood pressure, respiratory rate, oxygen saturation, and end tidal carbon dioxide) are not considered valid indicators for pain in critically ill patients and should only be used as cues to initiate further evaluation using one of the validated assessment measures.[14] In unresponsive or paralyzed patients in which the validated scales are impossible to use, no current assessment methods are available. Promising technology under development for this patient population includes measuring heart rate variability (Analgesia Nociception Index), incorporating several physiologic parameters (Nociception Level Index), and examining pupillary reflex dilation using video pupillometry.[33–38]

OPIOIDS

Historically, opioids were considered the mainstay of treatment for non-neuropathic pain in the critically ill patient population because of their high potency and efficacy.[14,39,40] Opioids act at specific G-protein–coupled receptors designated delta, kappa, and mu. These exist predominantly in the central nervous system, but also peripherally and in certain organs (notably the gastrointestinal tract and heart).[41] By acting at these receptors, opioids decrease the perception of pain without inducing loss of consciousness. All clinically relevant opioids are active at the mu receptor, and some have additional activity at other receptors.[41]

The decision regarding which opioid to prescribe is highly dependent on specific patient comorbidities and circumstances. When titrated appropriately, all intravenous opioids are considered equally

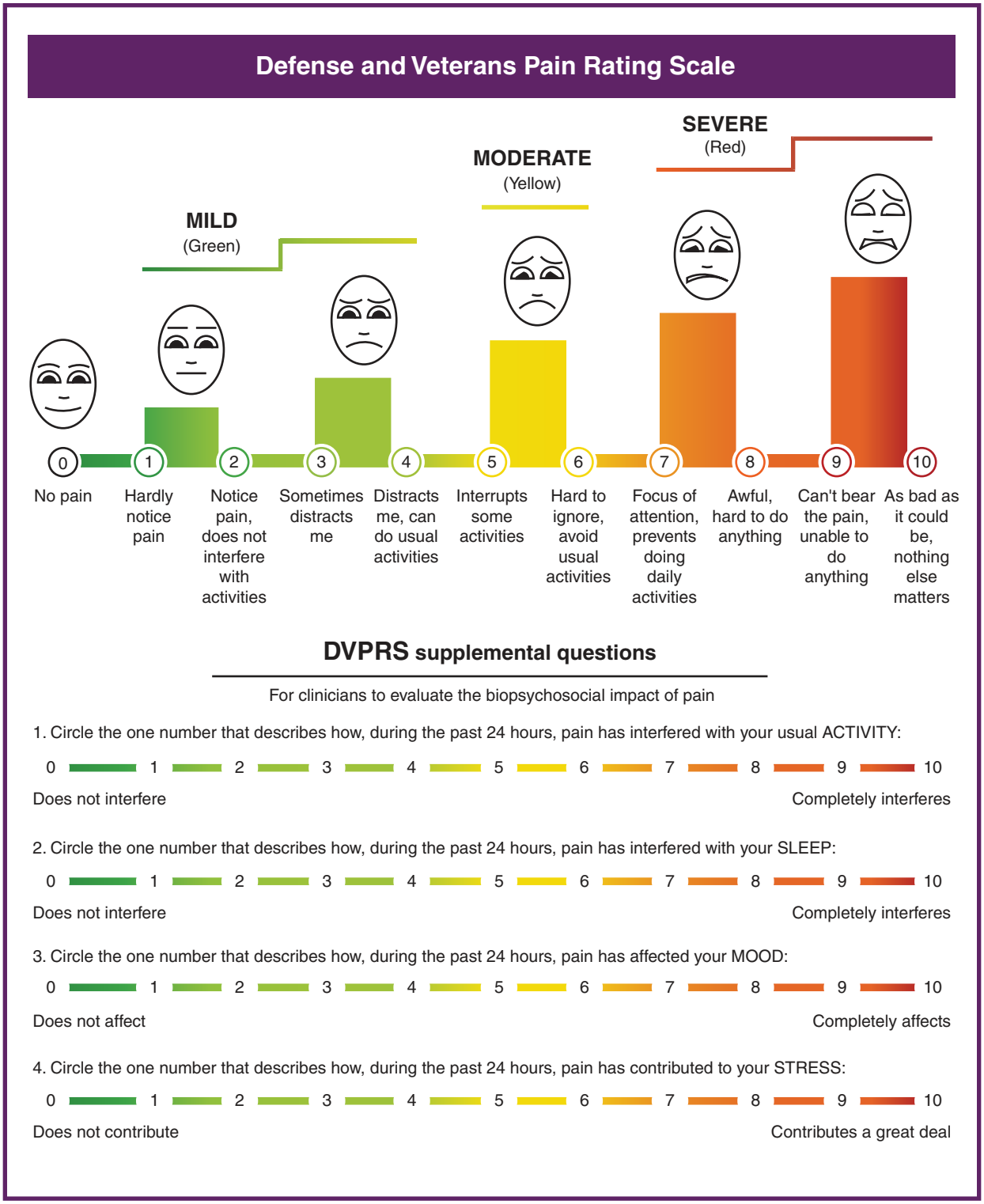

Fig. 3.1 The DVPRS is a graphic pain reporting tool for patients that can self-report. (From https://www.dvcipm.org/site/assets/files/1084/dvprs_single_page.pdf.)

Critical Care Pain Observation Tool

Indicator	Description	Score	
Facial expression	No muscular tension observed	Relaxed, neutral	0
	Presence of frowning, brow lowering, orbit tightening, and levator contraction	Tense	1
	All of the above facial movements plus eyelid tightly closed	Grimacing	2
Body movements	Does not move at all	Absence of movements	0
	Slow, cautious movements, touching or rubbing the pain site, seeking attention through movements	Protection	1
	Pulling tube, attempting to sit up, moving limbs/thrashing, not following commands, striking at staff, trying to climb out of bed	Restlessness	2
Muscle tension Evaluation by passive flexion and extension of upper extremities	No resistance to passive movements	Relaxed	0
	Resistance to passive movements	Tense, rigid	1
	Strong resistance to passive movements, inability to complete them	Very tense or rigid	2
Compliance with the ventilator (intubated patients)	Alarms not activated, easy ventilation	Tolerating ventilator or movement	0
	Alarms stop spontaneously	Coughing but tolerating	1
	Asynchrony: blocking ventilation, alarms frequently activated	Fighting ventilator	2
OR Vocalization (extubated patients)	Talking in normal tone or no sound	Talking in normal tone or no sound	0
	Sighing, moaning	Sighing, moaning	1
	Crying out, sobbing	Crying out, sobbing	2
Total, range			0–8

Behavioral Pain Scale

Item	Description	Score
Facial expression	Relaxed	1
	Partially tightened (e.g., brow lowering)	2
	Fully tightened (e.g. eyelid closing)	3
	Grimacing	4
Upper limbs	No movement	1
	Partially bent	2
	Fully bent with finger flexion	3
	Permanently retracted	4
Compliance with ventilation	Tolerating movement	1
	Coughing but tolerating ventilation for most of the time	2
	Fighting ventilator	3
	Unable to control ventilation	4

Fig. 3.2 Critical Care Pain Observation Tool (CPOT) and Behavioral Pain Scale (BPS) are two commonly used tools for monitoring pain in those patients that are unable to self-report. (Adapted from Gelinas C, Fillion L, Puntillo KA, et al. Validation of the critical-care pain observation tool in adult patients. *Am J Crit Care*. 2006;15(4):420–427 and Payen JF, Bru O, Bosson JL, et al. Assessing pain in critically ill sedated patients by using a behavioral pain scale. *Crit Care Med*. 2001;29(12):2258–2263.)

TABLE 3.1 Opioid Agents and Considerations for Use

Opioid	Dosage Forms	Onset	Pharmacokinetics	Considerations
Fentanyl	IV, IM, intranasal, transdermal, transmucosal	1–2 min	• Metabolized by the liver • No active metabolites	• Very potent (100 times the potency of morphine) • Rapid onset and short duration • Prolonged use leads to accumulation in peripheral compartments • Less association with histamine release
Hydromorphone	PO, IV, IM, SQ	5–15 min (IV) 30 min (PO)	• Metabolized by the liver into weak metabolites • Excreted renally	• Potent (7–10 times the potency of morphine) • Improved safety profile over morphine in renal impairment • Less association with histamine release
Morphine	PO, IV, IM, SQ, transdermal, transmucosal	5–10 min (IV) 15–60 min (PO)	• Metabolized by the liver into potent metabolites • Excreted renally	• Use with extreme caution in renal impairment • Use with caution in hepatic impairment • High association with histamine release (can lead to bronchospasm and hypotension)
Oxycodone	PO	10–30 min	• Metabolized by the liver to multiple metabolites (oxymorphone)	• Available in combination or alone
Hydrocodone	PO	15–30 min	• Metabolized by the liver to multiple metabolites (hydromorphone)	• Only available as a combination currently • Use with caution in those with severe asthma
Methadone	PO	30–60 min	• Metabolized by the liver • No active metabolites • Excreted in feces	• Plasma levels and risk of death peak 5 days after start • Respiratory depressant effect occurs later than analgesic effect • Watch for QTc prolongation • Inhibits serotonin reuptake and can also produce analgesia via NMDA receptor antagonism
*Tramadol**	PO	60 min	• Metabolized by the liver into O-desmethyl tramadol • Excreted renally	• Also modulates serotonin and norepinephrine uptake (can lead to seizures) • Less respiratory depression and fewer GI side effects than pure opioids

*Although not a typical opioid, tramadol is structurally related to morphine and has effects at opioid receptors
GI, Gastrointestinal; *IM,* intramuscular; *IV,* intravenous; *NMDA,* N-methyl-D-aspartate; *PO,* oral; *SQ,* subcutaneous.

effective with regard to analgesic efficacy and clinical outcomes.[39] However, studies have shown patients may demonstrate variability in opioid pharmacodynamics and pharmacokinetics, resulting in more favorable reactions to one opioid over another.[42] Thus providers must be comfortable with many different opioids, depending on the patient's reaction and clinical course. Common parenteral and oral opioids are summarized in Table 3.1.

Though opioids remain a cornerstone of pain management, considerable attention is now focused on limiting the opioids required through the use of multimodal therapy. This is primarily because of the many side effects of opioid-centered analgesia. Short term, these can include physical dependence, ileus, constipation, nausea and vomiting, respiratory depression, sedation, pruritus, and urinary retention.[43] Opioids may increase ICU length of stay and worsen post-ICU patient outcomes. Long-term sequelae of opioid use include addiction, immunosuppression, and opioid-induced hyperalgesia. These complications are prevalent, regardless of the specific opioid used or the route of administration.

Particular attention should be paid to bowel dysfunction associated with opioids secondary to binding of mu receptors in the enteric nervous system.[44] Opioids often induce constipation or worsen preexisting constipation; prevalence of these conditions with opioid use vary in the literature from 22% to 81% of patients.[44] Thus prevention via a robust bowel regimen that includes laxatives and/or bulking agents is an essential consideration when prescribing opioids.

ACETAMINOPHEN

Despite being a commonly used analgesic and antipyretic, acetaminophen's exact mechanism of action remains unknown. It has consistently been shown to reduce opioid requirements when used as an adjunct; furthermore, acetaminophen has minimal side effects. For the critically ill patient, acetaminophen offers an advantage in that it can be administered via multiple routes of administration (intravenous [IV], orally [PO], nasogastric [NG], per rectum [PR]). Although the IV formulation has a slightly faster onset when used as a first dose, there is minimal difference between the IV and enteral/rectal formulations when administered in a scheduled manner.[45] Acetaminophen carries a risk of hepatotoxicity, though this is more commonly noted when high doses are used for chronic pain rather than short-term acute pain. In 2011, the Food and Drug Administration (FDA) released a recommendation to reduce the maximum daily dose of acetaminophen from 4000 mg/day to 3000 mg/day; however, it is important to note that this recommendation was aimed at consumers exposed to numerous over-the-counter acetaminophen-containing combination products. In the inpatient setting, the maximum daily dose should remain 4000 mg/day.[46]

NSAIDs

NSAIDs work as analgesics and antipyretics by inhibiting cyclooxygenase (COX) enzymes, thereby reducing the formation of prostaglandins.

A wide variety of NSAIDs are available with numerous routes of administration (IV, PO, NG, PR, topical) and varying degrees of selectivity to COX-1 and COX-2.

Historically, there has been a reluctance to use NSAIDs in the acute pain setting because of their adverse effects, including increased risk of gastrointestinal bleeding, nephrotoxicity, impaired platelet function, and impaired wound healing. NSAIDs have long been avoided in the setting of fractures because of the risk of nonunion; however, more recent literature reviews have shown that this does not appear to be a long-term issue, particularly with early postinjury or postoperative administration.[47–49] Thus the most recent guidelines support their use in this setting.[50]

Platelet inhibition is primarily associated with inhibition of COX-1 and can be avoided with the use of COX-2 selective agents such as celecoxib. Unfortunately, COX-2 selective agents are not without risk—they are contraindicated after coronary artery bypass graft surgery and carry a risk of cardiovascular thrombotic events, such as myocardial infarction and stroke. Despite their known risks, NSAIDs can be beneficial in mitigating opioid exposure in select patient populations.

GABAPENTINOIDS

Opioids and other medications that often work well for nociceptive pain offer minimal benefit for neuropathic pain. For patients who suffer from diabetic neuropathy, spinal cord injury, burn pain, phantom limb, post-stroke central pain, postherpetic neuralgia, or other forms of neuropathic pain, gabapentinoids should be considered.[51–53] Gabapentin and its prodrug, pregabalin, work by inhibiting presynaptic calcium channels. Originally developed as antiepileptic medications, these agents have shown to be effective in the management of chronic neuropathic pain.[54] Although less data are available regarding their use for acute pain, gabapentinoids should be considered when a source of neuropathic pain is suspected. Caution should be exercised when initiating gabapentin or pregabalin in the elderly, as these agents are known to cause somnolence and dizziness. In patients with renal dysfunction, doses should be adjusted accordingly.

MUSCLE RELAXANTS

Patients who experience pain secondary to muscle spasm may find benefit from antispasmodic agents such as methocarbamol, cyclobenzaprine, baclofen, or diazepam. However, literature regarding their efficacy is scant, particularly in the acute pain setting. Careful consideration must be given before using these agents, given the associated risk of sedation. This is especially a concern in the older adult patient.

KETAMINE

Ketamine is a phencyclidine derivative that acts as an N-methyl-D-aspartate (NMDA) antagonist and has been used in the perioperative and procedural setting for its anesthetic and analgesic effects. More recently, subanesthetic doses of ketamine have been used in a continuous fashion to provide analgesia without eliciting hallucinations or other psychomimetic effects. Benefits of ketamine in the critically ill setting include its neutral hemodynamic effects and its lack of respiratory suppression. Traditionally, ketamine has been avoided in patients with cardiovascular comorbidities and patients with elevated intracranial pressure (ICP); however, recent literature suggests that ketamine may be used safely in patients with ICP concerns.[55]

At higher steady-state levels, magnesium has been shown to exhibit similar anti-NMDA activity in the perioperative setting.[56] Although this effect has not yet been demonstrated in the ICU setting, studies are currently ongoing.

LIDOCAINE

Topical lidocaine patches can be used for localized pain to avoid systemic effects, but their efficacy remains unclear, and caution should be exercised near open wounds. Lidocaine drips have been used in the perioperative setting to reduce opioid requirements and ileus recovery time, but its role in the critical care setting remains largely unknown.[57,58]

α_2 AGONISTS

Centrally acting α_2 agonists, such as dexmedetomidine and clonidine, may offer analgesic effects while avoiding respiratory depression. However, data regarding their use for acute pain in the critically ill population are minimal, and cardiovascular effects such as hypotension and bradycardia limit their use in hemodynamically unstable patients.

A summary of the previously discussed nonopioid analgesics can be found in Table 3.2.

REGIONAL ANESTHESIA

Regional anesthesia techniques include neuraxial blocks (such as spinal and epidural catheters), paravertebral blocks, intercostal nerve blocks, transversus abdominis plane blocks, and peripheral nerve blocks of the extremities. The use of regional anesthesia is associated with improved analgesia in many patient populations, including postoperative and polytrauma patients. Many studies have also shown that the use of regional anesthesia leads to decreases in opioid-related side effects.[43] Of special interest within the critically ill population is the association between epidural analgesia and improved global pulmonary outcomes.[59]

Despite the many benefits of regional anesthesia documented in the literature, it remains generally underused in the critically ill population for a multitude of reasons. Hemodynamic instability and sepsis are considered relative contraindications to neuraxial techniques.[60] Critically ill patients may also require anticoagulation or develop coagulopathy, both of which may limit the ability of providers to perform neuraxial techniques safely. Finally, caution must be exercised in patients at risk for developing compartment syndrome because of the potential masking of symptoms. Of note, however, this can also be a concern with systemic analgesia.

MUSIC MODALITIES

Music modalities for pain management can broadly be separated into music medicine and music therapy. Music medicine uses music to promote relaxation, provide distraction, and/or alleviate tension.[61] Music therapy is instead a holistic approach involving a music therapist that focuses on the healing process of music via personal interaction.

Within the critically ill population, three small studies have found minimal to moderate improvements in self-reported and assumed pain scores through various forms of music medicine.[62–64] Two of these studies even found temporary improvement in pain scores for mechanically ventilated patients undergoing music medicine.[63,64] In postoperative patients, a recent meta-analysis of 97 studies found that music medicine had a small to moderate effect on reducing opioid usage, and music therapy was found to decrease patient perception of pain intensity.[61] Music interventions generally had a stronger impact

TABLE 3.2 Nonopioid Agents and Considerations for Use

Class	Medication	Dosage Forms	Considerations
Acetaminophen	Acetaminophen	PO, IV, rectal	• Caution in hepatic dysfunction • IV formulation associated with hypotension
NSAIDs	Nonselective Ibuprofen	PO, IV, topical, rectal	• Caution in patients with gastrointestinal bleeding, acute kidney injury, and cardiovascular events • Ketorolac carries a black box warning cautioning against more than 5 days of use to mitigate these risks
	(COX-1 selective) Ketorolac Naproxen		
	(COX-2 selective) Celecoxib	PO	
Gabapentinoids	Gabapentin	PO	• Consider for neuropathic pain • Caution in elderly patients and renal dysfunction • Monitor for dizziness and drowsiness
	Pregabalin		
	Venlafaxine		
Muscle relaxants	Baclofen	PO	• Caution in elderly patients and renal dysfunction • Tolerance/dependence may develop with prolonged use of baclofen
	Methocarbamol		
	Cyclobenzaprine		
	Diazepam	PO, IV	• Associated with sedation and respiratory depression
NMDA antagonists	Ketamine	IV, IM, PO	• Contraindicated in history of CVA, severe cardiac decompensation, or conditions in which an increase in blood pressure may be harmful • Increased risk of laryngospasm (procedural doses) • Potential for tolerance with long-term use • Monitor for emergence reactions
	Magnesium (high dose)	IV, PO	• Contraindicated in patients with bradycardia • IV bolus can be associated with hypotension • Caution in patients with renal dysfunction and neuromuscular disease
Sodium channel blockers	Lidocaine	IV, topical	• IV product contraindicated in heart block • Monitor for neurologic and cardiac toxicity
α_2 agonists	Dexmedetomidine	IV	• Associated bradycardia and hypotension • Potential for tachyphylaxis to develop with long-term use
	Clonidine	PO	• Associated hypotension and sedation

COX, Cyclooxygenase; *CVA*, cerebrovascular accident; *IM*, intramuscular; *IV*, intravenous; *NSAID*, nonsteroidal antiinflammatory drug; *PO*, oral.
Data from Erstad BL. Attempts to limit opioid prescribing in critically ill patients: Not so easy, not so fast. *Ann Pharmacother*. 2019;53:716–725; O'Connor A, Dworkin R. Treatment of neuropathic pain: An overview of recent guidelines. *Am J Med.* 2009;122, S22—S32; See S, Ginzburg R. Skeletal muscle relaxants. *Pharmacotherapy.* 2008;28(2):207–213.

on acute or procedural pain versus chronic or cancer pain. Given these results, and the fact that music modalities are inexpensive and safe, consideration should be given to employing these modalities in the ICU, pending availability and institutional logistics.

COGNITIVE BEHAVIORAL MODALITIES

Cognitive behavioral modalities include hypnosis, guided imagery, and relaxation methods. Although these modalities have been extensively studied as an adjunct for both acute and chronic pain management, there is unfortunately a paucity of evidence within the critically ill population. Examining the postoperative literature, cognitive behavioral modalities frequently are found to improve postoperative pain and analgesic use.[65] Thus clinical practice guidelines from several prominent medical societies recommend cognitive behavioral therapy as adjunctive treatments in the postoperative patient.[65] As these modalities are noninvasive and associated with minimal harm, the critical care provider may consider incorporating these techniques into pain management.

AROMATHERAPY

Aromatherapy involves the inhalation, topical application, or injection of plant oils with pleasant smells. Common fragrances include bergamot, rose, orange, and mint, though lavender essential oil is one of the most frequently discussed in the literature. Although evidence examining aromatherapy for pain management in the ICU is lacking, a systematic review of randomized controlled trials found that aromatherapy reduces anxiety and improves sleep in critically ill patients.[66] This effect has also been noted in the mechanically ventilated subpopulation.[67]

PHYSICAL MODALITIES

Physical modalities include techniques such as acupuncture, cold or heat therapy, and massage. Although these interventions are generally safe and inexpensive, there is scant scientific literature in the critically ill population. One small study found acupuncture in the ICU to be feasible and safe, but effectiveness of the technique in this setting has not been studied.[68] Furthermore, the impact of physical modalities for

pain management in other patient populations is highly variable. As such, clinical practice guidelines neither recommend nor discourage the use of these techniques for postoperative pain management.[65] Whether the critically ill patient would benefit from these physical modalities is currently unknown.

KEY POINTS

- Pain management in the ICU patient is complex because of unique sociodemographic, pharmacokinetic, and pharmacogenomic variables that are coupled with underlying psychosocial and medical comorbidities.
- The costs of inadequate pain control are high and include the development of delirium, cardiac instability, respiratory distress, and immunosuppression.
- Valid pain assessment tools are important, as they help guide analgesia while avoiding excess medication administration in those patients with adequately controlled pain.
- Multimodal analgesia regimens are highly recommended because of their improved efficacy and an associated decrease in opioid consumption, with resultant reduction in opioid-related side effects.
- Nonpharmacologic modalities for pain control should not be underestimated and may have a role in a well-rounded regimen for pain management.

References for this chapter can be found at expertconsult.com.

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4

Fever and Hyperthermia

Paul Young

> "*Humanity has but three great enemies: fever, famine and war; of these by far the greatest, by far the most terrible, is fever.*"
>
> ***William Osler, from his address to the 47th annual meeting of the American Medical Association, 1896***

Fever is defined as an increase in body temperature as a result of a pathophysiologic response that increases the body's normal thermoregulatory set point. This set point varies with age, gender, the time of the day, and other factors.[1] Although there is no universally agreed-upon definition of what constitutes a febrile temperature,[1] a threshold of ≥38.3°C is perhaps the most commonly applied.[2] Whatever threshold is used, it is important to remember that body temperature varies depending on the route by which it is measured.[3] Because peripheral temperature measurements such as via the axilla or elsewhere on the skin can underestimate core temperature by 1°C or more,[3] continuous monitoring of core temperature is recommended in patients at risk of life-threatening temperature elevations and when precise control of temperature is desirable.

In clinical practice, fever is not always readily distinguishable from hyperthermia. Hyperthermia occurs when the body temperature is elevated but the thermoregulatory set point is normal. It is the result of environmental exposure to heat, increased heat generation, impaired heat loss, or a combination of these, and it implies that normal homeostatic thermoregulatory mechanisms have been overwhelmed. Elevated body temperature, caused by either fever or hyperthermia, is commonly encountered in patients who are in the intensive care unit (ICU). Although infection must always be at the front of one's mind when an elevated body temperature is encountered, there is also a broad differential diagnosis of noninfectious etiologies to consider (Box 4.1). Although many patients develop a fever during the course of an ICU admission, persistent fever is uncommon,[4] except in patients with neurologic conditions. In patients who do not have such conditions, fever typically abates within a day or two unless there is an undrained collection of pus. There are exceptions, and a few of these are notable. High fevers that persist for days or weeks are often a feature of influenza pneumonitis and are almost invariably encountered in patients with severe necrotizing pancreatitis. Among patients with a range of neurologic conditions, including subarachnoid hemorrhage, stroke, and traumatic brain injury, fever is particularly common and often persistent. In young patients with severe traumatic brain injury, persistent high fevers, tachycardia, and hypertension sometimes present a difficult management problem in the weeks after the primary brain injury. One uncommon neurologic condition where persistently elevated body temperature is routinely encountered is anti–N-methyl-D-aspartate (NMDA) receptor autoantibody encephalitis.[5] This condition warrants specific mention because patients with it often need prolonged intensive care, and potentially life-threatening body temperature elevation is sometimes a feature of the disease.[5]

An elevated body temperature in an ICU patient should prompt a clinical assessment undertaken with the differential diagnosis in mind (Box 4.2). Although fever is seen in patients with large myocardial infarctions and thromboembolic disease, the occurrence of fever alone is insufficient reason to undertake diagnostic testing for these because the presence of fever has a low specificity for these conditions. Because fever is a cardinal sign of infection and sepsis is a frequent and often lethal complication of critical illness, particular care should be taken to note new or worsening organ dysfunction and potential sites of infection. Although other diagnostic possibilities should always be considered, in practical terms, the occurrence of elevated body temperature in a critically ill patient is a key trigger for investigation for sepsis. In this regard, the threshold temperature value to trigger such investigation should be reduced as the clinician's view as to the likelihood of infection rises. If the probability of infection is judged to be sufficiently high, investigations for possible sepsis should occur irrespective of the body temperature, and antibiotics should be commenced promptly.

Beyond endeavoring to establish and treat the cause of an elevated body temperature, a key consideration for clinicians is whether to intervene to reduce the temperature.[6] Here the clinician should consider both the degree of temperature elevation and the strength of the evidence to intervene for the particular condition in question (Fig. 4.1).

A diagnosis of hyperthermia indicates that normal thermoregulation has been overwhelmed. Intervention with physical cooling should be initiated. The higher the elevation in body temperature in a patient with hyperthermia, the more rapidly and aggressively one should intervene. If malignant hyperthermia is the diagnosis, dantrolene should be administered promptly.[7]

If the elevation of body temperature is caused by a fever, one needs to consider the possibility that the fever might be beneficial for the patient. In the setting of infection, there is a substantial body of evidence that supports the notion that fever can be adaptive. Fever is a broadly conserved biologic response to infection that is seen in almost all animals. The conservation of a metabolically costly response like fever across biology suggests that it confers some evolutionary advantage. In ICU patients, in keeping with the hypothesis that fever might be of benefit in the setting of infection, increasing fever in the first 24 hours in the ICU is generally associated with reducing mortality risk after adjusting for illness severity in patients.[8] This is the case even for patients with brain infections.[9] In comparison, in the absence of infection, increasing fever is associated with increasing mortality risk.[8,9] Reassuringly, administration of the antipyretic acetaminophen (paracetamol) to febrile patients with known or suspected infection in the ICU in a randomized placebo-controlled trial appeared to be

BOX 4.1 Noninfectious Causes of Elevated Body Temperature

Central Nervous System
Subarachnoid hemorrhage
Intracerebral hemorrhage
Infarction
Hypoxic ischemic encephalopathy
Anti-NMDA receptor autoantibody encephalitis

Cardiac
Myocardial infarction
Pericarditis

Pulmonary
Atelectasis
Pulmonary embolism
Fibroproliferative phase of acute respiratory distress syndrome

Hepatobiliary and Gastrointestinal
Acalculous cholecystitis
Acute pancreatitis
Active Crohn disease
Toxic megacolon
Alcoholic hepatitis

Rheumatologic Syndromes
Vasculitides (e.g., polyarteritis nodosa, temporal arteritis, granulomatosis with polyangiitis)
Systemic lupus erythematosus
Rheumatoid arthritis
Goodpasture syndrome

Endocrine
Hyperthyroidism
Adrenal insufficiency
Pheochromocytoma

Other
Drug reactions ("drug fever")
Transfusion reactions
Neoplasms (especially lymphoma, hepatoma, and renal cell carcinoma)
Malignant hyperthermia
Neuroleptic malignant syndrome
Serotonin syndrome
Opioid withdrawal syndrome
Ethanol withdrawal syndrome
Transient endotoxemia or bacteremia associated with procedures
Devitalized tissue secondary to trauma
Hematoma

NMDA, N-methyl-D-aspartate.

BOX 4.2 Evaluation of New-Onset Fever/Hyperthermia in ICU Patients

History
Is the patient known to have a condition that causes fever?
Are there features in the history that suggest a particular diagnosis?
Is there a change in volume or purulence of respiratory secretions?
Is this a long-stay patient at particular risk of nosocomial infection and/or multidrug-resistant organisms?
Has the patient had a recent exposure to a drug that might be causing fever?

Infusions
Is the patient receiving blood? Consider a transfusion reaction.
Is the patient receiving vasopressors? New vasopressors or escalating vasopressors should prompt consideration of urgent administration of antibiotics.

Ventilator
What is the current level of support in terms of inspired oxygen and PEEP? What is the respiratory system compliance? Has there been a deterioration in pulmonary function that might point to a pulmonary cause for fever?

Monitor
Is the core temperature being continuously monitored? Does the clinical situation warrant consideration of such monitoring? How high is the temperature?
Is there tachycardia? Is the degree of tachycardia of clinical concern?
Is the blood pressure stable? A fall in blood pressure may indicate septic shock.

Equipment
Does the patient have venous or arterial lines? How long have they been in situ? Are there signs of infection like redness or discharge?
Note the amount and appearance of fluid from abdominal drains and intercostal catheters.
If the patient has an external ventricular drain, review recent cell counts and culture results and collect a new sample (unless one was taken recently).
Is there a rectal tube? If the patient has diarrhea, send a specimen to evaluate for *Clostridioides difficile*.
If the patient has an epidural catheter, inspect the insertion site, and examine the patient's lower limb neurology while considering the possibility of an epidural abscess.
If there is a urine catheter, examine urine for both volume and appearance. Oliguria may be a sign of impending sepsis; myoglobinuria may indicate rhabdomyolysis, which can complicate severe hyperthermia.

Key Elements of the Patient Examination
Perform a focused cardiorespiratory and abdominal examination, looking for causes and consequences of fever.
Look for signs of pneumonia.
Look for organomegaly and lymphadenopathy.
Look for signs of endocarditis.
Look at surgical and traumatic wounds (if necessary, remove bandages or dressings).
Note any areas of tenderness. Bony tenderness and joint pain in a patient with *Staphylococcus aureus* bacteremia generally indicates seeding of the infection to that site.
Examine the limbs for signs of deep vein thrombosis.
Perform a vaginal examination to exclude a retained tampon if appropriate.

Investigations
Will vary based on the clinical situation, but most often will include blood cultures, sputum cultures, urine cultures, a full blood count, and a chest x-ray.

ICU, Intensive care unit; *PEEP,* positive end-expiratory pressure.

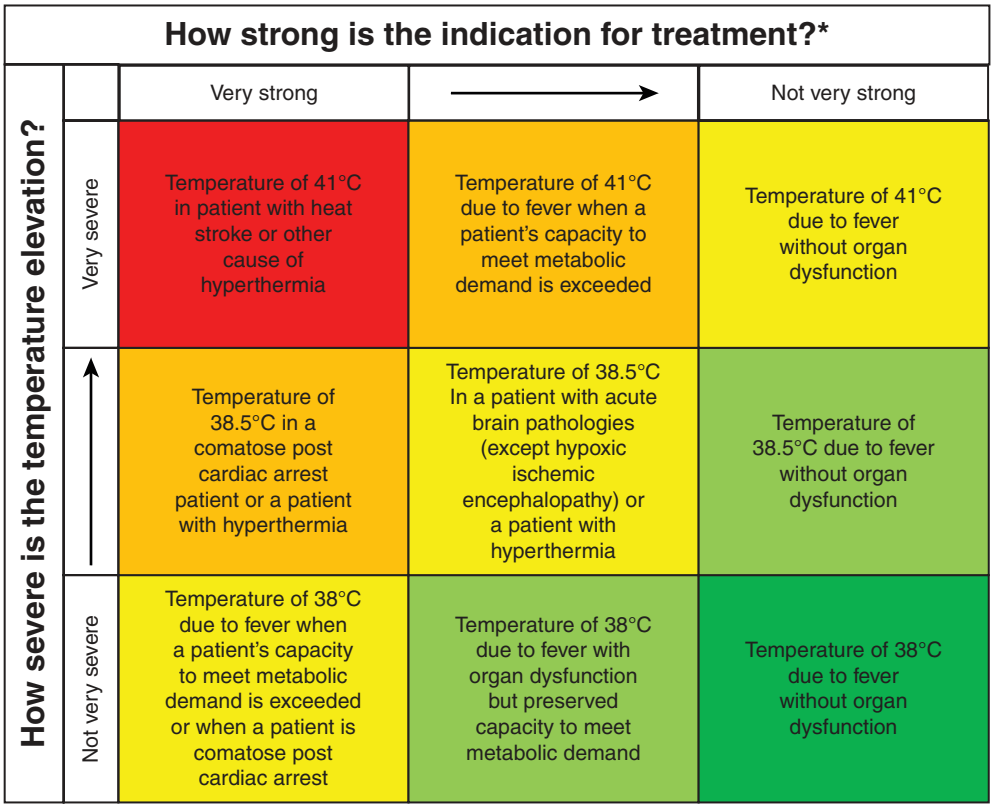

Fig. 4.1 When to Initiate Active Management of Elevated Body Temperature in the Critically Ill. *A strong indication for treatment combined with a severely elevated temperature is reflected by *red shading,* which corresponds to a situation where active management of elevated body temperature is reasonable; *dark green shading* indicates situations where active temperature management may be less desirable; *other shades* indicate different degrees of certainty about the appropriateness of treatment. (Reproduced from Young PJ & Prescott HC. When less is more in the active management of elevated body temperature of ICU patients. *Intensive Care Medicine*. 2019;45[9]:1275–1278.)

safe and was well-tolerated.[10] Such use of acetaminophen neither increased nor decreased days alive and free from intensive care.[10] Mortality rates were similar for patients who received acetaminophen to treat fever and for patients who did not.[10] Although these data do not provide a strong impetus for clinicians to give acetaminophen, they provide a degree of reassurance that if acetaminophen is administered to treat fever in the setting of an infection or given for another reason to a patient who happens to have fever and infection, such as for analgesia, harm is unlikely to result. Despite the considerations outlined earlier, there is an argument for treating fever in the ICU, even in patients with infections.[11] Patients in the ICU are supported beyond the limits of normal homeostasis. As fever increases metabolic demand, its presence may increase physiologic demands beyond the limits of supportive care. This is particularly true for patients who are the most unwell and for those who have limited reserves. Treating fever significantly reduces heart rate.[4] In patients who have limited cardiovascular reserves, such as those who have recently had a myocardial infarction, treatment of fever is reasonable, although evidence to support temperature control measures in this specific clinical setting is lacking.

For patients with infections, the authors of the SEPSIS-COOL trial reported that cooling patients with septic shock who were ventilated and sedated to normothermia might improve outcomes compared with not treating fever at all.[12] However, these findings were not reproduced in a subsequent similar trial, the REACTOR trial,[4] which randomized patients to normothermia or usual care. Overall, in patients without brain diseases, aggressive treatment of fever does not appear to alter outcomes compared with less aggressive approaches to temperature control.[4,13] For critically ill patients who have infections, a reasonable, albeit somewhat nebulous, approach is to treat fever routinely when it exceeds, say, 39°C core temperature and to treat fever at a lower level when it is judged to be of clinical concern. A more aggressive approach to fever control may be warranted in patients without infection, but this is not certain.[13]

Given the evidence supporting its safety,[3,10] acetaminophen is a reasonable first-line therapy to treat fever. Although aspirin is an effective antipyretic,[14] its use for this indication in the ICU has not been studied in randomized controlled trials. Of the nonsteroidal antiinflammatory drugs, ibuprofen has been most extensively studied in ICU patients. In patients with sepsis, ibuprofen decreases fever, tachycardia, oxygen consumption, and lactic acidosis but does not appear to improve survival.[15] Overall, irrespective of the antipyretic used, evidence suggests that physical cooling methods are more effective at reducing body temperature than antipyretic drugs.[16] That said, if fever is treated with physical cooling in an attempt to reduce physiologic demand, it is important that shivering, which markedly increases metabolic demand, is treated aggressively with opioids and/or sedatives. Neuromuscular paralysis may even be required. Because of the need to control shivering, physical cooling devices like cooling blankets are most useful in patients who are sedated.

In patients with traumatic brain injuries, acetaminophen alone is insufficient to prevent fever.[3] Strict avoidance of fever in such patients necessitates physical cooling. In the early period of management, this can be achieved because patients are often heavily sedated. However, during the recovery phase, the desire to control body temperature to attempt to prevent secondary brain injury often competes with the desire to reduce sedation and assess the patient's brain function. In this setting, nonsteroidal antiinflammatory drugs occasionally result in prompt abatement of fever, allowing physical cooling and associated sedation to be ceased. Interestingly, despite the fact that most clinicians consider temperature control to be desirable in patients who have traumatic brain injuries, fever of up to 38.5°C in the first 24 hours in the ICU is not associated with increased mortality risk after adjustment for illness severity.[9] A reasonable approach for patients with traumatic brain injuries is to seek to avoid both fever and hyperthermia whenever possible. Continuous monitoring of core body temperature is desirable in this setting. One approach is to administer acetaminophen regularly to reduce the burden of fever and to initiate physical cooling early if the body temperature exceeds 38°C.

In patients with subarachnoid hemorrhage, fever is particularly common, and the most appropriate way to treat it is not known. acetaminophen is an appropriate first-line therapy and can reasonably be administered regularly, given its favorable safety profile. Fever is common in patients with subarachnoid hemorrhage who are awake and, in the absence of high-quality evidence demonstrating that control of such fever improves neurologic outcomes, intervening in a manner that is likely to prolong mechanical ventilation time and associated complications is undesirable. Thus, although physical cooling to control fever in an effort to prevent secondary brain injury is appropriate for patients who are sedated for other reasons, it is undesirable to sedate patients with subarachnoid hemorrhage simply to control their body temperature. Fever is somewhat less common in patients with hemorrhagic and ischemic stroke, but in both of these conditions, the principles outlined in relation to subarachnoid hemorrhage apply.

For patients who have hypoxic ischemic encephalopathy, strict avoidance of fever is recommended. Routine use of therapeutic hypothermia does not appear to improve patient outcomes compared to early treatment of fever.[19]

KEY POINTS

- There is no universally agreed-upon definition of what constitutes a febrile temperature.
- Continuous monitoring of core temperature is recommended in patients at risk of life-threatening temperature elevations and when precise control of temperature is desirable.

KEY POINTS—cont'd

- Because fever is a cardinal sign of infection and sepsis is a frequent and often lethal complication of critical illness, particular care should be taken to note new or worsening organ dysfunction and potential sites of infection when a fever is present.
- A diagnosis of hyperthermia indicates that normal thermoregulation has been overwhelmed. Intervention with physical cooling should be initiated. The higher the elevation in body temperature in a patient with hyperthermia, the more rapidly and aggressively one should intervene.
- If the elevation of body temperature is caused by a fever, one needs to consider the possibility that the fever might be beneficial for the patient.
- Treating fever significantly reduces heart rate. In patients who have limited cardiovascular reserves, such as those who have recently had a myocardial infarction, treatment of fever is reasonable, although evidence to support temperature control measures in this specific clinical setting is lacking.
- Evidence supports the safety of using acetaminophen to treat fever in the critically ill. However, available evidence also suggests that physical cooling methods are more effective at reducing body temperature than antipyretic drugs.
- In patients with traumatic brain injuries, a reasonable approach is to administer acetaminophen regularly to reduce the burden of fever and to initiate physical cooling early if the body temperature exceeds 38°C.
- For patients who have hypoxic ischemic encephalopathy early treatment of fever is recommended.

References for this chapter can be found at expertconsult.com.

ANNOTATED REFERENCES

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5

Very High Systemic Arterial Blood Pressure

Michael Donahoe

Hypertensive emergency (HE) is a severe elevation in systemic blood pressure combined with new or progressive end-organ damage most frequently in the cardiac, renal, and central nervous systems. HE is an infrequent clinical presentation of acute hypertension that requires immediate, titrated blood pressure reduction.[1] Although HE is often associated with a blood pressure elevation >180/110 mm Hg, the diagnosis of HE is based upon the patient's clinical signs and symptoms rather than a specific blood pressure measurement. Clinical conditions associated with HE include hypertensive encephalopathy, intracranial hemorrhage (IH), acute coronary syndrome, acute pulmonary edema, aortic dissection, acute renal failure, and eclampsia.

The term *hypertensive urgency* (HU) has been historically used to describe critically elevated blood pressure (>180/110 mm Hg) without evidence for acute and progressive dysfunction of target organs. In HU, a more gradual reduction of blood pressure over several hours to days is the therapeutic target. A rapid decrease in blood pressure in HU has no proven benefit, and cerebral or myocardial ischemia can be induced by aggressive antihypertensive therapy if the blood pressure falls below a level needed to maintain adequate tissue perfusion. HU can progress to end-organ damage if blood pressure remains uncontrolled over a sustained interval. As urgent, titrated therapy is indicated only in patients with end-organ damage (i.e., HE), some groups divide high systemic arterial blood pressure into the two categories of HE and uncontrolled hypertension.[2] The majority of hospitalized patients with an elevation in systemic arterial blood pressure have uncontrolled hypertension.

A 25-institution US analysis of patients with HE reported a hospital mortality rate of 6.9%, with an aggregate 90-day mortality rate of 11% and a 90-day readmission rate of 37%.[3] Although the frequency of hospitalization for HE might be increasing, the all-cause hospital mortality for these patients continues to decrease.

Malignant hypertension refers to HE with advanced retinopathy, defined as flame-shaped hemorrhages, cotton wool spots, or papilledema. *Thrombotic microangiopathy* is an HE with active Coombs-negative hemolysis and thrombocytopenia in the absence of another cause, that improves with the lowering of the blood pressure.

PATHOPHYSIOLOGY

An acute elevation in systemic arterial blood pressure fundamentally involves an increase in systemic vascular resistance. This increase in vascular resistance results from a complex interaction of vascular mediators with a triggering factor in the setting of preexisting hypertension. Vasoconstriction can be promoted by circulating catecholamines, angiotensin II (ATII), vasopressin, thromboxane (TxA_2), and endothelin 1 (ET1). In contrast, compensatory production of local counter-regulatory vasodilators, including nitric oxide (NO) and prostacyclin (PGI_2), is inadequate to maintain homeostatic balance. The early stage of HE is associated with a pressure-induced natriuresis that further stimulates the release of vasoconstrictor substances from the kidney.

Specific cellular mechanisms of vascular injury in HE involve proinflammatory responses incorporating cytokine secretion, monocyte activation, and upregulation of endothelial adhesion molecules.[4] These proinflammatory factors extend the endothelial injury by promoting endothelial permeability and activating the coagulation cascade.

This cascade of intravascular events leads to the characteristic pathologic findings of obliterative vascular lesions. The vascular changes, evident to the clinician during an examination of the retina, are mirrored by similar changes in the kidney, leading to proliferative arteritis and, in advanced stages of the process, fibrinoid necrosis. A state of relative ischemia results in the affected organs, leading to end-organ dysfunction. The thrombotic microangiopathy (TMA) that characterizes the advanced stages of HE is a prothrombotic state characterized by endothelial dysfunction, platelet activation, and thrombin generation, with enhanced fibrinolytic activity.[3]

The potential adverse effects of aggressive blood pressure control have been most carefully studied in the cerebral circulation. The cerebrovascular arteriolar tone is adjusted over a range of cerebral perfusion pressures (CPPs) to maintain constant cerebral blood flow (CBF). Increases in CPP promote an increase in vascular resistance, whereas decreases in CPP act to vasodilate the cerebral vasculature. Steady flow is therefore maintained over a range of mean arterial pressure (MAP) from approximately 60 mm Hg to 150 mm Hg.[5] As MAP increases to values >180 mm Hg or above the upper limit of autoregulation, cerebral hyperperfusion, can occur, resulting in cerebral edema. Conversely, when CPP falls below the lower limit of autoregulation, CBF decreases, and tissue ischemia may occur. In patients with long-standing hypertension, a rightward shift of the CPP–CBF relationship occurs such that the lower limit of autoregulation occurs at a value higher than that in normal subjects. Comparative studies in hypertensive and normotensive patients suggest that the lower limit of autoregulation is about 20% below the resting MAP for both, although the absolute value is higher for the hypertensive patient. These data support the standard recommendation that a safe level of blood pressure reduction in HE is a 10% to 20% reduction of MAP from the highest values on clinical presentation, or a diastolic blood pressure typically in the 100 to 110 mm Hg range.

CLINICAL PRESENTATION

The history and physical examination in the patient with an acute elevation in systemic arterial blood pressure will focus on signs and symptoms of acute organ dysfunction. No specific blood pressure

threshold defines an HE. At identical blood pressure levels, end-organ damage may be present or absent.

According to the Studying the Treatment of Acute Hypertension (STAT) registry, the most common presenting symptoms in HE include shortness of breath (29%), chest pain (26%), headache (23%), altered mental status (20%), and a focal neurologic deficit (11%).[3] The most common admitting diagnoses are severe hypertension (27%), subarachnoid hemorrhage (11%), acute coronary syndrome (10%), and heart failure (8%). In approximately 25% of patients with HE, there is a history of either chronic or current medication nonadherence, and 11% of patients are current drug abusers. The mean systolic blood pressure in the STAT registry was 200 mm Hg (interquartile range [IQR], 186–220), and the median diastolic blood pressure was 110 mm Hg (IQR, 93–123).[3]

The patient evaluation must include a detailed medication history with attention to medications associated with blood pressure elevation (e.g., nonsteroidal antiinflammatory drugs [NSAIDs], calcineurin inhibitors, sympathomimetics). For patients with preexisting hypertension, the possibility of hypertensive medication nonadherence and withdrawal is considered.[6]

HEs may develop as secondary hypertension in association with such diverse etiologies as renal vascular disease, sleep apnea, hyperaldosteronism, pheochromocytoma, and pregnancy (preeclampsia). Also, illicit drug use is a significant risk factor for the development of HEs.

Blood pressure should be measured in both arms using an appropriately sized cuff and in a lower limb to detect differences associated with aortic dissection. Repeated blood pressure measurements are indicated, as a significant fraction of patients will resolve hypertension with bed rest and initial observation. Physical examination, including a fundoscopic examination, should focus on the identification of signs suggesting end-organ dysfunction.

HYPERTENSION AND CEREBROVASCULAR DISEASE

Hypertensive Encephalopathy

Acute elevations in systemic arterial blood pressure can lead to hypertensive encephalopathy (HEN). The clinical manifestations of HEN include headache, confusion, or a depressed level of consciousness; nausea and vomiting; visual disturbances (cortical blindness); or seizures (generalized or focal). Patients may present with focal neurologic deficits, although this finding is more common in cerebrovascular accidents. Rarely, HEN can show brainstem involvement manifesting as ataxia and diplopia.[7] If left untreated, the condition can progress to coma and death. Retinal findings, including arteriolar spasm, exudates or hemorrhages, and papilledema, may be present but are not a requirement. Magnetic resonance imaging (MRI) studies show edema involving the subcortical white matter of the parieto-occipital regions best seen on T2 and fluid-attenuated inversion recovery (FLAIR) imaging; a finding termed *posterior leukoencephalopathy*. Approximately two-thirds of patients will also have hyperintense lesions on T2 and FLAIR imaging in the frontal and temporal lobes, and one-third will have brainstem, cerebellum, or basal ganglia involvement.[8] The imaging findings are typically bilateral but can be asymmetric. HEN is the most common cause of reversible posterior leukoencephalopathy syndrome (RPLS).[6] Improvement or resolution of the radiographic findings is often delayed in comparison with clinical improvement.

The diagnosis of HEN is confirmed by the absence of other conditions and the prompt resolution of symptoms and neuroimaging abnormalities with effective blood pressure control. The failure of a patient to improve within 6–12 hours of blood pressure reduction should suggest an alternative cause of the encephalopathy. The condition is typically reversible with no observable adverse outcomes.

Acute Stroke

As blood pressure management differs significantly between acute ischemic stroke and acute hemorrhagic stroke, early imaging is required to guide treatment. The majority of patients with acute ischemic stroke have elevated systolic blood pressure on presentation to the hospital that declines to normal within 48 hours of presentation. Current data are contradictory whether hypertension in the early phase of acute stroke contributes to a worse patient outcome or is a surrogate marker of stroke severity.

During an acute stroke, cerebral autoregulation may be compromised in ischemic tissue, and lowering of blood pressure may further compromise CBF and extend ischemic injury. Medications used to treat hypertension may lead to cerebral vasodilation, augmenting CBF and leading to progression in cerebral edema. Ideally, a "correct" level of MAP should be maintained in each stroke patient to maintain CPP without worsening cerebral edema or progression of the lesion. Still, the clinical determination of this ideal value is often difficult.

Consensus guidelines recommend that blood pressure not be treated acutely in the patient with ischemic stroke unless the hypertension is extreme (systolic blood pressure >220 mm Hg or diastolic blood pressure >120 mm Hg) or the patient has active end-organ dysfunction in other organ systems.[1,2] When treatment is indicated, cautious lowering of blood pressure by approximately 15% during the first 24 hours after stroke onset is suggested. Antihypertensive medications can be restarted at around 24–48 hours after stroke onset in patients with preexisting hypertension who are neurologically stable unless a specific contraindication to restarting treatment exists. Special considerations are patients with extracranial or intracranial stenosis and candidates for thrombolytic therapy. The former group may be critically dependent on perfusion pressure so that blood pressure therapy may be further delayed. In contrast, treatment is recommended before lytic treatment is started, so that systolic blood pressure is ≤185 mm Hg and diastolic blood pressure is ≤110 mm Hg before lytic therapy administration.[1,2] The blood pressure should be stabilized and maintained below 180/105 mm Hg for at least 24 hours after intravenous (IV) lytic therapy.

Blood pressure is frequently elevated in patients with acute IH, often to a greater degree than seen in ischemic stroke. Theoretically, severe elevations in blood pressure may worsen IH by creating a continued force for bleeding. However, the increased arterial pressure may also be necessary to maintain cerebral perfusion in this setting, and aggressive blood pressure management could lead to worsening cerebral ischemia. For patients with suspected elevated intracranial pressure (ICP), ICP monitoring may be indicated to help maintain CPP during therapeutic interventions. American Heart Association guidelines, admittedly arbitrary and not evidence-based, suggest a target MAP of less than 110 mm Hg or a blood pressure of less than 160/90 mm Hg while maintaining a reasonable CPP in patients with suspected elevated ICP.[9] Based upon the results of INTERACT 1 and 2—which showed a decreasing trend in the primary outcome of death or severe disability, significant improvements in secondary functional outcomes, and reassuring safety data—many investigators advocate acute blood pressure reduction to a target systolic blood pressure of ~140 mm Hg for patients with spontaneous IH.[10]

HYPERTENSION AND CARDIOVASCULAR DISEASE

Acute Coronary Syndrome

Patients presenting with acute myocardial ischemia or infarction frequently suffer from an elevated MAP. The increased afterload raises the myocardial oxygen demand. Decreasing the heart rate and blood pressure in these patients will favorably reduce the myocardial oxygen demand and infarct size. However, a reduction in arterial pressure in this

setting should be made cautiously. Potent systemic vasodilation without coronary vasodilation can lead to a decrease in coronary artery perfusion pressure and infarct extension. For this reason, nitroglycerin (NTG), a robust coronary vasodilator, is often the antihypertensive agent of choice in acute coronary syndromes. In combination with beta-blocker therapy, this approach can reduce cardiac workload significantly in the setting of ischemia.

Acute Left Ventricular Dysfunction

Hypertension in acute left ventricular dysfunction (LVD) may be the inciting event with secondary myocardial dysfunction, or a secondary component of acute pulmonary edema resulting from the sympathoadrenal response to hypoxemia, increased work of breathing, and anxiety. Regardless, efforts to control hypertension in LVD are essential to resolve increased myocardial workload and diastolic dysfunction. However, the use of vasodilators in patients with LVD and normal to low blood pressure can lead to hemodynamic instability, impaired organ perfusion, and, potentially, shock.

IV vasodilators, including NTG and calcium channel antagonists, which permit rapid titration of blood pressure, are generally preferred in the setting of acute LVD. The dihydropyridine calcium antagonists nicardipine (NIC) and clevidipine (CLV) have been associated with reduced systemic arterial pressure, with the preservation of coronary blood flow. Patients with LVD may initially be hypertensive secondary to high initial catecholamine levels. With effective treatment or control of hypoxemia and anxiety, blood pressure may fall rapidly, especially in the setting of concomitant diuresis. Thus longer-acting medications such as angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blocker (ARB) therapy are avoided early in the treatment period. Noninvasive continuous positive pressure therapy will increase intrathoracic pressure and acutely reduce venous return and left ventricular afterload. This form of positive airway pressure can offer immediate benefit in the patient with acute pulmonary edema and elevated left ventricular filling pressures.

Patients with HE, in particular, may have suffered a natriuresis resulting in elevated levels of renin production by the kidney and, hence, increased circulating levels of the potent endogenous vasoconstrictor AII. Further reductions in intravascular volume and renal perfusion can lead to further increases in circulating AII levels. Therefore aggressive diuresis before blood pressure control is not advised. Medications that increase cardiac work (e.g., hydralazine) or impair cardiac contractility (e.g., labetalol) are contraindicated as primary therapy for hypertension in the setting of LVD.

Acute Aortic Dissection

Aortic dissection results from an intimal tear in the aortic wall. The primary morbidity and mortality result from the extension of that tear. The extension is promoted by factors that increase the rate of change of aortic pressure (dp/dt), including elevation in blood pressure, heart rate, and myocardial stroke volume. A high clinical suspicion is required, as the classic triad of chest pain, arm–leg blood pressure differential, and a widened mediastinum is present in only one-quarter of cases.

Heart rate and blood pressure in aortic dissection should be promptly reduced. Titratable combined modality therapy to promote vasodilation (NIC or nitroprusside) and control cardiac contractility (esmolol) is advocated for this disorder, with initial aggressive control of the heart rate and blood pressure (~60 beats per min and <120 mm Hg systolic pressure). Isolated treatment with a vasodilator alone could precipitate a reflex tachycardia, increasing dp/dt. Therefore initiate therapy first directed at heart rate control with the addition of vasodilator therapy as needed to achieve the blood pressure target. Effective pain control can also aid with patients achieving specific hemodynamic targets.

HYPERTENSION AND RENOVASCULAR DISEASE

The kidney is both a source of mediators that promote hypertension (i.e., AII) and a target of high systemic arterial pressure. Chronic hypertension is second to diabetes mellitus as a primary cause of renal insufficiency. Elevated systemic arterial pressure should be regulated in patients with underlying renal insufficiency, and a comprehensive workup initiated to determine the cause and effect relationship. Restrict the evaluation of patients for a renovascular cause of hypertension to patients likely to benefit from a correction procedure. Traditional vasodilator medications are preferred to ACE inhibitors for blood pressure control in the setting of renovascular disease, as ACE inhibitors can further compromise renal function.

Scleroderma Renal Crisis

Scleroderma renal crisis (SRC) is characterized by acute renal failure associated with the abrupt onset of moderate to severe hypertension, elevated plasma renin activity, and a normal to minimally abnormal urine sediment. Significant risk factors for SRC are the presence of diffuse scleroderma skin involvement and recent treatment with high-dose corticosteroids.[11] SRC results in a marked activation of the renin–angiotensin system. Aggressive control of blood pressure using ACE inhibitors, particularly early in the disease process, controls blood pressure in up to 90% of patients and promotes recovery in renal function.[11]

HYPERTENSION IN EXCESS CATECHOLAMINE STATES

Pheochromocytoma

Pheochromocytoma is frequently suspected in the setting of acute paroxysmal hypertension, although, in reality, the condition is quite rare. Pheochromocytoma results in the production of circulating catecholamines, which causes hypertension, diaphoresis, tachycardia, and paresthesias of the hands and feet. The classic triad of pheochromocytoma includes headaches, palpitations, and diaphoresis. These attacks can last from minutes to days and occur as frequently as several times a day or as infrequently as once per month. Operative manipulation of the tumor can result in perioperative hypertension. Hypertension therapy in this disorder must avoid the use of isolated treatment with a beta-blocker. This strategy can lead to unopposed alpha-adrenergic stimulation with the risk of further vasoconstriction and blood pressure elevation. The preferred agents for the treatment of hypertension resulting from pheochromocytoma are nitroprusside, NIC, and phentolamine, a potent alpha-adrenergic antagonist. If necessary, phentolamine can be combined with a beta-blocker.

PHARMACOLOGICALLY MEDIATED HYPERTENSION

The administration of exogenous substances (medications or illicit drugs) or abrupt withdrawal of substances can be associated with a hypertensive crisis. Rapid withdrawal or tapering of clonidine has been associated with a hyperadrenergic state characterized by hypertension, diaphoresis, headache, and anxiety. The syndrome is best treated by restarting the clonidine. If the symptoms are extreme, treatment is similar to that for the patient with pheochromocytoma. Hypertension can also occur during the withdrawal phase of alcohol abuse.

Monoamine oxidase (MAO) inhibitors can be associated with hypertension if the patient consumes foods or medications containing tyramine or other sympathomimetic amines. MAO inhibitors interfere with the degradation of tyramine in the intestine, leading to excess absorption and tyramine-induced catecholamine activity in the circulation.

Other medications—including metoclopramide; calcineurin inhibitors; cyclosporine; tacrolimus; and drugs of abuse, such as cocaine,

phenylpropanolamine, phencyclidine, and methamphetamine—must all be considered as possible factors in the intensive care patient with elevated systemic arterial pressure.

Hypertensive states may occur after spinal cord injury, particularly with stimulation of dermatomes and muscles below the level of the injury. The blood pressure elevation is believed to result from excess stimulation of sympathetic neurons. The hypertension is accompanied by bradycardia through stimulation of the baroreceptor reflex. Treatment is focused on minimizing stimulation and providing medical therapy as necessary. Patients with Guillain-Barré can manifest a similar syndrome.

HYPERTENSION AND MISCELLANEOUS CONDITIONS

Preeclampsia/Eclampsia

Hypertension can occur in pregnant women or women in the postpartum period. Acute severe hypertension in the second half of gestation may occur in preeclampsia, gestational hypertension, or HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome. Hypertension occurs as one manifestation of preeclampsia in the pregnant patient; the other key feature is evidence for end-organ dysfunction. Severe hypertension, particularly systolic hypertension in pregnancy, can be associated with central nervous system injury, including cerebral infarction and hemorrhage.

The optimal treatment of preeclampsia is delivery of the fetus, an approach that prevents progression to eclampsia. However, blood pressure should be regulated to avoid end-organ damage. The treatment goal is to achieve a range of 140–150/90–100 mm Hg.[12] IV labetalol, methyldopa, and hydralazine have been considered the first-line medications for the management of severe hypertension in pregnant and postpartum women. However, more recent guidelines have included nifedipine.[12] Magnesium sulfate is not considered an antihypertensive agent, but rather is administered for seizure prophylaxis in severe preeclampsia and eclampsia. Sodium nitroprusside (SNP) (fetal defects), ACE inhibitors (renal dysfunction in the fetus), and trimethaphan (meconium ileus) should be avoided.

Postoperative Hypertension

Postoperative hypertension most often occurs after vascular surgery procedures in patients with a background history of hypertension. The duration of postoperative hypertensive crisis is often brief (2–6 hours) but has been linked to postoperative cardiac and renal complications, including bleeding from suture lines, intracerebral hemorrhage, stroke, and LVD.[13]

Factors such as pain, anxiety, hypervolemia, hypoxemia, hypercarbia, and nausea are reversible factors that can contribute to postoperative hypertension and should be addressed. Postoperative hypertension is often limited in duration (2–12 hours), and aggressive attempts to lower blood pressure acutely can lead to delayed hypotension.

ANTIHYPERTENSIVE MEDICATIONS

A summary of the medications available for the treatment of elevated systemic arterial pressure is outlined in Table 5.1. Currently, the

TABLE 5.1 Intravenous Antihypertensive Therapy

Medication (Route)	Pharmacology	Dosing	Indication	Contraindication
Nitric Oxide Vasodilators				
Nitroprusside (IV infusion)	Onset: 2–3 min Duration: 2–3 min	Init: 0.25–0.5 mcg/kg/min Titrate: 0.5 mcg/kg/min Max: 2 mcg/kg/min	Most hypertensive emergencies	Contraindication in pregnancy. Use with caution in the settings of cerebral edema, acute coronary syndrome, or azotemia. Cyanide toxicity with prolonged use.
Nitroglycerin (IV infusion)	Onset: 2–5 min Duration: 5–10 min	Init: 5 mcg/min Titrate: 5 mcg/min q3–5min Max: 200 mcg/min	Acute coronary syndromes	Contraindication in pregnancy. Caution with use in a volume-contracted patient.
Calcium Channel Blockers				
Nicardipine (IV infusion)	Onset: 5–15 min Duration: 4–6 h	Init: 5 mg/h Titrate: 2.5 mg/h q5min Max: 15 mg/h	Most hypertensive emergencies	Contraindicated in advanced aortic stenosis.
Clevidipine (IV infusion)	Onset: 2–4 min Duration: 5–15 min	Init: 1–2 mg/h Titrate: 2× infusion rate every 90 sec Max: 32 mg/h	Most hypertensive emergencies	Contraindicated with allergy to soybean or egg products. Contraindicated with defective lipid metabolism. Contraindicated with advanced aortic stenosis.
Miscellaneous Medications				
Labetalol (IV infusion, oral)	Onset: 2–5 min Duration: 2–4 h	Init: IV bolus 20 mg Repeat bolus 20–80 mg q10min Infusion: 0.5–2 mg/min	Most hypertensive emergencies	Contraindication in airflow obstruction, acute heart failure, heart block, or in patients nontolerant of beta-blockers.
Phentolamine (IV)	Onset: 1–2 min Duration: 10–30 min	Test dose: 1 mg Repeat 5-mg boluses or continuous infusion may be provided	Pheochromocytoma Catecholamine withdrawal Catecholamine excess	Contraindicated with coronary artery disease.
Enalapril (oral)	Onset: 15 min Duration: 12–24 h	1.25–5 mg q6h	Scleroderma renal crisis	Use with caution in acute coronary syndrome. Not titratable.
Hydralazine (IV, oral)	Onset: 10–20 min Duration: 2–4 h	Init: 10 mg IV q20min Max: 20-mg dose Repeat q4–6h as needed	Pregnancy	Hydralazine is not recommended for hypertensive emergency in the general population due to an unpredictable effect duration

clinician has minimal comparative data to guide initial therapy for the patient with hypertension. Patients without end-organ dysfunction (HU) are best treated with oral agents, allowing a gradual reduction in blood pressure over 24–48 hours. In contrast, for patients with an HE, short-acting titratable medications provided in a monitored environment are preferred, as hypotension and compromised organ perfusion must be avoided. The sublingual and intramuscular routes should be avoided because of unpredictable pharmacokinetics. The conversion to oral therapy is timed to stable blood pressure readings and no further progression in end-organ dysfunction.

Patients with specific conditions (i.e., aortic dissection, severe preeclampsia, pheochromocytoma crisis) should have their systolic blood pressure reduced to <140 mm Hg during the first hour of treatment and to <120 mm Hg for aortic dissection. For the majority of adults without a specific condition, systolic blood pressure should be reduced by no more than 25% within the first hour; then, if stable, to 160/100 mm Hg within the next 2–6 hours; and then cautiously to normal during the following 24–48 hours.[1] Blood pressure–lowering medication is often withheld in the acute phase of patients with ischemic stroke.

Patients receiving NIC were more likely to have their blood pressure controlled to prospectively defined target ranges at 30 minutes compared with those receiving labetalol in one of the few comparative effectiveness trials of NIC versus IV labetalol in the emergency department management of acute hypertension.[14]

CLV was compared with three commonly employed medications for the treatment of postoperative hypertension (NTG, SNP, and NIC.[15] The primary endpoint was safety, as assessed by the incidence of death, stroke, myocardial infarction (MI), and renal dysfunction from the initiation of study drug infusion through postoperative day 30. There was no difference in the CLV-treated patients compared with the other treatment groups. However, mortality was significantly higher for SNP-treated patients compared with CLV-treated patients.

Nitric Oxide Vasodilators

SNP is a potent arterial and venous vasodilator that reduces preload and afterload. SNP was once the gold standard for the treatment of HE because of its short duration of action, allowing careful titration. The blood pressure response to SNP is rapid and mandates its use in a well-monitored environment with frequent blood pressure monitoring. The arteriolar and venous vasodilating activity of SNP may not be uniform, however. Redistribution of oxygenated blood flow from nonresponsive ischemic regions to vasodilated nonischemic coronary arteries can reduce CPP, resulting in a "coronary steal" syndrome. A similar "cerebral steal" syndrome has been suggested with the use of SNP because of preferential vasodilation in systemic vascular beds versus cerebral vessels. Through the dilation of large-capacitance vessels, SNP can increase cerebral blood volume, leading to an increase in ICP that raises additional concerns in patients with increased ICP. SNP is rarely associated with cyanide or thiocyanate toxicity, occurring primarily in patients receiving infusions for greater than 24–48 hours, in the setting of underlying renal insufficiency, or the use of doses that exceed the capacity of the body to detoxify cyanide (more than 2 μg/kg per min). Despite the marked potency and rapidly titratable characteristics of SNP, the recognized adverse effects on cerebral and coronary blood flow combined with the potential toxicities have made newer alternative agents favored over SNP for the treatment of HE.

NTG is a coronary vascular dilator and a systemic venodilator that reduces myocardial preload. NTG demonstrates arterial smooth muscle effects only at higher-dose infusions. The drug is contraindicated in patients with significant volume depletion, as venodilation in these patients will further lower preload, reduce cardiac output, and compromise overall systemic perfusion. When administered by the IV route, the medication has a relatively short duration of action. The drug has favorable effects for patients with acute coronary syndromes, including reducing myocardial oxygen demand via its effects on preload and afterload and augmenting myocardial oxygen delivery through its impact on the coronary circulation. Headache is the most common adverse effect of NTG, and methemoglobinemia is a rare complication of prolonged NTG therapy.

Calcium Channel Blockers

Calcium channel blockers (CCBs) are a heterogeneous class of medications used in the treatment of HE. Dihydropyridines, a specific class of CCB (e.g., NIC and CLV), are selective for vascular smooth muscle over the myocardium, with little, if any, activity in cardiac muscle or the sinoatrial node; thus they have little effect on heart rate and no effect on myocardial contractility.[16] The vascular smooth muscle relaxation without associated cardiac effects makes this class favorable for the treatment of HEs.

NIC is a dihydropyridine CBB that acts primarily as a systemic, cerebral, and coronary artery vasodilator. The greater water solubility of this drug compared with other CCBs (e.g., nifedipine) allows IV administration with a short onset (5–15 minutes) and short duration of action; therefore titration to a therapeutic effect is easy. NIC readily crosses the blood–brain barrier and relaxes vascular smooth muscle, especially in regions of ischemic tissue. The medication acts as a vasodilator of small-resistance cerebral arterioles but does not change intracranial volume or ICP with the preservation of cerebral oxygenation.[17] In comparison with SNP, NIC appears to offer equal efficacy with the advantage of avoiding the toxic metabolites of SNP, less frequent dose adjustments, and a decreased risk of increased ICP as reported with SNP. NIC has been shown to increase coronary blood flow with a favorable effect on myocardial oxygen demand.[18] NIC is metabolized by the liver, and excretion can be impaired in patients with liver disease.

CLV is a third-generation dihydropyridine CCB available as a racemic mixture with poor water solubility, so the drug is administered by continuous IV infusion in a lipid emulsion. A new formulation of CLV has been available in the United States since 2011 and contains a retardant (0.005% disodium edetate) that inhibits microbial growth for up to 12 hours. CLV reduces afterload without adversely affecting cardiac filling pressures or causing reflex tachycardia.[19] It has a rapid onset (~2–4 minutes) and offset of action (~5–15 minutes). It undergoes rapid ester hydrolysis by arterial blood esterases to form inactive metabolites, making medication clearance independent of renal or hepatic functional status.

CLV is contraindicated in patients with allergies to soybeans, soy products, eggs, or egg products and patients with defective lipid metabolism. Because of lipid-load restrictions, no more than 1000 mL, or an average of 21 mg/h of CLV infusion, is recommended per a 24-hour period.

CLV has shown favorable results in adult cardiac surgery patients with acute perioperative or postoperative hypertension, in acute hypertensive heart failure, and in patients with intracranial hemorrhage.[20,21] Elevated triglyceride levels have been reported in patients who received CLV, but these resolved with discontinuation of the medication.

Beta-Blockers

Esmolol is a short-acting, cardioselective beta-blocker with a rapid onset (<1 minutes) and short duration of action (10–20 minutes) that is only administered by continuous infusion. The short half-life requires bolus administration with each infusion titration. Esmolol reduces blood pressure, heart rate, and cardiac output and must be avoided in patients with bradycardia or impaired left ventricular function. Esmolol is optimally used in patients with tachycardia, hypertension, and normal to elevated

cardiac output. It is rapidly cleared by red blood cell esterases and is independent of renal or hepatic function.

Labetalol is an oral and parenteral agent that acts as an alpha- and nonselective beta-adrenergic blocker with an alpha-to-beta blocking ratio of 1:7.[22] The blood pressure–lowering effect is produced through a reduction in systemic vascular resistance without a compensatory increase in heart rate. In contrast to traditional beta-blockers, labetalol is associated with the preservation of cardiac output. The hypotensive effect of labetalol has an onset of 2–5 minutes, peak effect at 5–15 minutes, and duration of ~2–6 hours. Labetalol has minimal effect on cerebral circulation and is thus not associated with an increase in ICP in the normal brain. The drug has minimal placental transfer and has been used effectively in pregnancy-associated hypertension. It has been used effectively in patients with end-organ dysfunction in the setting of acute neurologic injury, pheochromocytoma, dissecting aneurysm, and eclampsia. The primary contraindication to the use of the medication relates to its nonselective beta-blocking properties. The drug should be used cautiously in patients with reactive airway disease and heart block.

Miscellaneous Medications

Enalapril is an intravenously administered ACE inhibitor. This medication reduces renin-dependent vasopressor activity, blocks the conversion of angiotensin I to AII, and blocks the degradation of bradykinin. ACE inhibitor administration is associated with a decrease in systemic vascular resistance, with minimal change in heart rate, cardiac output, or left ventricular filling pressure. Enalapril is effective in patients with low to normal renin levels and hypertension. The peak effect of enalapril may not be seen for up to 4 hours, with a duration of 12–24 hours. These pharmacokinetic parameters limit drug titration in the acute setting of an HE. ACE inhibitors are contraindicated in the setting of renal artery stenosis and pregnancy.

Phentolamine is a rapid-acting, alpha-adrenergic blocker. It is often considered the drug of choice for HEs secondary to pheochromocytoma, MAO–tyramine interactions, and clonidine rebound hypertension.

Hydralazine is a direct-acting vasodilator with a latent onset (5–15 minutes) and a prolonged effect (~12-hour half-life) that can be highly variable. Because of hydralazine's prolonged and unpredictable antihypertensive effects, this medication is best avoided in the management of an HE.

Diuretics should be avoided initially in the acute management of HE in the absence of pulmonary edema or renal parenchymal disease. Volume depletion is typical in HE patients, and these patients are susceptible to hypotension and compromised perfusion if vasodilators and diuretics are initiated together.

KEY POINTS

- Although HE is typically associated with a blood pressure elevation >180/110 mm Hg, the diagnosis is based on the patient's clinical signs and symptoms rather than a specific blood pressure level.
- Clinical conditions associated with HE include hypertensive encephalopathy, intracranial hemorrhage, acute coronary syndrome, acute pulmonary edema, aortic dissection, acute renal failure, and eclampsia.
- Patients with HU (without end-organ dysfunction) are best treated with oral agents, allowing a gradual reduction in the blood pressure over 24–48 hours.
- Patients with an HE should be treated with short-acting, titratable medications that are administered in a monitored environment, as hypotension and compromised organ perfusion must be avoided.

References for this chapter can be found at expertconsult.com.

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6

Low Systemic Arterial Blood Pressure

Joseph A. Hamera, Anna W. McLean, Lakhmir S. Chawla, and Kyle J. Gunnerson

INTRODUCTION

Assessment of hemodynamics is an important skill in the critical care setting. The goal of hemodynamic monitoring in a critically ill patient is to ensure adequate tissue oxygen delivery and end-organ perfusion. Low systemic arterial blood pressures are commonly encountered in the clinical setting, and a thoughtful, systematic approach should be used.

INITIAL EVALUATION

Initial evaluation usually begins with assessment of blood pressure (BP) readings. However, one should not rely solely on these readings, as there is no "normal" BP for all patients, and a BP value in the "normal" range does not always equate with adequate tissue perfusion. For example, a patient with a history of poorly controlled chronic hypertension may be normotensive, not yet in critical condition, but cannot meet his or her body's oxygen demand, resulting in evidence of significant anaerobic metabolism referred to as *cryptic shock*.[1] Conversely, a patient with cirrhosis or a pregnant patient may have adequate perfusion despite having a lower-than-normal BP.

Additionally, attention should be given to the mean arterial pressure (MAP). It is important to keep in mind that the MAP is the sum of two-thirds diastolic and one-third systolic pressure. The MAP is the main determinant of the perfusion pressure, or what pressure the organ sees. Safe levels of hypotension have historically been estimated to be anything greater than two-thirds of MAP.[2,3] Even more recently, it was found that an MAP less than 55 mm Hg during noncardiac surgery is independently associated with an increased risk of kidney and myocardial injury and has a moderate association with duration of surgery.[4] A good initial goal should be to restore the patient to an MAP of 65–70 mm Hg, but the level should be adjusted to restore tissue perfusion as assessed on the basis of mental status, appearance, urine output, etc.[5] Therefore hypotension triage needs to be quick and purposeful in order to prevent potentially damaging long-term sequelae.

An initial bedside assessment of tissue perfusion should include evaluation of mental status, urine output, and skin findings (e.g., temperature, diaphoresis, mottling, and capillary refill). If any of these parameters is abnormal, a more urgent approach to treatment must be taken. A focused cardiac and pulmonary examination is essential: presence of jugular venous distention; an S3 or S4 heart sound; new or worsening murmurs; or muffled heart sounds, crackles, or rales. Furthermore, a finding of absent breath sounds could be equally important, suggesting a pneumothorax.

All patients should have adequate intravenous (IV) access, preferably two patent 18-gauge or larger catheters. The patient should be monitored using a standard electrocardiogram (ECG) monitor and pulse oximetry. A 12-lead ECG should be performed, looking for evidence of myocardial ischemia. Chest radiography should be done, and supplemental oxygen should be given as needed. Complete blood counts, serum chemistry, lactate, arterial blood gas, random cortisol, coagulation panels, procalcitonin, and cardiac enzymes may be considered as part of the initial workup.

If equipment and a qualified operator are available, bedside ultrasound can form a useful part of the diagnostic workup of hypotension by demonstrating evidence of diminished cardiac contractility or pulmonary edema suggestive of cardiac failure, right ventricular findings consistent with pulmonary embolism, pneumothorax, or unexpected intraperitoneal fluid collections concerning for hemorrhage.[6] As with the physical examination, diligent attention must be paid to the proper performance of image acquisition and interpretation, as incorrect technique can lead to incorrect diagnosis and errors of commission or omission. A systematic approach to using ultrasound in hypotension is essential to avoid missed findings or misinterpretation. Multisystem examinations such as the Rapid Ultrasound in Shock and Hypotension (RUSH) protocol have been developed to aid in undifferentiated hypotension evaluation and, if possible, should be performed to completion to avoid premature closure.[7] As always, imaging findings do not stand alone and require interpretation in a clinical context to guide management decisions.[8]

WHAT IS THE CAUSE?

A review of cardiovascular physiology is essential in order to help focus the differential diagnosis of a hypotensive patient. A clinician's initial evaluation should be a global assessment (Fig. 6.1) of systemic vascular resistance (SVR) and cardiac output (CO). It is important to recall that *pressure = flow × resistance,* where flow is CO and resistance is SVR. Because CO is determined by stroke volume (SV) × heart rate (HR), the presence of hypotension means that at least one of these parameters (e.g., SV, SVR, or HR) is abnormal.[9] Assessment of HR is obvious by palpation of pulses or cardiac monitoring; however, assessing SV and SVR can be more challenging. Attention should be paid to systolic blood pressure (SBP) and diastolic blood pressure (DBP) in the context of pulse pressure (PP = SBP − DBP). DBP is a reasonable surrogate for SVR.

During systole, the SV is ejected into the proximal arterial conduits. Because more blood is being ejected than the peripheral circulation can accommodate in the arterioles, the arterial walls distend, increasing SBP in a way that is directly proportional to the SV and indirectly proportional to the capacitance (C) of the arterial wall. This relationship is represented by the following formula[9]:

$$SBP = SV \div C$$

That is, for a fixed SV, if capacitance is higher, the SBP is lower.

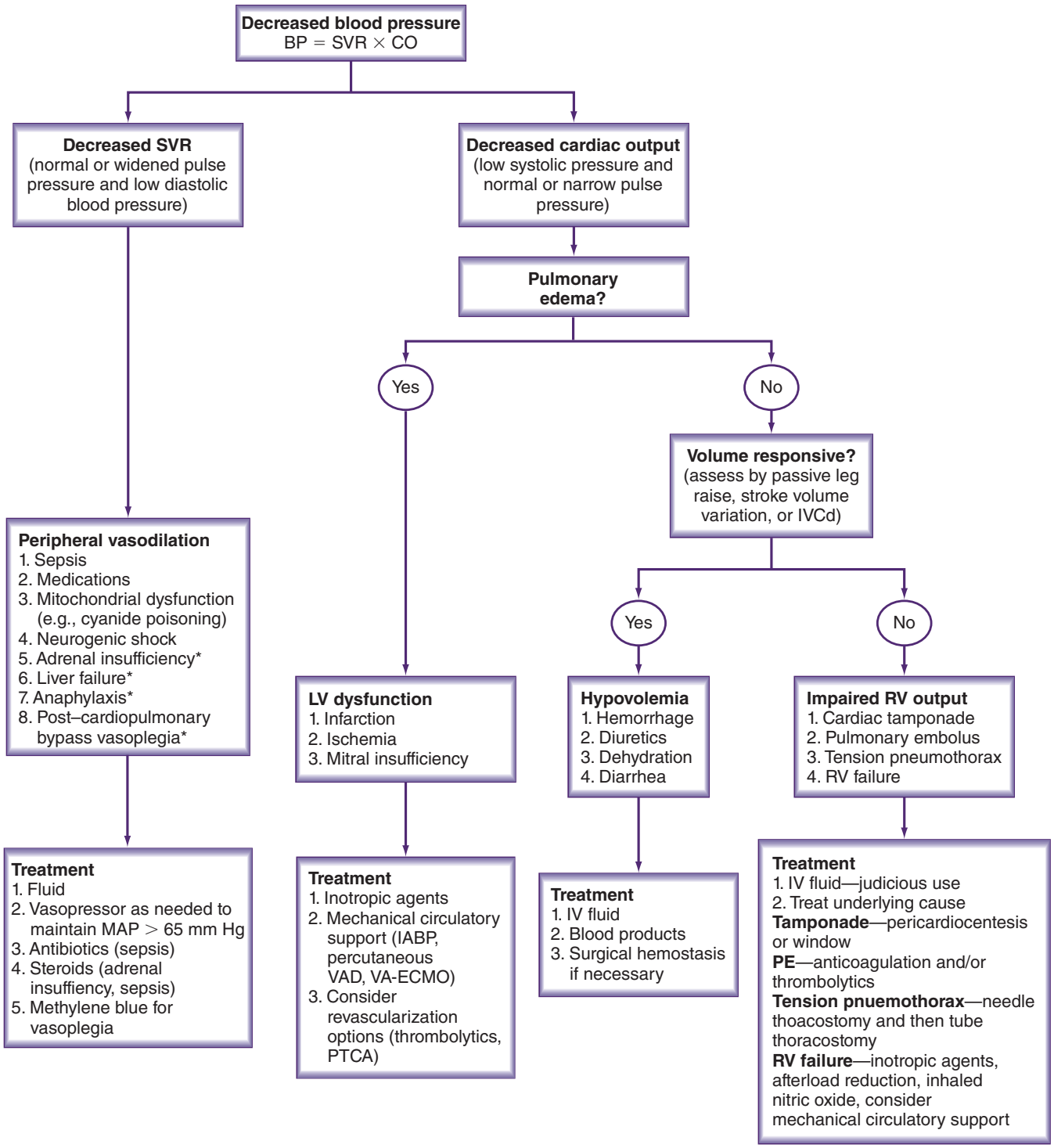

Fig. 6.1 Initial approach to a patient with low systemic arterial blood pressure. *Adrenal insufficiency, liver failure, post–cardiopulmonary bypass vasoplegia, and anaphylaxis are commonly listed as vasodilatory shock; however, data are inconclusive, and components of other types of shock (hypovolemic, cardiogenic) may also be present. *BP,* Blood pressure; *CO,* cardiac output; *IABP,* intraaortic balloon pump; *IV,* intravenous; *IVCd,* inferior vena cava diameter; *LV,* left ventricle; *MAP,* mean arterial pressure; *PE,* pulmonary embolism; *PTCA,* percutaneous transluminal coronary angioplasty; *RV,* right ventricle; *SVR,* systemic vascular resistance; *VAD,* ventricular assist device; *VA-ECMO,* venovenous extracorporeal membrane oxygenation.

During diastole, the portion of the SV that was "stored" by the distention of the arterial walls during systole fills the peripheral arterioles, leading to a progressive decrease in BP until the next systolic phase. This is the diastolic pressure, a parameter that is directly related to the SVR and capacitance (i.e., low diastolic pressure = low SVR and/or capacitance).[9] When using these basic cardiovascular principles to understand the cause of hypotension, it is important to remember the following: (1) capacitance does not change from heartbeat to heartbeat and (2) SV depends on preload, afterload, and contractility.

Low SVR is characteristic of a number of pathologic conditions, including sepsis, adrenal insufficiency, vasodilating medications, neurogenic shock, post–cardiopulmonary bypass (CPB) vasoplegia, and severe liver dysfunction. Decreased SVR (and aortic valve insufficiency) should be suspected in the presence of a widened PP and low DBP.[10,11]

Reduced SV can be the result of decreased preload, decreased contractility, or increased afterload. The most common cause of inadequate preload is hypovolemia. Other causes of inadequate preload include increased intrathoracic pressure caused by dynamic hyperinflation in mechanically ventilated patients[12,13] or tension pneumothorax, pulmonary embolism,[14] mitral valve stenosis,[15] cardiac tamponade,[16] and right ventricular failure.[17] Decreased contractility can be caused by myocardial ischemia or infarction, cardiomyopathy, myocarditis, negative inotropic drugs, myocardial stunning after CPB, and direct myocyte toxins such as chemotherapeutic agents and inflammatory mediators (e.g., tumor necrosis factor [TNF] and interleukin 1-beta [IL-1β]).[18] A reduction in SV can be identified by decreased SBP and normal or narrow PP.

Reduced HR is a relatively uncommon cause of low BP. Causes include structural damage to the conducting system; metabolic derangements such as hyperkalemia; autonomic dysregulation, as seen in central neurologic injury; and pharmacologic poisoning of the conduction system, as in the case of beta-blocker or calcium channel blocker overdose.[19] Shock states driven primarily by bradycardia, like other forms of cardiogenic shock, can initially manifest with relatively normal BP despite inadequate forward flow caused by the preservation of systemic vascular tone.

TREATMENT

Hypotension has been associated with higher morbidity and mortality in a variety of disease states, so until proven otherwise, hypotension should be considered synonymous with hypoperfusion and thus treated aggressively. A trial of at least 1.0 L of crystalloid should be infused to treat hypotension; the fear of pulmonary edema should not preclude the use of volume expanders in a patient who is not perfusing adequately.[1]

In a large series of intensive care unit (ICU) patients in shock, 78% were in either septic or hypovolemic shock.[20] Because treatment for both states requires intravascular volume resuscitation and clinical examination is unreliable for determining the need for and endpoint of volume resuscitation, several adjunctive tools have been developed to assist in decision making surrounding fluid administration.[21,22] The use of ultrasound at the bedside to evaluate inferior vena cava diameter (IVCd) has proven to be an accurate metric of volume responsiveness in mechanically ventilated and spontaneously breathing patients.[23] IVCd is measured subcostally, approximately 0.5–4.0 cm below the junction of the IVC and right atrium, in the longitudinal direction at a perpendicular angle to the IVC, and is calculated as "the change" in IVCd during inspiration as compared with expiration.[23] Patients with variation >50% will most likely respond to additional volume.[24]

Another method by which the clinician can evaluate volume responsiveness is the passive leg raise (PLR) test. In the nonintubated patient sitting with the head of the bed at 45 degrees, laying the patient flat and elevating the patient's legs at a 45-degree angle above the plane of the bed will cause a rapid temporary increase in venous return to the heart and an increase in CO, which has been shown to correlate with a 500-cc bolus of normal saline.[23] This maneuver increases PP in "responders." An increase in PP of more than 9% noted before and after the passive leg lifts will identify patients who are likely to respond to additional IV fluid administration.[25,26]

Although more invasive than the PLR, pulse contour analysis (PCA) has emerged as an accurate method for measuring cardiac performance (SV, CO, cardiiac index [CI]) and also measures PP or SV variation in the intubated and mechanically ventilated patient. By observing the undulation of the arterial line monitor for 30 seconds and the variability throughout the respiratory cycles, a decrease of 13% or more in SV during the inspiratory cycle correlates with preload responsiveness of SV. This variation represents a decrease in venous return in conjunction with the increased intrathoracic pressure during the inspiratory phase of ventilation. This measurement is only accurate when the heart rhythm is regular, so it is an unreliable index of preload responsiveness in patients with many kinds of arrhythmias, in the presence of an intraaortic balloon pump (IABP), or when there is loss of integrity in the arterial waveform. It is also only accurate in mechanically ventilated patients who are not experiencing large variations in intrathoracic pressures.[27,28]

In those patients where a low SVR is suspected as the primary cause of hypotension, the treatment is different. Large amounts of additional IV fluid alone will not adequately increase the BP to maintain tissue perfusion. Vasoconstrictor agents (e.g., norepinephrine, dopamine, phenylephrine, angiotensin II, and vasopressin) will be required in these patients. In certain specific cases, other pharmacologic adjuncts may be helpful. Low-dose hydrocortisone in vasoconstrictor-resistant septic shock[29] and methylene blue in post-CPB vasoplegia are two examples.[30]

In cases where hypotension is suspected to be caused by low SV, attention must be paid to the central cardiovascular system. These cases can be divided into failure of contractility or obstructive shock. In cases of primary left or right ventricular failure, steps must be taken to improve the performance of the heart either pharmacologically or mechanically. Optimization of a failing left ventricle involves reduction in preload and afterload with escalation to inotropic support if hypotension is present.[31] Management of primary right ventricular failure requires judicious optimization of preload, consideration of reduction in pulmonary arterial pressure, and inotropic support.[32] If pharmacologic means fail, escalation to mechanical circulatory support should be considered. Various forms of mechanical support are currently in use, including IABP, percutaneous ventricular support devices, and venous-arterial extracorporeal membrane oxygenation (VA-ECMO). The exact system required depends on which side of the heart requires support and the magnitude of support required.[31] Obstructive shock requires emergent disease-directed treatment. In cases of tension pneumothorax or cardiac tamponade, procedural decompression of the space is mandatory.[33,34] In cases of pulmonary embolism causing acute right ventricular failure, in addition to systemic anticoagulation, consideration of systemic thrombolysis or catheter-directed treatment should be made to offload the failing right ventricle.[35,36]

Hypotension mediated by bradycardia is typically managed by correction of the underlying cause. In metabolic causes, the underlying cause should be corrected. In pharmacologic cases, temporary management should include antidotes if available in addition to positive chronotropic agents such as atropine or beta-agonists. In cases caused by damage to the conduction system by ischemia or infiltrative disease, chronotropic agents are indicated temporarily, but clinicians should be prepared to start temporary pacing in the event these fail.

Many occurrences of hypotension may have some qualities of both decreased SV and decreased SVR. However, by using a systematic approach, the clinician can rapidly start diagnostic and therapeutic measures needed to treat tissue hypoperfusion.

KEY POINTS

- Assessment of any BP requires clinical consideration of the adequacy of tissue perfusion.
- BP goals in the ICU typically start around MAP 65–70 mm Hg, but must be individualized to patient needs using clinical markers of tissue perfusion.
- The assessment of hypotension should include making preparations for resuscitation, clinical examination, laboratory and radiographic testing, and the employment of bedside diagnostics where able to accelerate directed interventions.
- The physiology of hypotension necessarily involves derangement in HR, SV, or SVR. Diagnosing which perturbation(s) are present and for what reason can help focus management.
- Initial management of hypotension should usually involve a fluid challenge, with subsequent fluid administration directed by serial assessment of volume responsiveness. Early administration of pharmacologic vasopressors and/or inotropic support is indicated for inadequate response.

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7

Tachycardia and Bradycardia

Bryan T. Romito and Joseph S. Meltzer

The resting adult heart rate normally ranges from 60 to 100 beats per minute (bpm). Heart rate and rhythm abnormalities occur frequently in critically ill patients, and the incidence of sustained arrhythmias can approach 40% in some intensive care unit (ICU) settings.[1,2] Common arrhythmia risk factors in the critically ill include advanced age, sepsis, myocardial ischemia, respiratory failure, renal insufficiency, acute brain injury, polypharmacy, metabolic disturbances, cancer, trauma, and burns.[2,3] Prompt recognition and treatment are essential, as the presence of tachyarrhythmias (characterized by heart rates >100 bpm) and bradyarrhythmias (characterized by heart rates <60 bpm) is associated with both significantly increased hospital length of stay and in-hospital mortality rates in the critically ill.[2]

TACHYARRHYTHMIAS

For classification purposes, tachyarrhythmias can be subdivided into those with a narrow QRS complex (≤120 milliseconds [ms]) and those with a wide QRS complex (>120 ms). In general, narrow QRS complex tachyarrhythmias are supraventricular tachycardias (SVTs), involving tissue from the His bundle or above.[4] Wide complex tachyarrhythmias typically represent ventricular tachycardias (VTs) or SVTs with abnormal conduction patterns.[5]

Sinus Tachycardia

Sinus tachycardia is an atrial supraventricular tachyarrhythmia with a narrow QRS complex. On the electrocardiogram (ECG), the P wave is positive in leads I, II, and aVF and biphasic/negative in lead V1.[4] The vast majority of sinus tachycardia is physiologic and associated with catecholaminergic triggers.[6] Sinus tachycardia may result from pain, physical activity, fever, or hyperthyroidism. Simulants, caffeine, anticholinergics, and beta-receptor agonists can all produce transient sinus tachycardia.[7] In critically ill patients, sinus tachycardia may signify a normal adaptive response to maintain cardiac output in the setting of decreased stroke volume, oxygen-carrying capacity, or arterial vascular tone. Although nonspecific, tachycardia can represent an early sign of impending cardiopulmonary instability, and it is an independent risk factor linked to several worse clinical outcomes in the ICU.[8] The development of sinus tachycardia in critically ill patients is often multifactorial, and appropriate management includes identification of risk factors, discontinuation of offending agents, and treatment of underlying causes (Table 7.1).[4]

Atrioventricular Nodal Reentrant Tachycardia

Atrioventricular nodal reentrant tachycardia (AVNRT) is the most common type of the "classical" SVTs.[5] It occurs as a result of a reentry circuit present either within or near the atrioventricular (AV) node. ECG findings of typical AVNRT include a regular tachycardia with indiscernible P waves and narrow QRS complexes.[4] The risk of developing AVNRT is almost twice as high in women as in men.[9] Vagal maneuvers (i.e., Valsalva and carotid sinus massage) in the supine position and/or intravenous (IV) adenosine are recommended for the acute treatment of patients with stable SVT.[7] If refractory, IV diltiazem, verapamil, or beta-blockers can be administered to hemodynamically stable patients. Calcium channel blockers are not appropriate for patients with suspected systolic heart failure. Synchronized direct current cardioversion (DCCV) is recommended for hemodynamically unstable patients with SVT or for stable patients when pharmacologic therapy is ineffective or contraindicated.[7]

Atrial Fibrillation

Atrial fibrillation (AF) is the most common sustained arrhythmia, with a lifetime risk of 25% in the general population.[10] ECG characteristics of AF include an irregularly irregular rhythm with no discernible P waves because of rapid atrial oscillations that vary in timing, amplitude, and shape.[5] Critically ill patients encounter multiple risk factors for developing new-onset AF. Inflammation; electrolyte abnormalities; hypervolemia; sepsis; excessive adrenergic stimulation; and receipt of beta-receptor agonists, vasopressors, and certain antiarrhythmics can all trigger AF in ICU patients.[10] Accelerated ventricular rates and loss of the normal atrial contribution to ventricular filling ("atrial kick") during AF may lead to rapid hemodynamic deterioration, especially in patients with diastolic dysfunction. The development of new-onset AF is associated with increased hospital mortality rates and long-term risks of ischemic stroke, heart failure, and death.[10]

New-onset AF in critical illness is often reversible. The majority of patients will spontaneously convert to sinus rhythm within 72 hours of treatment of the underlying causes or removal of the offending agent.[2] Otherwise, management of the hemodynamically stable patient with AF involves three treatment principles: rate control, rhythm control/cardioversion, and anticoagulation. Beta-receptor antagonists are particularly effective for rate control in the setting of increased sympathetic tone from critical illness, sepsis, or the postoperative state.[10,11] Nondihydropyridine calcium channel blockers may be used for rate control in patients intolerant of beta-receptor antagonists, and digoxin can be considered as third-line therapy.[2] Calcium channel blockers are contraindicated in patients with acute heart failure, and the use of digoxin in patients with AF has been associated with sudden cardiac death.[12] In patients with permanent AF, targeting a resting heart rate <110 bpm is as effective as targeting a resting heart rate <80 bpm.[13] Amiodarone is an effective rhythm control agent, and it offers the additional benefit of rate control if both beta-receptor antagonists and calcium channel blockers are contraindicated. Pulmonary and thyroid toxicity have been described after its administration. IV magnesium, either as monotherapy or in combination with other agents, may provide greater rate and

TABLE 7.1 Common Causes of Arrhythmias in the ICU

Tachyarrhythmias	Bradyarrhythmias
Advanced age	Advanced age
Myocardial ischemia	Myocardial ischemia
Respiratory failure	Respiratory failure
Kidney failure	Kidney failure
Postcardiac surgery	Postcardiac surgery
Heart failure	Heart failure
Electrolyte abnormalities	Electrolyte abnormalities
Increased catecholamines: pain, exercise, anxiety	Increased vagal tone
Hyperthyroidism	Hypothyroidism
Hyperthermia	Hypothermia
Hypovolemia	Increased intracranial pressure
Anemia	Hypertension
Sepsis	Obstructive sleep apnea
Cancer	Infiltrative diseases: cardiac amyloidosis, sarcoidosis, hemochromatosis, lymphoma
Trauma/burns	Inflammatory diseases: Lyme disease, Chagas disease, myocarditis, endocarditis
Intoxication: alcohol, cocaine, stimulants	Rheumatologic diseases: rheumatoid arthritis, scleroderma, systemic lupus erythematosus
Medications: anticholinergics, beta-receptor agonists, chemotherapy agents, antiarrhythmics, vasopressors, inotropes	Medications: beta-receptor antagonists, calcium channel blockers, digoxin, dexmedetomidine, antiarrhythmics, opioids, tricyclic antidepressants, clonidine, lithium, phenytoin

rhythm control.[10,14,15] In patients with heart failure, treatment of AF with catheter ablation may be associated with improved clinical outcomes.[16,17]

Hemodynamically unstable patients with AF should be treated with synchronized DCCV. Even with multiple attempts, the reported success rates for electrical cardioversion of AF during critical illness range from 30% to 37%.[2] Concurrent administration of rate or rhythm control agents should be considered, given the high likelihood of recurrence.[10] In patients with a recurrence of persistent AF after electrical cardioversion, rate control is not inferior to rhythm control.[18] For prevention of thromboembolism, anticoagulation should be considered for all patients with AF. The risk of stroke may be greater in patients with higher CHA_2DS_2-VASc scores and with AF duration ≥48 hours. Overall, the risk of thromboembolic events should be weighed against the risk of anticoagulant-related bleeding for the individual patient.[19]

Atrial Flutter

Typical atrial flutter (AFl) is a macroreentrant, narrow complex atrial tachycardia that is characterized by a regular sawtooth pattern on the ECG.[4] Atrial rates usually range from 250 to 330 bpm.[7] The acute management of AFl is largely similar to the management of AF; however, ventricular rate control may be more difficult to achieve in AFl.[2] Patients with AFl are thought to have the same risk of thromboembolism as patients with AF, so anticoagulation should be considered accordingly.[7] Finally, DCCV of AFl can often be accomplished with lower energies compared with AF.[2]

Ventricular Tachycardia

Ventricular tachycardia (VT) is characterized by ≥3 consecutive complexes originating in the ventricles at a rate >100 bpm.[20] It is the most common cause of wide QRS complex tachycardia. VT is classified as sustained when it lasts >30 seconds or requires termination because of hemodynamic compromise in <30 seconds. Conversely, nonsustained VT (NSVT) has a duration of <30 seconds and terminates spontaneously. VT can also be classified as monomorphic (i.e., stable single beat-to-beat QRS morphology) or polymorphic (i.e., changing or multiform beat-to-beat QRS morphology).[20]

Hemodynamically stable patients with asymptomatic NSVT usually do not require treatment other than correction of any precipitating cause. The in-hospital mortality rate for patients with sustained monomorphic VT is approximately 50%.[2] In patients with stable monomorphic VT, administration of IV procainamide, amiodarone, or sotalol can be used to terminate the rhythm.[20] Amiodarone is often better tolerated in patients with systolic dysfunction.[2] In addition to antiarrhythmic administration, correction of electrolyte abnormalities and discontinuation of offending agents should be performed concurrently. DCCV and catheter ablation can be undertaken in refractory cases of sustained monomorphic VT. Patients with unstable monomorphic VT should be treated with DCCV.[20]

Polymorphic VT can occur in the setting of a normal (<460 ms) or prolonged (>460 ms) QT interval. Unstable patients with normal QT interval–associated polymorphic VT require immediate defibrillation. Recurrent polymorphic VT can be caused by ongoing myocardial ischemia that resolves with coronary revascularization.[20] Polymorphic VT associated with QT interval prolongation is termed *torsades de pointes.* It is characterized by a waxing and waning QRS amplitude.[20] Treatment of torsades de pointes includes discontinuing QT-prolonging agents, correcting electrolyte derangements, administering magnesium, and increasing the ventricular rate with isoproterenol or temporary pacing.[2]

BRADYARRHYTHMIAS

Abnormalities of the sinus node, atrial tissue, AV nodal tissue, or conduction system can contribute to the development of bradyarrhythmias.[21] Bradyarrhythmias are more common in older patients because of age-related degeneration and fibrosis of the conduction system. Other risk factors for the development of bradyarrhythmias include hypertension, respiratory failure, and ischemic heart disease (see Table 7.1).[22]

Sinus node dysfunction (SND) can manifest with sinus bradycardia, sinus pauses, or tachycardia–bradycardia syndrome.[21] Asymptomatic sinus bradycardia has not been associated with adverse outcomes, and treatment is not recommended. Symptoms attributable to SND can range from mild fatigue to syncope.[21] Correction of reversible causes is key to the acute management of SND. If symptoms persist despite conservative treatment, medications with chronotropic effects such as atropine, dopamine, isoproterenol, or epinephrine can be administered. Severe refractory SND associated with hemodynamic instability should be treated with pacing.[21]

AV nodal disease presents as variable heart block with specific ECG patterns. In first-degree AV block, P waves are associated with 1:1 AV conduction and a prolonged PR interval of >200 ms.[22] Second-degree AV block is characterized by intermittent AV conduction and can be divided into two subtypes. Second-degree AV block Mobitz type 1 (Wenckebach) presents with progressive PR interval lengthening followed by a nonconducted P wave. Second-degree AV block Mobitz type

II presents with fixed PR intervals and periodic nonconducted P waves. Third-degree (complete) AV block presents with AV dissociation.[21,22]

The acute treatment of bradycardia attributed to AV block is similar to that of SND. In addition to addressing reversible causes, chronotropic agents such as atropine, isoproterenol, dopamine, dobutamine, and epinephrine can be administered. Temporary pacing may be needed in patients who are hemodynamically unstable or with refractory symptoms.[21,23] Depending on the scenario, this can be accomplished using transcutaneous, transvenous, or epicardial modalities. Irrespective of symptoms, permanent pacemaker implantation is indicated for patients with second-degree AV block Mobitz type II, high-grade AV block, or third-degree AV block.[22] Additionally, a transthoracic echocardiogram is recommended in order to evaluate for the presence of structural heart disease.[21]

KEY POINTS

- Tachyarrhythmias and bradyarrhythmias are both associated with increased in-hospital mortality rates in the critically ill.
- Sinus tachycardia may represent a normal adaptive response to maintain cardiac output in the setting of decreased stroke volume, oxygen-carrying capacity, or arterial vascular tone.
- Beta-receptor antagonists are particularly effective for AF rate control in the setting of increased sympathetic tone from critical illness, sepsis, or the postoperative state.
- Treatment of torsades de pointes includes correcting electrolyte abnormalities, administering magnesium, discontinuing QT-prolonging agents, and increasing the ventricular rate.
- Symptomatic SND and AV block can be treated with chronotropic agents.

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8

Arterial Hypoxemia

Jean-Louis Vincent

Normal cell function requires an adequate oxygen supply. Lack of oxygen at the cellular level is called *hypoxia.* Oxygen delivery (DO_2) to the tissues is determined by cardiac output and the arterial oxygen content, which in turn is determined by the hemoglobin concentration and its oxygen saturation. *Hypoxemia* is defined by a significantly low partial pressure of oxygen (PaO_2; less than about 75 mm Hg), regardless of the inspiratory oxygen fraction (FiO_2). Hypoxemia can be compensated for by an increase in cardiac output, so that DO_2 may not be critically reduced by its presence. The increase in cardiac output that accompanies hypoxemia is mediated by an increase in sympathetic tone, resulting in combined increases in heart rate and contractility. Impaired O_2 delivery to the tissues is more often the result of decreased cardiac output or altered vascular tone than of a decrease in PaO_2. Tissue hypoxia is a hallmark of shock and is associated with altered cellular metabolism that results in increased blood lactate levels. To avoid confusion, the word *hypoxia* should not be used to characterize a low PaO_2.

Hypoxemia is almost always the result of respiratory failure, but it can also be the result of cardiac abnormalities. A low cardiac output can aggravate hypoxemia via a reduction in oxygen saturation of the mixed venous blood (SvO_2) (see later). Moderate hypoxemia must be compensated for by an increase in cardiac output, which may be poorly tolerated in frail patients. When that compensatory mechanism is exhausted or when there is concurrent anemia, hypoxia can develop and result in multiple organ failure and cardiac arrest.

The nonlinear relationship between SaO_2 and PaO_2 is affected by body temperature, partial pressure of carbon dioxide in arterial blood ($PaCO_2$), pH, and 2,3-diphosphoglycerate concentration (Fig. 8.1). As a result, patients can have a higher or lower SaO_2 for a given PaO_2, depending on the existing conditions. The critical PaO_2 value is approximately 60 mm Hg, because a further decline in PaO_2 results in a steep fall in SaO_2.

Although PaO_2 reflects pulmonary function, it must be related to FiO_2 when judging oxygenating efficiency. (The PaO_2/FiO_2 ratio is one indicator commonly employed for that purpose.) The SaO_2 is the primary determinant of oxygen content and strongly influences DO_2. (Dissolved oxygen is a negligible fraction of the total oxygen transported per milliliter of blood.) Thus, giving supplemental oxygen to increase PaO_2 to supranormal levels does not appreciably increase DO_2 and is generally inadvisable except in the context of life-threatening anemia. Nevertheless doing so may have marginal utility if used immediately before interventions that may result in hypoxemia, such as endotracheal intubation or bronchoscopy.

PaO_2 and SaO_2 are measured by arterial blood gas analysis, which requires invasive sampling and is not performed continuously. Capillary blood oxygen saturation (SpO_2) can serve as a surrogate measure of SaO_2 and can be measured noninvasively and continuously with a pulse oximeter. Pulse oximetry uses spectrophotometry to detect oxyhemoglobin (peak absorption at 940 nm) and deoxyhemoglobin (peak absorption at 660 nm) via a pulsatile optical signal directed through tissue, with their ratio reflecting the SpO_2 in that tissue (e.g., fingertip or earlobe). However, this measurement can be affected by various factors. The SpO_2 may give a falsely low indication of the SaO_2 if there is poor pulsatility of the waveform: for example, in the presence of altered cutaneous perfusion. Light transmission through the tissues of the fingertip can be decreased by dark nail polish, again affecting that measurement. Methemoglobinemia can also result in a falsely low SpO_2 reading, whereas carboxyhemoglobinemia can result in a falsely elevated SpO_2 reading.[1]

Another issue with pulse oximetry, notably in critically ill patients, is that it takes many seconds for the SpO_2 to reflect acute changes in PaO_2, including those occurring as a result of alterations of oxygen administration and/or positive end-expiratory pressure (PEEP). Response times are even more prolonged when there is reduced cardiac output.[2,3]

CAUSES OF ARTERIAL HYPOXEMIA

Causes of hypoxemia can be categorized into four groups (Fig. 8.2).

1. Decreased Alveolar Oxygen Content (PAO_2)

According to the alveolar gas equation, the alveolar PAO_2 is determined by:

$$PAO_2 = FiO_2(P_{atm} - PH_2O) - PaCO_2/RQ,$$

where FiO_2 is the concentration of inspired oxygen, P_{atm} is the atmospheric pressure, PH_2O is the partial pressure of water (typically 47 mm Hg at ambient temperature), and RQ is the respiratory quotient[4,5] (i.e., the amount of oxygen consumed relative to the amount of carbon dioxide produced when nutrients are metabolized). RQ is generally assumed to be 0.8, although it may vary. Under normal conditions at sea level,

$$PAO_2 = 0.21\ (760\ \text{mm Hg} - 47\ \text{mm Hg}) - (40\ \text{mm Hg}/0.8) \approx 100\ \text{mm Hg}.$$

The first part of the equation can be affected by altitude because P_{atm} decreases.[6] The second part of the equation is primarily affected by $PaCO_2$, which typically results from hypoventilation (e.g., central respiratory depression, neuromuscular weakness). Hence, unless there is an increase in the concentration of inspired oxygen, PAO_2 can decrease in the presence of an increased $PaCO_2$, which in turn is determined by the following equation:

$$PaCO_2 = CO_2\ \text{production} \div (\text{respiratory rate} \times [\text{tidal volume} - \text{dead space}]).$$

Thus $PaCO_2$ can rise with an increase in CO_2 production (increased metabolism), a decrease in minute ventilation (e.g., because of central respiratory depression or neuromuscular weakness), and/or an increase in dead space ventilation.

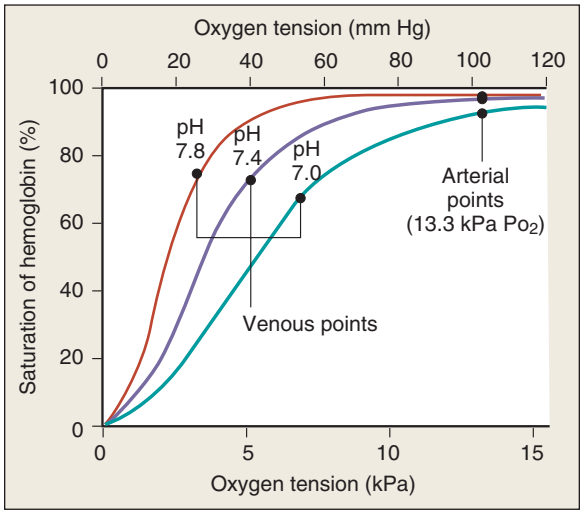

Fig. 8.1 Oxygen saturation varies with the PaO_2 in a nonlinear relationship and is affected by temperature, $PaCO_2$, pH, and 2,3-diphosphoglycerate (2,3-DPG) concentration.

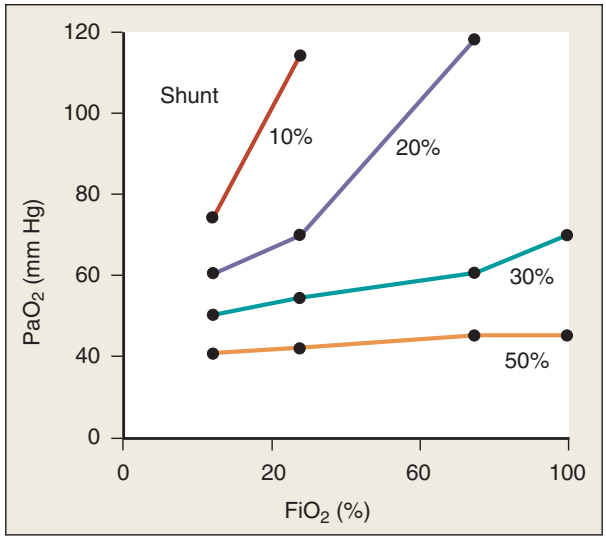

Fig. 8.3 Blunted response to increasing inspired oxygen concentration. A patient with a shunt greater than 50% has little response to increasing FiO_2.

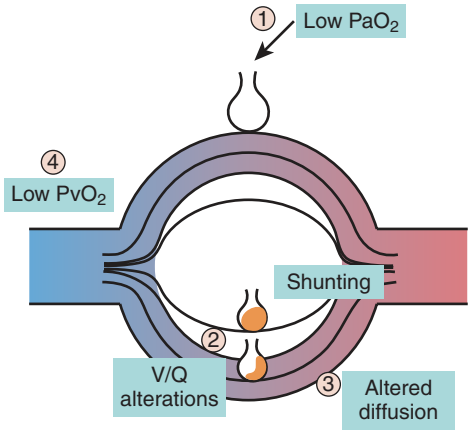

Fig. 8.2 The four mechanisms of hypoxemia. *V/Q,* Ventilation/perfusion.

2. Ventilation/Perfusion (V/Q) Mismatch and Presence of a Pulmonary Shunt

This is the most common cause of hypoxemia and arises when perfusion is maintained in regions that are no longer participating effectively in gas exchange: for example, atelectasis, pneumonia, or lung edema. Some therapeutic interventions may also contribute: in normal conditions, the presence of hypoxic pulmonary vasoconstriction reduces perfusion to underventilated areas of lung, but this mechanism can be altered by vasoactive medications (vasodilators in particular). Hence, a substantial fraction of the cardiac output will not participate in gas exchange and will be "shunted" to cause "venous admixture." The normal shunt fraction is approximately 3%–4% and arises primarily in the bronchial arterial circulation. Reduced ventilation of perfused alveoli increases the shunt fraction and thus decreases PaO_2. If V/Q alterations are partial, an increase in FiO_2 can largely correct this effect, but when the shunt is complete, an increase in FiO_2 will not improve PaO_2 (Fig. 8.3).

Right-to-left shunts can also be anatomic (e.g., intracardiac shunts and intrapulmonary shunts resulting from arteriovenous malformations). Anatomic shunting can also develop in end-stage liver disease.

Pulmonary perfusion is not homogeneous: dependent areas are preferentially perfused compared with nondependent ones. As a result, changes in the patient's position can alter arterial oxygenation, depending on the location and distribution of the underventilated lung areas or the regions of intrapulmonary shunt. If the patient is placed in a position in which the underventilated areas of the lung (often gravitationally dependent zones in the setting of lung injury) are also the ones receiving rich perfusion, hypoxemia will worsen. Placing a patient with severe acute respiratory distress syndrome (ARDS) in the prone position can therefore improve gas exchange.[7]

In the presence of severe respiratory failure, pulmonary hypertension resulting in elevated right heart pressures may reopen a patent foramen ovale, thereby creating an intracardiac right-to-left shunt. This possibility should be considered when an increase in PEEP therapy worsens gas exchange.

Of note, the opposite of shunt is increased dead space, where preserved alveolar ventilation is associated with reduced perfusion. This predisposes to increased $PaCO_2$, which can be compensated for by increasing minute ventilation. Massive pulmonary embolism and diffuse lung injury that reduces the capacity of the "baby lung" are typical causes of increased dead space. Hypoxemia commonly observed in this condition is not straightforward.

3. Impaired Diffusion

Acting alone, this is a rare cause of hypoxemia in the acutely ill. It can result from an increase in the diffusion distance between the alveolar space and the capillary lumen. A reduction in the capillary transit time can occur as a result of a dramatic increase in cardiac output during strenuous exercise. Combinations of rapid transit coupled with the innately impaired diffusing properties of injured tissue may accentuate hypoxemia.

4. A Decrease in the Oxygen Saturation of Mixed Venous Blood (SvO_2) Can Contribute to the Severity of Hypoxemia

This is usually because of inadequate cardiac output, anemia, or increased oxygen consumption by body tissues. However, in the absence of parenchymal damage or admixture/shunt from other causes, low

SvO_2 does not alter the effectiveness of oxygenating blood passing through the gas exchanger of the healthy lung.

MANAGEMENT OF ARTERIAL HYPOXEMIA

The first action to increase PaO_2 is to increase the FiO_2 If the response is unsatisfactory, one can consider increasing the flow rate of supplemental oxygen or using a mask with an oxygen reservoir (i.e., a "nonrebreather mask"). If the response is still poor, then the patient is likely to have severe V/Q mismatching or a true right-to-left shunt. The next step should be to try to reopen closed alveoli by repositioning and applying positive pressure ventilation using continuous positive airway pressure (CPAP) in the absence of endotracheal intubation, or PEEP if the patient is receiving mechanical ventilation (noninvasive or invasive). Relief of an excessive breathing workload and a high oxygen consumption often helps restore the balance, allowing effective O_2 delivery. Prone positioning improves arterial oxygenation in the majority of ARDS patients.

KEY POINTS

- PaO_2 (in relation to FiO_2) primarily reflects the lung function, and SaO_2 the amount of oxygen carried to the tissues.
- Hypoxemia is the result of four major mechanisms.
- The primary action to correct hypoxemia is to increase the FiO_2, increase the oxygen flux, or increase the intrathoracic pressure.

References for this chapter can be found at expertconsult.com.

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9

Acute Respiratory Failure

Igor Barjaktarevic, Roxana Cortes-Lopez, and Tisha Wang

Acute respiratory failure (ARF) is defined by the sudden onset of severe impairment of pulmonary gas exchange and is characterized by the inability of the lungs to meet the body's metabolic needs for the transport of oxygen (O_2) into the blood and/or removal of carbon dioxide (CO_2) from the blood. The diagnosis of ARF is based on the measurements of arterial blood gas (ABG) parameters (i.e., partial pressure of oxygen [PaO_2], partial pressure of carbon dioxide [$PaCO_2$], and pH), and these values must always be interpreted in relation to the patient's baseline status. As a final common pathway for a variety of illnesses, ARF is one of the most frequently encountered diagnoses in the intensive care unit (ICU), and its management represents one of the key challenges of critical care medicine. This chapter aims to tie the physiology of breathing to the pathologic processes that lead to ARF and will also discuss the clinical approach to the patient with ARF.

ARF is one of the most common reasons for admission to the ICU and accounts for ~2 million admissions per year in the United States.[1] More than half of all patients admitted to the medical ICU with stays >48 hours have ARF at some point during their hospitalization,[2] with overall mortality rates of >33%.[2–5] Mortality significantly increases with age, preexisting comorbidities, and the presence of shock or multisystem organ failure.[6] With the aging population in the United States, the incidence of patients with ARF is expected to increase by 80% over the next two decades.

COMPONENTS OF THE RESPIRATORY SYSTEM

Understanding the process of respiration is a key step in understanding and managing ARF. Respiratory control is established by the tight coordination of three groups of neurons in the medulla oblongata: a dorsal respiratory center that controls inspiration, a ventral respiratory group that controls expiration, and a pneumotaxic center that controls the rate and depth of breathing. In addition to neurons in the brainstem, a peripheral chemoreceptor system is located outside the brain in the form of carotid bodies and aortic bodies that detect subtle changes in PaO_2. The neural impulses from the central nervous system (CNS) traverse the spinal cord and motor neurons, reaching and activating the diaphragm and other respiratory muscles. Contraction of the inspiratory muscles creates negative pleural pressure by expanding the chest cavity and pushing the abdominal contents caudally. The negative pressure created in the thorax during inspiration leads to subatmospheric pressure in the alveoli, creating a gradient for the flow of inspired air toward the alveoli. Oxygen-rich inspired air allows the diffusion of O_2 from the alveoli to the blood through the alveolar–capillary membrane, where deoxygenated hemoglobin becomes saturated with O_2 to form oxyhemoglobin.

O_2 is consumed by all human tissues, and the ability to do so depends on gas exchange in the lungs. The average O_2 uptake of an adult is approximately 250 mL/min, although this rate depends on numerous factors.[7] Most (~98.5%) O_2 is carried to peripheral tissues via oxyhemoglobin, whereas the remainder is transported as O_2 dissolved in the fluid phase of blood. The total transport of O_2 by the arterial system is termed *oxygen delivery* (DO_2) and is normally several-fold higher than the O_2 demand of the peripheral tissues. However, O_2 utilization (VO_2) can become dependent on DO_2 in pathologic conditions such as ARF.[7–9] In these states, the normally balanced relationship between oxygen delivery and oxygen demand can be disrupted by decreased O_2 delivery or increased O_2 demand (Fig. 9.1).

DO_2 is the product of cardiac output and arterial oxygen content (CaO_2), a value determined by the concentration of hemoglobin (Hgb) and oxygen saturation (SaO_2) (Fig. 9.2). Adequate perfusion of capillaries in the peripheral tissues allows for the liberation of O_2 from oxyhemoglobin.

PATHOPHYSIOLOGIC PROCESSES LEADING TO ARF

ARF can be a consequence of a wide range of tissue defects, which can have both pulmonary and extrapulmonary etiologies. It is important to understand the mechanisms leading to hypoxemia, as the best therapeutic approach may require targeting the appropriate etiology. This, however, is often difficult in the early stages of managing a patient with acute hypoxemia. Considering a broad differential diagnosis for ARF is crucial to appropriate management of the underlying condition (Table 9.1).

CLASSIFICATION OF ARF

Respiratory failure can be classified as acute or chronic. The clinical presentation of ARF is typically dramatic and obvious, often with profound derangements in ABG values. "Acute on chronic" respiratory failure represents an acute deterioration in the presence of preexisting chronic pulmonary disease and chronic respiratory dysfunction. Chronic respiratory dysfunction may present with markers of chronic hypoxemia (e.g., polycythemia, or *cor pulmonale*) and may or may not require ICU care. Regardless of acuity, respiratory failure represents a potentially life-threatening group of disorders for which inadequate management may lead to rapid clinical deterioration.

ARF has been classically described as one of two types: hypoxemic or hypercarbic failure. More recent classifications categorize ARF into four different types, based on the mechanism of hypoxemia.[10] Table 9.2 describes differences among the four types of ARF with regard to the mechanism of hypoxemia, location of the abnormality, and most commonly seen clinical syndromes. Despite these categories, considerable overlap exists in the different types of ARF. Furthermore, a given patient can have multiple types of ARF contributing to their clinical presentation.

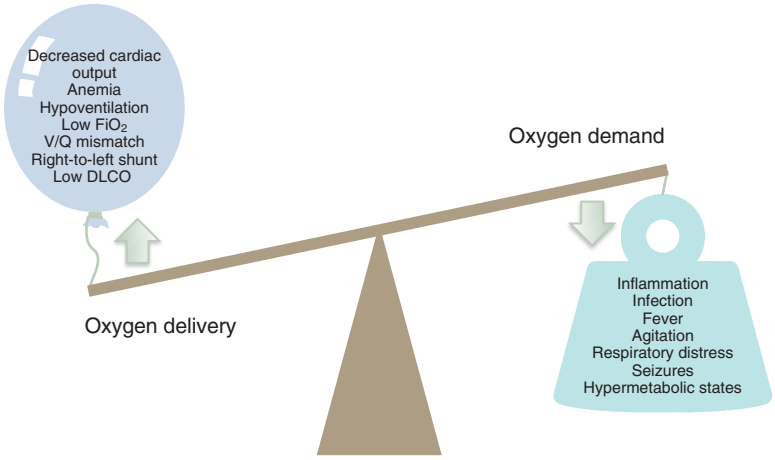

Fig. 9.1 Compromised oxygenation of peripheral tissues may be the consequence of inadequate O_2 delivery or increased O_2 demand. *DLCO*, diffusing capacity for carbon monoxide; *FiO_2*, fraction of inspired oxygen; *V/Q*, ventilation perfusion.

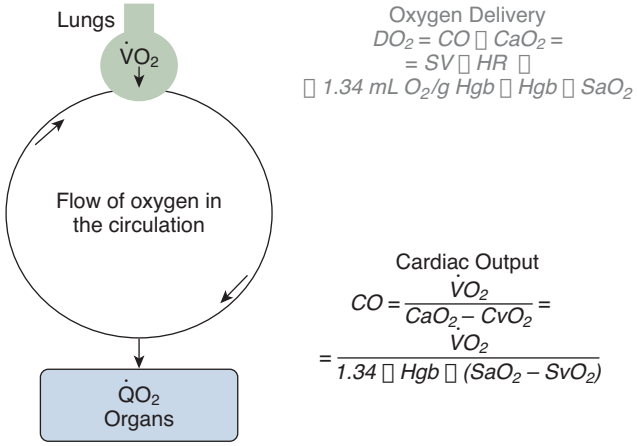

Fig. 9.2 The Fick principle underlies the relationship of O_2 uptake/consumption by peripheral tissues to cardiac output and the oxygen content in arterial and venous compartments. *CaO_2*, arterial oxygen content; *CO*, cardiac output; *DO_2*, oxygen delivery; *Hgb*, hemoglobin; *HR*, heart rate; *SV*, stroke volume; *$\dot{Q}O_2$*, oxygen consumption rate; *SaO_2*, arterial oxygen saturation; *SvO_2*, mixed venous oxygen saturation *$\dot{V}O_2$*, oxygen uptake.

Type I or Classic "Hypoxemic" Respiratory Failure

Type I ARF is the most common form of respiratory failure and at sea level is defined by PaO_2 <60 mm Hg, with normal or decreased $PaCO_2$. The primary abnormality originates in one of three dysfunctions: (1) inadequately oxygenated alveoli (because of low fraction of inspired oxygen [FiO_2] and/or alveolar collapse and/or the presence of alveoli filled with fluid, cells, debris, or blood); (2) compromised transition of oxygen from the alveoli to the blood (because of interstitial processes or pulmonary vascular disease); or (3) compromised ability of the blood to oxygenate (because of obstructed blood flow, shunting, low Hgb concentration, or the presence of dysfunctional Hgb). The analysis of ABG values and calculation of the alveolar-arterial (A-a) gradient are important in the assessment of type I ARF.

Type II or "Hypercarbic" Respiratory Failure

Type II ARF ($PaCO_2$ >45 mm Hg) represents the failure of the lungs to remove a sufficient amount of CO_2 in a given time interval and is characterized by decreased alveolar minute ventilation. An increase in $PaCO_2$ leads to hypoxemia because CO_2 displaces O_2 and effectively reduces the alveolar partial pressure of oxygen (PAO_2). In contrast to some cases of type I ARF, hypoxemia in type II ARF is rather easily corrected with supplemental oxygen. This type of respiratory failure is frequently the result of acute or chronic neuromuscular dysfunction or

TABLE 9.1 Pathophysiologic Mechanisms That Lead to Hypoxia and Respiratory Insufficiency

1. Extrapulmonary processes, including chest wall and skeletal abnormalities (hypoxic hypoxia)
   a. Deficiency of oxygen in inspired air (high altitude, suffocation)
   b. Hypoactive hypoventilation (central nervous system trauma, drug toxicities, and neuromuscular and skeletal disorders)
   c. Upper airway obstruction leading to hypoventilation (trauma and angioedema)
2. Pulmonary etiologies (hypoxic hypoxia)
   a. Hypoventilation caused by increased airway resistance (chronic obstructive pulmonary disease and asthma)
   b. Abnormal alveolar ventilation–perfusion ratio (pulmonary embolism, pneumonia, aspiration, and emphysema)
   c. Diminished diffusing capacity via the alveolar–capillary membrane (interstitial lung disease and pulmonary vascular disease)
   d. Pulmonary shunting (atelectasis, pneumonia, hepatopulmonary syndrome, and arteriovenous malformations)
3. Cardiac right-to-left shunts (e.g., atrial septal defect [hypoxic hypoxia])
4. Inadequate capacity of blood to transport oxygen (anemic hypoxia)
   a. Anemia
   b. Hemoglobinopathies (methemoglobinemia and carbon monoxide poisoning)
5. Inadequate oxygen transport because of a circulatory defect (static hypoxia)
   a. General circulatory deficiency or collapse (shock or cardiac failure)
   b. Localized circulatory deficiency (peripheral, cerebral, and coronary vessels)
6. Abnormal tissue capability for using oxygen (histotoxic hypoxia)
   a. Late-stage irreversible shock
   b. Poisoning of cellular oxidation enzymes (cyanide or arsenic toxicity and heavy ethanol intoxication)
   c. Diminished cellular metabolic capacity for using oxygen

TABLE 9.2 Classification of Acute Respiratory Failure (Modified From[10])

	Type I	Type II	Type III	Type IV
Mechanism of hypoxemia	Low FiO_2 ventilation/perfusion (V/Q) mismatch Shunting Reduced diffusing capacity	Hypoventilation	Shunting Hypoventilation V/Q mismatch	Hypoperfusion or inadequate oxygenation of peripheral tissues
Location of pathologic process	Inhaled air composition Alveolar–capillary unit Oxygen-carrying capacity of blood	Airway Central nervous system (CNS) Neuromuscular system Chest wall	Alveolar–capillary unit collapse with regional hypoventilation	Cardiovascular system Peripheral tissues
Clinical syndromes	Cardiogenic pulmonary edema Acute respiratory distress syndrome (ARDS) Pneumonia Interstitial lung disease Pulmonary embolism Pulmonary hypertension Atelectasis Alveolar hemorrhage Carbon monoxide poisoning Anatomic shunts	Chronic obstructive pulmonary disease (COPD) Asthma CNS depression (intoxication) CNS trauma or injury Neuromuscular disorders Skeletal disorders Obesity–hypoventilation syndrome	ARDS Thoracic or upper abdominal surgery or trauma Inadequate postoperative analgesia Pleural tumor or inflammation Trapped lung Subdiaphragmatic tumor or inflammation Obesity	Septic (distributive) shock Hypovolemic shock Cardiogenic shock Compromised cellular oxidation Hypermetabolic states

FiO_2, Fraction of inspired oxygen.

the inability of the airways or lungs to ensure adequate ventilation and CO_2 exchange.

Type III or "Perioperative" Respiratory Failure

Type III respiratory failure is synonymous with perioperative respiratory failure and is related to atelectasis of the lung. It is often a consequence of abnormal abdominal and chest wall mechanics in the setting of surgery or trauma, especially those characterized by intrapleural or subdiaphragmatic pathologies. The patient usually splints the chest to limit involuntary movement of the injured region, leading to inadequate expansion of the dependent parts of the lungs, with resultant regional atelectasis and hypoventilation. As a result, type III ARF shares features with both type I (hypoxemic) and type II (hypercarbic) ARF. This type of ARF can be prevented or ameliorated by certain anesthetic strategies in addition to perioperative measures such as elevating the head of the bed, early ambulation, incentive spirometry, avoiding excessive sedation, and lowering intraabdominal pressure.

Type IV or "High-Demand" Respiratory Failure

Type IV respiratory failure is related to an inability of normal or relatively normal lungs to keep up with increased ventilatory demands associated with systemic hypermetabolism (e.g., secondary to sepsis). In other words, peripheral tissue demands cannot be satisfied by cardiorespiratory compensatory mechanisms. Under these conditions, respiratory muscle fatigue can lead to a requirement for mechanical ventilation (MV) to support adequate minute ventilation.

DIAGNOSTIC WORKUP

Obtaining a relevant history is crucial in narrowing down the etiology of ARF. A focused physical examination also helps assess the severity of respiratory failure and determine the need for immediate interventions. Common signs include tachypnea; the use of accessory respiratory muscles; nasal flaring; abdominal paradoxical breathing; and retractions in the intercostal, suprasternal, or supraclavicular areas. At times, irregular breathing patterns or poor chest wall excursion may be observed in addition to cough, wheezing, copious secretions, or cyanosis. A detailed examination of the upper airway and chest in addition to careful neurologic, cardiovascular, abdominal, skin, and musculoskeletal system examinations may also help narrow down the differential diagnosis. Table 9.3 lists common clues obtained from the history and physical examination of the patient, which can help diagnose the etiology of respiratory failure.

Before the comprehensive diagnostic workup, it is important to remember that establishing a diagnosis should not delay intervention in cases of severe ARF. ABG analysis should be obtained in all patients with suspected ARF. The ABG helps determine the chronicity of the respiratory failure and, more importantly, the extent and severity of the ARF. Fig. 9.3 schematically displays the changes in ABG parameters in acute and chronic respiratory disorders. Laboratory workup should also include complete blood count, basic metabolic profile, cardiac enzymes, and microbiologic evaluation. Chest imaging, including computed tomography (CT) when needed, can help with the diagnosis of a primary pulmonary pathology. Evaluating cardiac function with echocardiography can significantly narrow down the differential diagnosis in patients with systemic disease and shock. Increasing availability and accumulated evidence about the role of point-of-care ultrasound (POCUS) in the ICU has had a significant impact on the management of ARF. In addition to the broad cardiovascular assessment of critically ill patients with protocols such as Rapid Ultrasound for Shock and Hypotension (RUSH)[11] or Focused Assessment with Sonography in Trauma (FAST),[12] which are recommended aids to rapid recognition of the pathophysiologic processes leading to ARF, lung-centered POCUS techniques have also significantly evolved. The Bedside Lung Ultrasound Emergency (BLUE) protocol[13] for the immediate diagnosis of ARF has been widely implemented, and the ability of POCUS to facilitate more prompt and early management of ARF has become evident in recent years (Table 9.4).[14]

MANAGEMENT

Appropriate management of a patient with ARF usually requires admission to an ICU setting, where adequate support and close monitoring are available. Management should focus on stabilization of the patient's ventilatory and hemodynamic status in addition to

TABLE 9.3 Common Clues Obtained From the History, Symptoms, and Clinical Examination Findings That Can Help in the Initial Diagnostic Workup and Management of Acute Respiratory Failure

History and Symptoms	Signs on Physical Examination	Diagnosis
Cough, sputum, secretions	Rales or wheezing	Pneumonia, COPD exacerbation, bronchiectasis
Sudden onset of shortness of breath	Normal auscultation and percussion, possible signs of leg swelling to suggest deep vein thrombosis	Pulmonary embolism
History of heavy smoking	Wheezing, rhonchi	Emphysema, chronic bronchitis
Orthopnea, chest pain, paroxysmal nocturnal dyspnea	Arrhythmia, peripheral edema, jugular venous distention, peripheral hypoperfusion	Congestive heart failure or acute coronary syndrome
Trauma, aspiration, blood transfusions	Diffuse crackles	ARDS
History of allergies, wheezing or airway disease	Wheezing	Asthma, COPD
Exposure to heavy metals, handling of animals, dust, or other significant environmental exposures	"Velcro" rales, clubbing	Chronic interstitial lung disease
Choking, aspiration, vomiting, dental procedures	Inspiratory stridor, poor air entry	Foreign body
Drug abuse	Constricted or dilated pupils, altered mental status, skin marks, perforated nasal septum, hypersalivation, decreased respiratory frequency	CNS depression, intoxication
Exposure to a new drug/chemical or foods known to be allergenic	Swollen oral mucosa and tongue; stridor or wheezing	Angioedema, anaphylaxis
Progressive muscle weakness or immobility	Sensory abnormalities	Neuromuscular disorders
Trauma, procedures, inhalational injury	Absent breath sounds unilaterally, hypertympanic, tracheal deviation	Pneumothorax
Trauma, procedures	Absent breath sounds, dull on percussion, tracheal deviation	Hemothorax

ARDS, Acute respiratory distress syndrome; *CNS,* central nervous system; *COPD,* chronic pulmonary obstructive disease.

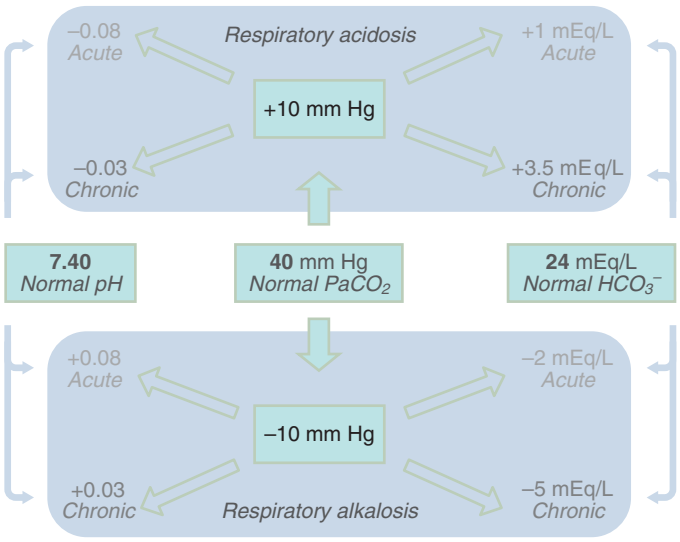

Fig. 9.3 Interpretation of an arterial blood gas in the setting of respiratory failure.

correction of the pathophysiologic process underlying the respiratory failure. Prioritizing airway patency, breathing, and circulation has long been a basic tenet in the management of ARF, or the so-called "ABC" of ARF management (not to be confused with the American Heart Association's guidelines for cardiac arrest management).[15]

TABLE 9.4 Ultrasound Findings of Common Etiologies of Acute Respiratory Failure

Clinical Finding	Ultrasound Finding
Pneumothorax	Absence of "lung sliding" "Lung point" Absence of "comet tail" artifact "Bar code" sign on M-mode
Pleural effusion	Hypoechoic space "Quad" sign "Sinusoid" sign on M-mode
Pneumonia	Consolidation Hepatization of lung Dynamic air bronchograms
Pulmonary embolism	Peripheral wedge-shaped consolidation RV dysfunction (RV dilation, >1:1 RV:LV ratio, bowing of interventricular septum into LV) Pleural effusion
Pulmonary edema	>3 B-lines per intercostal space
Interstitial lung disease	Irregular pleural line Subpleural cysts Decreased lung sliding B-lines

LV, Left ventricle; *RV,* right ventricle.
Table modified from Wallbridge P, Steinfort D, Tay TR, et al. Diagnostic chest ultrasound for acute respiratory failure. *Respir Med.* 2018;141:26–36.

Airway Patency

Securing airway patency is the first step in the management of ARF. This usually requires interventions such as positioning, suctioning of secretions, treatment with bronchodilators, and/or placement of an oral airway. When physical obstruction of the upper airway by a foreign body or mass is suspected, advanced invasive procedures, such as laryngoscopy or bronchoscopy, may be necessary. In cases of severe respiratory compromise that require more invasive ventilatory management, endotracheal intubation is indicated. This can be achieved via orotracheal or nasotracheal intubation or, in difficult cases when an endotracheal tube cannot be advanced through the vocal cords, emergency cricothyroidotomy. The inability of a patient to protect their airway because of compromised mental status (usually with a Glasgow Coma Scale score <8) also warrants endotracheal intubation to secure the airway. The process of securing the airway in ARF requires an understanding of the ongoing pathologic process and an advanced knowledge of the anatomy of the upper airway. Appropriate monitoring and measures to maintain adequate oxygenation during the process should be undertaken.

Breathing

Breathing encompasses oxygenation and ventilation and is based on the movement of fresh, oxygenated air into and out of the lungs, enabling gas exchange by bringing in oxygen and flushing out carbon dioxide. Breathing assistance is required for both oxygenation and ventilation disorders. Treating hypoxemia should be the first step, which usually can be achieved with supplemental oxygen. Oxygen can be provided via nasal cannula, face mask, Venturi mask, nonrebreather mask, or high-flow oxygen delivery devices. When hypoxemia cannot be corrected with supplemental oxygen alone or ventilation is compromised, transition to MV may be necessary. MV may be provided via noninvasive ventilation (NIV) or via invasive MV through an endotracheal tube. Severe respiratory failure with an inability to oxygenate and/or ventilate despite MV may occasionally require assisted gas exchange by extracorporeal membrane oxygenation (ECMO).[16]

Circulation

Natural breathing without positive airway pressure not only provides gas exchange but also affects hemodynamics on a breath-to-breath basis, allowing unimpeded venous return and cardiac output. Circulation affects our respiratory patterns, and they are also affected by ventilatory mechanics. Treating hypotension or hypertension and optimizing cardiac output may help treat the underlying etiology of ARF and offset the potentially adverse effects of positive pressure ventilation on cardiac preload and afterload. Also, anesthetics and sedatives used for mechanically ventilated patients, in addition to paralytics used for intubation, often have significant hemodynamic effects that should be anticipated and aggressively corrected as necessary.

Further Management and Monitoring

Along with focusing on the "ABC" of ARF, the treatment of its underlying cause is of paramount importance to the patient's outcome. Antibiotics and source control for the management of infections, cardiac or inotropic medications, revascularization, air or fluid evacuation, anticoagulation or thrombolysis, fluid expansion, diuretics, vasodilators, bronchodilators, and glucocorticoids, in addition to many other medications and interventions, may be required to treat the underlying etiology.

The success and adequacy of the management of ARF should be continuously monitored. Multiple blood gas analyses may be required to ensure that both oxygenation and ventilation are maintained within desired limits. In general, PaO_2 should be maintained at >55–60 mm Hg, a range that represents a threshold for severe hypoxemia. Arterial blood oxygen saturation (SpO_2) can be tested and correlated to PaO_2 and can be used as a surrogate marker for the adequacy of oxygenation, with a general recommended goal of >88%. pH and arterial or central venous PCO_2 values reflect the adequacy of MV and are also useful in the setting of a metabolic acid-base disorder. ABG goals should in general be individualized. For example, permissive hypercapnia may be appropriate for some patients, whereas other patients may benefit from therapeutic hyperventilation.

Ventilatory/Oxygenation Support Strategies and Mechanical Ventilation

The purpose of MV is to improve oxygenation and ventilation to correct respiratory acidosis and hypoxemia, meet metabolic demands, rest respiratory muscles, and optimize cardiac function and blood circulation. MV allows for augmented or controlled minute ventilation and the provision of high concentrations of oxygen and positive end-expiratory pressure (PEEP). MV may therefore positively affect gas exchange and the regional distribution of lung aeration and ventilation.[17] MV can be *noninvasive,* involving a variety of interfaces such as nasal or face masks, or *invasive,* involving endotracheal intubation. General indications for intubation and invasive MV are described in Table 9.5.

NIV has been increasingly used in the past two decades as an alternative to endotracheal intubation and MV in appropriate clinical settings.[18] NIV with continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) modalities benefits selected cases of chronic obstructive pulmonary disease (COPD) exacerbation, cardiogenic pulmonary edema, obesity hypoventilation, decompensated obstructive sleep apnea, and neuromuscular disease.[18,19] It has also been used successfully for respiratory failure in postoperative patients,[20] immunocompromised patients,[21] or in patients with a do-not-intubate (DNI) code status.[22]

NIV requires the patient's cooperation and an anatomically preserved, functional upper airway. It is not a replacement for invasive MV, nor is it suitable for all patients with ARF. Significantly depressed mental status with an inability to protect the airway, copious secretions, massive hemoptysis or hematemesis, recent upper gastrointestinal and facial surgery, bowel obstruction, facial trauma or deformity, cardiopulmonary arrest, and severe arrhythmias are contraindications to its use.[19] NIV is not always prudent as the first step in advanced hypoxemic respiratory failure, as it may lead to a more difficult transition to MV in cases of NIV failure.[23] There is some evidence, however, that it can be of benefit in the setting of severe hypoxemia during the

TABLE 9.5 General Indications for Intubation and Mechanical Ventilation

Cardiopulmonary arrest or impending arrest
Respiratory distress/tachypnea with increased ventilatory demand and breathing effort leading to respiratory muscle fatigue
Severe hypercarbic respiratory failure with either poor candidacy for NIV or failure of NIV
Severe refractory hypoxemia with failure of noninvasive oxygen delivery devices
Severe refractory metabolic acid-base disorder
Inability to protect the airway
Inability to clear secretions
Need for therapeutic hyperventilation or hypoventilation
Upper airway obstruction with poor airway patency
Decreased respiratory drive with bradypnea
Coma with Glasgow Coma Scale score of <8
Severe trauma
Surgery requiring general anesthesia

NIV, Noninvasive ventilation.

process of *transitioning* to invasive MV.[24] In circulatory shock states that lead to type IV ARF, NIV may adversely affect venous return and pulmonary hemodynamics in volume-depleted patients.[25]

A recent alternative to NIV and perhaps to MV has been the use of high-flow nasal cannula (HFNC). This newer oxygen delivery system provides heated and humidified air at 21%–100% of FiO_2 with flow rates of up to 60 liters per minute (L/min). Oxygen-enriched gas is delivered through a large-bore nasal cannula that helps prevent entrainment of room air. Mechanisms by which HFNC helps improve oxygenation and ventilation include provision of heated, humidified gas that aids mucociliary clearance; delivery of gas at high-flow rates to match patient demand; generation of low-level PEEP; washout of dead space from the upper airway; minimization of oxygen dilution; and improved patient comfort when compared with other options for respiratory support.[26]

A prospective, multicenter, randomized controlled trial published in 2015 evaluated patients admitted to the ICU with acute hypoxemic respiratory failure and determined that HFNC as compared with NIV and standard oxygen therapy alone did not reduce intubation rates but did reduce ICU mortality at 90 days.[27] HFNC was especially beneficial in patients with severe hypoxemia, defined as PaO_2:FiO_2 ≤200 mm Hg, in whom HFNC also reduced the rate of intubation.

Retrospective studies have also investigated the use of HFNC in critically ill patients during hypercarbic respiratory failure, with possible benefits.[28] The use of HFNC in this population, however, is not well-established.

Invasive MV requires an endotracheal or tracheostomy tube to seal the interface between the patient and the ventilator. Before initiation of invasive MV, a careful assessment of risks and benefits needs to be undertaken, as both intubation and MV carry risks of potentially fatal complications. Although it is clearly a lifesaving measure when appropriately used, invasive MV may lead to significant hemodynamic compromise that results from the sedative effects of medications used for intubation and MV; abrogation of the patient's inspiratory drive; and changes in cardiac preload, afterload, and interventricular dependence.[29,30] MV also increases the risks of ventilation-associated lung injury, dynamic hyperinflation, and pneumonia, in addition to the discomfort of patient–ventilator asynchrony. Importantly, in situations involving terminal illnesses or irreversible etiologies of ARF, a discussion with the patient and family regarding the appropriateness and expectations of invasive MV is warranted.

Evaluation of the patient's anatomy, such as the presence of facial hair; oral cavity inspection, including dentition; neck shape and mobility; and the presence of secretions or obstruction, is helpful for predicting the odds of a difficult intubation and for planning the specific intubation approach. Before intubation, the operator needs to carefully choose sedatives and anesthetics, secure vascular access, prepare hemodynamic support, adequately preoxygenate the patient, and prepare for supportive manual bag–valve mask ventilation.[23] It is important to remember that every intubation in the setting of ARF may become a difficult intubation,[31] and experienced operators and rescue strategies for securing the airway need to be available. Upon endotracheal intubation, the tube position should be confirmed and secured to avoid accidental extubation.

While attached to a ventilator, the patient's comfort, gas exchange, mechanics, and ventilator waveforms need to be continuously monitored. Adequate analgesia must be provided while using the least sedation required to achieve comfort and ventilator synchrony.[32–34] Spontaneous breathing trials should be initiated daily once the patient's condition is stable.[34–36] With few exceptions, the upper body should be elevated to >30 degrees, and daily prophylaxis for deep venous thrombosis should be provided.

In patients with or at high risk for acute lung injury and acute respiratory distress syndrome (ARDS), a lung-protective ventilation strategy should be used. This entails using low tidal volumes (5–7 mL/kg of ideal body weight), permissive hypercapnia, PEEP of 5–15 cm H_2O to best compliance, and maintaining noninjurious inspiratory driving and plateau pressures (<15 and 30 cm H_2O, respectively).[37,38] In patients without ARDS but with respiratory failure, strict adherence to low tidal volumes may be less crucial, as recent data suggest that an intermediate tidal volume ventilation strategy may keep safe airway pressure targets and have similar outcomes in this patient population.[39] Early neuromuscular paralysis can be used in cases of severe ARDS or in patients experiencing ventilator dyssynchrony despite high doses of sedatives.[40] In cases of refractory hypoxemia, additional strategies,[41] including prone positioning,[42] pulmonary vasodilators (e.g., inhaled nitric oxide),[43] recruitment maneuvers,[44] high-frequency oscillatory ventilation,[45] or airway pressure release ventilation (APRV or bilevel ventilation),[46] have been used but with variable success rates.

In patients with severe ARDS, early use of paralytics for brief periods (,48 hours) had been previously accepted as the standard of care after the ACURASYS trial demonstrated a decrease in 90-day mortality.[32,40] The Prevention and Early Treatment of Acute Lung Injury (PETAL) network has since conducted the ROSE trial, a larger trial of ARDS patients examining paralysis versus usual care with lighter sedation. This more recently published trial did not confirm benefit of routinely initiating paralytics on mortality or other secondary outcomes.[47]

Prone positioning is another adjunctive therapy used in the treatment of hypoxic respiratory failure. Prone positioning recruits dependent lung regions, which helps improve ventilation–perfusion matching and may help gas exchange by more equally distributing tidal volumes and associated transpulmonary pressures. The latter reduces average tissue stress on the lung, helping in the "lung protective" strategy. In a large trial using prone positioning for ≥16 hours a day in patients with severe ARDS (PaO_2:FiO_2 ≤150 mm Hg), a significant reduction in 90-day mortality was observed.[42] However, in a subsequent Cochrane review of nine trials of varying quality that looked at the effects of prone positioning on outcomes, no consistent evidence of benefit or harm was found.[48] Differences in patient selection, duration, and severity of disease may help explain this apparent discord.

Patients with profound nonresolving ARF despite the previously mentioned strategies should be considered for ECMO if the underlying etiology is considered reversible.[49] Although no clear evidence of a mortality benefit exists for the early implementation of ECMO in patients with severe ARDS, the EOLIA trial showed increases in prone positioning–free days, renal failure–free days, and renal replacement–free days in patients with early referral to an ECMO center.[50]

CONCLUSION

ARF is one of the most common conditions encountered in critical care medicine and is associated with significant morbidity and mortality. Understanding the pathophysiology of ARF with regard to oxygen consumption, delivery, and transport; the etiologies of ARF (types I–IV); and the clinical presentation (acute or acute on chronic) is essential for the skilled management of these patients. The priority in the management of ARF is to focus on the "ABC" approach, with efficient and effective decision making regarding the use of HFNC, NIV, and/or invasive MV. Finally, therapies need to be directed at both the ARF itself and the underlying condition in order to optimize patient outcomes.

KEY POINTS

- ARF is one of the most common indications for admission to the ICU and carries a high morbidity and mortality.
- An understanding of the pathophysiology of respiratory failure and a focus on the stabilization of oxygenation, ventilation, and hemodynamics are essential in the management of ARF.
- Respiratory failure can be divided into four categories: hypoxemic, hypercarbic, perioperative, and high-demand respiratory failure, although in practice, it is often a combination of multiple categories.
- The use of HFNC can be considered a noninferior alternative to NIV for acute hypoxic respiratory failure and may have a survival benefit in patients with severe hypoxemia.
- NIV in select cases of acute hypercarbic respiratory failure has been shown to reduce dyspnea, ICU length of stay, need for mechanical intubation, and mortality.
- Adjunctive therapies for the treatment of moderate to severe ARDS include prone positioning, early paralytic use, and lung-protective ventilation.
- Although without clear evidence to support a mortality benefit, data suggest that the early implementation of ECMO for patients with severe ARDS may lead to improved outcomes.

References for this chapter can be found at expertconsult.com.

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This prospective, multicenter cohort study of 36 French ICUs evaluated the prevalence and outcome of patients with ARDS requiring mechanical ventilation using the American-European Consensus Conference definition of ARDS. Patients were categorized into three groups depending on the severity of hypoxemia and whether they met ARDS criteria and were followed for 28 days. The prevalence of ARDS was 6.9% of all ICU admissions and accounted for 15.8% of mechanically ventilated patients. Mortality rate was highest among the group with hypoxemia who met ARDS criteria (60%) when compared with other hypoxemic, non-ARDS ventilated patients. Three variables were independently linked to mortality: SAPS II score at inclusion, septic shock, and immunosuppression.

Slutsky AS. Mechanical ventilation. American College of Chest Physicians' Consensus Conference. *Chest*. 1993;104(6):1833–1859.
This article summarizes key concepts of mechanical ventilation to provide recommendations on the management of mechanical ventilation in specific situations. These recommendations were a result of an international consensus committee meeting consisting of specialists within anesthesia, critical care, and pulmonary and respiratory therapy. This meeting provided the basis of some of the most important concepts of mechanical ventilation that are still used today.

The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *New England Journal of Medicine*. 2000;342(18):1301–1308.
This multicenter, randomized controlled trial served to create a paradigm shift in the traditional approach to mechanical ventilation. It sought to compare ventilation with traditional lung volumes (10–15 mL/kg of predicted body weight) versus lower tidal volumes (4–6 mL/kg of predicted body weight) to determine if there was a difference in mortality and ventilator-free days. The trial was stopped early, as mortality was significantly lower in the low tidal volume ventilation group.

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Hyperbaric Oxygen in Critical Care

Kinjal N. Sethuraman and Stephen R. Thom

Hyperbaric oxygen (HBO_2) treatment involves intermittent breathing of pure oxygen at greater than ambient pressure (>1.4 atmospheres absolute [ATA]). Over the past 20 years, HBO_2 has undergone refinement, with an increased understanding of the mechanisms of action and clinical applications.

APPLICATIONS

HBO_2 treatment is carried out in either a monoplace (single person) or multiplace (typically two or more) chamber. Pressures applied while in the chamber are usually 2–3 ATA, representing the sum of the atmospheric pressure plus additional hydrostatic pressure equivalent to 1 or 2 atmospheres. Treatments are usually for 2–8 hours, depending on the indication, and may be performed between 1 and 3 times daily. Monoplace chambers are usually compressed with pure oxygen. Multiplace chambers are pressurized with air, and patients breathe pure oxygen through a tight-fitting face mask, hood, or endotracheal tube. Multiplace chambers require an inside tender to manage the starting and stopping of supplemental oxygen. Patient selection is important when choosing a monoplace vs. multiplace chamber for treatment. During treatment, arterial oxygenation as indexed by the PaO_2, typically exceeds 2000 mm Hg and levels of 200–400 mm Hg occur in tissues.[1]

HBO_2 should be viewed as a drug and the hyperbaric chamber as a dosing device. Elevating tissue oxygen tension is a primary effect. Although this may alleviate physiologic stress in hypoxic tissues, lasting benefits of HBO_2 must relate to an abatement of the underlying pathophysiologic processes. As knowledge surrounding the biochemical effects of HBO_2 grows, there may be an increase in the list of indications for it. The current accepted indications comprise a heterogeneous group of disorders (Box 10.1), thus implying that there are several mechanisms of action for HBO_2 (Box 10.2).[1–3]

In this chapter, we discuss the most common emergent indications for HBO_2.

Arterial Gas Embolism and Decompression Sickness

Among the earliest applications of hyperbaric therapy was to treat disorders related to gas bubbles in the body. Compressed air construction work required exposure to elevated ambient pressure within compartments (caissons) for many hours to excavate tunnels or bridge foundations in muddy soil that otherwise would flood. In the 19th century, workers were noted to frequently experience joint pain, limb paralysis, or pulmonary compromise when they returned to ambient pressure. This condition—decompression sickness (DCS), caisson disease, or bends—was later attributed to nitrogen bubbles in the body, and recompression was found to relieve symptoms. Recompression to treat DCS, based purely on Boyle's law with a reduction of gas bubble volume caused by pressure, was later improved by adding supplemental oxygen. Doing so hastens inert gas diffusion out of the body and may exert beneficial effects by additional therapeutic mechanisms. Similar observations were made at later times for scuba divers who also are prone to DCS and may develop arterial gas embolism (AGE) caused by pulmonary overpressurization on decompression.

Iatrogenic AGE has been reported in association with different types of interventions that include cardiovascular, obstetric/gynecologic, neurosurgical, and orthopedic procedures. AGE can occur whenever disruption of a vascular wall separating blood from gas occurs. Nonsurgical processes reported to cause AGE include overexpansion during mechanical ventilation, hemodialysis, and after accidental opening of central venous catheters.[4]

Treatment of gas bubble disorders includes standard support of airway, ventilation, and circulation plus prompt application of HBO_2. Gas bubbles may persist for several days, and although delays should be avoided, HBO_2 may be beneficial even when begun after long delays.[5–9] Controlled animal trials support the efficacy of HBO_2, but randomized clinical trials have not been conducted.[10] Yet in their review of 27 case series, Moon and Gorman described the substantial benefit of HBO_2 treatment, in which 78% of 441 cases receiving HBO_2 fully recovered and 4.5% died, whereas only 26% of 74 cases not undergoing HBO_2 treatment fully recovered and 52% died.[4]

Mechanisms of action of HBO_2 in AGE and DCS treatment include the reduction of gas bubble size according to Boyle's law, hyperoxygenation to hasten inert gas diffusion, inhibition of leukocyte adherence to injured endothelium, and inhibition of inflammatory microparticle formation.[11] Endothelial dysfunction occurs in association with mechanical interactions of bubbles at vessel walls and lumen occlusion.[12–16] Neutrophil activation and perivascular adherence occur and are associated with functional deficits post decompression.[4,17,18] Animals depleted of leukocytes before experimental cerebral air embolism suffer less severe reduction in cerebral blood flow and better neurologic outcome.[19] HBO_2 has been shown to temporarily inhibit human beta-2-integrin adhesion function.[20] Inhibition of neutrophil beta-2-integrin adhesion by HBO_2 has been described in a number of animal models, including skeletal muscle ischemia-reperfusion, cerebral ischemia-reperfusion, pulmonary smoke inhalation injury, and brain injury after carbon monoxide (CO) poisoning.[21–24] The mechanism for this effect involves *S*-nitrosylation of cytoskeletal beta-actin, which impedes the coordinated cell-surface beta-2-integrin migration required for firm adherence.[25]

Carbon Monoxide Poisoning

CO is the leading cause of injury and death by poisoning in the world.[26] The affinity of CO for hemoglobin to form carboxyhemoglobin (COHb), is more than 200-fold greater than that of O_2. CO-mediated hypoxic stress is a primary insult, but COHb values correlate poorly with clinical outcome.[27–33] Pathologic mechanisms, in addition to elevations of COHb, include intravascular platelet-leukocyte aggregation,

BOX 10.1 Accepted Indications for Hyperbaric Oxygen Therapy

- Air or gas embolism
- Carbon monoxide poisoning
- Clostridial myositis and myonecrosis
- Crush injury, compartment syndrome, acute traumatic ischemia
- Decompression sickness
- Enhancement of healing in selected problem wounds
- Severe anemia
- Intracranial abscess
- Necrotizing fasciitis
- Refractory osteomyelitis
- Radiation necrosis
  - Delayed radiation injury
- Compromised skin grafts and flaps
- Thermal burns
- Central retinal artery occlusion
- Idiopathic sudden sensorineural hearing loss

Data from Weaver, LK, ed. *Hyperbaric Oxygen Therapy Indications*, 13th ed. Durham, NC: Undersea and Hyperbaric Medical Society; 2014.

BOX 10.2 Mechanisms of Action of Hyperbaric Oxygen

Related to Hyperoxygenation of Tissues

- Angiogenesis/neovascularization/osteogenesis/epithelization in ischemic tissues (mechanisms likely include O_2 behaving as an intracellular signal transducer, leading to augmentation of one or more growth factors and mobilization of vasculogenic stem cells)
- Bacteriostatic/bactericidal actions
- Carboxyhemoglobin dissociation hastened
- Inhibition of *Clostridium perfringens* alpha toxin synthesis
- Improved phagocytic bacterial killing
- Temporary inhibition of neutrophil beta-2-integrin adhesion
- Vasoconstriction
  - Induction of growth factors and growth factor receptors
  - Inhibition of neutrophil adhesion
  - Reduction of ischemia reperfusion injury
  - Reduction in inflammation and edema

Related to Pressurization

- Reduction of gas bubble volume (Boyle's law)

leukocyte-mediated oxidative injury to the brain, the excessive release of amino acids (e.g., glutamate), impaired mitochondrial oxidative phosphorylation, and possible myocardial calcium overload.[34–40]

Survivors of acute CO poisoning are at risk for developing delayed neurologic sequelae (DNS) that include cognitive deficits, memory loss, dementia, parkinsonism, paralysis, chorea, cortical blindness, psychosis, personality changes, and peripheral neuropathy. DNS typically occurs from 2 to 40 days after poisoning, and its incidence is from 25% to 50% after severe poisoning.

Administration of supplemental oxygen is the cornerstone of treatment for CO poisoning. Oxygen inhalation will hasten the dissociation of CO from hemoglobin and provide enhanced tissue oxygenation. HBO_2 causes COHb dissociation to occur at a rate greater than that achievable by breathing pure oxygen at sea level. Additionally, HBO_2, but not ambient pressure oxygen treatment, has several actions that have been demonstrated in animal models to be beneficial in ameliorating pathophysiologic events associated with central nervous system (CNS) injuries mediated by CO. These include an improvement in mitochondrial oxidative processes,[41] inhibition of lipid peroxidation,[42] and impairment of leukocyte adhesion to injured microvasculature.[23] Animals poisoned with CO and treated with HBO_2 have been found to have more rapid improvement in cardiovascular status,[43] lower mortality,[44] and diminished incidence of neurologic sequelae.[45] A large study from China comparing patients with carbon monoxide toxicity who received HBO_2 and those who did not showed decreased mortality.[46]

Despite criticisms of their analysis, a meta-analysis by the Cochrane Library concluded that it is unclear whether HBO_2 reduces the incidence of adverse CO-mediated neurologic outcomes.[47] Five prospective, randomized trials have assessed the clinical efficacy of HBO_2 for acute CO poisoning.[31–33,48,49] Several studies failed to find a benefit,[31,49] but methodologic weaknesses discussed by several authors[40,50] diminish their clinical impact. Only one clinical trial satisfies all characteristics deemed necessary for the highest quality of randomized controlled trials.[51] The variation in patient selection, hyperbaric oxygen dose, and methodology contribute to the skepticism that these studies create. Overall, patients who received 2.8 ATA of HBO_2 had better outcomes than those who received 2.0 ATA, implying a dose-dependent response to treatment. In patients exposed to smoke and fire, careful attention needs to be paid to the patient's airway, and early intubation should be strongly considered. Some patients being treated for CO toxicity become more alert during HBO_2 therapy, and therefore in ventilated patients, adequate sedation should be prioritized because of the risk of dislodging the endotracheal tube and patient safety. Some burn centers employ adjunctive HBO_2 for severe burns. Animal models have documented benefits with HBO_2 in reducing partial- to full-thickness skin loss, hastening epithelialization, and lowering mortality.[1] Randomized clinical trials, albeit with small patient numbers, have reported improved rates of healing of burns with shorter hospitalization stays and therefore reduced costs.[52–55] The rationale for treatment has been based on reducing tissue edema and increasing neovascularization. There is growing evidence that HBO_2 benefits patients with severe burns. A comparative study of patients with 20%–60% body surface area thermal burns showed that patients receiving 6–10 HBO_2 treatments over 2 weeks had lower levels of proinflammatory cytokines, reduced length of stay in the hospital, and fewer complications.[56]

Clostridial Myonecrosis (Gas Gangrene)

Successful treatment of gas gangrene depends on prompt recognition and aggressive intervention. Early treatment with HBO_2 is recommended to inhibit the production of alpha-toxin by *Clostridium perfringens*. Mortality rates with conventional therapy from 11% to 52% have been reported. Currently, there are five retrospective comparisons using HBO_2 and 13 case series in the literature. These have been discussed in several reviews.[1,57,58] Because of difficulties with comparison among patient groups, impartial assessment of HBO_2 efficacy based on mortality or "tissue salvage" rates is difficult. Most authors comment on clinical benefits associated with treatment. Temporal improvement of vital signs in patients with gangrene can be among the most dramatic observations in day-to-day practice.

Progressive Necrotizing Infections

The use of HBO_2 for treatment of necrotizing fasciitis and Fournier gangrene, which are mixed aerobic-anaerobic infections, has been reported in six nonrandomized comparisons and four case series.[59–68] As with gas gangrene, variations in time of diagnosis and clinical status on admission compromise assessment of the existing literature. Most studies have reported that when HBO_2 is added to surgery and antibiotic therapy,

mortality is reduced versus surgery and antibiotics alone. Animal trials have been difficult to assess because synergistic bacterial processes are difficult to establish and model. One report has found HBO_2 to potentiate antibiotics in streptococcal myositis,[69] and several animal models of polymicrobial bacteremia and sepsis have reported increased survival with HBO_2.[70–72] Mechanisms of action may include the suppressed growth of anaerobic microorganisms and improved bactericidal action of leukocytes (which function poorly in hypoxic conditions).[12,73–75]

CRITICAL CARE IN HYPERBARIC MEDICINE

Preparations for treatment begin while the patient is still in the intensive care unit (i.e., before transport to the hyperbaric chamber is initiated). Issues to be addressed include informed consent, a determination that all intravenous/arterial lines and nasogastric tubes/Foley catheters are secured, capping all unnecessary intravenous catheters, placing chest tubes to one-way Heimlich valves, and adequately sedating or paralyzing the patient as clinically indicated.

The environment of the hyperbaric chamber imposes limitations on equipment, including space restrictions, fire codes, and the effect of pressure on equipment function. Electrical components of equipment are located outside the hyperbaric chamber. Cables penetrate the chamber bulkhead to make a connection to the pneumatic portion of ventilators, internal cardiac pacer wires, electrocardiogram attachments, and arterial line transducers. The patient is attached to equipment at ambient pressure before treatment. Once the treatment pressure is achieved, all settings are verified and transducers recalibrated. It is especially important to remember to check the cuff pressure of endotracheal tubes. Many centers make it a practice to replace the air in these cuffs with an equivalent volume of sterile saline before treatment to avoid volume changes related to pressurization.

Several intravenous infusion pumps operate normally in the multiplace chamber environment. If glass bottles, pressure bags, or any other gas-filled equipment is used inside a hyperbaric chamber, it must be adequately vented and closely monitored during treatment. There are limited numbers of ventilator brands approved for the high-pressure environment, and pressure cycle modes function more reliably than do those targeting tidal volume. Furthermore, patients with severe lung disease and high mean airway pressures often cannot be treated under hyperbaric conditions until pulmonary function improves.

Bed type, size, and timing of treatment around other procedures and diagnostic testing can limit the number of HBO_2 treatments the patient receives. The recent trend to place very ill patients with elevated creatinine levels on continuous dialysis has also hindered the ability to treat patients at regular intervals.

ADVERSE EFFECTS

The inherent toxicity of O_2 and potential for injury caused by elevated ambient pressure must be addressed whenever HBO_2 is used therapeutically. Middle ear barotrauma is the most common adverse effect of HBO_2 treatment.[76] As the ambient pressure within the hyperbaric chamber is increased, a patient must be able to equalize the pressure within the middle ear by auto-insufflation. Standard protocols include the instruction of patients on auto-insufflation techniques and adding oral or topical decongestants when needed. When these interventions fail, tympanostomy tubes must be placed. Intubated patients have difficulty with equalization, and the tympanic membrane must be examined after each treatment. The incidence of tympanostomy tube placement has been reported to be approximately 4% in one series.[77] Others report an overall incidence of aural barotrauma to be between 1.2% and 7%.[78,79]

Pulmonary barotrauma during HBO_2 treatment is extremely rare but should be suspected when any significant chest or hemodynamic symptoms occur during or shortly after decompression. Because the offending gas in virtually all cases will be pure O_2, absorption within the body occurs rather quickly in most cases. If symptoms do develop, however, decompression should be prevented or interrupted and the patient carefully evaluated. If the pneumothorax is suspected, placement of a chest tube is appropriate. Preexisting pneumothorax should be treated with chest tube drainage before initiating therapy.

Biochemical toxicity resulting from O_2 can be manifested by injuries to the lungs, CNS, and eyes. Pulmonary insults can impair mechanics (elasticity), vital capacity, and gas exchange.[79] These changes are typically observed only when treatment duration and pressures exceed typical therapeutic protocols. CNS O_2 toxicity manifests as a grand mal seizure. This occurs at an incidence of approximately 1–4 in 10,000 patient treatments.[78,80,81] The risk is higher in hypercapnic patients and possibly those who are acidotic or compromised as a result of sepsis, because an incidence of 7% (23 in 322 patients) was reported in a case series of HBO_2 treatment of gas gangrene.[57] Anecdotally, intubated patients seem to be at higher risk of seizures because of the greater oxygen concentrations to which they are exposed. Seizures are managed by reducing the inspired O_2 tension while leaving the patient exposed to the same ambient pressure (to avoid pulmonary overexpansion injury when a patient is in the tonic convulsion phase).

Progressive myopia has been reported in patients who undergo prolonged daily therapy, but this typically reverses within 6 weeks after termination of treatments.[82] There is a risk for nuclear cataract development, most typically when treatments exceed a total of 150–200 hours, but cataracts may arise with less provocative exposures.[83,84] Although there is a theoretical risk of retrolental fibroplasia in neonates,[85] there are no reports of this having occurred. Currently, the experimental and clinical evidence does not indicate that typical HBO_2 therapy protocols have detrimental effects on neonates or the unborn fetus.[86] This apparent tolerance is likely caused by the relatively short duration of hyperoxia.

OTHER RISKS

Confinement anxiety for patients may occur and is typically managed with the use of sedating agents. Any environment with an elevated concentration of O_2 presents a risk for fire. Scrupulous attention to avoiding an ignition source is standard in HBO_2 therapy programs.[87]

The risk for acquiring respiratory diseases in a confined environment needs to be considered. Patients and their accompanying tenders should wear surgical masks at all times in a multiplace chamber. Patients using head tents, hoods, or fitted masks for oxygen delivery are in a closed circuit and offer reduced risk for transmitting disease; however, when a respiratory illness is suspected in a patient, N95 masks should be worn by staff. N95 mask fit should be tested under hyperbaric conditions to ascertain proper fit and protection.

KEY POINTS

- Several therapeutic mechanisms of action for HBO_2 therapy stem from hyperoxygenation of perfused tissues, reduction of gas bubble volumes, and decrease in proinflammatory processes.
- Safe treatment of critically ill patients can be accomplished in either one-person "monoplace" or larger multiple-person hyperbaric chambers.
- Efficacy of hyperbaric oxygen therapy has been documented by randomized clinical trials for a heterogeneous group of disorders.

References for this chapter can be found at expertconsult.com.

ANNOTATED REFERENCES

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Pulmonary Edema

Sonal R. Pannu, John W. Christman, and Elliott D. Crouser

BACKGROUND AND EPIDEMIOLOGY OF PULMONARY EDEMA

Acute pulmonary edema is a commonly occurring emergency that demands immediate medical attention.[1,2] It is broadly classified into cardiogenic (increased hydrostatic pressure) or noncardiogenic (increased microvascular permeability) causes; however, it is common for critically ill patients to present with pulmonary edema arising from a combination of cardiogenic and noncardiogenic etiologies. It is a major health problem, accounting for ~10% of intensive care unit (ICU) admissions,[3] and is associated with an estimated acute hospital mortality of ~10%–25%[4–6] and 1-year mortality exceeding 40%.[5,7,8]

PATHOPHYSIOLOGY OF PULMONARY EDEMA

The alveolar-capillary microcirculation regulates the amount of fluid within the lung. Normal pulmonary physiology is governed by Starling forces that favor a small net extravasation of fluid from the alveolar capillaries into the lung interstitial space that is facilitated by hydrostatic forces and by the presence of microscopic gaps between the capillary endothelial cells.[9] The rate of fluid influx is mitigated by a protein osmotic pressure gradient favoring movement of fluid from the interstitial space back into the circulating plasma. The resulting relatively small physiologic fluid movement from the vasculature into the lungs is normally offset by fluid efflux via the pulmonary lymphatic system, which ultimately drains back into the systemic venous circulation. In normal adults, interstitial fluid volume is strictly controlled because the physiologic extravasation is exactly balanced by lymphatic clearance[10]; as fluid passes through the lung interstitium, it is excluded from the alveolar space (AS) by occlusive tight junctions between alveolar epithelial cells.[1,11] The Starling equation for filtration mathematically represents the fluid balance between the pulmonary vasculature and interstitium, which "depends on the net difference in hydrostatic and protein osmotic pressures and permeability of the capillary membrane."[12]

$$Q = K[(Pmv - Ppmv) - (\pi mv - \pi pmv)]^{9}$$

where:
Q = net transvascular filtration of fluid into the IS
K= filtration coefficient
Ppmv = hydrostatic pressure in perimicrovascular IS
Pmv = hydrostatic pressure within the capillaries (e.g., the pulmonary capillary wedge pressure [PCWP])
πmv = protein osmotic pressure in the circulation
πpmv = protein osmotic pressure in the perimicrovascular IS

Although the Starling equation is conceptually useful in understanding the mechanisms favoring pulmonary edema formation, it is impractical to accurately measure most of these parameters clinically. Among the four forces, only the pulmonary artery occlusion pressure (PAOP) can be measured clinically. It is derived from the pulmonary artery catheter balloon wedged into a pulmonary artery segment, is a reflection of left atrial filling pressure, and is thought to be a useful but imperfect estimate of the hydrostatic pressure of the lung microcirculation. In the absence of acute lung injury (e.g., capillary damage), changes in the rate of fluid flux through the lungs are dictated primarily by changes in hydrostatic pressure. Nonetheless, a basic understanding of this equation is needed to understand the mechanisms governing the development of pulmonary edema.

In the presence of factors altering the Starling equation, the surplus fluid in the capillaries results in interstitial edema, which is reflected in chest images as peribronchial and perivascular cuffing. Pathologically, dilation of lymphatics may be noted as the lymphatic capacitance increases and is eventually overwhelmed as it attempts to accommodate the additional interstitial fluid. Ongoing accumulation of excess fluid in the interstitium overcomes the tight junctions in the alveolar epithelium, and subsequent alveolar edema results. Alveolar edema results in marked changes in lung water that are clinically manifested as increased work of breathing and hypoxemia. Lack of ventilation in the flooded alveolar units results in variable degree of right-to-left shunting of the pulmonary arterial blood flow, which contributes to hypoxemia.

CARDIOGENIC PULMONARY EDEMA (INCREASED CAPILLARY HYDROSTATIC PRESSURE)

Increased hydrostatic pressure in the pulmonary capillaries increases transvascular fluid filtration and is most often caused by volume overload or impaired left ventricular function (elevated filling pressures) that elevates pulmonary vascular pressures. Mild elevations of left atrial pressure, reflected by a PAOP of 18–25 mm Hg, cause edema formation and engorgement of the perimicrovascular and peribronchovascular interstitial spaces. As left atrial pressure rises further (PAOP >25 mm Hg), the capacitance of the lymphatics and lung interstitium (estimated at ~500 mL fluid) is exceeded and fluid overwhelms the lung epithelial barrier, flooding the alveoli with protein-poor fluid.[13,14] The development of edema with increases in the hydrostatic pressure is also a function of the acuity of pressure elevation. In the setting of gradual pressure changes associated with valvular deformities, the gradually proliferating collaterals of the lymphatic system prevent rapid edema formation and prevent overt symptoms of pulmonary edema at even high PAOP. On the other hand, sudden impairment of left ventricular function or massive fluid overload may lead to rapid development of the pathophysiologic changes described earlier.

Light and electron microscopic changes in animal lung tissue with hydrostatic lung edema indicate statistically significant increase in nonparenchymal interstitium: that is, the interlobular septa and the connective tissue sleeves that surround conducting portions of the respiratory tree and extraalveolar pulmonary blood vessels.[15] The thickness of the air–blood barrier, which consists primarily of matrix or ground substance in the interstitium, is significantly greater in the edematous lungs. Interestingly in high-pressure edema, barrier lesions have also been noted in both endothelial and alveolar epithelial regions. Frank disruptions of the thin and thick sides of the blood-gas barrier suggest capillary stress fractures. In moderate-pressure edema, epithelial blebs may be noted. These findings imply that barrier leaks may result from hydrostatic pulmonary edema, based on the severity and chronicity of the disease.[16] Thus interstitial edema from capillary injury is an alternative mechanism, in addition to the hydrostatic and osmotic pressure variations, which may explain or contribute to edema formation in some cases of cardiogenic pulmonary edema.

Hypoxemia results clinically from the development of alveolar and interstitial fluid accumulation, destabilization of alveolar units (impaired surfactant function), and consequent ventilation–perfusion (V/Q) mismatching. Gas exchange is severely impaired as a result of alveolar flooding, and intrapulmonary shunting ensues. The presence of edema fluid reduces pulmonary distensibility and moves the lung's pressure–volume curve rightward. The loss of surfactant plays an important role in the reduction of the total lung volume and related alveolar ventilation because of the instability and collapse of alveoli. Airway resistance is associated with the development of hydrostatic pulmonary edema caused by peribronchiolar fluid accumulation.[17] Consequently, patients developing pulmonary edema have to breathe more rapidly and have to work harder to expand their lungs, leading to increased work of breathing.

Occasionally noncardiogenic causes, such as rapid resuscitation with fluids or administered blood products (specifically in the setting of renal failure), cardiac valvular diseases, or rarely, pulmonary veno-occlusive diseases may cause pulmonary edema by similar mechanisms; however, given that cardiac etiology is by far the most common, we broadly refer to high capillary pressure pulmonary edema as cardiogenic pulmonary edema.

NONCARDIOGENIC PULMONARY EDEMA (INCREASED VASCULAR PERMEABILITY)

This mechanism of pulmonary edema features an abnormal increase in the microvascular permeability of the lung, as opposed to elevated capillary pressures, thereby promoting greater fluid and protein flux into the interstitial and alveolar spaces. In terms of the Starling equation, pulmonary vascular damage results in an increase in the filtration coefficient and the leakage of larger solutes (proteins). This decompartmentalization increases the interstitial osmotic pressure, helping to favor lung edema formation. During permeability pulmonary edema, increasing interstitial hydrostatic pressures associated with proteinaceous fluid eventually disrupt tight junctions in the alveolar epithelial barrier.[18] However, increased interstitial hydrostatic pressure is not the only proponent of increasing extravascular lung water. Important synergy exists between increased vascular permeability and hydrostatic pressure in the lungs. In the presence of increased barrier permeability and absence of oncotic forces that resist transvascular fluid transfer, hydrostatic capillary pressure is relatively unopposed. This tendency for seepage at normal hydrostatic vascular pressure is further exacerbated by decreases in colloidal oncotic pressure (COP) that result from low albumin levels.[19,20]

ACUTE RESPIRATORY DISTRESS SYNDROME: A PROTOTYPICAL MANIFESTATION OF NONCARDIOGENIC PULMONARY EDEMA

Permeability pulmonary edema resulting from injury to the lung capillary endothelium and/or alveolar epithelium is a classical feature of the acute lung injury that characterizes acute respiratory distress syndrome (ARDS). The very first description of ARDS depicted areas of alveolar atelectasis, hyperemia, and alveolar and interstitial hemorrhage, with a striking presence of alveolar neutrophils along with hyaline membranes.[21] Consequences of disruption of the alveolar epithelial barrier include loss of surfactant and impairment of the endothelial lining, favoring alveolar collapse during normal tidal breathing.

Causes of direct injury to the alveolar epithelium include gastric aspiration, bacterial pneumonia, and the neutrophilic alveolitis that is characteristic of ARDS. Other conditions that promote acute lung capillary endothelial injury include systemic infections (sepsis), severe burns, polytrauma, and other systemic inflammatory conditions. Varied etiologic insults, individually or in combination, lead to represent a spectrum of progressive noncardiogenic lung injury associated with impaired gas exchange (shunting, V/Q mismatching) and reduced lung compliance (increased work of breathing).[13,14]

High-permeability pulmonary edema markedly affects gas exchange and lung mechanics. Decrease in static respiratory compliance is notable and may be attributable to loss of aerated units (alveolar atelectasis) and, to some extent, to surfactant reduction.[22] Both interstitial lung parenchymal and chest wall edema contribute to reduced thoracic compliance.[23] As noted previously, ventilation–perfusion mismatch with variable degrees of shunting and increased dead space is conspicuous and directly proportionate to the severity of lung injury.

Certain causes of noncardiogenic pulmonary edema deserve special consideration because of their unique clinical presentations.

TRANSFUSION-RELATED ACUTE LUNG INJURY

Transfusion-related acute lung injury (TRALI) is an adverse response to transfusion of blood products containing plasma that is characterized by the acute (within 6 hours) onset of dyspnea, hypoxemia, and bilateral pulmonary infiltrates. Injury is mediated mechanistically by anti–human leukocyte antigen (HLA) antibodies, neutrophil activation, and related endothelial barrier damage.[24,25] The diagnosis of TRALI is supported clinically and by the exclusion of cardiogenic edema or fluid overload. Thus a low brain natriuretic peptide (BNP) (<250 pg/mL) supports the diagnosis.[26] Treatment includes immediate discontinuation of any transfusing blood products, followed by supportive care, which often requires intubation and mechanical ventilation. Duration of symptoms is typically limited (48–96 hours).[25]

VAPING-ASSOCIATED LUNG INJURY

Use of vaping devices (electronic cigarettes) containing nicotine, cannabis, and other products rapidly increased after their introduction in 2007. By 2018 vaping had affected more than 3.6 million US youths, with a majority of these being school-age adolescents and children. As of February 18, 2020, a total of 2807 hospitalized vaping-associated lung injury (VALI) cases or deaths have been reported to the Centers for Disease Control and Prevention (CDC), with 68 confirmed deaths.[27] Lung tissue of patients with respiratory failure reveals diffuse alveolar damage, acute fibrinous pneumonitis, or organizing pneumonia.[28] Foamy macrophages and pneumocystis-like vacuolization have been seen consistently. The exact pathology of acute lung injury is yet

to be determined. It has been speculated, however, that noncardiogenic edema results from alveolar epithelial injury by inhaled toxic nanoparticles of diluents such as propylene glycol and vegetable glycerin. These may eventually decompose at the parenchymal level, generating potentially harmful carbonyl compounds.[29] Taking a thorough history of any use of vaping products in the 90 days before presentation is key. Hypoxemia is consistently present, with constitutional symptoms, cough, and dyspnea preceding it. Imaging findings on high-resolution computed tomography include ground-glass opacities and fluffy nodules centered on terminal airways.[30] Ruling out other differential diagnoses and providing supportive respiratory assistance is the recommended management approach, followed by absolute abstinence.

OTHER MECHANISMS RESULTING IN PULMONARY EDEMA

PULMONARY EDEMA ASSOCIATED WITH DECREASED INTERSTITIAL HYDROSTATIC PRESSURE

NEUROGENIC PULMONARY EDEMA

Neurogenic pulmonary edema may occur after a significant central nervous system insult[31] and is most often triggered by conditions associated with rapid and extreme elevations in intracranial pressure (ICP),[31,32] in addition to acute spinal cord injury, intracranial hemorrhage, or status epilepticus. Sympathetic nervous system activation and intense catecholamine release are thought to be the primary mechanisms.[33] The condition typically resolves within 48 hours of ICP normalization.[34]

RE-EXPANSION PULMONARY EDEMA

Rapid expansion of a collapsed lung after draining a large pleural effusion or pneumothorax may cause unilateral lung edema. The incidence of re-expansion pulmonary edema (RPE) is quite uncommon when appropriate precautions are taken.[35,36] We typically note RPE occurring within hours of draining a large pleural effusion in cases of sustained (>72 hours) lung collapse. It is seen more commonly after draining spontaneous pneumothorax and correlates to the pneumothorax size and prior symptom duration.[37] Associated symptoms range from mild to life-threatening, including dyspnea, cough with frothy sputum production, chest discomfort, and hypoxemic respiratory failure. A unilateral edema pattern of the re-expanded lung is typical on chest x-ray (CXR), but infiltrates occasionally occur in the contralateral lung or in both lungs.[38,39] Most patients completely recover with supportive care within a few days. Preventive strategies include discontinuing pleural fluid removal at the onset of any signs of chest discomfort, limiting volume removal to <1.5 L, and avoiding high negative pressure (less than −20 cm H_2O).[40]

NEGATIVE-PRESSURE PULMONARY EDEMA

Negative-pressure pulmonary edema (NPPE) may present in the immediate postextubation period after the acute development of negative intrathoracic pressure generated during respiratory efforts against an obstructed upper airway. NPPE occurs in less than 0.1% of all elective surgeries and is most common in young, healthy, and athletic patients during postextubation laryngospasm. Other causes of NPPE include strangulation (or hanging), severe sleep apnea, endotracheal tube occlusion, or epiglottitis.[41] As with RPE, the condition typically resolves within several days.

ESTABLISHING THE ETIOLOGY OF PULMONARY EDEMA IN THE CLINICAL SETTING

It is important for care providers to quickly establish the cause of acute pulmonary edema so that appropriate therapy can be rapidly initiated to avoid serious, life-threatening complications. For instance, a patient with an acute rupture of mitral valve chordea tendineae would benefit from afterload reduction (e.g., peripheral vasodilators, intraaortic balloon pump [IABP]) and immediate mitral valve surgery,[42] whereas a patient with ARDS related to sepsis would benefit from judicial use of supplemental inspired oxygen, positive-pressure ventilation, and treatment of infections with early antibiotics. Unfortunately, the cause of pulmonary edema can be difficult to establish in the critical care setting and requires a skilled clinician with appropriate diagnostic tools.

Common clinical manifestations of pulmonary edema (of any cause) include the acute onset of dyspnea, anxiety, orthopnea, and in some cases pink (blood-tinged) frothy sputum. On examination, patients have signs of increased sympathetic tone (tachycardia, hypertension), increased work of breathing (e.g., accessory muscle use and diaphoresis), inspiratory crackles of the lung, and peripheral cyanosis.

CLINICAL FEATURES FAVORING CARDIOGENIC PULMONARY EDEMA

Beyond the clinical features of pulmonary edema previously mentioned, historical information, such as a recent myocardial infarction; new onset of cardiac arrhythmias; and examination findings of elevated jugular venous pressures, a third heart sound (S3), new cardiac murmurs, and/or dependent edema would favor the diagnosis of cardiogenic over noncardiogenic pulmonary edema. CXR findings of cardiomegaly, centralized pattern of interstitial and alveolar opacities, Kerley lines, and/or the presence of pleural effusions further support the diagnosis of cardiogenic pulmonary edema (Fig. 11.1).[43] Other supporting evidence includes elevated BNP and NT-pro BNP (BNP >1200 pg/mL, NT-pro BNP levels >1800 pg/mL)[44] or troponin, a marker of acute myocardial injury. However, these biomarkers lack diagnostic specificity.[45] Factors such as age, obesity, and renal failure can affect BNP levels and should be taken into account.[46] Given the lack of specificity, BNP levels are most beneficial in dyspneic patients with at least an intermediate probability of cardiogenic pulmonary

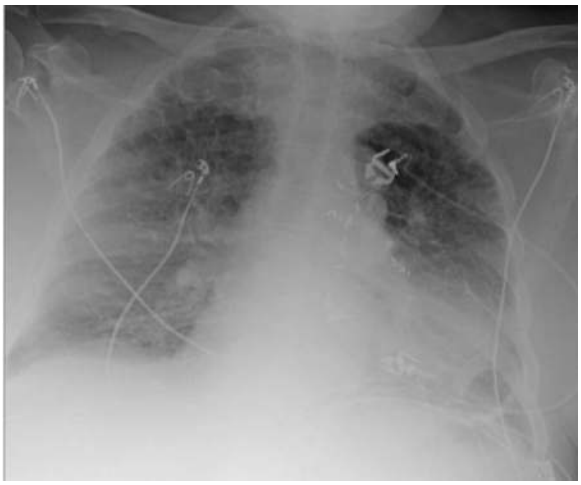

Fig. 11.1 This chest x-ray image is an anteroposterior (AP) view denoting bilaterally increased interstitial opacities with hilar prominence in the setting of cardiomegaly. Also Kerley lines, thin 1–2-cm hyperechoic lines indicating thickened interlobular septae, are noted.

edema. On the other hand, low levels (BNP <100 pg/mL;[47] NT-pro BNP <300 pg/mL) help to rule out a cardiogenic etiology of pulmonary edema. Cardiac imaging, particularly echocardiography, is very useful diagnostically and is shown to alter the management of a high percentage of critically ill patients presenting with acute pulmonary edema.[48,49] In recent years, bedside ultrasound (point-of-care ultrasound) has evolved significantly as an adjunct for diagnosing pulmonary edema when used by experienced operators. Thoracic bedside ultrasound relies on a combination of artifacts and related findings.[50] "B" lines are artifacts that run perpendicular to the pleura, and these "comet tails" obliterate the "A" lines that reverberate in diminishing fashion from the pleura and move in synchrony with pleural sliding. The presence of more than four B lines suggest thickened subpleural interlobular septae. A "B" profile, described as a bilateral anterior symmetrical B pattern with lung sliding that is present in at least two regions of the lung, suggests cardiogenic edema.[51,52] In noncardiogenic pulmonary edema, B lines are few and nonhomogeneous, and pleural sliding is affected (Video 11.1). Other features suggestive of noncardiogenic edema are discussed later. Bedside lung ultrasound not only has higher sensitivity (96%) compared with routine chest radiography (65%; P <.001) for detecting cardiogenic pulmonary edema but also its integration with clinical assessment may be more accurate than chest radiography and NT-pro BNP used together.[53]

CLINICAL FEATURES FAVORING NONCARDIOGENIC PULMONARY EDEMA

ARDS encompasses a spectrum of moderate to severe gas exchange abnormalities consequent to altered pulmonary vascular permeability, which often is further complicated by alveolar epithelial damage. Clinical features are based on the underlying etiology. The differential diagnosis of ARDS is broadly categorized as processes that cause direct versus indirect lung injury (Box 11.1). The most common direct causes are bacterial and viral pneumonia and aspiration pneumonitis, whereas nonpulmonary sources of sepsis, multiple transfusions, and trauma comprise the most common causes of indirect ARDS. Onset of symptoms (typically dyspnea, tachypnea, or related to their clinical insult) for not more than a week, presence of bilateral radiographic opacities, and exclusion of a primarily cardiogenic etiology of respiratory failure summarize the definition of ARDS. The Berlin definition (Box 11.2) categorizes ARDS into mild, moderate, and severe based on the arterial oxygen tension (PaO_2) and the fraction of inspired oxygen (FiO_2) while receiving positive end-expiratory pressure (PEEP) (Fig. 11.2 and Video 11.2).[54]

Highly specific diagnostic tests for ARDS are lacking, and the differentiation of ARDS from cardiogenic edema largely relies on the clinical acumen of the critical care providers. Details of the present illness as it relates to known risk factors for acute lung injury often provide important clues (see Box 11.1), as do certain test results (e.g., BNP <200 pg/mL)[45] (Table 11.1). On bedside ultrasound, findings such as limited pleural sliding, scattered or inhomogeneous B lines, pleural effusions, and

BOX 11.1 Common Causes of Cardiogenic and Noncardiogenic Pulmonary Edema

Cardiogenic Pulmonary Edema
- Acute exacerbation of heart failure
- Acute valve dysfunction (e.g., mitral valve chordae tendineae rupture)
- Arrhythmia/myocardial infarction
- Hypertensive crisis
- Fluid overload after aggressive volume resuscitation (e.g., postoperative)
- Ventricular septal rupture
- Pericardial tamponade

Noncardiogenic Pulmonary Edema
- Direct lung injury
  - Pneumonia
  - Gastric aspiration
  - Toxic inhalation
  - Negative pressure related (e.g., strangulation)
  - Vaping/electronic cigarette use
- Indirect causes of lung injury
  - Sepsis
  - Trauma
  - Pancreatitis
  - Multiple blood transfusions
  - Burn injury

BOX 11.2 Management of Cardiogenic Pulmonary Edema

Decrease Preload
- Diuretics (e.g., furosemide): decrease systemic venous tone and extracellular volume/volume overload[6]
- Opiates (e.g., morphine sulfate): reduce sympathetic tone
- Nitrates (e.g., nitroglycerin): venous and arterial vasodilator,[31] reduce myocardial oxygen demand[42]
- Nesiritide: recombinant BNP that results in vasodilation and diuresis[31]
- Ultrafiltration (volume removal)

Afterload Reduction
- ACE inhibitor/ARB: reduce preload and afterload[42,43]
- Nitroprusside (decreases venous return and afterload)
- Intraaortic balloon pump

Inotropic Support
- Dobutamine
- Dopamine
- Phosphodiesterase inhibitors (e.g., milrinone)
- Vasopressin (e.g., tolvaptan)

ACE, Angiotensin-converting enzyme; *ARB*, angiotensin receptor blocker; *BNP*, brain natriuretic peptide.

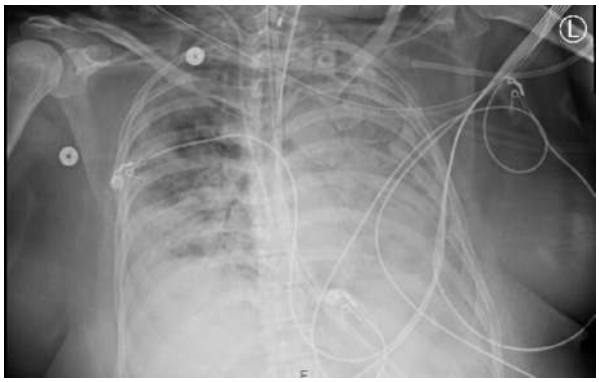

Fig. 11.2 This chest x-ray image is an anteroposterior (AP) view denoting bilateral interstitial and alveolar opacities, left side more prominent than the right side. Almost confluent alveolar opacities are noted on the left side with accompanying pleural effusion, suggestive of a left-sided pneumonia as the suggestive etiology for ARDS.

TABLE 11.1 Distinguishing Cardiogenic and Noncardiogenic Pulmonary Edema

	History	Examination	Laboratory Tests	Imaging	Pulmonary Artery Catheter
Cardiogenic	Heart disease Renal disease Uncontrolled HTN Edema Orthopnea Recent administration of IV fluids or blood products	Heart failure examination findings: Distended neck veins S3 heart sound Dependent edema Elevated blood pressure Cool extremities	*↑BNP >1200 pg/mL ↑Creatinine (in setting of volume overload) †↑Troponin	CXR: CMG pleural effusions ‡Kerley B lines Bedside USG: homogenous B lines and sliding pleura in at least two lung regions TEE: ↓LVEF Diastolic filling defect Severe mitral or aortic valvular disease Pericardial effusion with tamponade VSD	PCWP >18 mm Hg Prominent V waves (mitral regurgitation) Elevation and equilibration of right atrial pressure, pulmonary artery diastolic and PCWP (tamponade physiology) CVP >12 mm Hg
Noncardiogenic	Sepsis Aspiration event Trauma (long bone fractures) Burn injury Pancreatitis Multiple transfusions	Signs of active infection Extensive burn injury Evidence of trauma (absence of heart failure examination findings)	↑WBC *BNP <200 pg/mL	CXR: Diffuse central and peripheral infiltrates Normal heart size No or minimal pleural effusions Bedside USG: Presence of nonhomogeneous B lines, limited pleural sliding, and other patterns such as subpleural consolidations in at least two to three lung regions TEE: Normal LV and valvular function No evidence of volume overload	PCWP <18 mm Hg CVP <12 mm Hg

* Brain Natriuretic Peptide.
‡ Kerley lines, thin 1–2 cm hyperechoic lines indicating thickened interlobular septae in the lung apices, or bases.

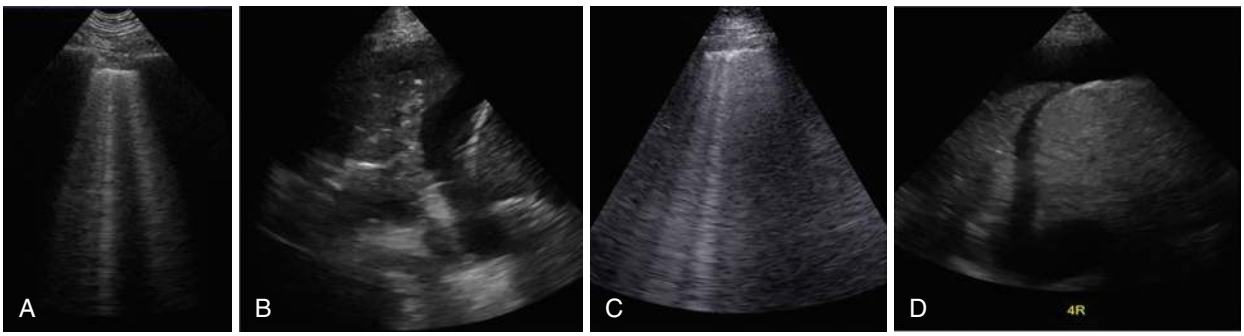

Fig. 11.3 Bedside Lung Ultrasound Images Suggestive of acute respiratory distress syndrome (ARDS). Lung ultrasound is an adjunct to the clinical examination for the diagnosis of ARDS. ARDS ultrasonic images reflect nonhomogeneous lung disease by combining normal A lines (spared areas) with the B pattern, and subpleural and translobar consolidation characterized by abolished lung sliding and irregular and thickened pleural lines in at least two regions. **(A)** Nonhomogeneous B lines; **(B)** thickened irregular pleura, **(C** and **D)** consolidative pattern ("C" profile).

presence of a consolidative or tissue-like pattern observed in more than one lung zone constitutes the "C" profile and provides a complementary diagnostic tool for clinicians at experienced centers (Fig. 11.3).[50,55]

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS OF PULMONARY EDEMA

Table 11.1 summarizes the typical clinical findings that distinguish cardiogenic from noncardiogenic pulmonary edema. Ironically, pulmonary artery (PA) catheterization, the most definitive diagnostic modality, is no longer routinely used at the bedside because of the perceived incidence of complications (e.g., bleeding, pneumothorax, arrhythmias, infections, vessel trauma) and unreliability resulting from improper calibration or misinterpretation of the data.[56–58] Thus less-invasive techniques have largely replaced PA catheters for the routine evaluation of cardiogenic etiology for pulmonary edema in the ICU setting.

Echocardiography, both transthoracic (TTE) and transesophageal (TEE), is the most widely used tool for the definitive evaluation of critically ill patients with suspected cardiac disease. In the context of

PE, TEE can rapidly detect serious cardiac diseases associated with elevated left ventricular filling pressures, including impaired left ventricular ejection fraction (LVEF) caused by ischemic (typically causing regional wall motion abnormalities) or nonischemic (diffuse wall motion abnormalities) muscle disease, significant valvular disease, or pericardial effusions that cause tamponade physiology.[59]

Alternative modalities have evolved over the last decade to quantitatively diagnose pulmonary edema and differentiate cardiogenic from noncardiogenic forms. Determination of excessive extravascular lung water by the transpulmonary thermodilution (TPTD) technique may suggest the diagnosis of pulmonary edema. Several large case studies have shown the expected extravascular lung water (EVLW, 7.3–8.0 mL/kg predicted body weight) in lungs without pulmonary edema (area under the curve, 0.90; 95% confidence interval [CI], 0.88–0.91).[60,61] A national registry showed that >9.8 mL/kg represented the optimal threshold for distinguishing pulmonary edema, with an EVLW level of 14.6 mL/kg yielding a 99% positive predictive value.[60]

A pulmonary vascular permeability index may point toward ARDS if elevated, cardiogenic pulmonary edema if low, and a combination of both if the pulmonary vascular permeability index is within intermediate ranges.[62] Several limitations in the technology impede its deployment. These include the need for central venous and thermistor-tipped arterial catheters, accuracy and timing of evaluation, and the need for larger randomized clinical trials to prove benefit over current standard of care. In addition, limitations of the TPTD technique, such as vascular obstruction, focal injury, other contributors to extravascular water, and confounding are associated with the ranges and variations of tidal volume, PEEP, and so on.[63,64]

MANAGEMENT OF PULMONARY EDEMA

Therapeutic approaches are classified as either cardiovascular or pulmonary interventions. Cardiovascular interventions aim to reduce transcapillary fluid flux into the lung by reducing pulmonary capillary pressures. As shown in Fig. 11.4 and Box 11.2, such interventions aim to reduce preload (e.g., loop and proximal tubular diuretics, nitrates, or ultrafiltration in renal failure), reduce afterload (systemic vasodilating agents including nitrates and angiotensin-converting enzyme [ACE] inhibitors), or optimize cardiac contractility during impaired left ventricular function (catecholamines, phosphodiesterase [PDE] inhibitors, IABP). Although most effective in the setting of cardiogenic edema, pulmonary capillary hydrostatic pressure reduction can also mitigate the severity of noncardiogenic edema.

Pulmonary interventions are designed to optimize gas exchange, particularly oxygenation, by recruiting unstable, collapsed, or fluid-filled alveolar units, primarily through the administration of PEEP. PEEP, typically 5–15 cm H_2O, counteracts alveolar collapse during the ventilator cycle to enhance V/Q matching and consequently oxygen transfer from the alveoli to the blood. Alveolar stabilization also reduces the work of breathing by improving CO_2 exchange (i.e., lower ventilatory rates) and lung compliance. In addition to PEEP, it is often necessary to cautiously increase the fraction of inspired oxygen (FiO_2) to maintain adequate oxygenation (see Fig. 11.4). PEEP may be provided by a tight-fitting, occlusive face mask in the form of continuous positive airway pressure (CPAP) or noninvasive positive-pressure ventilation (NIPPV), wherein inspiratory support is added to PEEP (bilevel ventilation). Positive-pressure ventilation further mitigates cardiogenic pulmonary edema by decreasing both preload and afterload.[13] Early use of CPAP or NIPPV for respiratory distress in cardiogenic pulmonary edema should be strongly considered, as it provides support while awaiting the benefits of the aforementioned medical interventions. Based on the analysis of over 2900 patients, NIPPV has been shown to reduce both the need for endotracheal intubation and the likelihood of mortality.[65] The European Respiratory Society guidelines strongly recommend CPAP or NIPPV for cardiogenic edema[66]; however, it is unclear if bilevel NIPPV is superior to CPAP in improving dyspnea, work of breathing, oxygenation, and partial pressure of carbon dioxide ($PaCO_2$) retention.[67,68] Endotracheal intubation and sedation may be required for patients with intolerably high work of breathing or altered mental status.

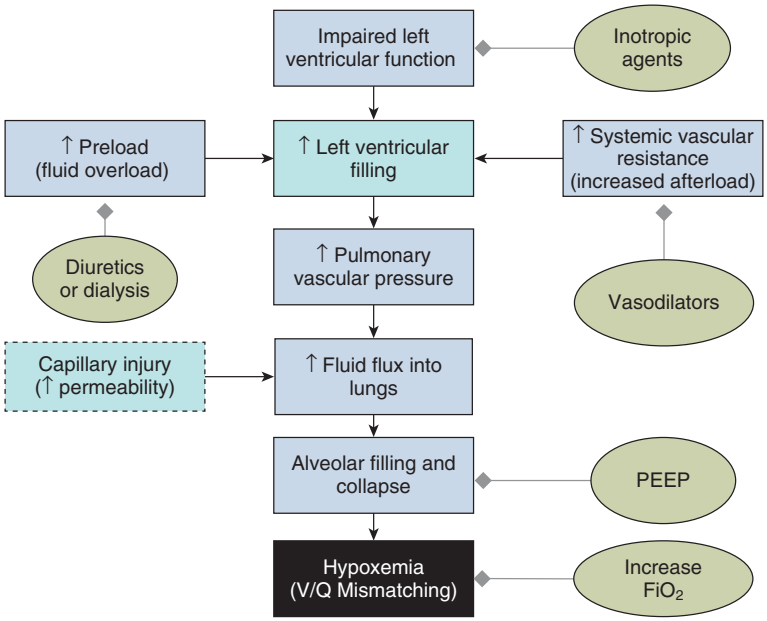

Fig. 11.4 Acute Management of Pulmonary Edema. This schematic represents basic mechanisms distinguishing cardiogenic and noncardiogenic pulmonary edema *(red boxes)* and the contributing factors *(blue boxes)* that ultimately lead to impaired gas exchange *(black box)*. The *green circles* represent treatments that are available in the intensive care unit setting to reduce pulmonary edema or to mitigate its adverse consequences. *FiO_2*, fraction of inspired oxygen; *PEEP*, positive end-expiratory pressure; *V/Q*, ventilation–perfusion.

A trial of high-flow nasal cannula or NIPPV may be given in the setting of noncardiogenic pulmonary edema. However, because of the etiologic heterogeneity, an individualized approach should be maintained with a low and early threshold for initiating mechanical ventilation.[69,70] When ventilator support is required, a lung-protective ventilation strategy that incorporates relatively low tidal volumes (4–8 mL/kg ideal body weight or less) is recommended to minimize ventilator-associated lung injury.[71]

KEY POINTS

- Pulmonary edema is broadly classified into cardiogenic (increased hydrostatic pressure) or noncardiogenic (increased microvascular permeability) causes; however, it is common for critically ill patients to present with pulmonary edema arising from a combination of cardiogenic and noncardiogenic etiologies.
- Common clinical manifestations of pulmonary edema (of any cause) include the acute onset of dyspnea, anxiety, orthopnea, and in some cases pink (blood-tinged) frothy sputum. On examination, patients have signs of increased sympathetic tone (tachycardia, hypertension), increased work of breathing (e.g., accessory muscle use and diaphoresis), inspiratory crackles of the lung, and peripheral cyanosis.
- In addition to the history and physical examination, laboratory testing (troponin, BNP) and imaging (CXR, bedside ultrasound, and echocardiogram) may be helpful in differentiating between cardiogenic and noncardiogenic causes of pulmonary edema.
- Management should be directed at the causes of the pulmonary edema. In addition, early use of NIPPV for respiratory distress in cardiogenic pulmonary edema should be strongly considered because it provides support while awaiting the benefits of the medical interventions described earlier.

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12

Pleural Effusion in the Intensive Care Unit

Peter K. Moore, Hunter B. Moore, and Ernest E. Moore

EPIDEMIOLOGY

Pleural effusions are common in the intensive care unit (ICU). Estimated incidence depends on screening method and ranges from 8% by physical examination to 60% by ultrasound.[1,2] Transudative causes of effusion (heart failure, hypoalbuminemia) predominate in the medical ICU, whereas hemothorax and postsurgical effusions occur more frequently in trauma and cardiac ICUs.[3] In any setting, 83% of patients with acute respiratory distress syndrome have pleural effusions as assessed by computed tomography (CT) scan.[4]

PATHOPHYSIOLOGY

The pleural space is bound by the visceral pleural lining of the lung and the parietal pleura that covers the internal thoracic cavity. During health, a small amount of fluid within the pleural space is maintained by a balance between pleural fluid generation and removal. Approximately 0.01 mL/kg/hr of pleural fluid is generated per day (~16 mL/day in a 70-kg adult) from the vascular space.[5] Pleural fluid removal occurs via pores in the parietal pleura, which are large enough to allow egress of erythrocytes. Pleural fluid resorption has a remarkable capacity, with the ability to increase approximately 30 times the basal rate.[6] Because of the slow rate of fluid production and large capacitance for removal, pathologic pleural effusions usually result from both an increase in the production of fluid and a decrease in absorption.

Pleural effusions are best classified as transudates or exudates by Light's criteria (Table 12.1).[7] In general, etiologies that primarily affect hydrostatic pressure (e.g., heart failure) or intravascular oncotic pressure (e.g., nephrotic syndrome) will result in transudative effusions, whereas disease that causes increased vascular permeability and obstruction of parietal pleural lymphatics (e.g., infection, malignancy) will result in exudative effusions. Occasionally, an abnormal connection between the pleural space and an extrathoracic compartment will result in pleural effusion, such as seen in hepatic hydrothorax (Table 12.2).

Mechanical changes to the lung, chest wall, and diaphragm occur when fluid collects in the pleural space. Because of the outward recoil of the chest wall and inferior displacement of the diaphragm, the lung volume decreases approximately one third. In a healthy lung, the reduction in lung volume usually does not cause gas exchange derangements likely because ventilation and perfusion are reduced similarly in the areas of lung collapse.[8] Studies in patients with pleural effusions and normal underlying lungs have demonstrated that removal of pleural fluid can worsen gas exchange.[9] There is inconsistent evidence with regard to the benefit of evacuation of pleural effusion in mechanically ventilated patients. Several studies have demonstrated improvement in oxygenation and respiratory mechanics when effusions are drained in ventilated patients, but whether this translates to meaningful improvement in clinical outcomes is not clear.[10–12]

DIAGNOSTIC EVALUATION

Physical Examination

Physical examination findings of pleural effusion include reduced breath sounds, dullness to percussion, decreased tactile fremitus, and asymmetric chest expansion.[13] However, many physical examination maneuvers are difficult to perform accurately in critically ill patients because of many factors, including altered breath sounds from mechanical ventilation, difficulty with positioning, and presence of surgical drains and dressings.

Imaging

Chest x-ray has long been used to evaluate for suspected pleural effusions. Conventional upright x-rays can detect effusions of approximately 50 mL in the lateral view and 200 mL in the posteroanterior projection.[14] Lateral decubitus can detect even smaller volumes but is difficult to perform in most critically ill patients. On upright or semi-recumbent films, blunting of the costophrenic angles may be the only sign of small pleural effusion. Larger effusions can cause obliteration of the hemidiaphragm and mediastinal shift away from the effusion. The sensitivity of x-ray for diagnosing pleural effusion in the critically ill is lower because of the inability to position correctly, lung opacification from alternative causes, and lower quality of portable x-rays. Commonly, free-flowing pleural effusions will appear as hazy lower lobe opacities with indistinct diaphragm on portable anteroposterior semi-upright x-rays (Fig. 12.1A). Loculated effusions can appear as a "D" shape with the flat portion against the lateral edge of the pleura. Pleural fluid isolated to the fissure, so called "pseudotumor," can have the appearance of an intraparenchymal mass or consolidation on x-ray (see Fig. 12.1B).

Point-of-care ultrasound can be performed at the bedside in the ICU with ease and has increased sensitivity for pleural fluid. Ultrasound for pleural effusion can detect as little as 5 mL of fluid and has sensitivities similar to that of chest CT.[15] Ultrasound can differentiate consolidated or atelectatic lung from pleural fluid. In addition, features of pleural effusions, including debris, loculations, and pleural thickening on ultrasound, can assist with classifying collections as complex rather than simple effusion (Fig. 12.2).[16] Pleural thickening and nodularity on ultrasound are suggestive of cancer and should trigger further diagnostic evaluation with advanced imaging and/or pleural biopsy.[17]

Chest CT allows for the best visualization of size and characteristics of pleural effusions (Fig. 12.3). Contrast examination is not necessary in all pleural effusions but is useful to distinguish atelectatic or consolidated lung (which will enhance with pleural timed intravenous [IV] contrast) from pleural fluid.[18] Hounsfield units >15.6 in the pleural fluid is suggestive of hemothorax.[19]

TABLE 12.1 Light's Criteria for Exudative Pleural Effusion. Exudate If One or More Criteria Are Met

Exudative Pleural Effusion	Value
Pleural fluid-to-serum ratio of total protein	>0.5
Pleural fluid-to-serum ratio of LDH	>0.6
Pleural fluid LDH level	More than two-thirds upper limit of normal for serum

LDH, Lactate dehydrogenase.

TABLE 12.2 Causes of Pleural Effusions

Transudative	Exudative
Intrathoracic	
Congestive heart failure	Infection
Nephrotic syndrome	Bacterial
Cirrhosis	Tuberculosis
Iatrogenic volume overload	Fungal
Central venous occlusion	Viral
	Parasitic
	Malignancy
	Pulmonary embolism
	Rheumatologic disorder
	Post–cardiac injury or surgery
	Uremia
	Asbestos
	Drug-induced
	Radiation
	Yellow nail syndrome
	Hemothorax
	Chylothorax
	Esophageal rupture
Extrathoracic	
Hepatic hydrothorax	Pancreaticopleural fistula
Peritoneal dialysis	Feeding tube migration
Urinothorax	
Bilothorax	
Cerebrospinal fluid leak	
Central venous catheter migration	

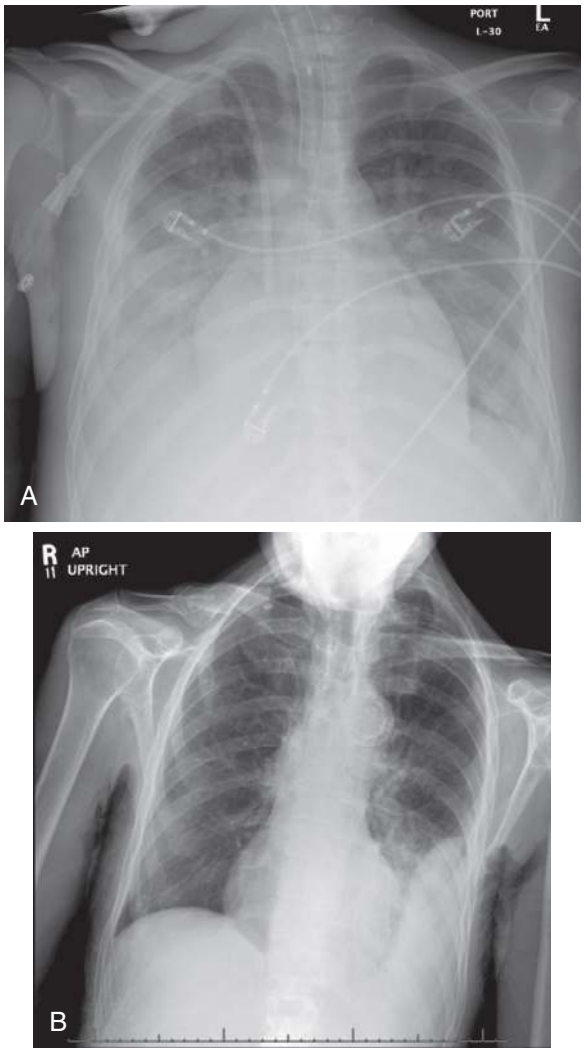

Fig. 12.1 A, Semi-recumbent portable chest x-ray demonstrates bilateral basilar hazy opacities silhouetting the diaphragm. Large bilateral pleural effusions were confirmed on bedside ultrasound. **B,** Loculated effusion with "D-sign."

Thoracentesis

Pleural fluid sampling through thoracentesis can be safely accomplished at the bedside in patients with >2 cm of pleural fluid between parietal and visceral pleura on bedside ultrasound. Fluid sampling can be deferred in patients with pleural effusions thought to be simply related to volume overload. However, if there is clinical concern for infection in the pleural space (i.e., ipsilateral pneumonia, unexplained fever, elevated white blood cell count) or hemothorax, prompt evaluation should be pursued. Ultrasound guidance is the preferred method for thoracentesis, as there are lower rates of pneumothorax with the use of ultrasound. Marking of the skin for thoracentesis location should be performed with bedside ultrasound while the patient is in the correct position for the procedure to ensure that the overlying skin does not shift with patient movement before sampling.[20] Although coagulopathy, thrombocytopenia, and use of antiplatelet agents previously were thought to increase the risk of bleeding, several recent studies have challenged that notion.[21,22]

PLEURAL FLUID EVALUATION

Pleural Fluid Gross Characteristics

At the time of thoracentesis characteristics of pleural fluid will often guide laboratory analysis and management. For example, purulent fluid with a putrid odor should be treated as an empyema with prompt chest tube drainage, bloody fluid should have its hematocrit analyzed (>50% of the blood hematocrit is diagnostic of hemothorax), milky appearance should prompt evaluation for chylothorax, and fluid that smells like ammonia should lead to evaluation for possible urinothorax. Pleural fluid is routinely sent for total protein and lactate dehydrogenase (LDH) levels to help classify as exudative vs. transudative (see Table 12.1), and cell count differential can further assist with

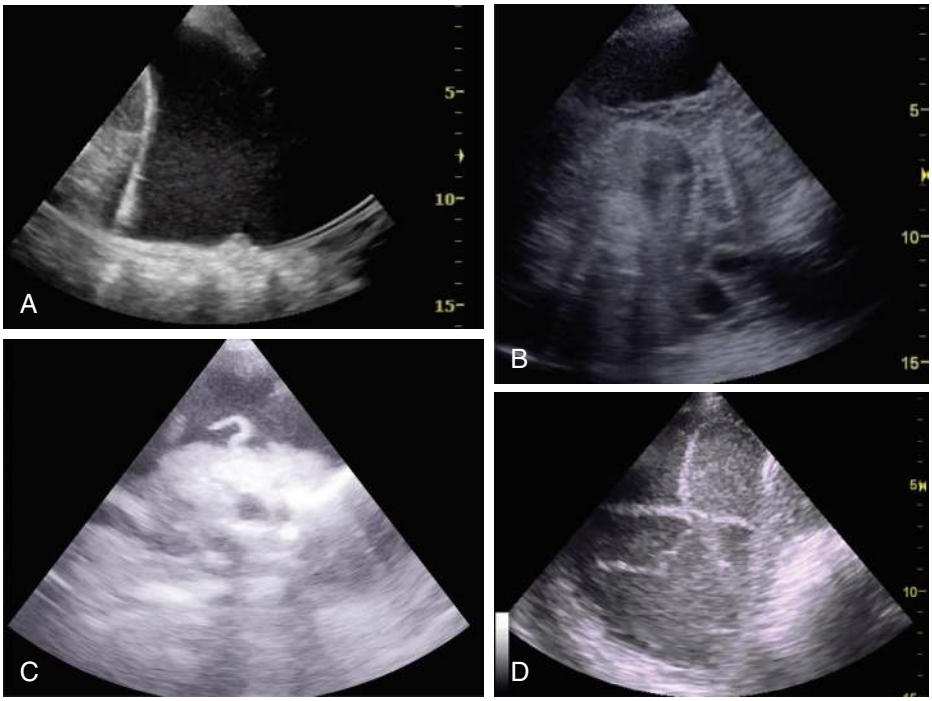

Fig. 12.2 Point-of-care ultrasound of pleural space shows **(A)** anechoic simple effusion, **(B)** complex effusion with multiple septations, **(C)** complex effusion with debris (blood clot in this example), and **(D)** empyema with septations and increased echogenicity of pleural fluid.

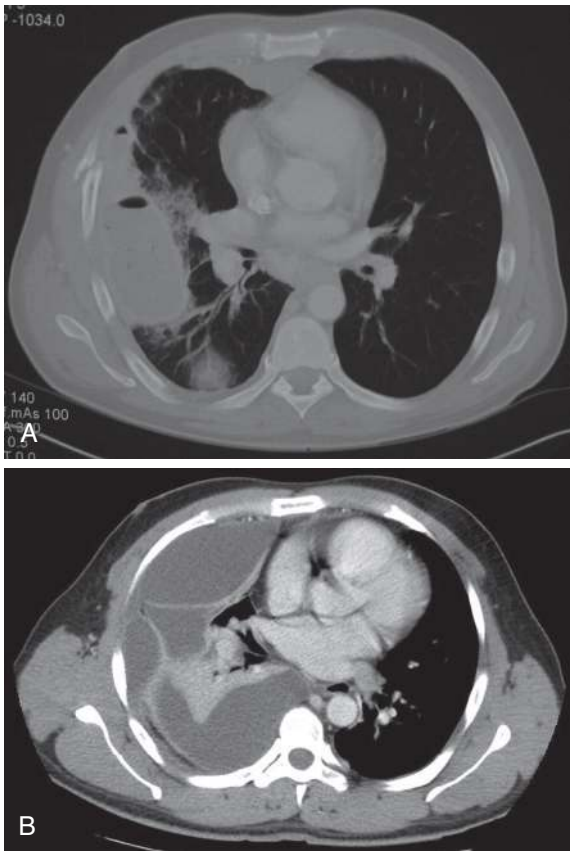

Fig. 12.3 Contrast-enhanced CT scan of the chest shows **(A)** simple loculated effusion and **(B)** organized multiloculated effusion. The multiloculated effusion is unlikely to resolve with tube thoracostomy and fibrinolytics; early VATS should be considered in these scenarios.

diagnostic evaluation of exudates. Any effusion that is sampled for concern for infection should have aerobic and anaerobic cultures, glucose, and pH evaluated to guide management.

Total Protein and Lactate Dehydrogenase

Elevation of pleural fluid total protein and LDH in relation to the serum is reflective of increased vascular permeability, which can be seen with inflammatory, infectious, or malignant conditions. In addition, as LDH is a marker of cellular breakdown, pleural LDH elevation can reflect increased inflammation within the pleural space.[23] Thus if LDH levels continue to rise on repeated pleural fluid sampling, there should be suspicion that inflammation is worsening within the pleural space.

Up to 25% of pleural effusions from transudative etiology can be misclassified as exudative using Light's criteria.[7] This is frequently encountered in the setting of heart failure when diuresis has concentrated the pleural space.[24] In this setting the patient's clinical symptoms and signs will usually lead to the correct diagnosis. Pleural N-terminal pro-brain natriutetic peptide (NT-ProBNP) has sensitivity and specificity of 94% for diagnosing heart failure–associated effusions. However, pleural levels of NT-proBNP correlate strongly with serum levels, and blood tests alone likely suffice in this scenario.[25] Pleural to serum albumin or protein gradient above 1.2 g/dL or 3.1 g/dL, respectively, in the setting of heart failure will correctly classify the effusion as transudative after diuresis.[26,27]

Leukocyte Count and Differential

At homeostasis, the leukocyte count is approximately 1700 WBC/μL with a macrophage and monocyte predominance.[28] Elevations in pleural fluid absolute leukocyte count are usually indicative of an exudative process but are otherwise nonspecific. Pleural fluid differential can be useful for differentiating causes of exudative effusions (Table 12.3). Neutrophil predominance is commonly seen in the setting of infection and infarction. Very high lymphocyte counts (>85%) are seen in tuberculosis and malignancy.[29] Eosinophilic pleural effusions

TABLE 12.3 Causes of Exudative Effusions by Pleural Leukocyte Differential

Neutrophil Predominant	Lymphocyte Predominant (>80%)	Eosinophil Predominant (>10%)
Parapneumonic effusion	Malignancy	Hemothorax
Acute inflammation of lung or pleura (e.g., ARDS)	Tuberculosis	Parasitic infection
Pulmonary embolism	Connective tissue disease	Fungal infection
	Chylothorax	Tuberculosis
	Yellow nail syndrome	Drug reaction
		Pulmonary embolism
		Eosinophilic polyangiitis with granulomatosis
		Malignancy

ARDS, Acute respiratory distress syndrome.

(eosinophils >10%) are less specific but can be seen 2 weeks after hemothorax or with drug reactions, pulmonary embolism, malignancy, parasitic infection, and eosinophilic granulomatosis with polyangiitis.[30,31]

pH and Glucose

In the absence of disease, the pleural space is basic, with a pH of approximately 7.6.[32] Pleural pH <7.3 is considered abnormal and is usually indicative of an exudative effusion, with the notable exception of the transudative urinothorax.[33] Low pleural pH has been shown to have negative prognostic value in the setting of parapneumonic effusions and malignancy-associated effusions.[34,35] Although parapneumonic effusions with pH <7.15 have a likelihood ratio of about 6 for requiring chest tube drainage, the relationship of pleural pH to the need for chest drainage is linear, and a strict cutoff for drainage based solely on pH may not be appropriate.[35–37] The exception is a pH >7.2 that can occur with *Proteus* infection because of ammonia production via urease.

Pleural glucose <60 mg/dL or pleural to serum glucose ratio of <0.5 is suggestive of a small number of inflammatory lung conditions. These include complicated parapneumonic effusion, esophageal rupture, malignancy, tuberculous pleuritis, or rheumatoid- or lupus-associated pleuritis. Pleural glucose <40 mg/dL in the setting of parapneumonic effusion predicts need for chest tube drainage but is less sensitive than pH.[37] Rheumatoid pleural effusions are notable for extremely low glucose levels and low pH and can imitate biochemical characteristics of an empyema.[38]

Culture

Pleural Gram stain and culture should be obtained in exudative effusions of unclear etiology. Fungal and mycobacterial samples should be sent in the appropriate clinical scenario. In the setting of pleural bacterial infection, inoculation of blood culture bottles with pleural fluid in addition to standard sterile bottles increased identification of bacterial pathogens from 38% to 59%.[39]

Cytology

Exudative pleural effusions of unclear etiology should undergo cytologic examination. Cytology has approximately 60% sensitivity for diagnosis of malignancy, but sensitivity varies significantly based on the type of cancer and location of metastasis (visceral versus parietal pleura).[40,41] Sending cytology on three separate samples increases sensitivity to approximately 90%.[23]

Triglycerides and Cholesterol

Triglycerides and cholesterol distinguish chylothorax from pseudochylothorax (also known as *cholesterol effusion*). Triglyceride levels >110 mg/dL are diagnostic of chylothorax, and levels <50 mg/dL effectively rule out the diagnosis. Levels between 50 and 110 mg/dL should be evaluated for chylomicrons by lipoprotein electrophoresis.[42] Cholesterol levels >200 mg/dL are consistent with pseudochylous effusions. Cholesterol/triglyceride ratio >1 is the most sensitive test for pseudochylous effusions, which result from chronic inflammation, most often from tuberculosis or rheumatoid arthritis.[43]

Other Pleural Fluid Tests

Adenosine deaminase (ADA) testing is most useful for distinguishing between tuberculosis and malignancy in lymphocytic effusions with negative mycobacterial cultures and cytology. ADA <35 U/L has a negative predictive value of approximately 95% in countries with low to intermediate rates of tuberculosis.[44] Although Xpert MTB/RIF PCR (GeneXpert) in the sputum is a highly sensitive test for active pulmonary tuberculosis, its sensitivity is only 50% for the diagnosis of tuberculous pleuritis when evaluated in the pleural fluid.[45]

Amylase from salivary or pancreatic sources will be in the pleural fluid in the setting of esophageal rupture or pancreaticopleural fistula. Pleural amylase to serum ratio >1 is generally considered positive. Malignancy can also result in amylase elevation.[46]

Pleural to serum creatinine ratio >1 is diagnostic of urinothorax, which is further supported by transudative fluid characteristics by Light's criteria with pH <7.4.[33]

There is interest in biomarkers of cancer (e.g., CEA, mesothelin) and infection (e.g., procalcitonin) in the pleural space, but at this time there have not been conclusive studies to support their routine clinical use.

Invasive Diagnostics

Pleural biopsy is often needed to diagnose tuberculous pleurisy and malignancy (either metastatic or primary pleural based). Methods of biopsy from least invasive to most invasive are closed (blind) needle pleural biopsy, image-guided needle biopsy, thoracoscopy/video-assisted thoracoscopic biopsy, and open pleural biopsy. In general, sensitivity for malignancy and tuberculosis increases with a more invasive diagnostic approach. Open pleural biopsy is only indicated with progressive pleural disease that cannot be approached thoracoscopically or with previous nondiagnostic thoracoscopic biopsy.

MANAGEMENT

Management of pleural fluid collections is targeted at the specific cause. For example, transudative effusions from congestive heart failure will resolve with diuresis, whereas moderate to large hemothoraces will require tube thoracostomy drainage. Extravascular causes of

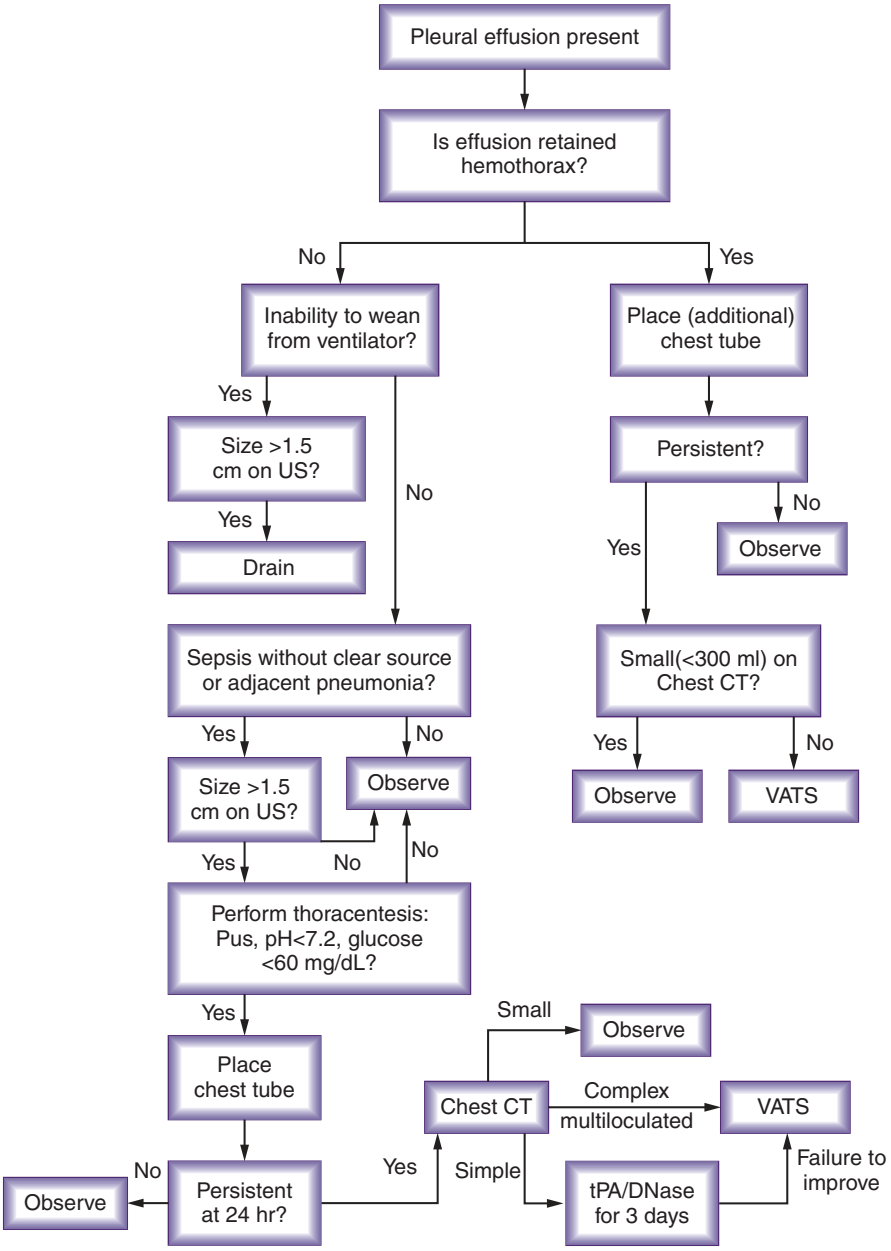

Fig. 12.4 General approach to pleural effusion in the ICU. This algorithm can serve as a general guide, but is not applicable to all clinical scenarios.

pleural effusions, such as those caused by esophageal rupture, pancreaticopleural fistula, and urinothoraces, often require endoscopic or surgical repair. A general approach to guide pleural space interventions in critically ill patients is outlined in Fig. 12.4. This chapter will focus on specifics of management of uncomplicated effusions in patients with refractory hypoxemia undergoing mechanical ventilation, parapneumonic effusion, hemothorax, and chylothorax.

Transudative and Uncomplicated Effusions in Mechanically Ventilated Patients

As accumulation of free-flowing fluid in the pleural space is accommodated by outward recoil of the chest and downward deflection of the diaphragm, the lung is only displaced by about one-third of the volume taken up by the effusion. In the setting of intact vasoregulatory mechanisms, ventilation/perfusion matching is maintained. Consequently, atelectasis from pleural effusion alone rarely causes significant hypoxemia, but does alter respiratory muscle mechanics.[8]

In the setting of mechanical ventilation, optimal treatment of uncomplicated effusion is controversial. In a recent prospective multicenter observational evaluation of patients weaning from mechanical ventilation, moderate to large pleural effusions were present in one-third of patients by ultrasound at the initiation of weaning. Moderate to large effusions were associated with increased rates of failure of first spontaneous breathing trials, increased weaning failures, and fewer ventilator-free days.[47] Although drainage of pleural effusions in the setting of mechanical ventilation has been demonstrated to improve oxygenation and respiratory mechanics, there have been no studies showing improvement in clinically significant outcomes such as duration of mechanical ventilation or mortality.[10–12] Prospective trials are needed to evaluate whether drainage of

pleural effusions in ventilated patients results in clinically meaningful outcomes.

Complicated Parapneumonic Effusion and Empyema

Close to half of patients admitted with bacterial pneumonia will develop a pleural effusion, with approximately 10% of these effusions becoming complicated (i.e., requiring chest tube drainage for resolution or having positive pleural fluid cultures).[48,49] Risk factors for development of complicated pleural space infections in the setting of pneumonia include diabetes, alcohol use, drug addiction, and poor dentition with aspiration.[49–51] Nosocomial pneumonias are more likely to result in complicated pleural effusions or empyema and have a high rate of requiring surgical decortication.[52] Retained hemothorax is the biggest risk factor for empyema, with an incidence of greater than 25%.[53]

Complicated parapneumonic effusions, and ultimately empyema, develop in three conceptual phases. The early exudative phase consists of sterile fluid accumulation from alterations in capillary permeability and reduced lymphatic clearance.[54] Most of these effusions resolve on their own if pneumonia is treated with appropriate antibiotics.[48] The second "fibropurulent" phase is initiated by bacterial invasion with resultant activation of the innate immune system and coagulation system. During this time, bacterial and neutrophil metabolism acidify the fluid, consume glucose, increase protein content, and release LDH from cellular apoptosis and necrosis. Because of the integrated responses of the innate immune and coagulation systems, hypercoagulability with resultant suppression of the fibrinolytic system occurs.[55] As this stage progresses, pleural effusions develop septations and loculations and become unlikely to resolve with antibiotics alone. If left untreated, the pleural effusion will go through an "organization" stage with formation of a fibrous rind that encases the lung, resulting in significant restriction of lung function and sequestration of bacteria within the pleural space.[56]

Parapneumonic effusions can be separated into three categories: uncomplicated parapneumonic effusion, complicated parapneumonic effusion, and empyema. Radiographic, biochemical, and microbiologic characteristics and risk of adverse outcome are described in Table 12.4.[57] Uncomplicated parapneumonic effusions are exudative effusions related to adjacent parenchymal inflammation will resolve with appropriate medical therapy. Approximately 90% of parapneumonic effusions are uncomplicated.[48] Of note persistent uncomplicated parapneumonic effusions can progress. Repeat pleural fluid sampling or advanced imaging should be pursued if a patient has enlarging effusion or sepsis with unclear source. Complicated parapneumonic effusions will either become infected (positive Gram stain/culture) or require drainage either with chest tube thoracostomy or thoracoscopic decortication. Empyema is defined by the presence of frank pus.

Gram stain and bacterial cultures of the pleural space at the time of thoracentesis can be helpful in guiding therapy for complicated parapneumonic effusions and empyemas. However, there will be no identifiable pathogen in up to 80% of cases.[58] As mentioned previously, direct inoculation of blood culture bottles with pleural fluid increases the yield of bacterial pathogens.[39] Empiric therapy should be initiated based on patient risk factors. In community-acquired pleural infections *Streptococcus* species are responsible for approximately 50% of infections. *Streptococcus anginosus* group (formerly *Streptococcus milleri*) is the most common pathogen (20%–30% of total cases) followed by other *Streptococcus* species, including *Streptococcus pneumoniae* and, less frequently, *Streptococcus pyogenes* and other *Streptococci (maskall, chen 2000)*.[50,59] The remaining cases are usually caused by *Staphylococcus aureus* (~10%), gram negatives (~10%), and anaerobes (~20%). Methicillin-resistant *S. aureus* (MRSA) is rare in the community-acquired empyema and was responsible for 2% of cases in one study.[50] Polymicrobial infections are frequent, especially when anaerobes are present. Hospital-acquired pleural infections have higher rates of MRSA (~25% of cases) and gram-negative organisms (~25%). The risk of death is approximately fourfold higher in nosocomial cases when compared with community-acquired cases.[50,58] Of note, although most antibiotics penetrate the pleura well, aminoglycosides may be inactivated at the lower pH present in pleural infections.[60]

Once complicated effusion or empyema is identified, pleural fluid must be evacuated from the pleural space for infection source control and prevention of fibrous rind formation. Historically, larger-bore chest tubes (>32 French) were used to treat pleural space infection, but clinical practice has shifted toward insertion of small-bore tubes. This is largely because of the relative ease of placement of smaller-bore tubes with less pain at the insertion site rather than results of a randomized clinical trial. The best current data for noninferiority of small-bore chest tubes come from post hoc analysis of 405 patients in the Multicenter Intrapleural Sepsis Trial I (MIST I) in which there were no differences in the rates of clinical failure in patients with small- versus large-bore chest tubes (size <10 36%; size 10–14F 36%; size 15–20F 40% and size >20F 44%, $P = 0.27$), but there was significantly less pain in the smaller-bore groups.[61]

After thoracostomy tube placement, output and radiologic assessment of the pleural space should be undertaken. If there is persistent pleural fluid after 24 hours, it is reasonable to initiate therapy with fibrinolytics/DNase to break down fibrin and clear cellular debris. Although initial trials with DNase or fibrinolytics had inconsistent evidence for benefit, they were limited by power or poor study design.[62] In 2011, the Multicenter Intrapleural Sepsis Trial II (MIST 2) randomized 210 patients with intrapleural infection to one of four therapies for 3 days: intrapleural tissue plasminogen activator (tPA) and placebo, intrapleural DNase and placebo, intrapleural tPA and DNase, or double placebo.[63] The primary outcome was the percentage of hemithorax occupied by pleural effusion at day 7 compared with day 1 (at randomization) as assessed by chest x-ray. The authors found that the tPA + DNase group had significantly reduced the size of pleural effusion when compared with the double-placebo group. tPA alone

TABLE 12.4 Radiographic and Biochemical Characteristics of Uncomplicated and Complicated Pleural Effusions

	Radiographic	pH	Glucose	Drainage Recommended
Uncomplicated small	<1 cm on bedside ultrasound	not assessed	not assessed	no
Uncomplicated moderate	>1 cm on ultrasound and less than half the hemithorax	>7.2	>60 mg/dL	no
Complicated	septation, debris, pleural thickening on ultrasound or volume more than one-half the hemithorax	<7.2	<60 mg/dL	yes
Empyema	similar to complicated	pus on aspiration		yes

or DNase alone did not significantly reduce the size of the pleural effusion when compared with placebo. Secondary outcomes of hospital length of stay and referral for thoracic surgery at 3 months were significantly lower in the tPA + DNase group when compared with double placebo. Notably, patients treated with DNase alone had a threefold increase in thoracic surgery referral at 3 months.

Surgical evacuation of pleural infections is often reserved for those who have failed tube thoracostomy with medical therapy or those who present late with multiloculated, organized empyemas. However, there have been six small randomized controlled trials of early video-assisted thoracoscopic surgery (VATS) decortication versus conventional tube thoracoscopy with fibrinolytics, mostly in children. A Cochrane review and meta-analysis of these studies concluded that early VATS was associated with significant reduction in hospital length of stay (−2.5 days) with no difference in mortality. The studies had significant heterogeneity and were limited by a relatively small sample size. A large randomized clinical trial of early VATS versus intrapleural fibrinolysis/DNase in adults fit for surgery should be pursued.[64]

When operative management of pleural infection is pursued, the preferred procedure is VATS decortication. The objectives of VATS are to unroof all loculated collections, including fissural loculations, and to free the lung from visceral pleural fibrous casing. After the procedure, the thorax is usually drained with three relatively large chest tubes (28F) to facilitate removal of debris and blood associated with the intervention. When a dense, fibrous peel prevents successful VATS decortication, a lateral muscle-sparing thoracotomy ("mini-thoracotomy") can be pursued. In the rare case of chronic empyema, standard posterolateral thoracotomy is often required. Occasionally patients with necrotic infections of the lung and pleural space require chronic open thoracic drainage with an Eloesser flap, in which marsupialization of the thoracic cavity is accomplished via segmental rib resection and ligation of skin to the underlying parietal pleura.[65] Alternatively, thoracostoma-mediated open drainage with suturing the skin margin to the chest wall and use of vacuum-assisted wound closure have been implemented with success.[66]

Hemothorax

Hemothorax in the surgical ICU (SICU) is predominantly the result of trauma. Blunt trauma–induced hemothorax is usually related to motor vehicle crashes, assaults, and falls. Falls in the elderly are becoming a more frequent cause of rib fractures because of the aging population. The dominant source of bleeding is the chest wall, and specifically rib fractures.[67] Sternal fractures, however, may be associated with internal mammary arterial transection, which can manifest as life-threatening delayed bleeding.[68] Delayed bleeding from a torn thoracic aorta is rare because routine whole-body CT scanning is done for major trauma evaluation before SICU admission.[69] Hemothorax after penetrating trauma is also frequently the result of rib fractures but may result from persistent lung parenchymal bleeding.[69] In the medical ICU, hemothoraces are rare, occur most often in patients with chronic kidney disease, and are usually iatrogenic from thoracentesis or chest thoracostomy.[70]

The first management decision is when to decompress a hemothorax. Traditionally, hemothoraces have been considered small if <500 mL, moderate at 500–1000 mL, and large at >1000 m:. But more recently the classification has been small <300, medium 300–900, and large >900.[71] A plain chest radiography usually requires >300 mL of blood to be recognized, although ultrasound is more sensitive.[72] CT scanning can assist in quantifying the size of the hemothorax if an intervention is considered (volume = $d^2 \times l$; d = depth, l = length).[73] The primary complication of a hemothorax is empyema, although a lung-restricting fibrothorax is a theoretical complication with larger collections. Experimentally,[74] and clinically,[75] it has been established that a normal pleural cavity can absorb a sizable hemothorax without adverse sequela. Factors that may impair resorption of a hemothorax include rib fractures, lung contusion, or diaphragm injury. Associated pneumothorax may also increase the risk of secondary infection. In general, most recommend that a hemothorax >300 mL should be evacuated by tube thoracostomy, but there are no randomized studies to indicate a limit for safe observation.

The second decision is the size of the tube for thoracostomy. For decades, a 36F chest tube was considered standard for any hemothorax to ensure rapid and complete evacuation. However, randomized trials have established a 28F tube is as effective and less traumatic to introduce.[76] In fact, recent studies suggest a 14F catheter may be sufficient.[77] Another contemporary issue has been the role of intrathoracic irrigation of the pleural space at the time of chest tube placement to minimize the risk of retained hemothorax.[78]

The third decision is the rare event of the need for operative intervention because of massive or ongoing pleural bleeding. The indications for emergent thoracotomy are based on data for initial presentation in the emergency department. In general, the indications for surgical intervention are an acute large-volume collection (>20 mL/kg, ~1500 mL), persistent bleeding (>3 mL/kg/hr for >3 hr, ~250 mL), or a caked hemothorax.[79] A caked hemothorax is the failure to evacuate a large blood collection with a second tube thoracostomy.

A more common problem in the ICU is a retained hemothorax (i.e., a persistent blood collection despite a well-positioned tube thoracostomy). Retained hemothoraces are often progressive blood collections, but may be a result of delayed bleeding, usually from displaced rib fractures. "Retained hemothorax" is often a misnomer in the setting of blunt trauma where ongoing inflammation causes collection of exudative fluid rather than true blood. Regardless, the scenario is compounded by a chest tube that may serve as a conduit for bacteria to infect the hematoma. Fibrinolytic therapy would appear optimal for a retained hemothorax, but the ability for tPA to enter a mature clot is limited. Unfortunately, most reported experience represents small, nonrandomized series, although some with compelling results.[80] In general, most intensivists will attempt tPA and DNase via the chest tube for simple collections. But large, persistent, or complex collections require VATS evacuation. Collective experience suggests early intervention (<day 4) is more successful in complete clot removal with less risk of pleural damage, so the "3-day rule for VATS" is widely accepted to prevent empyema or the theoretical restrictive fibrothorax.[81] The technical aspects of VATS are similar to those for any complicated pleural collection, although the dominant clot burden will usually exist in the dependent inferior pleural space.

Chylothorax

Chylothorax is the collection of chyle in the pleural space. Unlike chyle within the peritoneal space, which typically resolves without intervention, chyle in the chest is more persistent because of negative intrathoracic pressure. In the pleural cavity, the source of chyle is the thoracic duct, which extends from the cisterna chyli in the retroperitoneum via the mediastinum to empty into the venous system at the juncture of the left subclavian and jugular veins. Chyle consists of triglycerides in the form of chylomicrons, T lymphocytes, proteins, immunoglobulins, fat-soluble vitamins, and electrolytes; the predominant contents are derived from the intestine to be delivered to the bloodstream.[82] Chyle also contains constituents from the lymphatics of the other abdominal viscera, lung, and lower extremities. Total flow in the thoracic duct normally ranges from 1500 to 2500 mL/day and is augmented by dietary intake of fat.

The etiology of chylothorax can be broadly divided into trauma and nontrauma causes.[83–85] Trauma is usually the result of thoracic surgery, direct injury from penetrating wounds, or less commonly, blunt rupture. Iatrogenic injuries of the thoracic duct can occur with left-sided central venous access, and extravasation of lipid-containing total parenteral nutrition (TPN) can confuse the diagnosis. Nontraumatic etiology is most often malignancy, but there are a myriad of benign immune/inflammatory sources. Interestingly, an idiopathic cause is reported in 5%–15%. Consequently, the etiology of chylothorax varies considerably between medical intensive care units (MICUs) and SICUs.

The clinical manifestations of chylothorax are initially those resulting from a pleural effusion, as discussed previously. The side of the chylothorax is dependent on the location of the thoracic duct pathology. The thoracic duct traverses the mediastinum at approximately the fifth thoracic vertebra (i.e., lesions below T5 produce right pleural effusions and above T5 left effusions).[82] Chest pain and fever are unusual because there is a limited inflammatory response to the chyle that remains sterile as a result of the immunoglobulin content. On the other hand, chronic loss of immunoglobulins, T cells, and protein may produce immunosuppression and malnutrition, increasing the risk of infection in extrapleural locations and poor wound healing.[83–85] Tube thoracostomy output of a milky fluid is a hallmark of chylothorax, but is not clinically apparent in half of the patients. Furthermore, cholesterol pleural effusion and empyema may produce the same appearance.[86] The pleural volume output varies substantially depending on the etiology and size of the thoracic duct lesion. In patients with nontraumatic chylothorax, the course is often indolent, whereas postsurgical or postinjury chylothorax usually presents within the first week and the chest tube output often exceeds 500 mL/day.[87]

The diagnosis of chylothorax is established by analysis of the pleural fluid.[42] Triglyceride and cholesterol levels are determined in addition to the standard tests for pleural fluid, as discussed previously. The pH of a chylothorax exceeds 7.4, thus distinguishing it from an empyema (except for infections involving *Proteus* species). The LDH is low, and electrolytes and glucose levels reflect those in the plasma. However, the protein content of chylothoraces is usually elevated sufficiently to qualify as exudative. The white blood differential has a predominance of lymphocytes, which are largely polyclonal T cells. Lipid analysis is the most definitive for the diagnosis of chylothorax. Triglycerides generally exceed >110 mg/dL and cholesterol is <200 mg/dL. Triglycerides can be <110 mg/dL, but a cholesterol >200 mg/dL suggests a cholesterol effusion.[42,86] In the event of equivocal results, chylomicrons can be measured by lipoprotein electrophoresis.

With the diagnosis of chylothorax established, the next step is to identify the source. A chest CT scan is usually the first step for any chylothorax. The location of trauma-induced effusions is further pursued based on the side of injury—left-sided are usually the result of lesions above T5. Considering the innumerable causes of nontraumatic chylothorax, the evaluation is targeted sequentially to the most likely etiology. In the event of an unhelpful chest CT scan, alternative diagnostic tests include lymphangiography, lymphoscintigraphy, or magnetic resonance (MR) lymphangiography.[88]

The management of chylothorax varies substantially based on the etiology and rate of chyle accumulation. Low-output chylothorax is defined as <1000 mL/day. In general, the initial approach consists of continuous thoracostomy tube or catheter drainage, oral or enteral diet with high protein and low fat (<10 gm fat/day, minimizing long-chain triglycerols),[89] and somatostatin or octreotide.[90] For prolonged leaks, medium chain triglycerols can be added to the diet to avoid essential fatty acid deficiency because they are absorbed from the intestine and transported directly to the liver via the portal vein.[91] An essential component is treatment of an underlying medical disorder that is driving the chyle leak if present.

The management strategy for a high-volume chylothorax (>1000 mL /day) is more aggressive. Usually patients are placed immediately on TPN,[92] which has no fat restrictions, and administered octreotide.[90] Interventions are frequently done early for postoperative persistent high-volume leaks because of progressive morbidity from chyle content loss.[93] Percutaneous lymphatic interventions are usually attempted first where the capabilities exist.[94] The procedures include thoracic duct embolization or ablation and therapeutic lymphangiography.[95,96] For those who fail, an operative approach is needed, which usually consists of thoracic duct ligation and glue application and often combined with pleurodesis. VATS is an option for a clearly defined leak. For failures of this step-up approach or for high-risk patients, pleuroperitoneal or pleurovenous shunts are options.[97]

KEY POINTS

- Pleural effusions are classified as transudative or exudative by Light's criteria.
- Treatment of pleural effusion is targeted at the specific etiology of the effusion.
- Drainage of uncomplicated effusions in mechanically ventilated patients is controversial: It may improve oxygenation and respiratory mechanics, but it is unclear whether this facilitates liberation from the ventilator.
- Parapneumonic effusions with pH <7.2, glucose <60 mg/dL, and complex appearance on ultrasound or chest CT require drainage with tube thoracostomy.
- Community-acquired pleural space infections are usually caused by *Streptococcal* species.
- Hospital-acquired pleural space infections are often caused by methicillin-resistant *S. aureus* and resistant gram-negative rods.
- Moderate (>300 mL) and large hemothoraces should be drained with tube thoracostomy.
- Small-bore chest tubes appear to have similar efficacy to larger chest tubes in complicated parapneumonic effusion, empyema, and hemothorax.

References for this chapter can be found at expertconsult.com.

ANNOTATED REFERENCES

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Bauman et al. prospectively evaluated the outcomes in patients who had small-bore (14F) pigtail catheters versus larger-bore chest thoracostomy tubes in the setting of traumatic hemothorax and hemopneumothorax at a single level-1 trauma center from 2008 to 2014. The authors found that although there were some baseline differences between patients who received pigtail catheters and chest thoracostomy tubes (pigtails were placed in older patients and more frequently with blunt trauma), there were no differences in procedure-related complications or failure rates.

Chakko SC, Caldwell SH, Sforza PP. Treatment of congestive heart failure. Its effect on pleural fluid chemistry. *Chest*. 1989;95(4):798–802.
Chakko et al. report a longitudinal study of pleural fluid biochemical characteristics in eight patients with congestive heart failure and pleural effusions. They demonstrated that treatment of heart failure with diuretics leads to an increase in pleural total protein and LDH levels. Three out of eight patients with heart failure–related pleural effusions were misclassified as exudative based on Light's criteria after diuresis.

Goligher EC, Leis JA, Fowler RA, et al. Utility and safety of draining pleural effusions in mechanically ventilated patients: A systematic review and meta-analysis. *Crit Care*. 2011;15(1):R46.

This systematic review identified 19 observational studies of drainage of pleural effusions in mechanically ventilated patients. The conclusion was that the PaO_2/FiO_2 ratio appeared to improve and the procedure was safe. However, there were insufficient data to suggest whether this translated to reduced duration of mechanical ventilation, ICU or hospital length of stay, or mortality.

Light RW, Macgregor MI, Luchsinger PC, et al. (1972). Pleural effusions: The diagnostic separation of transudates and exudates. *Ann Intern Med.* 1972;77(4):507–513.

Light et al. define criteria that separate transudative and exudative pleural effusions. Exudative effusions are defined by any of the following three criteria: ratio of protein in the pleural space to the serum >0.5, ratio of LDH in the pleural space to the serum >0.6, or LDH in the pleural space more than two-thirds the upper limit of normal LDH for the serum.

Rahman NM, Maskell NA, West A, et al. Intrapleural use of tissue plasminogen activator and DNase in pleural infection. *New Engl J Med.* 2011;365(6):518–526.

The MIST2 trial was a randomized, blinded, 2 × 2 factorial trial of a combination of intrapleural tPA and DNase, intrapleural tPA + placebo, intrapleural DNase + placebo, or double placebo in 210 patients with complicated parapneumonic effusion or empyema. The primary outcome of change in the area of pleural opacity on chest x-ray was significantly improved with use of the combination of intrapleural tPA and DNase when compared with placebo (−29.5% versus −17.2%). The rate of surgical referral at 3 months was lower in the combination tPA and DNase group than placebo (4% versus 16%), and hospital length of stay was shortened in the combination tPA and DNase group (−6.7 days). There were no significant differences in primary or secondary outcomes in the tPA- and DNase-alone groups with the exception of increase in surgical referral in the DNase-alone group (39%).

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13

Polyuria

Ramesh Venkataraman and John A. Kellum

PATHOPHYSIOLOGY AND CLASSIFICATION

The daily urine output is determined predominantly by the daily intake of fluids, daily solute excretion, and the urine-concentrating ability of the nephrons. The average person excretes about 600–800 mOsm of solutes per day, and average urine output is about 1.5–2.5 L/day. Polyuria happens usually because of one or more of the following mechanisms:

- Increased fluid intake, necessitating excretion of a large volume of urine (primary polydipsia)
- Increased glomerular filtration rate (rare)
- Increased solute excretion (solute or osmotic diuresis)
- Inability of the kidney to reabsorb water (central or nephrogenic diabetes insipidus [DI])

Polyuria is hence broadly classified into *solute diuresis* or *water diuresis*. When increased solute excretion drives the polyuria, it is termed *solute diuresis.* Increased urine output secondary to increased water intake or impaired water reabsorption is termed *water diuresis.* However, some patients have mixed water and solute diuresis.

RECOGNITION OF POLYURIA

In critically ill patients, polyuria is usually easy to identify in patients with an indwelling urinary catheter. Careful measurement of urine volume passed or placement of a urinary catheter should be undertaken in patients who have increased urinary frequency; who are passing large volumes of urine; and who are severely hyperglycemic, hypercalcemic, or hypokalemic. Importantly, because intensive care unit (ICU) patients frequently receive in excess of 3 L a day in total input, urine output may exceed 3 L without pathology. Therefore clinical context and clinical judgement are required.[1,2]

SOLUTE DIURESIS

Total daily urinary solute excretion varies widely varies different ethnicities, cultures, and dietary habits. The average urinary solute excretion in a healthy American adult is between 500 and 1000 mOsm/d. Solute or osmotic diuresis causing polyuria is due to solute excretion in excess of the usual excretory rate.[3] The primary abnormality in such conditions is the inability for the kidney to reabsorb a large proportion of the solute filtered. Increased solute load can be secondary to excess solute intake or increased generation of solutes because of metabolism. Increased solute intake can occur after administration of intravenous fluids (saline, dextrose, or bicarbonate); enteral or parenteral nutrition; or ingestion of exogenous proteins, sugars, or alcohols. Increased solute generation from metabolism is seen in hyperglycemia and azotemia.

Solute excretion increases urine output in a linear fashion,[4] and solute diuresis impairs the ability of the kidney to concentrate the urine. Solute diuresis can be quite severe and can be caused by more than one solute concurrently. Unless there is an adequate replacement of solute and water, a persistent solute diuresis contracts extracellular volume, leading to severe dehydration and hypernatremia.

Multiplying urine osmolality by the 24-hour urine volume gives an estimate of total urine solute concentration. If urinary total solute concentration is abnormally large, a solute diuresis is present. Solute diuresis is caused by either excessive electrolyte excretion or excessive nonelectrolyte solute excretion. If the total urinary electrolyte excretion exceeds 600 mOsm/d, then an electrolyte diuresis is present. The total urinary electrolyte excretion (in mOsm/d) can be estimated as $2 \times (\text{urine } [Na^+] + \text{urine } [K^+]) \times \text{total urine volume}$.[5] Electrolyte diuresis is generally driven by a sodium salt, usually because of iatrogenic administration of excessive normal saline or sodium bicarbonate solutions, excessive salt ingestion, and repetitive administration of loop diuretics. However, salt-losing nephropathies usually do not cause polyuria because the increased delivery of chloride to the macula densa cells triggers tubuloglomerular feedback, causing afferent arteriolar constriction and resulting in decreased glomerular filtration rate (GFR) and an overall decrease in sodium excretion.

Cerebral salt wasting (CSW) is a clinical syndrome characterized by excess renal sodium excretion, polyuria, hypovolemia, and hyponatremia.[6] Although most often seen in patients with aneurysmal subarachnoid hemorrhage (SAH), it can occur in any primary neurologic illness, including central nervous system (CNS) tumors, infectious or carcinomatous meningoencephalitis, and after neurosurgical procedures. Normally, the sympathetic nervous system promotes reabsorption of sodium directly at the proximal tubule. During CSW, increased sodium excretion occurs possibly because of impaired sympathetic neural input to the kidney related to the brain injury. Another putative mechanism involves release of brain natriuretic peptide (BNP) leading to decreased sodium reabsorption and renin release. The resulting solute diuresis and polyuria cause hypovolemia, which then stimulates antidiuretic hormone (ADH) release via a baroreceptor-mediated mechanism, leading to water retention and hyponatremia. Often CSW and syndrome of inappropriate ADH secretion (SIADH) overlap and are difficult to distinguish biochemically. Clinical evidence of volume contraction suggests a diagnosis of CSW, whereas patients with SIADH are usually euvolemic.

A clearly excessive value for urine nonelectrolyte excretion (i.e., >600 mOsm/d) implies that nonelectrolytes are the predominant solutes contributing to the diuresis. The urinary nonelectrolyte excretion can be calculated by subtracting urine electrolyte excretion from the total urine solute excretion. The most common nonelectrolyte solute causing excessive diuresis is glucose, although its incidence is

decreasing in critically ill patients because of tighter glycemic control practices. Conditions associated with glucose-induced diuresis include diabetic ketoacidosis or hyperosmolar state.[7] Excessive excretion of urea is another important cause of solute diuresis. This problem can occur after relief of urinary tract obstruction, as a consequence of enteral nutrition using a high-protein tube feeding formula, or during recovery from acute tubular necrosis. Mannitol administration (e.g., as a therapy for intracranial hypertension) also can lead to significant solute diuresis. This issue is pertinent because mannitol is often administered to patients with head trauma, who are at risk for development of nephrogenic DI.

The correct diagnosis of solute diuresis depends on a clear systematic approach as discussed earlier. Management usually involves treatment of the underlying disorder and repletion of extracellular volume by hydration.

WATER DIURESIS

Definition and Pathophysiology

When polyuria occurs because of excess water intake or impaired water reabsorption, it is called *water diuresis.* The latter is usually secondary to impaired ADH release (central DI) or resistance to the action of ADH (nephrogenic DI). The usual hallmark is polyuria associated with a dilute urine (urine osmolality <300 mOsm/L). In general, diuresis is marked, and urine osmolality (Uosm) is often less than 100 mOsm/L.

A good understanding of water homeostasis is critical for recognizing and managing water diuresis. The normal plasma osmolality is 275–285 mOsm/L. To maintain this steady state while maintaining solute balance, water intake must equal water excretion. The primary stimulus for water ingestion is thirst, mediated either by an increase in effective osmolality or a decrease in blood pressure or effective circulating volume. Under normal circumstances, water intake generally exceeds physiologic requirements.

Unlike water intake, water excretion is very tightly regulated by multiple factors. The most dominant regulating factor affecting water excretion is arginine vasopressin (AVP) or ADH, a polypeptide synthesized in the hypothalamus and secreted by the posterior pituitary gland. The major stimulus for ADH release is plasma hypertonicity. ADH release is also affected by other nonosmotic factors, such as the effective circulating volume, hypoglycemia, and drugs. Once released, ADH binds to vasopressin-2 (V2) receptors located on the basolateral membranes of renal epithelial cells lining the collecting ducts. Binding of ADH to V2 receptors initiates a sequence of cellular events, ultimately resulting in the insertion of water channels called *aquaporins* into the luminal cell membrane. The presence of these water channels permits passive diffusion of water (hence its reabsorption) across the collecting duct. Any derangement in this process results in a lack of or inadequate water reabsorption by the collecting duct and will result in water diuresis.

In summary, water diuresis occurs either because of excessive water intake sufficient to overwhelm the renal excretory capacity (primary polydipsia) or the impairment of renal water reabsorption itself (DI). Impaired renal water reabsorptive capacity (leading to water diuresis) in turn can occur either as a result of failure of ADH release in response to normal physiologic stimuli (central or neurogenic DI) or failure of the kidney to respond to ADH (nephrogenic DI). In most patients, the degree of polyuria is primarily determined by the degree of ADH deficiency or AVP resistance.

Primary Polydipsia

Primary polydipsia, although rare in the ICU, can be clinically recognized based on the history of the patient. Usually there is a history of psychiatric illness, especially when phenothiazines are being used. Some patients with chronic psychiatric illnesses have a moderate to marked increase in water intake (up to 40 L/day).[8,9] It is presumed that a central defect in thirst regulation plays an important role in the pathogenesis of primary polydipsia. In some cases, the osmotic threshold for thirst is reduced below the threshold for the release of ADH. The mechanism responsible for abnormal thirst regulation in this setting is unclear. There is evidence that these patients have other defects in central neurohumoral control as well.[10] Hyponatremia, when present, also points to the diagnosis of primary polydipsia. The diagnosis of primary polydipsia is usually evident from low urine and plasma osmolalities in the face of polyuria. Hypothalamic diseases such as sarcoidosis, trauma, and certain drugs (e.g., phenothiazines) can lead to primary polydipsia (Table 13.1). There is no proven specific therapy for psychogenic polydipsia. Free water restriction is the mainstay of treatment.

Central Diabetes Insipidus

The osmotic threshold for ADH release is a serum osmolality of 280–290 mOsm/kg. Failure to maximally concentrate the urine (urine osmolality >1000 mOsm/kg) despite a serum osmolality above the osmotic threshold indicates DI. Central DI occurs when there is a defect in the secretion of ADH. Inadequate secretion of ADH (central DI) can be caused by a large number of disorders that act at one or more of the sites involved in ADH secretion, interfering with the physiologic chain of events that lead to the release of this hormone. However, the most common causes of central DI account for the vast majority of cases. Polyuria occurs when >80% of neurons secreting ADH are damaged.[11] These common causes include neurosurgery, head trauma, brain death, primary or secondary tumors of the hypothalamus, and infiltrative diseases such as Langerhans cell histiocytosis (see Table 13.1).

TABLE 13.1 Cause of Polyuria

1. Polyuria secondary to water diuresis
   - a. Excessive intake of water
     - i. Psychogenic polydipsia
     - ii. Drugs—anticholinergic drugs, thioridazine
     - iii. Hypothalamic diseases—trauma, sarcoidosis
   - b. Defective water reabsorption by the kidney
     - i. Central diabetes insipidus (vasopressin deficiency)
     - ii. Renal tubular resistance to AVP
2. Congenital nephrogenic diabetes insipidus
3. Acquired nephrogenic diabetes insipidus
   - a. Hypercalcemia
   - b. Hypokalemia
   - c. Drugs—lithium, demeclocycline
   - d. Chronic renal diseases—postobstructive diuresis, polyuric phase of ATN
   - e. Other systemic diseases—amyloidosis, sickle cell anemia
4. Polyuria secondary to solute diuresis
   - a. Electrolyte-induced solute diuresis
     - i. Iatrogenic—excessive sodium chloride load, loop diuretic use
     - ii. Salt-wasting nephropathy (rarely causes polyuria)
   - b. Nonelectrolyte solute–induced diuresis
     - i. Glucosuria—diabetic ketoacidosis, hyperosmolar coma
     - ii. Urea diuresis—high-protein diet, ATN
     - iii. Iatrogenic—mannito

ATN, Acute tubular necrosis; *AVP,* arginine vasopressin.

Nephrogenic Diabetes Insipidus

Nephrogenic DI refers to a decrease in urinary concentrating ability because of renal resistance to the action of ADH. In some cases, collecting duct cells fail to respond to ADH. Other factors that can cause renal resistance to ADH are problems that interfere with the renal countercurrent concentrating mechanism, such as medullary injury or decreased sodium chloride reabsorption in the medullary aspect of the thick ascending limb of the loop of Henle.

The most common cause of nephrogenic DI in adults is chronic lithium ingestion (see Table 13.1). Polyuria occurs in about 20%–30% of patients on chronic lithium therapy. The impairment in the nephrons' concentrating ability is thought to be the result of decreased density of V2 receptors or decreased expression of aquaporin-2, a water channel protein. Other secondary causes of nephrogenic DI include hypercalcemia, hypokalemia, sickle cell disease, and other drugs (see Table 13.1). Hypercalcemia-induced nephrogenic DI occurs when the plasma calcium concentration is persistently above 11 mg/dL (2.75 mmol/L). This defect is generally reversible with correction of hypercalcemia. The mechanism(s) responsible for hypercalcemia-induced nephrogenic DI remain incompletely understood. Compared with hypercalcemia-induced DI, hypokalemia-induced nephrogenic DI is less severe and often asymptomatic. Water diuresis can also follow relief of obstructive nephropathy. A rare form of nephrogenic DI can occur during the second half of pregnancy (gestational DI). This condition is thought to be caused by release of a vasopressinase from the placenta, leading to rapid degradation of endogenous or exogenous AVP.[12]

In children, nephrogenic DI is usually hereditary. Congenital or hereditary nephrogenic DI is an X-linked recessive disorder resulting from mutations in the V2 AVP receptor gene.[13] The X-linked inheritance pattern means that males tend to have marked polyuria. Female carriers are usually asymptomatic but occasionally have severe polyuria. In addition, different mutations are associated with different degrees of ADH resistance. Nephrogenic DI can also be inherited as an autosomal recessive disorder because of mutations in the aquaporin gene that result in absent or defective water channels, thereby causing resistance to the action of ADH.[14]

Approach to Polyuria (Fig.13.1)

Polyuria in a critically ill patient should be evaluated in a timely manner and the underlying cause determined and rectified. For all practical purposes, polyuria should be suspected in patients with urinary volume >200 mL/h for 2 or more consecutive hours in the absence of diuretic administration. A thorough review of patient history, medication list, and clinical and laboratory parameters often reveals the underlying cause of polyuria in a large proportion of critically ill patients. Common causes of solute diuresis, such as hyperglycemia, hypercalcemia, mannitol use or intravenous saline or bicarbonate use, and azotemia, are apparent by routine review of laboratory studies. History of an intervention to relieve bilateral urinary tract obstruction points toward solute diuresis because of increased sodium and urea excretion. Post-neurosurgery status, presence of traumatic brain injury, and clinical brain death suggest central DI as the likely cause of polyuria. History of a primary neurologic insult can suggest polyuria either because of CSW or central DI. The presence of severe hypothermia or hypokalemia and a history of lithium intake make nephrogenic DI the likely reason for polyuria. The rate of onset of polyuria can sometimes provide a clue about the diagnosis; when central DI is the problem, the onset of polyuria is generally abrupt, whereas when nephrogenic DI or primary polydipsia is the problem, the onset of polyuria tends to be more gradual.

When the cause of polyuria is not readily apparent, as a first step, spot urine osmolality should be measured. When urine osmolality is low (<300 mOsm/kg), it suggests a water diuresis from primary polydipsia or DI. On the other hand, when the urine osmolality is high (>600 mOsm/kg), it usually indicates the presence of solute diuresis. Urine osmolality values between 300 and 600 mOsm/kg could be the result of solute diuresis, water diuresis, or mixed diuresis. Plasma sodium concentration, along with urine osmolality, often helps in identifying the underlying pathophysiology. A low serum sodium with dilute urine indicates primary polydipsia. A normal plasma sodium may indicate solute or water diuresis. In such patients, if the urine osmolality is >600 mOsm, it usually indicates a solute diuresis and no further testing is necessary. If urine osmolality is indeterminate (300–600 mOsm/kg), total daily osmolar output can be calculated (Uosm × 24-hour urine volume) and if it is >1000 mOsm, solute diuresis can be diagnosed. A high plasma serum sodium in the presence of dilute urine indicates excretion of excess amounts of free water and favors a diagnosis of DI. In a patient with a neurologic disorder, it is important to differentiate polyuria caused by central DI from that caused by CSW (Table 13.2). Although both conditions lead to hypovolemia, CSW has increased urine osmolality from decreased sodium and urea reabsorption, whereas urine osmolality is very low because of water diuresis in central DI. CSW presents with hyponatremia, whereas patients with central DI often have hypernatremia.

When the diagnosis is unclear (plasma sodium is normal and urine osmolality is indeterminate), the diagnosis can be confirmed by determining the urinary response to an acute increase in plasma osmolality induced either by water restriction or, less commonly, by administration of hypertonic saline. When the patient is evaluated after water restriction, the urine osmolality, plasma osmolality, and plasma sodium should be measured. Achievement of a serum sodium >145 mEq/L and serum osmolality >295 mOsmol/kg ensures maximal ADH release and response in normal individuals with no additional effect with external ADH administration. Hence, if the urine osmolality reaches a normal value (>700 mOsmol/kg) after water restriction, this indicates that both ADH release and its action on collecting ducts are intact and the diagnosis is primary polydipsia. However, if urine osmolality is <700 mOsm despite a serum osmolality >295 mOsm/kg and serum sodium >145 mEq/dL, it denotes a blunted ADH release or ADH effect, and hence administration of exogenous ADH is recommended. Desmopressin nasal spray or as a subcutaneous or intravenous injection is preferred over aqueous vasopressin injections because of its shorter half-life. Urine volume and osmolality should be monitored every 30 minutes for the first 2 hours after exogenous ADH administration. Urine osmolality will be doubled after ADH administration in patients with central DI. In patients with complete nephrogenic DI, no significant change (<15%) in urine osmolality is seen after exogenous ADH administration. A small increase in urine osmolality (<45%) is seen in patients with partial nephrogenic DI. In contrast to patients with partial central DI, in patients with partial nephrogenic DI, urine remains dilute with osmolality not >300 mOsm/kg despite desmopressin administration. An alternative to performing a therapeutic trial of desmopressin is to measure plasma copeptin levels after infusing hypertonic saline to stimulate ADH release. However, copeptin assays are not yet widely available for clinical use. Copeptin is the C-terminal glycoprotein moiety of the ADH prohormone and therefore a surrogate marker of ADH.15 To distinguish central DI from primary polydipsia, hypertonic saline is infused to raise the serum sodium to >145 mEq/L, at which point plasma copeptin is measured. Copeptin levels ≤4.9 pmol/L indicate central DI, whereas higher levels suggest primary polydipsia.

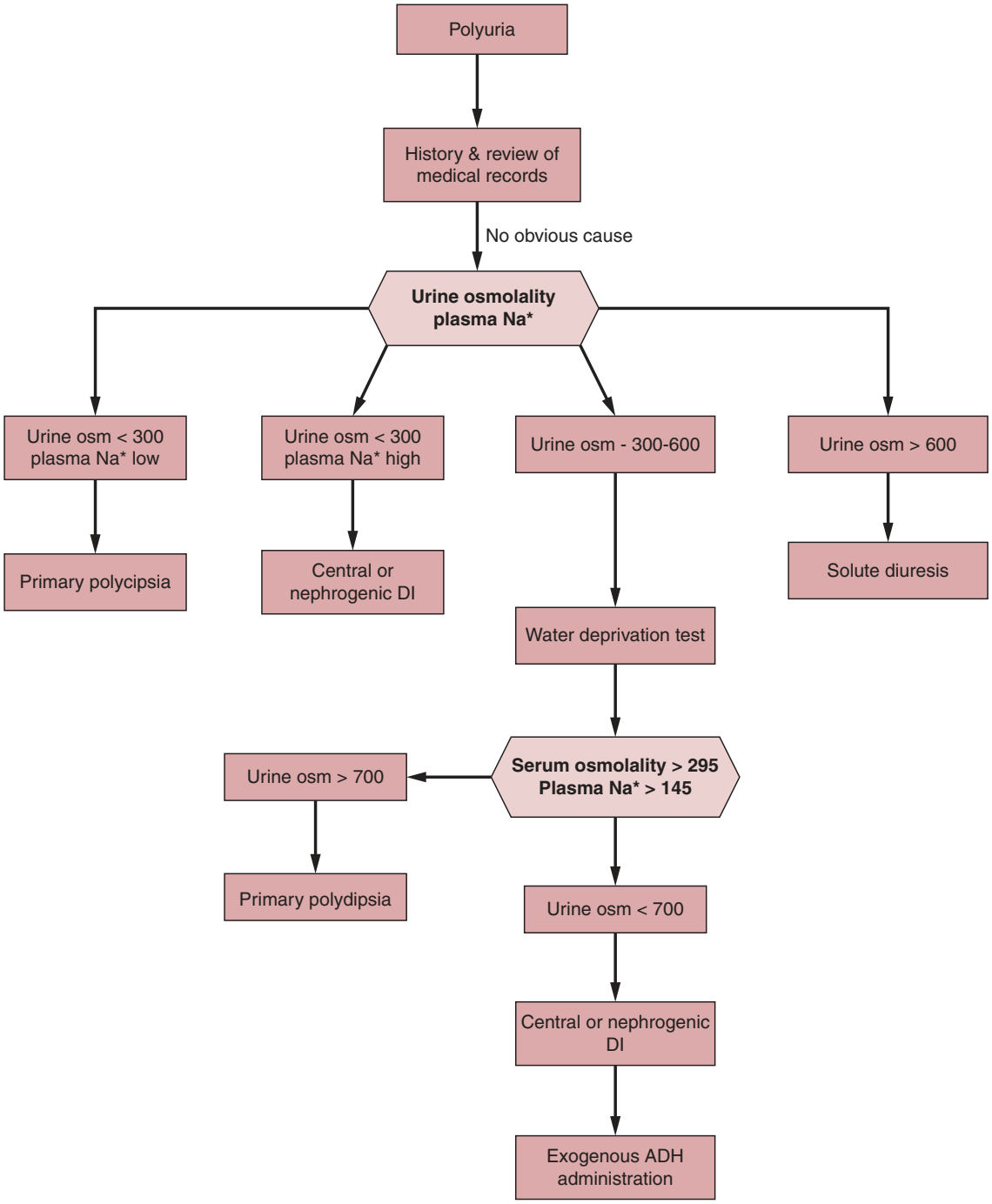

Fig. 13.1 Approach to polyuria.

TABLE 13.2 Differentiation of Cerebral Salt Wasting vs. Central DI

	Cerebral Salt Wasting	Central DI
Urine osmolality	High (>300 mOsm)	Low (<300 mOsm)
Serum osmolality	Low	High
Urine sodium	High (>40 mEq/L)	Low (<20 mEq/L)
Serum sodium	Low	High
Intravascular volume	Low	Low

DI, Diabetes insipidus.

Treatment of Polyuria

Primary polydipsia can only be treated by eliminating the underlying cause and by water restriction. In patients with schizophrenia and polydipsia, clozapine has been shown to have a beneficial effect. Treatment of the underlying cause will resolve polyuria in patients with solute diuresis. In patients with postobstructive diuresis, urine output is often very high because of combined sodium and urea diuresis. In such situations, attempting to replace the urine volume by intravenous infusion of isotonic saline to prevent hypovolemia will delay resolution of polyuria. A fluid infusion at a maintenance level, such as 75 mL of one-half isotonic saline per hour, is generally recommended and will

suffice to help resolve polyuria quickly without causing hypotension.[16] Because solute diuresis is often accompanied by hypernatremia, and very rapid correction of hypernatremia can have disastrous consequences (e.g., cerebral herniation), it is crucial to carefully monitor serum Na^+. The serum Na^+ should not be permitted to decrease more than 0.5–1 mEq/L per hour.

Central DI can be treated by replacing ADH. The agent of choice is desmopressin, because it has prolonged antidiuretic activity and a very minimal vasopressor effect. It is usually administered intranasally at doses of 10–20 μg once or twice a day. Patients with central DI with some residual releasable ADH can be treated with drugs, such as carbamazepine (100–300 mg twice daily), clofibrate (500 mg every 6 hours), or chlorpropamide (125–250 mg once or twice a day), that stimulate ADH release.

The mainstay of treatment of nephrogenic DI is solute restriction and diuretics. Thiazide diuretics in combination with a low-salt diet can diminish the degree of polyuria in patients with persistent and symptomatic nephrogenic DI. Thiazide diuretics (e.g., hydrochlorothiazide) act by inducing mild volume depletion. Hypovolemia induces an increase in proximal sodium and water reabsorption, thereby diminishing water delivery to ADH-sensitive sites in the collecting tubules and reducing the urine output. The potassium-sparing diuretic, amiloride, also may be helpful.[17] In patients with partial nephrogenic DI, exogenous administration of ADH can be attempted.

CONCLUSION

Polyuria is common in the ICU setting. Immediate recognition, determination of the underlying cause, and specific management will prevent significant hypotension and hypernatremia. A systematic approach based on pathophysiology is recommended to guide therapy.

KEY POINTS

- Urine output of > 3 L/day is defined as polyuria. However, any urine output >200 mL/h for 2 or more consecutive hours in the absence of diuretic administration warrants further evaluation and may require prompt treatment.
- Most causes of polyuria in the critically ill patient can be identified by a careful review of patient history and medical records, including medication list.
- When the cause of polyuria is unclear, urine osmolality along with plasma sodium should be performed.
- Very low urine osmolality (<300 mOsm/kg) indicates water diuresis, whereas urine osmolality >600 mOsm indicates solute diuresis.
- When untreated, polyuria leads to significant hypotension and hypernatremia.

References for this chapter can be found at expertconsult.com.

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14

Oliguria

Ramesh Venkataraman and John A. Kellum

Oliguria is one of the most common problems faced by clinicians in the intensive care unit (ICU). The goal of this chapter is to understand the reasons for oliguria and provide an evidence-based, practical, physiology-based approach to diagnosing and treating it.

DEFINITIONS AND EPIDEMIOLOGY

An average person excretes 600 mOsm of solute/day, and the maximal urinary concentration that can be achieved is 1200 mOsm/L. Hence a urine output of at least 500 mL per day is obligatory for excreting the average daily solute load. Therefore oliguria has generally been defined as urine output less than 500 mL per 24 hours.

The incidence of oliguria has been variedly reported in the literature, mainly because of the different definitions used. Some studies have estimated that up to 18% of medical and surgical ICU patients with intact renal function exhibit episodes of oliguria.[1] Furthermore, 88% of ICU patients who develop acute kidney injury (AKI) have a urine output of <0.5 mL/kg/h for 6 hours or more, and 18% have a urine output of <0.3 mL/kg/h for 24 hours or longer.[2]

To standardize the definition across different studies and populations, the Acute Dialysis Quality Initiative (ADQI) adopted a definition of *oliguria* as urine output of less than 0.3 mL/kg/h for at least 24 hours (www.ADQI.org). For all practical purposes, however, urine output under 0.5 mL/kg/h is usually considered inadequate for most critically ill patients. This is in part because fluid input resulting from medications, nutrition, and other reasons typically exceeds this threshold in critically ill patients, and fluid overload may result if urine output is inadequate to maintain fluid balance. Hence any urine output <0.5 mL/kg/h should immediately be evaluated and therapy initiated to reverse the inciting mechanism when feasible.

OLIGURIA IN ACUTE KIDNEY INJURY

Oliguria is often treated as an early marker of AKI. However, AKI need not manifest as oliguria in the intensive care setting, and oliguria is an insensitive and nonspecific clinical manifestation of AKI. Moreover, other factors, such as profound hypokalemia, hypothermia, hyperglycemia, and medications, can all lead to good urine output even in the presence of AKI, confounding the assessment of AKI severity. Although currently Kidney Disease: Improving Global Outcomes (KDIGO) definitions of AKI give equal weight to change in serum creatinine and reduction in urine output, these two measures differ significantly in terms of pathophysiology and their relationship to clinical outcomes. Although a rise in serum creatinine likely implies a true reduction in glomerular filtration, oliguria could just represent a stress response or imply an actual decrease in glomerular filtration. However, several studies have clearly demonstrated that even isolated oliguria (no creatinine criteria) is associated with significant short- and long-term adverse consequences, including death or permanent dialysis.[2] When associated with increased serum creatinine, oliguria seems to denote worse prognosis[2] and likely represents irreversible kidney injury. Ability of urine output to predict AKI also seems to vary across different patient cohorts, with better predictive ability in medical than surgical patients. When oliguria is prolonged, it almost always implies ongoing kidney injury, and the likelihood of reversibility of oliguria diminishes over time. Prowle et al. demonstrated that oliguria of longer than 12 hours' duration predicted stage 2 AKI better, and oliguria of lesser duration, although common, did not lead to biochemical AKI.[3] Hence although any oliguria (urine output <0.5 mL/kg/h) warrants a prompt assessment for risk of AKI, the presence of oliguria in itself does not imply occurrence of renal structural injury.

Pathophysiology of Oliguria

Oliguria can occur because of decreased glomerular filtration rate (GFR), increased tubular reabsorption of filtrate, or a combination of both. Factors that decrease GFR in ICU patients include overt hypovolemia related to fluid losses, hemorrhage, third-spacing, low cardiac output states, and systemic vasodilatation, as seen commonly in patients with sepsis or secondary to sedatives. In hypovolemic patients, release of antidiuretic hormone (ADH) and activation of the renin–angiotensin system lead to increased reabsorption of water and oliguria with a high urine osmolality. Similarly, other stressors such as surgery, pain, and trauma also release ADH and along with sympathetic stimulation can lead to oliguria as a physiologic response. Under these circumstances, oliguria can be easily reversed with the timely resolution of the inciting stress and/or volume replacement.

Although oliguria is simplistically perceived as a decline in glomerular filtration, multiple mechanisms have been implicated for oliguria in the critically ill patient with AKI, including overall reduction in renal blood flow, regional intrarenal variation in blood flow and redistribution, alteration in glomerular hemodynamics, direct glomerular injury, ischemia to the proximal tubule (S3 segment), renal interstitial edema, inflammatory insult, and tubular obstruction.[4] Not uncommonly, increased abdominal pressure decreases GFR by direct compression on the kidneys, leading to increased renal venous pressures. Fluid overload has been consistently shown to worsen renal functions in critically ill patients by increasing renal intracapsular and renal venous outflow pressures and is strongly associated with worsening of AKI and mortality.

Mechanical obstruction to urine flow is common and usually caused by obstruction or malposition of a urinary catheter, urethral or bladder neck obstruction from an enlarged prostate or malignancy, or tubuloureteral obstruction as seen in papillary necrosis.

DIAGNOSTIC APPROACH TO OLIGURIA

The diagnosis of oliguria necessitates an integrated approach as outlined in Fig. 14.1. Accurate monitoring of intake and output is required, usually with a urinary catheter in place. Intensive urine output monitoring has been shown to improve the detection of AKI and improve outcomes.[5] The risks of urinary catheter–associated urinary tract infections must be balanced against the benefit of hourly urine output monitoring in patients with high risk for the development of AKI. In general, patients in stage 1 KDIGO AKI or higher will benefit from accurate urine output monitoring and warrant a urinary catheter.[6] Transient oliguria is common and may not be an independent risk factor for morbidity and mortality in critically ill or injured patients, but sustained oliguria (at least 6 hours' duration) often indicates AKI and has been shown to be independently associated with hospital mortality. Oliguria mandates immediate evaluation for reversible causes and a risk assessment for AKI. The main goal of managing oliguria is to rapidly determine and correct the underlying cause(s), to halt the progression of kidney injury. Merely reacting to every oliguria with either fluid and/or diuretic therapy should be condemned, and efforts should be taken to understand and address the underlying pathophysiology. Targeted therapy to reverse the inciting events should be applied rapidly.

Clinical History and Examination

Evaluation of a patient with oliguria should start with a focused history taking, chart review, and clinical examination. A history suggestive of overt intravascular volume depletion such as history of vomiting and/or diarrhea, evidence of ongoing bleeding, perioperative fluid losses or deficits (e.g., gastric/ileostomy losses or vomiting), or extravascular fluid sequestration can point to a functional cause of oliguria with or without changes in serum creatinine or urea. History of patient comorbidities, prior or present myocardial infarction, or left ventricular systolic or diastolic dysfunction can provide clues to impaired cardiac output as a cause of oliguria. History of fever with localizing symptoms with or without hypotension makes septic AKI likely. A history of recent contrast administration for imaging, of intraoperative hypotension, or administration of nephrotoxic agents can suggest an intrarenal cause of oliguria in an adequately volume-resuscitated patient. Chart review should involve capturing of episodes of hypotension, duration of any hemodynamic instability, cumulative fluid balance, previous use of diuretics, use of nephrotoxic agents, and dosing of medications.

Routine clinical examination for volume status, including skin turgor, dry mucosa, and the presence of pedal or sacral edema, are insensitive and nonspecific and can be misleading. In critically ill patients, functional hemodynamic monitoring has become the standard for

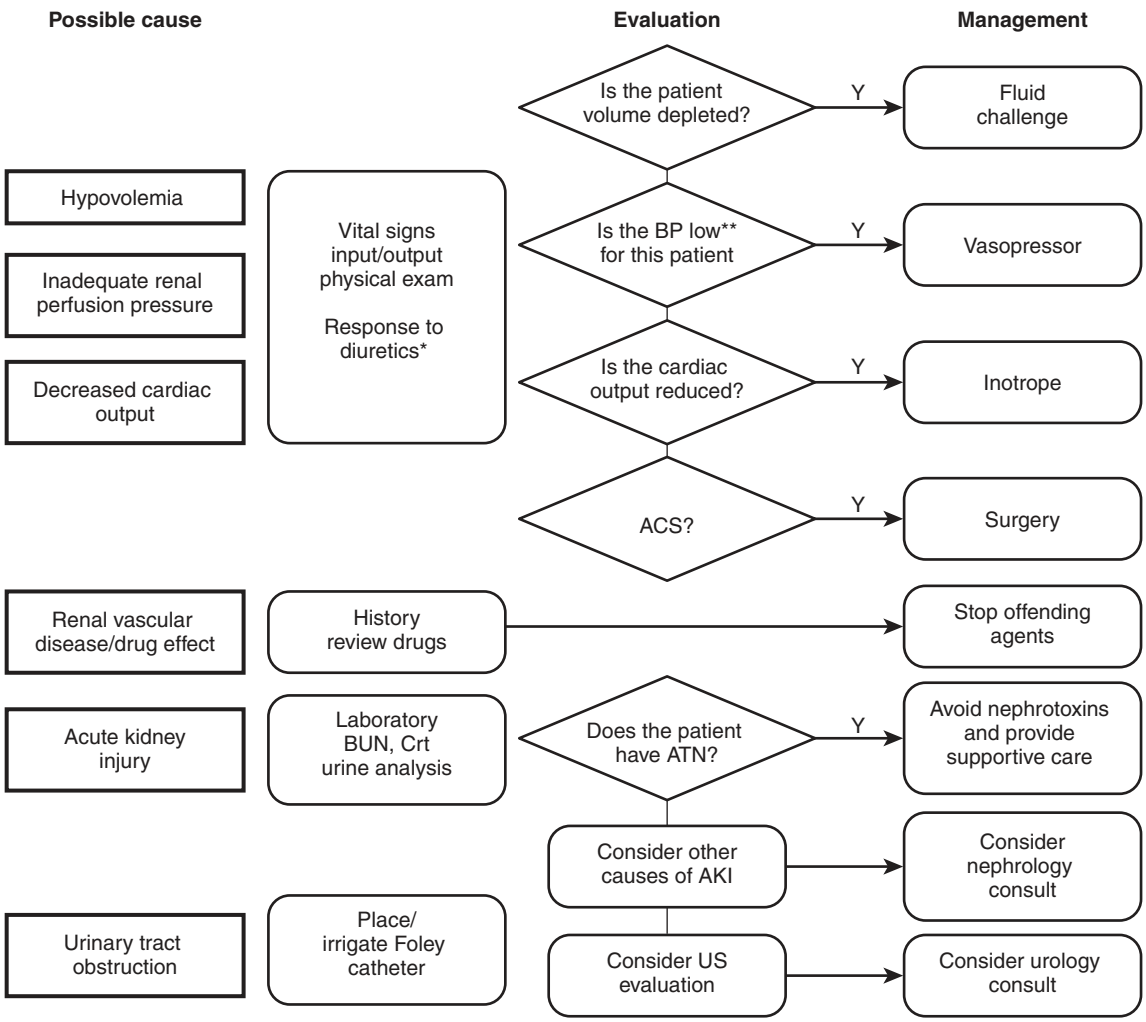

Fig. 14.1 Diagnostic Approach to Oliguria. *ACS,* Abdominal compartment syndrome; *AKI,* acute kidney injury; *ATN,* acute tubular necrosis or tubular injury; *BP,* blood pressure; *BUN,* blood urea nitrogen; *Crt,* creatinine; *US,* ultrasound.

assessment of fluid responsiveness (see later). A tense abdomen can be a very early and important clue for the onset of abdominal compartment syndrome (ACS) and should trigger frequent measurements of intraabdominal pressure (IAP) and hourly urine output monitoring.

Rule Out Urinary Obstruction

Acute oliguria in the ICU with no obvious inciting event should prompt an evaluation for postrenal obstruction. Elderly men with a prior history of prostatic hypertrophy/malignancy and elderly women with bladder neck obstruction are at high risk for such obstruction. Clinical palpation for a distended bladder and bladder ultrasound to determine residual urine volume should be immediately performed and the need for urinary catheterization decided. In critically ill patients with a urinary catheter already in place, obstruction of the urinary catheter by clots or sediments should be ruled out by flushing the catheter. Although uncommon in the acute setting, complete or severe partial bilateral ureteral obstruction may also lead to acute, "acute on chronic" failure.

Renal Imaging

An early diagnosis of urinary tract obstruction (UTO) with renal ultrasound and timely relief of obstruction will prevent further progression and secondary infections. Renal ultrasound also can be useful to assess for the presence of a chronic component to the kidney injury (decreased size of kidney and cortical thinning) and for detecting other causes of renal disease such as polycystic kidney disease (Table 14.1). In patients with severe hypovolemia and early obstruction, hydronephrosis may not be seen on the initial ultrasound examination but may appear later in the course of the disease. Computed tomography (CT) scanning should be performed if the ultrasound results are equivocal or if the kidneys are not well visualized.

Laboratory Parameters

Evaluation of new-onset oliguria not secondary to obstruction and obvious hypovolemia should start with the measurement of serum urea and creatinine concentrations. Often acute oliguria may not be accompanied by creatinine elevation and under these circumstances may be the earliest marker of impending AKI. When oliguria is associated with an elevation in serum creatinine, it implies ongoing AKI and a poorer outcome. Rate of rise of serum creatinine can also provide useful information regarding the severity and potential for reversibility of AKI. Elderly patients with less lean muscle mass, advanced liver disease, and fluid overload may have a falsely low serum creatinine for the degree of their renal injury, whereas patients with rhabdomyolysis may have a higher serum creatinine and a greater rate of rise disproportionate to the severity of their renal injury.

Although routine urine microscopy is generally recommended, the yield of urine microscopy in the ICU is very low. Urine sediment is typically bland or reveals hyaline and fine or coarse granular casts. However, the discrimination of these findings is limited and most often noncontributory in the management of oliguria. Rarely, urine microscopy reveals red cell casts indicating a primary glomerular pathology most commonly seen in patients with vasculitides. Eosinophilia, eosinophiluria, and hypocomplementemia, if present (although insensitive and nonspecific), point to the diagnosis of atheroembolic etiology of acute oliguria.[7] Urine eosinophilia is neither sensitive nor specific for acute interstitial nephritis and should not be relied on.

Urinary indices such as urinary sodium and fractional excretion of sodium (FE_{Na}) have been proposed to differentiate prerenal from intrinsic causes of AKI. Conventionally, an FE_{Na} of less than 1% has been used as a marker for a "prerenal" cause of oliguria, whereas a value of greater than 1% generally suggests a loss of tubular function and AKI. However, use of diuretics, agents interfering with the angiotensin–aldosterone axis, or osmotic agents such as mannitol interfere with sodium excretion and FE_{Na}. In patients who have received diuretics, fractional excretion of urea (FE_{urea}) may be useful. A low FE_{urea} ($\leq$35%) was a more sensitive and specific index than FE_{Na} in identifying intact tubular function, especially if diuretics were administered.[8] Urinary indices have not been validated in critically ill patients and have shown disparate results in patients with septic AKI. Systemic inflammation secondary to sepsis has been shown to cause conformational channels in the Na/H, chloride, and urea changes, thereby independently affecting their excretion. Recent studies have consistently demonstrated the limited diagnostic and prognostic utility of urine biochemistry in AKI,[9] and the routine use of these indices in patients with oliguria is not recommended.

Biomarkers

Several biomarkers have been evaluated in AKI and their utility in predicting progression of AKI in critically ill patients explored.[10] Biomarkers in AKI can be broadly stratified into those that primarily correspond to GFR (cystatin C) and those that reflect tubular damage (e.g., neutrophil gelatinase–associated lipocalcin [NGAL], kidney injury molecule-1 [KIM-1]) or stress (tissue inhibitor of metalloproteinases-2 [TIMP-2] and insulin-like growth factor binding protein-7 [IGFBP-7]). NGAL has been found to be a useful marker in predicting AKI onset and progression in varied populations.[11] A test using novel biomarkers, [TIMP-2]•[IGFBP-7], has been validated to predict moderate to severe (stage 2–3) AKI using both serum creatinine and urine output criteria and is Food and Drug Administration (FDA)–approved.[12]

TABLE 14.1. Diagnostic Tests and Their Utility in an Oliguric Patient

S. No.	Diagnostic Test	Comments
1	Urine microscopy	• Often noncontributory • RBC casts, when present, indicate glomerular pathology
2	Urine indices	• Very low utility in the ICU • Not recommended in the evaluation of oliguria
3	Renal ultrasound	• Should be routinely performed to rule out obstruction • Provides information on existence of chronic kidney disease
4	Biomarkers (NGAL, TIMP-2, and IGFBP-7)	• Consider when available • Elevation indicates structural kidney damage
5	Hemodynamic evaluation	• Mandatory to ensure fluid responsiveness and fluid tolerance
6	Measurement of intraabdominal pressure	• Suggested in patients with high risk for ACS

ACS, Abdominal compartment syndrome; *ICU,* intensive care unit; *IGFBP-7,* insulin-like growth factor binding protein-7; *NGAL,* neutrophil gelatinase–associated lipocalcin; *RBC,* red blood cell; *TIMP-2,* tissue inhibitor of metalloproteinases.

HEMODYNAMIC EVALUATION

Evaluation of hemodynamics and appropriate optimization is one of the logical important steps in the management of oliguria. Clinical

assessment of important hemodynamic variables such as preload, overall volume status, cardiac output, and tissue perfusion are all confounded by several factors, making them less useful in critically ill patients. Blood pressure and heart rate are affected by numerous physiologic and treatment variables and are unreliable measures of volume status. The presence or absence of jugular vein pressure (JVP) is not an accurate way to assess right ventricular or central venous pressures (CVPs) in the presence of positive pressure ventilation and positive end-expiratory pressure (PEEP). Similarly, peripheral edema is often the result of capillary leak and coexistent hypoalbuminemia and decreased oncotic pressure in critically ill patients. These patients can have an excessive volume of total body water and yet be intravascularly volume depleted.

It has been well established that measures such as CVP and pulmonary artery occlusion pressure (PAOP) do not provide reliable estimates of preload or preload responsiveness.[13] These static measures assume a linear pressure–volume relationship, which is often not the case in sick patients with comorbidities and are affected by the presence of atrioventricular valve abnormalities, compliance of the ventricle, and pericardial and abdominal pressures. Even when CVP is low, the value does not give any information on whether the patient will improve cardiac output in response to a fluid bolus (i.e., being preload responsive). The mixed venous oxygen saturation (SvO_2) or central venous oxygen saturation ($SCVO_2$) can serve as a surrogate for cardiac output, but again does not define optimal filling. Moreover, SvO_2 can be altered by the ability of tissues to extract and subsequently use delivered oxygen.

In patients on mechanical ventilation and without spontaneous triggering of the ventilator, an arterial pulse–pressure variation of >13% is strongly predictive of preload responsiveness.[14] However, the use of pulse contour analysis is limited in that it is applicable only in patients who receive >8 mL/kg tidal volume on the ventilator, who do not have arrhythmias, and in whom lung compliance is >30 cm of water. An easier and more applicable test of preload responsiveness in the ICU setting would be passive leg raising (PLR) and monitoring of change in cardiac index or pulse pressure.[15] This can be done in spontaneously breathing patients and in those with arrhythmias. However, any measurement of cardiac index, pulse pressure, or stroke volume variation warrants continuous cardiac output monitoring using one of the newer pulse contour techniques.

A bedside echocardiogram screening for inferior vena cava (IVC) size and respiratory variation in size, left and right ventricular size and function, and presence of pericardial tamponade can provide valuable information about preload and contractility and can rule out severe obstructive shock from massive pulmonary embolism and pericardial effusion. Ultrasound of the lungs looking for A profile vs. B profile along with extravascular lung water (EVLW) measurement, when available, will assist in determining fluid tolerance and should be routinely incorporated into the decision-making process before any empiric fluid bolus.

No one parameter individually can unequivocally predict fluid responsiveness, but when a combination of two or more are used, they can reliably predict fluid responsiveness. It is important to understand that improvement in cardiac output with a fluid bolus (fluid responsiveness) does not automatically predict improvement in urine output, and studies have shown little to no improvement in urine output when fluids were administered.

Evaluation for Intraabdominal Hypertension

An uncommon but often overlooked reason for acute oliguria is ACS. ACS should be suspected in any patient with a tensely distended abdomen, progressive oliguria, hypotension, and increased airway pressures (transmitted across the diaphragm). The mainstay of diagnosis is the measurement of IAP, and the most common way to assess IAP is to measure the pressure within the urinary bladder after transducing a fluid-filled urinary catheter.

ACS is defined as organ dysfunction that results from an increase in IAP. Normal IAP is 5–7 mm Hg. Abdominal perfusion pressure (APP) is the pressure difference between the mean arterial pressure (MAP) and IAP (APP = MAP − IAP). Sustained IAP >12 mm Hg is called *intraabdominal hypertension.* When the IAP is sustained >20 mm Hg with or without APP >60 mm Hg, it is called ACS.[16] ACS occurs in a wide variety of medical and surgical patients, including acute severe pancreatitis, major abdominal surgeries requiring large-volume resuscitation, emergent laparotomies with tight abdominal wall closures, or abdominal wall burns with edema. ACS leads to AKI and acute oliguria mainly by directly increasing renal outflow pressure and thus reducing renal perfusion. Other mechanisms include direct parenchymal compression and arterial vasoconstriction mediated by stimulation of the sympathetic nervous and renin–angiotensin systems. Cardiac output also can be compromised by impaired venous return.

TREATMENT OF OLIGURIA

Oliguria is a clinical sign that is often multifactorial in the critically ill patient, and no single therapeutic strategy can be universally applied to treat oliguric patients. A thorough evaluation and understanding of the underlying pathophysiologic processes responsible and specific strategies to attenuate and reverse them when possible should be employed.

Fluid Bolus

Oliguria is one of the most common indications for a fluid bolus in the ICU. However, routine empiric fluid therapy for every episode of oliguria should be strongly discouraged. Fluid bolus should be reserved only for oliguric patients with unequivocal evidence of hypovolemia and ongoing fluid losses (Table 14.2). In the absence of overt hypovolemia, fluid therapy should be considered only after careful hemodynamic evaluation and ensuring fluid responsiveness and fluid tolerance. A recent study that evaluated response to fluid bolus documented no change in cardiac output in most of the patients, with little or no improvement

TABLE 14.2 Effectiveness of Various Treatment Strategies in Oliguria

S. No.	Therapy	Indications
1	Fluid bolus	• Administer if overt hypovolemia and if fluid responsive and tolerant
2	Vasopressors	• In septic patients with MAP ≤65 mm Hg[1]
3	Inotropes	• If decreased LV and/or RV function with cardiorenal syndrome
4	Diuretics	• In fluid-overloaded patients • To prevent fluid overload • Once volume replete, consider FST[2] to assess response and risk stratify

FST, Furosemide stress test; *LV,* left ventricular; *MAP,* mean arterial pressure; *RV,* right ventricular.
1. In patients with known chronic hypertension, target MAP 70–75 mm Hg.

in urine output 1 hour after the fluid bolus.[17] Repeated fluid boluses for oliguria lead to fluid overload, which has been consistently shown to worsen AKI and mortality.[18] Fluid overload increases renal intracapsular and renal venous pressures, leading to renal hypoperfusion.

The type and volume of fluid administered have important therapeutic implications. When fluid therapy is indicated, 500 mL of a balanced crystalloid should be administered. Hyperchloremia induced by 0.9% saline has been shown to decrease renal blood flow and cause AKI[19,20] and hence should be avoided unless the patient is hyponatremic or hypochloremic. Starch preparations and hyperoncotic colloids such as 20% albumin have been shown to cause AKI, increase the need for renal replacement therapy (RRT), and increase mortality, and should not be administered.[21,22] Although 5% albumin has been shown to be equivalent to normal saline,[23] its relatively short intravascular half-life (only slightly longer than crystalloids) and higher cost make it the less preferred fluid compared with crystalloids.

Hemodynamic Manipulation

Autoregulatory mechanisms regulating renal blood flow are deranged in critical illness, making kidneys very sensitive to changes in MAP. In patients with vasodilatory shock, rapid restoration of perfusion pressure with vasoactive drugs is crucial to attenuate any renal injury. In critically ill patients, vasoactive drugs should be initiated early and concurrent volume expansion done to minimize the duration of hypotension. Norepinephrine is the drug of choice in sepsis-induced vasodilation and should be titrated to MAP >65 mm Hg. One multicenter randomized controlled study (SEPSISPAM study)[24] in septic patients demonstrated that higher MAP (70–75 mm Hg) may decrease the risk of renal injury in patients with chronic hypertension. Dopamine is ineffective in the prevention of AKI and should not be used to improve urine output or for renal protection.[25] Dopamine, being a weak diuretic, increases urine output without altering GFR and can lead to masking of the underlying pathology, causing worsening of AKI. Newer dopaminergic agonists (e.g., fenoldopam, dopexamine) increase renal blood flow without affecting medullary oxygenation and have not been shown to decrease the incidence of AKI.[26] They can induce significant hypotension, thereby further increasing the risk of renal injury, and hence these should not be used to treat oliguria. The renal-protective effect of vasopressin is debatable and hence not recommended as the primary or lone vasopressor in septic patients or for the sole purpose of improving renal function.

In patients with significant left and/or right ventricular dysfunction causing cardiorenal syndrome, inotropic support may improve renal perfusion and AKI. Dobutamine causes systemic vasodilatation and therefore should be initiated only after adequate volume repletion and in patients with vasodilatory shock after initiation of a vasopressor, preferably norepinephrine. In patients with cardiogenic shock, dopamine has been shown to worsen mortality and is not recommended for cardiorenal syndrome.[27]

Decompression of the abdomen with laparotomy, sometimes requiring that the abdomen be left open for a time, is the only definitive treatment for oliguria secondary to ACS.

Role of Diuretic Agents

The use of diuretic agents in oliguric renal failure is widespread despite the lack of convincing evidence supporting their efficacy. Traditionally, diuretics have been used in the early phases of oliguria to "jump start" the kidney and establish urine flow. Nonoliguric renal failure has a better prognosis than oliguric renal failure, and many clinicians believe that treating oliguria early also makes it easier to regulate intravascular volume status and avoid fluid overload imposed by the mandatory fluid requirements in the critically ill patient. Two large observational studies have evaluated outcomes related to diuretic use in AKI and have provided conflicting results. In the first cohort study (PICARD), patients were characterized based on exposure to diuretics on or before the day of nephrology consultation.[28] After adjustments of covariates and propensity scores, diuretic use was associated with increased risk of death and nonrecovery of renal function (odds ratio [OR], 1.77; 95% confidence interval, 1.14–2.76). A second large multicenter observational study (BEST kidney study) showed that the use of diuretics has no beneficial effect on clinical outcomes by three different multivariate models.[29] Furthermore, high doses of loop diuretics can be associated with ototoxicity.

There is a growing literature on the use of furosemide in the evaluation of oliguria and prediction of AKI progression. In a recent study, Koyner et al. employed a furosemide stress test (FST) to evaluate renal tubular functional integrity and its ability to predict progression of AKI and compared its performance with traditional biomarkers.[30] In this study, a standard intravenous dose of furosemide (1 mg/kg for furosemide-naïve patients and 1.5 mg/kg for furosemide-exposed patients) was administered to patients with stage 1 or 2 AKI, and the authors found a cutoff 2-hour urine output of <200 mL to be highly predictive of progression to stage 3 AKI (area under the curve [AUC], 0.87) and need for RRT (AUC, 0.86). In another study, FST nonresponse was used as a strategy to identify patients who might need RRT, and these patients were randomized to early vs. standard RRT.[31] FST seems to be a clinically applicable, functional marker of AKI that could potentially predict risk of progression of AKI and need for RRT. FST should not be attempted on hypovolemic patients, and ample care should be exercised when using it.

Renal Replacement Therapy

RRT should be considered when oliguric patients are unresponsive to optimization of volume status, hemodynamics, and a diuretic challenge. This will potentially avoid development of fluid overload and make management of volume status easier. There is no consensus on the timing of initiation of RRT in oliguric patients. One should consider the reasons for AKI, nature and severity of clinical and biochemical derangements, and underlying physiologic reserve of the patient to compensate for and tolerate homeostatic imbalances to decide on the timing of initiation of RRT. The elevation of biomarkers along with lack of response to FST may help identify patients who may benefit from early RRT.

CONCLUSION

The presence of oliguria should alert the clinician to undertake a diligent search for any correctable underlying causes and to assess the risk of AKI. Although oliguria is often multifactorial, reversible causes such as obstruction to the lower urinary tract or urinary catheter, hypovolemia, low cardiac output state, and increased IAP should be ruled out. Relieving urinary obstruction, optimization of fluid status, and hemodynamics remain the cornerstone in the management of oliguria. Instinctive use of fluid boluses and diuretics should be avoided. Use of isotonic-balanced crystalloids is recommended when fluid bolus is needed. Diuretics should be used in oliguric patients with fluid overload and in volume-replete patients to assess response and progression of AKI. When all these strategies fail, RRT should be considered.

KEY POINTS

- Oliguria in the ICU can be a physiologic response to stress or imply an impairment in glomerular function.
- Oliguria should prompt an immediate evaluation for reversible causes and a risk assessment for occurrence of AKI.
- Urinary biomarkers can help estimate structural damage and risk of progression of AKI.
- Empiric fluid boluses or diuretics for oliguria without comprehensive hemodynamic assessment should not be practiced.
- Balanced isotonic crystalloids are recommended when fluid bolus is indicated.
- Diuretics are indicated only in volume-replete patients to prevent and treat fluid overload and as a strategy for risk stratification.
- Early RRT may be considered in patients unresponsive to hemodynamic optimization and diuretic challenge.

References for this chapter can be found at expertconsult.com.

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15

Metabolic Acidosis and Alkalosis

Vinay Narasimha Krishna, Jared Cook, Keith M. Wille, and Ashita J. Tolwani

ACID-BASE DISORDERS

Acid-base disorders can be quantified by using the physiologic, base-excess, and physiochemical approaches (Stewart method).[1] The bicarbonate [HCO_3^-] buffer system plays a central role in the physiologic and base-excess methods. They share nearly common explanations while describing the types and mechanisms behind acid-base disturbances. However, Stewart's more recent (1980s) acid-base approach differs significantly from the other two approaches by not attributing a central role to [HCO_3^-], as HCO_3^- alone does not determine metabolic acid-base disorders. The Stewart approach adapts a method based on *charge differences between strong cations and anions.* According to Stewart, acid-base balance in the body is determined by "strong" and "weak" electrolytes that are present in body fluid compartments as cations and anions. Strong electrolytes are fully dissociated in aqueous solution, and weak electrolytes are partially dissociated. He proposed that changes in plasma [H^+] are related to water dissociation and not addition or removal of H^+ from the plasma.[2] Stewart derived six equations that, when solved simultaneously, yield the [H^+] of a solution, and these equations operate strictly under the physiochemical principles of electroneutrality (sum of cations is equal to sum of anions), conservation of mass (amount of substance in a solution is constant unless added or removed), and law of mass action (dissociation equiliriums of all incompletely dissociated substances must be met at all times).[2] Stewart proposed that [H^+] and HCO_3^- are dependent variables and that changes in hydrogen ion [H^+] and subsequently the pH are influenced by three independent variables: namely, partial pressure of carbon dioxide (pCO_2). When pCO_2 increases, [H^+] raises, and when it decreases, [H^+] decreases. Increases in pCO_2 define respiratory acidosis, and decreases in pCO_2 respiratory alkalosis.

Total concentration of weak acids [A_{TOT}]: weak acids are not completely dissociated in aqueous solution and are mainly represented by albumin and phosphate. Increase and decrease in [A_{TOT}] increases and decreases [H^+], respectively (e.g., hypoalbuminemia causes metabolic alkalosis and hyperphosphatemia results in metabolic acidosis).

Strong ion difference (SID): difference between the total concentration of strong cations (Na^+, K^+, Ca^{2+}, and Mg^{2+}) and strong anions (Cl^-, SO_4^-, and anions of organic acids). Concentrations of Na^+ and Cl^- are the main determinants of SID because of their magnitude, and normal values range from 39 to 42 mEq/L based on concentrations of Na^+ and Cl^- (SID = $Na^+ - Cl^-$ = 140 − 100 = 40 mEq/L). This simplest estimation is called *apparent SID* (SID_a). When other anions like plasma [HCO_3^-] and the anionic equivalence of albumin and phosphate are included in the calculation of SID, the estimation is called *effective SID* (SID_e). SID_e is difficult to calculate at the bedside and needs to be estimated from blood pH, pCO_2, and the plasma concentrations of albumin and phosphate using a formula or a nomogram. SID is always positive, as Na^+ concentration is greater than Cl^-. Because of the electroneutrality principle, SID is zero in healthy individuals, as the positivity is balanced by the negative charge present on HCO_3^-, albumin, and phosphate. Changes in SID result in metabolic acid-base disturbances. Metabolic acidosis develops because of a decrease in cations or increase in anions resulting in SID <39 mEq/L. Similarly, metabolic alkalosis develops when SID >42 mEq/L.

The difference between SID_a and SID_e is called strong anion gap (SIG) and represents unmeasured anions like ketones, SO_4^{2-}, and urate. SIG is similar to anion gap (AG) and ranges from 0 to 2 mEq/L. A SIG value >2 mEq/L reflects metabolic acidosis resulting from the presence of more anions than cations (e.g., ketones in diabetic ketoacidosis).[2]

The Stewart method describes six acid-base disorders based on variations in the three independent variables, as shown in Table 15.1.[1,2]

Stewart's methodology is mechanistic and useful in analyzing complex acid-base disorders, especially with SIG being superior to AG in detecting anions such as ketones. Compared with the traditional physiologic approach that is far more descriptive and widely adapted, the Stewart approach requires additional measurements of multiple ions and the use of complex calculations that hinder swift bedside clinical deployment. Interpreting SID with its two formulations, SID_a and SID_e, is cumbersome, and classification of metabolic acid-base disorders is unduly complex.[3] No quantitative assessment of the secondary compensatory responses to primary changes in SID_e, [A_{TOT}], and pCO_2 is offered by the Stewart approach. This is a major drawback and can risk misdiagnosis of the secondary responses as independent, simple acid-base disorders.[3] Hence this chapter focuses on the physiologic approach with the bicarbonate-carbonic acid buffer system that remains central in assessing acid-base disorders.

NORMAL ACID-BASE HOMEOSTASIS

On a daily basis, the body's metabolic processes generate 10,000–15,000 mEq of volatile acids and 1–2 mEq/kg of fixed acids that must be buffered and excreted to maintain the pH within a narrow range of 7.35–7.45. Chemical buffers and the pulmonary and renal systems operate interdependently to regulate and maintain acid-base balance. The most important buffer is the bicarbonate-carbonic acid (HCO_3^- and H_2CO_3) system, which acts immediately to buffer the extracellular fluid. The relationship between pH, HCO_3^-, and carbon dioxide (CO_2) is described by the Henderson-Hasselbalch equation:

$$pH = 6.10 + \log\left([HCO_3^-] \div [0.03 \times PaCO_2]\right)$$

The number 6.10 represents the dissociation constant for the reaction; 0.03 represents the solubility coefficient of CO_2 in blood. PCO_2 is the partial pressure of CO_2 in the blood.[4]

TABLE 15.1 Classification of Acid-Base Disorders Based on Three Independent Variables in Stewart's Method[1,2]

Independent Variable	Acidosis	Alkalosis
1. Respiratory pCO_2	↑pCO_2	↓pCO_2
2. Metabolic: abnormal SID		
Water excess	↓SID, [↓Na^+]	
Water deficit		↑SID [↑Na^+]
Hyperchloremia	↓SID	
Hypochloremia		↑SID
Lactic acidosis or ketoacidosis Unidentified anion excess	↓SID ↑SIG ↑ [XA]	
3. Nonvolatile weak acids: [A_{TOT}]		
Serum albumin	↑ [Alb]	↓ [Alb]
Inorganic phosphate	↑ [Pi]	↓[Pi]

[Alb], Albumin concentration; *[Pi],* inorganic phosphate concentration; *pCO_2,* partial pressure of carbon dioxide; *SID,* strong ion difference; *SIG,* strong ion gap; *[XA],* concentration of unidentified strong anion.

Normal acid-base status is maintained by pulmonary excretion of volatile acids and by renal excretion of fixed acids and the formation of bicarbonate. To maintain acid-base balance, the kidney must reabsorb all of the filtered bicarbonate (about 4000 mEq/day) and excrete the fixed daily acid load. Reabsorption occurs mostly in the proximal tubule (>90%) and, to a lesser degree, in the collecting tubule. Renal excretion of acid is achieved by combining hydrogen ions (H^+) with urinary buffers to be excreted as titratable acids, such as phosphate, urate, and creatinine, or with ammonia to form ammonium.[4] The ammonia buffering system is especially important because other buffers are filtered in fixed concentrations and can be depleted by high acid loads; by contrast, tubular cells actively regulate ammonia production in response to changes in acid load.

When acid-base derangements occur, the blood pH is returned toward normal, initially by chemical buffering, followed by pulmonary ventilation, and finally by renal regulation of acid-base excretion. The $PaCO_2$ is finely regulated by changes in tidal volume and minute ventilation. A decrease in pH is sensed by arterial chemoreceptors and leads to increases in tidal volume or respiratory rate. Pulmonary regulation occurs over minutes to hours. The kidney controls pH through the regulation of H^+ excretion, bicarbonate reabsorption, and the production of new bicarbonate. Reabsorption of bicarbonate is equivalent to removing free H^+. Changes in renal acid-base handling occur hours to days after changes in acid-base status.

ACID-BASE PATHOPHYSIOLOGY

Terminology and Classification

Acid-base disorders occur when a change in the normal value of the blood pH results from abnormal renal or pulmonary function or when an acid or base load overwhelms excretory capacity. *Acidemia* refers to a decrease in the blood pH below the normal range, whereas *alkalemia* refers to an increase in the blood pH above the normal range. *Acidosis* is a process that tends to decrease the blood pH and occurs by a fall in the plasma bicarbonate concentration and/or an elevation in $PaCO_2$. In contrast, *alkalosis* is a process that tends to raise the blood pH through an elevation in the plasma bicarbonate concentration and/or a fall in $PaCO_2$. Although acidemia cannot be present without acidosis and alkalemia cannot be present without alkalosis, acidosis or alkalosis can exist at any blood pH.

The four primary acid-base disorders are classified as respiratory or metabolic. A respiratory disturbance occurs when acidosis or alkalosis results from a primary change in the $PaCO_2$. Respiratory acidosis is a disorder that elevates the $PaCO_2$ and reduces the pH; respiratory alkalosis is a disorder that reduces the $PaCO_2$ and elevates the pH. A metabolic disturbance occurs when acidosis or alkalosis results from a primary change in the plasma bicarbonate concentration. Metabolic acidosis is a disorder that reduces the plasma bicarbonate concentration and pH; metabolic alkalosis is a disorder that elevates the plasma bicarbonate concentration and pH. Compensation refers to physiologic respiratory and renal changes by which the body attempts to return the pH toward normal in response to primary acidosis or alkalosis.[4,5] Compensation does not return the pH back to a completely normal value.

A simple acid-base disorder is a single primary acid-base disorder (respiratory acidosis, respiratory alkalosis, metabolic acidosis, or metabolic acidosis) with appropriate respiratory or renal compensation for that disorder. A mixed acid-base disorder is characterized as the simultaneous presence of two or more primary acid-base disorders and is frequently encountered in intensive care unit (ICU) patients. The arterial blood pH will depend on the direction and magnitude of disturbances. Mixed acid-base disorders can be suspected from the patient's history and whenever the measured compensatory values of either bicarbonate or $PaCO_2$ differ significantly from what is expected.

COMPENSATORY RESPONSES

Disturbances in acid-base balance lead to predictable responses that serve to limit the magnitude of change of the blood pH. The expected compensatory responses to primary acid-base disturbances are listed in Table 15.2.[5,6] The magnitude of the compensatory response is proportional to the severity of the primary acid-base disturbance. The Henderson-Hasselbalch equation shows that pH is determined by the ratio of the plasma HCO_3^- concentration and $PaCO_2$, not by either value in isolation.[6] In each acid-base disorder, compensatory renal or respiratory responses act to minimize the change in pH by minimizing alterations in the ratio. Metabolic disorders result in respiratory compensation (change in $PaCO_2$); respiratory acid-base disorders result in metabolic compensation (change in HCO_3^- concentration).

In metabolic acidosis, a low plasma HCO_3^- concentration decreases the pH, stimulating medullary chemoreceptors to increase ventilation and thereby decrease $PaCO_2$ and restore the pH toward normal. In general, for metabolic acidosis, respiratory compensation results in a 1.25 mm Hg decrease in $PaCO_2$ for every 1.0 mEq/L reduction in the plasma HCO_3^- concentration down to a minimum $PaCO_2$ of 10–15 mm Hg.[6] The expected $PaCO_2$ in a simple metabolic acidosis can be calculated by the Winters formula[5]:

$$PaCO_2 = 1.5 \times (HCO_3^-) + 8 \pm 2$$

This formula may be used in patients with metabolic acidosis to evaluate whether the observed $PaCO_2$ is an appropriate compensatory response or whether there is additional respiratory acidosis ($PaCO_2$ greater than predicted) or respiratory alkalosis ($PaCO_2$ less than predicted).[5]

Respiratory compensation to metabolic alkalosis should raise the PCO_2 by about 0.6–0.75 mm Hg for every 1 mEq/L increase in the plasma bicarbonate concentration.[6–8] The expected $PaCO_2$ may be estimated by the following formula:

$$PaCO_2 = 40 + ([\text{current } HCO_3^- - 24] \times 0.7)$$

TABLE 15.2 Acid-Base Abnormalities and Appropriate Compensatory Responses for Simple Disorders

Primary Acid-Base Disorders	Primary Defect	Effect on pH	Compensatory Response	Expected Range of Compensation	Limits of Compensation
Respiratory acidosis	Alveolar hypoventilation ($\uparrow P_{CO_2}$)	↓	↑ Renal HCO_3^- reabsorption (HCO_3^- ↑)	Acute: $\Delta[HCO_3^-] = +1$ mEq/L for each ↑ ΔP_{CO_2} of 10 mm Hg	$[HCO_3^-] = 38$ mEq/L
				Chronic: $\Delta [HCO_3^-] = +4$ mEq/L for each ↑ ΔP_{CO_2} of 10 mm Hg	$[HCO_3^-] = 45$ mEq/L
Respiratory alkalosis	Alveolar hyperventilation ($\downarrow P_{CO_2}$)	↑	↓ Renal HCO_3^- reabsorption (HCO_3^- ↓)	Acute: $\Delta [HCO_3^-] = -2$ mEq/L for each ↓ ΔP_{CO_2} of 10 mm Hg	$[HCO_3^-] = 18$ mEq/L
				Chronic: $\Delta [HCO_3^-] = -5$ mEq/L for each ↓ ΔP_{CO_2} of 10 mm Hg	$[HCO_3^-] = 15$ mEq/L
Metabolic acidosis	Loss of HCO_3^- or gain of H^+ ($\downarrow HCO_3^-$)	↓	Alveolar hyperventilation to ↑ pulmonary CO_2 excretion ($\downarrow P_{CO_2}$)	$P_{CO_2} = 1.5[HCO_3^-] + 8 \pm 2$ P_{CO_2} = last 2 digits of pH × 100 $P_{CO_2} = 15 + [HCO_3^-]$	$P_{CO_2} = 15$ mm Hg
Metabolic alkalosis	Gain of HCO_3^- or loss of H^+ ($\uparrow HCO_3^-$)	↑	Alveolar hypoventilation to ↓ pulmonary CO_2 excretion ($\uparrow P_{CO_2}$)	$P_{CO_2} = +0.6$ mm Hg for $\Delta [HCO_3^-]$ of 1 mEq/L $P_{CO_2} = 15 + [HCO_3^-]$	$P_{CO_2} = 55$ mm Hg

Adapted from Bidani A, Tauzon DM, Heming TA. Regulation of whole body acid-base balance. In: DuBose TD, Hamm LL, eds. *Acid Base and Electrolytes Disorders: A Companion to Brenner and Rector's The Kidney*. Philadelphia: Saunders; 2002:1–21.

In metabolic alkalosis, a high pH induces hypoventilation with a resultant rise in $PaCO_2$ and decrease in pH. However, hypoxemia induced by progressive hypoventilation eventually activates oxygen-sensitive chemoreceptors to stimulate ventilation and generally limits the compensatory pulmonary response to a $PaCO_2$ of <55 mm Hg.[7]

METABOLIC ACIDOSIS

Metabolic acidosis occurs via increased bicarbonate loss, decreased excretion of acid, an imbalance between production and consumption of endogenous acids, or administration of exogenous acid. The clinical significance of metabolic acidosis depends on the severity of the disorder. Without appropriate intervention, metabolic acidosis can progress to life-threatening changes in cardiac, neurologic, and metabolic function, as listed in Box 15.1.[9] Metabolic acidosis can be classified as high AG metabolic acidosis or non-AG (hyperchloremic) metabolic acidosis.

Serum Anion Gap

Calculation of the serum AG is a useful tool in the evaluation of metabolic acidosis. The serum AG represents the difference in the measured cations (mainly sodium) and the measured anions (chloride and bicarbonate). Mathematically, this is represented as follows:

$$AG = Na^+ - (Cl^- + HCO_3^-)$$

Based on the law of electroneutrality, the concentration of cations should be equal to the concentration of anions in the human body. Certain cations and anions are not measured on routine laboratory chemistry panels, and the serum AG quantifies these unmeasured anions. This can be represented as follows:

$$Na^+ + \text{Unmeasured Cations (UC)}$$
$$= Cl^- + HCO_3^- + \text{Unmeasured Anions (UA)}$$

Therefore:

$$AG = Na^+ - (Cl^- + HCO_3^-) = UA - UC$$

Box 15.1 Systemic Effects of Acidosis

Neurologic
- Obtundation and coma
- Hyperactivity of sympathetic nervous system
- Decreased cerebral metabolism
- Decreased response to catecholamines

Respiratory
- Increased minute ventilation
- Subjective dyspnea
- Respiratory muscle fatigue

Cardiovascular
- Decreased contractility of myocardium
- Core vasculature blood pooling (venoconstriction and arterial dilatation)
- Decreased cardiac response to catecholamines
- Tachyarrhythmias

Metabolic
- Hyperkalemia (inorganic acidemia)
- Hyperphosphatemia
- Increased protein catabolism

Adapted in part from Whitney GM, Szerlip HM. Acid-base disorder in critical care setting. In DuBose TD, Hamm LL, eds. *Acid-Base and Electrolytes Disorders: A Companion to Brenner and Rector's The Kidney.* Philadelphia: Saunders; 2002:165–183.

Calcium, magnesium, gamma globulins, and potassium are the major "unmeasured" cations and account for approximately 11 mEq/L under normal conditions (Fig. 15.1). Although potassium is routinely measured in chemistry panels, the concentration of potassium in the blood is negligible compared with that of sodium, chloride, and bicarbonate, so potassium is not typically included as a "measured" cation in the AG equation. Negatively charged plasma proteins (albumin), sulfates, phosphates, and other organic anions are the major "unmeasured" anions and account for 20–24 mEq/L. Thus the normal AG is

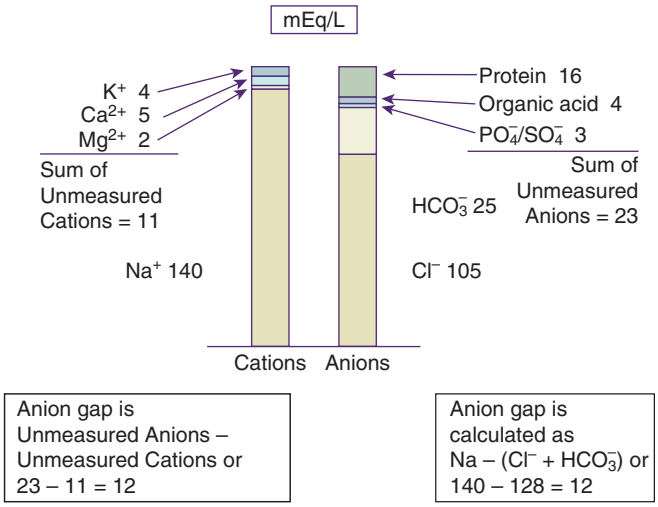


Fig. 15.1 Components of the serum anion gap.

about 12 mEq/L (23 − 11). Under normal circumstances, the serum AG is typically 12 ± 4 mEq/L but can vary depending on the laboratory method used.[10] Therefore the established normal range provided by the particular laboratory that performs the testing should be used.

The AG can be affected by increases or decreases in the UC or UA. The most important contributor to a normal serum AG is albumin, which has a negative charge at a physiologic pH. In patients with hypoalbuminemia, as commonly observed in critical illness or malnutrition, the AG must be corrected for low albumin. For each 1 g/dL fall in the plasma albumin concentration from a normal albumin concentration, the AG falls about 2.5 mEq/L.[10] This can be represented as follows:

$$\text{AG adjusted} = \text{AG} + 2.5 \times (\text{normal albumin} - \text{measured plasma albumin [g/dL]})$$

Other causes of a low or negative AG that may be important to consider for diagnostic and treatment purposes in ICU patients are listed in Table 15.3 and include hypercalcemia, hypermagnesemia, lithium intoxication, paraproteinemias such as multiple myeloma, and halide (bromide or iodide) intoxication.[11]

The contributors to serum AG in the normal physiologic state and in high AG and non-AG metabolic acidosis are depicted in Fig. 15.2.

HIGH–ANION GAP METABOLIC ACIDOSIS

High AG metabolic acidosis develops from excessive production, ingestion, or retention of a strong acid or a compound metabolized to a strong acid. These include negatively charged acids such as ketones, lactate, and sulfates, in addition to metabolites of methanol, ethylene glycol, or salicylate, which accumulate in place of the consumed HCO_3^- and cause a high AG. Other causes of an increased AG include hyperalbuminemia or uremia (increased anions) and hypocalcemia or hypomagnesemia (decreased cations)[11] (see Table 15.3).

The presence of a significantly elevated AG (AG >20 mEq/L) always represents metabolic acidosis, regardless of the pH or plasma bicarbonate concentration. In the event of a mixed acid-base disorder with a normal blood pH, a high AG points toward underlying metabolic acidosis, which otherwise may be missed. Therefore the serum AG should always be calculated when assessing acid-base disorders, especially in the ICU setting. The common causes of high AG acidosis in the ICU are lactic acidosis, ketoacidosis, toxin-induced acidosis, and renal failure (Box 15.2).

TABLE 15.3 Anion Gap in the Diagnosis of Metabolic Acidosis Anion Gap = $Na^+ - (Cl^- + HCO_3^-) = 9 + 3$ mEq/L

Decreased Anion Gap	Increased Anion Gap
Increased cations (not Na^+)	Increased anions (not Cl^- or HCO_3^-)
↑ Ca^{2+}, Mg^{2+}	↑ Albumin concentration
↑ Li^+	Alkalosis
↑ IgG	↑ Inorganic anions
Decreased anions:	Phosphate
(not Cl^- or HCO_3^-)	Sulfate
Hypoalbuminemia*	
Acidosis	↑ Organic anions
Laboratory error	L-Lactate
	D-Lactate
Hyperviscosity	Ketones
Bromism	Uremic
	↑ Exogenously supplied anions
	Toxins
	Salicylate
	Paraldehyde
	Ethylene glycol
	Methanol
	Toluene
	Pyroglutamic acid
	↑ Unidentified anions
	Uremic
	Hyperosmolar, nonketotic states
	Myoglobinuric acute renal failure
	Decreased cations (not Na^+)
	↓ Ca^{2+}, Mg^{2+}

Adapted from Emmett M, Narins RG. Clinical use of the anion gap. *Medicine.* 1997.56:38–54; Oh MS, Carroll HJ. The anion gap. *N Engl J Med.* 1977;297:814–817; Kraut JA, Madisa NE. Serum anion gap: its uses and limitations in clinical medicine. *Clin J Am Soc Nephrol.* 2007;2:162–174.

*Albumin is the major unmeasured anion. A decline in serum albumin of 1.0 g/dL from the normal value of 4.5 g/dL decreases the anion gap by 2.3–2.5 mEq/L. Correction is very important to diagnose anion gap acidosis in the setting of hypoalbuminemia.

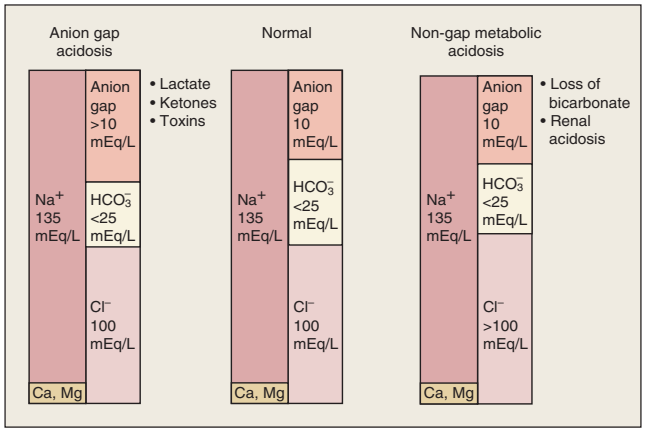


Fig. 15.2 Contributors to plasma anion gap in a normal physiologic state and in metabolic acidosis. (Data from Gamble JL. *Chemical Anatomy, Physiology, and Pathology of Extracellular Fluid.* 6th ed. Cambridge: Harvard University Press; 1954; Stewart PA. *How to Understand Acid-Base.* New York: Elsevier; 1981.)

Box 15.2 Clinical Causes of High Anion Gap and Normal Anion Gap Acidosis

High Anion Gap

Ketoacidosis

Diabetic ketoacidosis (acetoacetate)
Alcoholic (beta-hydroxybutyrate)
Starvation

Lactic Acid Acidosis (see Box 15.4)

L-Lactic acid acidosis (types A and B)
D-Lactic acid acidosis
Renal failure: sulfate, phosphate, urate, hippurate

Ingestions (Toxins and Their Metabolites)

Ethylene glycol → glycolate, oxalate
Methyl alcohol → formate
Salicylate → ketones, lactate, salicylate
Paraldehyde → organic anions
Toluene → hippurate (commonly presents with normal anion gap)
Propylene glycol → lactate
Pyroglutamic acidosis (acetaminophen use) → 5-oxoproline

Normal Anion Gap

Gastrointestinal Loss of HCO_3^- (Negative Urine Anion Gap)

Diarrhea
Fistula, external

Renal Loss of HCO_3^- or Failure to Excrete NH_4^+ (Positive Urine Anion Gap)

Proximal renal tubular acidosis (RTA type 2)
Acetazolamide
Classic distal renal tubular acidosis (low serum K^+) RTA type 1
Generalized distal renal tubular defect (high serum K^+) RTA type 4

Miscellaneous

NH_4Cl ingestion
Sulfur ingestion
Dilutional acidosis
Late stages in treatment of diabetic ketoacidosis

Adapted in part from DuBose TD Jr. Acid-base disorders. In Brenner BM, ed. *Brenner and Rector's The Kidney*. 8th ed. Philadelphia: Saunders; 2008:513–546.

LACTIC ACIDOSIS

L-Lactic Acidosis

L-lactic acidosis is among the most frequent causes of elevated AG metabolic acidosis in the ICU and is associated with a high mortality.[12,13] L-lactate refers to the L (levo) enantiomer of lactic acid and is directly measured by the standard serum lactate assay. Lactic acid concentration should be measured directly if lactic acidosis is expected because the serum AG has a sensitivity and specificity of <80% in identifying elevated lactate levels.[14] Thus a normal AG does not rule out lactic acidosis. Jansen et al. have shown that lactate levels serve as a prognosis indicator that can signal underlying deterioration, prompt more aggressive management, and help avoid unnecessary treatment when the condition stabilizes.[15] Lactic acidosis occurs whenever production of lactate exceeds its utilization. In most cases of clinically significant lactic acidosis, there is evidence of defective utilization and increased production, depending on the etiology of lactic acidosis.

Pyruvate is the precursor of lactate and is produced in the cytoplasm from glucose metabolism via glycolysis in the Embden-Meyerhof pathway. Pyruvate normally undergoes oxidative decarboxylation by mitochondrial pyruvate dehydrogenase (PDH) to acetylcoenzyme A and then ultimately to CO_2 and H_2O. This process results in the synthesis of 36 moles of adenosine triphosphate (ATP) and requires oxidized nicotinamide adenine dinucleotide (NAD^+). Pyruvate can also enter the Cori cycle in the liver and renal cortex and be converted back to glucose. Oxidative phosphorylation, ATP synthesis, and reoxidation of NADH are inhibited during hypoxia. This anaerobic metabolism leads to an increased NADH/NAD^+ ratio, increased conversion of pyruvate to lactate, and synthesis of 2 molecules of ATP, rather than the 36 generated via the tricarboxylic acid cycle. The overall result of anaerobic metabolism is increased lactate levels, an elevated lactate/pyruvate ratio, greater glucose utilization, and lower energy production.

Traditionally, lactic acidosis has been categorized as type A or type B. Type A lactic acidosis is characterized by an impaired mitochondrial oxidative capacity in the setting of tissue hypoxia, whereas type B lactic acidosis is the result of dysregulation of cell metabolism rather than hypoxia (Box 15.3). Most cases of type A lactic acidosis are the result of reduced oxygen delivery because of reduced tissue perfusion from shock or cardiopulmonary arrest. Other causes are carbon monoxide poisoning and severe anemia. Type B lactic acidosis is classified as type B1 (related to underlying diseases like malignancies or liver disease), type B2 (related to the effect of drugs and toxins), and type B3 (associated with inborn errors of metabolism).[16] The most common drugs associated with type B2 lactic acidosis include biguanides (e.g., metformin), reverse transcriptase inhibitors, acetylsalicylic acid (ASA), propofol, and linezolid, among others (see Box 15.3). Sepsis is a common cause of lactic acidosis in the ICU. Lactate level predicts increased mortality in patients with and without sepsis, even at 1 year post-hospitalization.[17] Sepsis-induced lactic acidosis has been conventionally classified as type A lactic acidosis because of inadequate oxygen supply and augmented anaerobic metabolism. However, the lack of response to increased oxygen delivery, the absence of tissue hypoxia, and normal tissue ATP levels suggest that lactate formation during sepsis may be the result of dysregulation of cellular metabolism.[18,19] Decreased clearance of lactate, rather than increased production, has been demonstrated in sepsis.[20] In addition, increased pyruvate production, decreased PDH activity, regional differences in lactate production, and decreased clearance of lactate have been implicated as possible contributors to lactic acidosis.[21–23] Decreased muscle PDH activity has been shown in sepsis, and it can be restored by dichloroacetate, suggesting that lactic acidosis during sepsis is the result of functional inhibition of PDH, leading to enhanced conversion of pyruvate to lactate.[24,25]

Treatment of lactic acidosis requires identification and correction of the underlying cause. The therapeutic goal in type A lactic acidosis is restoration of tissue oxygen delivery through hemodynamic and/or respiratory support. The use of sodium bicarbonate in lactic acidosis is controversial and not supported by clinical studies.[9] Intravenous (IV) administration of sodium bicarbonate may increase lactate production, decrease portal vein flow, decrease ionized calcium levels, lower intracellular pH, and worsen cardiac output.[9,26,27] Bicarbonate increases extracellular pH only if ventilation removes the excess CO_2 generated; otherwise, hypercapnia can lower intracellular pH and impair cellular function.[9,26,27] Bicarbonate can worsen tissue oxygen delivery if the arterial pH increases more than the intracellular pH, with a leftward shift in the oxyhemoglobin dissociation curve. If tissue hypoxia is present, the use of bicarbonate can stimulate glycolysis mediated by the pH-sensitive rate-limiting enzyme phosphofructokinase and paradoxically increase lactate production.[28] Sodium bicarbonate should be administered cautiously when the arterial pH is less

Box 15.3 Etiologies of Lactic Acidosis

L-Lactic Acidosis

Conditions Associated With Type A Lactic Acidosis

Poor tissue perfusion
Shock
Cardiogenic
Hemorrhagic
Septic
Profound hypoxemia
- Severe asthma
- Severe anemia

Carbon monoxide poisoning

Conditions Associated With Type B Lactic Acidosis

Liver disease
Diabetes mellitus
Catecholamine excess
- Endogenous
- Exogenous

Thiamine deficiency
Ketoacidosis
Seizure
Malignancy
Intracellular inorganic phosphate depletion
Intravenous (IV) fructose
IV xylose
IV sorbitol
Alcohols metabolized by alcohol dehydrogenase
- Ethanol
- Methanol
- Ethylene glycol
- Propylene glycol

Mitochondrial toxins
- Salicylate intoxication
- Cyanide poisoning
- 2,4-Dinitrophenol ingestion
- Nonnucleoside anti–reverse transcriptase drugs

Metformin
Inborn errors of metabolism
Pyroglutamic acidosis
Kombucha tea

D-Lactic Acidosis

Short bowel syndrome
Ischemic bowel
Small bowel obstruction

Adapted in part from DuBose TD Jr. Acid-base disorders. In Brenner BM, ed. *Brenner and Rector's The Kidney.* 8th ed. Philadelphia: Saunders; 2008:513–546.

than 7.15 because a pH below this value will promote the development of decreased responsiveness to catecholamines, arrhythmias, cardiac depression, and hemodynamic instability.[9]

Alternative buffering agents, such as tris-hydroxymethyl aminomethane (THAM), carbicarb, and dichloroacetate (DCA) have not shown any clinical benefit in patients with lactic acidosis. Carbicarb and DCA are unavailable in the United States.[29] THAM can bind to both CO_2 and metabolic acids. Protonated THAM is excreted by the kidney through glomerular filtration, together with bicarbonate or another anion. Thus THAM can increase the buffering capacity of blood without generating CO_2 but is less effective in patients with anuria. Reported toxicities of THAM include hyperkalemia, hypoglycemia, and respiratory depression.[9] THAM has not been specifically evaluated as a therapeutic agent for lactic acidosis in clinical trials. Carbicarb, an equimolecular mixture of sodium bicarbonate and sodium carbonate, has a buffering capacity similar to sodium bicarbonate but generates less CO_2. Animal studies have demonstrated inconsistent benefits of carbicarb in lactic acidosis, and one human study comparing the effects of sodium bicarbonate with carbicarb in metabolic acidosis found no benefit.[30,31] DCA stimulates the activity of the mitochondrial PDH enzyme complex indirectly through inhibition of the PDH kinase and hence decreases lactate production. Data from animal studies and one placebo-controlled double-blind clinical trial demonstrated that DCA improved acid-base status but not hemodynamics or survival.[28,32]

Dialysis can theoretically be used to treat lactic acidosis because it supplements bicarbonate, removes lactate, prevents decreased ionized calcium, avoids volume overload, and removes drugs associated with lactic acidosis such as metformin.[9,27] However, the same potential risks of worsening lactic acidosis with bicarbonate administration through the dialysate exist. Furthermore, in severe lactic acidosis, the quantity of lactate cleared by dialysis is much less than the quantity of lactate generated. Continuous dialysis modalities are preferred over intermittent dialysis in hemodynamically unstable patients and can deliver bicarbonate at a lower rate. Evidence supporting intermittent or continuous dialysis for treatment of lactic acidosis is anecdotal at best, and prospective controlled trials are warranted.[27]

D-Lactic Acidosis

D-lactate refers to the D (dextro) enantiomer of lactic acid. D-lactic acidosis is an uncommon form of lactic acidosis that occurs in patients with jejunoileal bypass, small bowel resection, or other causes of short bowel syndrome resulting from bacterial overgrowth. In these patients, abnormally large amounts of glucose and starch are metabolized to D-lactic acid by gram-positive intestinal anaerobes such as lactobacilli.[33,34] D-lactic acid is then absorbed into the systemic circulation and causes acidemia that tends to persist because D-lactate is not recognized by L-lactate dehydrogenase, the enzyme that converts L-lactate into pyruvate. Patients typically present with recurring episodes of metabolic acidosis after a carbohydrate meal in addition to neurologic abnormalities, including confusion, ataxia, slurred speech, and memory loss.[34] The diagnosis can be easily missed because the D-isomer responsible for the acidosis is not detected by the standard assay for lactate and requires a special assay for detection. Therapy for D-lactic acidosis includes administration of sodium bicarbonate to correct the acidosis, oral antibiotics to decrease gram-positive anaerobic colonic bacteria, and a low-carbohydrate diet to reduce carbohydrate delivery to the colon.[35] D-lactic acidosis has also been described in patients who have large amounts of propylene glycol and in those with diabetic ketoacidosis (DKA).[36,37]

KETOACIDOSIS

Ketoacidosis is a common complication in patients with insulin-dependent diabetes mellitus but can also be seen in chronic alcoholism and starvation (see Box 15.2). It results from the overproduction of ketone bodies, leading to accumulation of ketones in the plasma (ketonemia) and urine (ketonuria).

Diabetic Ketoacidosis

DKA occurs in patients with insulin-dependent diabetes mellitus and results from severe insulin deficiency in the setting of increased

metabolic demand, such as from a concurrent infection or myocardial infarction. It can also occur from poor compliance with insulin or missed injections. Insulin deficiency results in decreased glucose uptake, glycogen store depletion, lipolysis, and fatty acid oxidation leading to increased ketoacid production (acetoacetate and beta-hydroxybutyrate). Symptoms can progress from polydipsia, polyuria, nausea, vomiting, dyspnea, and diffuse abdominal pain to confusion, lethargy, and somnolence. Laboratory findings include hyperglycemia, increased serum AG, ketonemia, ketonuria, and increased plasma osmolality. The diagnosis is established by measuring plasma and urine ketone levels. However, clinicians must be aware that the nitroprusside reaction used in standard plasma and urine tests only measures acetone and acetoacetate levels and not beta-hydroxybutyrate levels, which is the predominant ketone in severe untreated DKA. Therefore laboratory analysis for ketones may be falsely negative. High plasma glucose levels can cause dilutional hyponatremia because the osmotic effect of hyperglycemia causes the movement of water into the intravascular space. For each 100 mg/dL of glucose over 100 mg/dL, the plasma sodium level is lowered by approximately 1.6 mEq/L. In spite of severely depleted total body potassium from osmotic diuresis, plasma potassium levels are initially elevated or within the normal range from insulin deficiency.[4,38]

The major goals of treatment are rapid volume expansion, correction of hyperglycemia, correction of acid-base and electrolyte disturbances, and identification and treatment of the precipitating cause. Adults should initially receive a rapid infusion of 1 L of isotonic saline with repeat boluses as necessary to prevent hemodynamic collapse. When the blood pressure and heart rate have stabilized and the patient is euvolemic, isotonic saline can be switched to 0.45% saline at a slower rate to replace the free water lost by osmotic diuresis. Insulin is typically administered as a 10- to 20-unit IV bolus (0.15 units/kg) followed by an infusion of 5–7 units/hour (0.1 unit/kg/hour). Insulin inhibits lipolysis and gluconeogenesis and allows for the conversion of ketones to bicarbonate. If the blood sugar falls below 250 mg/dL, the rate of insulin should be decreased to 0.03 u/kg/hour and 5%–10% dextrose should be added to the fluids. Once the AG normalizes, subcutaneous insulin should be administered while the insulin infusion is continued for another 1–2 hours. Potassium replacement should be administered at 10–20 mEq/hour if the plasma potassium level is less than 5.3 mEq/L and if renal failure is not present. Plasma potassium levels should be measured frequently, and the infusion should be stopped if hyperkalemia occurs. Small amounts of IV sodium bicarbonate should only be administered if the arterial pH is less than 6.9, with frequent monitoring of pH and serum AG. IV phosphate replacement can be given if the initial level is less than 1.0 mg/dL. Plasma phosphorus levels can be high initially because of the transcellular shift of phosphate out of the cell in the setting of acidosis and insulin deficiency.[38,39]

Hemodialysis-dependent patients with DKA are managed differently. Insulin administration is frequently the only treatment needed for DKA management in these patients. Anuric dialysis patients usually present with signs of extracellular volume (ECV) expansion rather than volume depletion because osmotic diuresis cannot occur in the absence of kidney function. Therefore dialysis patients do not require IV fluids unless they have evidence of extracellular fluid loss such as vomiting, diarrhea, or excessive insensible losses. If volume depletion is present, small amounts of isotonic saline should be carefully administered with close monitoring of respiratory and hemodynamic parameters. When volume overload is apparent, immediate hemodialysis is the therapy of choice. Hemodialysis will also help correct hyperglycemia resulting from diffusive clearance of glucose but must be performed in conjunction with insulin administration, as insulin is the only therapy that will halt lipolysis and gluconeogenesis. Dialysis-dependent patients with DKA should not receive routine potassium supplementation because total body potassium stores may be high and patients are unable to excrete a potassium load. Urgent dialysis is indicated if hyperkalemia is present with electrocardiographic findings. Similarly, significant metabolic acidosis can only be corrected with hemodialysis.[39,40]

Euglycemic DKA is an emerging entity that has been recognized in patients with both type 1 and type 2 diabetes mellitus who present with increased AG acidosis, ketosis, and relatively normal serum glucose <200 mg/dL.[41] The pathophysiology is thought to be related to decreased hepatic gluconeogenesis during fasting or enhanced urinary excretion of glucose. Common causes of euglycemic DKA include SGLT2 inhibitors, pregnancy, glycogen storage diseases, and chronic liver disease. Less common causes include pancreatitis, alcohol use, cocaine intoxication, gastroparesis, and Duchenne muscular dystrophy.[41]

Alcoholic Ketoacidosis

Alcoholic ketoacidosis (AKA) occurs in the setting of chronic alcoholism, recent binge drinking, minimal oral intake, and persistent vomiting. It is characterized by elevated plasma ketone levels, high AG, and normal or only slightly elevated plasma glucose level. Prolonged starvation results in decreased insulin activity, glycogen depletion, increased counterregulatory hormone production, dehydration, and increased lipolysis and fatty acid oxidation with accumulation of ketoacids. The metabolism of ethanol itself promotes ketoacidosis by leading to an accumulation in reduced NADH. Reduced NADH then results in impaired conversion of lactate to pyruvate, preferential conversion of pyruvate to lactate, and a shift toward beta-hydroxybutyrate production. Beta-hydroxybutyrate is the predominant ketone in AKA. As mentioned, the standard nitroprusside test for detecting ketones only detects acetoacetate and may be falsely negative or only minimally positive in AKA, leading to an underestimation of the degree of ketoacidosis.[42,43]

Patients with AKA frequently present with a mixed acid-base disturbance. They can have elevated AG metabolic acidosis from ketoacidosis and lactate, metabolic alkalosis from persistent vomiting, and chronic respiratory alkalosis from liver disease. Magnesium and phosphate levels may be low because of increased urinary excretion and poor nutrition.

The mainstay of treatment is hydration with 5% dextrose in isotonic saline. Before glucose administration, thiamine should be given to avoid precipitating Wernicke encephalopathy. Carbohydrate and fluid replacement reverse the pathophysiologic derangements that lead to AKA by increasing plasma insulin levels and suppressing the release of glucagon and other counterregulatory hormones. Dextrose stimulates the oxidation of NADH and aids in normalizing the $NADH/NAD^+$ ratio. Insulin should be avoided because it can lead to hypoglycemia, especially as the patient's endogenous insulin levels rise with carbohydrate and fluid repletion. Bicarbonate is only recommended if the plasma pH is less than 7.1 and the acidosis is not responding to IV fluids. Hypophosphatemia, hypokalemia, and hypomagnesemia should be corrected. Glucose infusion can exacerbate hypophosphatemia, resulting in rhabdomyolysis if not repleted.[44]

Starvation Ketoacidosis

Starvation, as mentioned earlier, results in ketoacidosis because of the increase in counterregulatory hormones and a decrease in insulin level, promoting fatty acid oxidation, gluconeogenesis, and ketone production. However, in comparison to the potentially severe ketoacidosis

that develops in uncontrolled diabetes and alcoholic states, ketoacid levels do not typically exceed 10 mEq/L with fasting. This is probably because of the insulin level, which, though lower, is still enough to limit the production of free fatty acids and thus ketoacidosis[45,46] (see Boxes 15.2 and 15.3).

TOXIC ALCOHOL INGESTIONS

Accumulation of the metabolites of methanol—ethylene glycol, diethylene glycol, and propylene glycol—causes a high AG and increased plasma osmolal gap. Intoxication should be suspected in any patient who presents with high AG metabolic acidosis, renal failure, and neurologic findings, and treatment should be initiated early.

The normal range of plasma osmolality is 285–290 mOsm/kg. Plasma osmolality (Posm) can be estimated from the following formula:

$$\text{Calculated Posm} = (2 \times \text{plasma [Na]}) + (\text{glucose mg/dL})/18 + (\text{BUN mg/dL})/2.8$$

The plasma osmolal gap represents the difference between the measured and calculated plasma osmolality. A difference of higher than 10 mOsm/kg is considered an osmolal gap. Accumulation of the noted alcohols will typically produce an osmolal gap of higher than 20 mOsm/kg. Methanol gives rise to the greatest increment in plasma osmolality, followed by ethylene glycol, propylene glycol, and finally diethylene glycol.[47] The absence of an osmolal gap does not exclude an alcohol-related intoxication. Furthermore, although the plasma osmolal gap may support the diagnosis of ingestion of a toxic alcohol, plasma toxicology screens specifically looking for the toxins are considered the gold standard.

Other causes of high AG metabolic acidosis that can be associated with an elevated plasma osmolal gap include lactic acidosis, ketoacidosis, advanced chronic kidney disease (CKD), formaldehyde ingestion, and paraldehyde ingestion. The plasma osmolal gap is usually less pronounced in these disorders (≤15–20 mOsm/kg), and plasma toxicology is not typically performed. Substances that can cause an osmolal gap without metabolic acidosis are ethanol, isopropyl alcohol ingestion, infusion of nonconductive glycine, sorbitol or mannitol solutions, severe hyperproteinemia, and severe hyperlipidemia.[47]

Methanol, used as a laboratory and industrial solvent, is commonly found in windshield wiper fluid, de-icing products, gas-line antifreeze, and various paint solvents and thinners. It is metabolized by alcohol dehydrogenase (ADH) to formaldehyde, which is further metabolized by aldehyde dehydrogenase (ALDH) to formic acid. The most common symptoms of methanol intoxication are abdominal pain and visual disturbances, including decreased visual acuity, photophobia, and blurred vision. Formic acid is the main toxic metabolite responsible for retinal, ophthalmic, and neural toxicity. Permanent blindness may occur because of optic nerve atrophy. High AG metabolic acidosis is the result of generation of formic acid and increased production of lactic acid. Lactic acidosis results from impaired cellular respiration by formate or increased generation of NADH during the metabolism of methanol.[47,48] Imaging findings in acute methanol intoxication include bilateral necrosis of the putamen, diffuse white matter necrosis, and subarachnoid hemorrhage on brain computed tomography (CT) and magnetic resonance imaging (MRI).[49]

Ethylene glycol is typically found in radiator antifreeze in addition to various solvents and paint formulations. It is metabolized by ADH to glycolaldehyde, then to glycolic acid by ALDH, which is further metabolized to glyoxylic acid and finally oxalic acid. The metabolites are responsible for neurologic, cardiopulmonary, and renal toxicity. Typically, neurologic abnormalities occur initially, followed by cardiopulmonary dysfunction, and finally renal dysfunction. Neurologic findings include coma, seizures, meningeal signs, external ocular paralysis, and delayed onset of cranial nerve deficits. Cardiopulmonary findings include tachycardia, hyperventilation, and heart failure. Oxalic acid combines with plasma calcium to form calcium oxalate, which leads to hypocalcemia, QTc prolongation, and risk of ventricular arrhythmias. Calcium oxalate crystals precipitate in the renal tubules, causing flank pain, oliguria, and renal failure. Calcium oxalate crystals are present in the urine 4–8 hours after ingestion of ethylene glycol and can be visualized by direct urine microscopy. High AG metabolic acidosis is the result of generation of glycolic, glyoxylic, and oxalic acids and increased production of lactic acid. Measurement of plasma ethylene glycol levels can confirm poisoning.[47,48]

Methanol and ethylene glycol poisoning are treated with fomepizole or ethanol, which inhibits ADH and prevents the formation of toxic metabolites. Fomepizole (15 mg/kg loading dose, then 10 mg/kg every 12 hours) is preferred over ethanol because of its easier dosing regimen and better side-effect profile. The indications for antidotal therapy are a plasma concentration of methanol or ethylene glycol higher than 20 mg/dL and two of the following: osmolal gap higher than 10 mOsm/kg, arterial pH lower than 7.3, plasma bicarbonate level lower than 20 mEq/L, and the presence of urinary oxalate crystals. Indications for hemodialysis are severe metabolic acidosis (pH <7.25), visual abnormalities, renal failure, electrolyte abnormalities not responsive to treatment, hemodynamic instability despite ICU treatment, and plasma concentration higher than 50 mg/dL. In ethylene glycol toxicity, pyridoxine and thiamine are administered to increase the metabolism of glycolic and glyoxylic acid to the less-toxic metabolites glycine and alpha-hydroxy-beta-ketoadipate. In methanol toxicity, folic acid or folinic acid increases the breakdown of formic acid to CO_2 and water.[47,48]

Diethylene glycol is present in brake fluid and is used as an illegal adulterant in ethanol spirits or in medication. Diethylene glycol is oxidized by ADH to 2-hydroxyethoxyacetaldehyde and then via ALDH to 2-hydroxyethoxyacetic acid. Acute oliguric and nonoliguric renal failure are frequent. Treatment consists of hemodialysis and fomepizole.[47]

Propylene glycol is a solvent for unstable drugs, including benzodiazepines, phenytoin, nitroglycerin, and some topical medications. The majority of intoxications have resulted from excessively large or rapidly infused IV injections of propylene glycol–containing medications such as benzodiazepines. Neurologic depression is the primary manifestation of acute propylene glycol poisoning. Metabolic acidosis is attributed to the generation of lactic acid during metabolism of propylene glycol. Discontinuation of propylene glycol–containing medication can lead to correction of the acidosis within 24 hours in most patients. In the face of extremely high blood concentrations, hemodialysis is extremely effective in rapidly reducing plasma propylene glycol levels.[47]

Use of isopropyl alcohol is the most common cause of toxic alcohol exposure in the United States; it is found in rubbing alcohol, hand sanitizer gels, and other antiseptic preparations. It is metabolized by ADH to acetone, without production of AG acidosis. Toxicity is mainly limited to gastrointestinal (GI) effects, such as hemorrhagic gastritis and neurologic depression. Isopropyl alcohol is the only toxic alcohol that causes ketosis without acidosis. In comparison to other toxic alcohols, isopropyl alcohol intoxication is usually managed supportively. Hemodialysis may increase the rate of elimination of both isopropyl alcohol and acetone and should be considered for patients with deteriorating mental status or hemodynamic instability.[47]

SALICYLATES

Salicylate toxicity may develop with either acute or chronic exposure to salicylates. Acute and chronic salicylate toxicity is associated with a high mortality if not recognized early and treated. Salicylates are found in over-the-counter medications such as aspirin, bismuth subsalicylate, effervescent antacids, ointments, liniments, and oil of wintergreen (methyl salicylate) and in numerous prescription medications. Patients with salicylate toxicity may present with neurologic symptoms (cerebral edema, coma, agitation, tinnitus, or seizures), pulmonary symptoms (hyperventilation/tachypnea or acute lung injury), and GI symptoms (nausea or vomiting). Nausea, vomiting, diaphoresis, and tinnitus are the earliest signs and symptoms of salicylate toxicity. Salicylates stimulate the respiratory center, leading to hyperventilation and respiratory alkalosis. They also uncouple oxidative phosphorylation and interfere with the Krebs cycle, leading to increased lactate production, ketosis, and high AG metabolic acidosis. Interference with aerobic respiration also causes hypoglycemia, fever, and fluid loss. Adult patients with acute poisoning usually present with mixed respiratory alkalosis and metabolic acidosis but can also present with primary respiratory alkalosis. In children, respiratory alkalosis may be transient, with metabolic acidosis occurring early in the course.[50]

The therapeutic range of salicylates is 10–30 mg/dL. Patients become symptomatic at concentrations higher than 40 mg/dL. Levels higher than 90–100 mg/dL usually have serious or life-threatening toxicity. In overdoses, the peak plasma concentration may not occur for 4–6 hours. Laboratory tests should be repeated every 4–6 hours until the level falls into the nontoxic range. Renal excretion of salicylic acid depends on urinary pH. Increasing the urine pH to 7.5 prevents reabsorption of salicylic acid from the urine. Because acidosis facilitates transfer of salicylate into tissues, especially in the brain, it must be treated aggressively by raising the blood pH higher than the brain pH, thereby shifting the equilibrium from the tissues to the plasma. Alkalinization with IV sodium bicarbonate is the mainstay of treatment in patients whose plasma pH is not already elevated (>7.5), and care should be taken not to raise plasma pH to inappropriately high levels (>7.55). Hypokalemia occurs commonly in salicylate-poisoned patients and prevents urinary excretion of salicylate unless corrected. Because intoxication can decrease cerebral glucose concentrations despite normal plasma glucose concentrations, adults who are hypoglycemic or have altered mental status, regardless of their plasma glucose concentration, should be treated with supplemental glucose. Indications for hemodialysis include a plasma level higher than 120 mg/dL (acutely) or higher than 100 mg/dL (6 hours post-ingestion), refractory acidosis, coma or seizures, noncardiogenic pulmonary edema, volume overload, and renal failure. In chronic overdose, hemodialysis may be required for a symptomatic patient with a plasma salicylate level higher than 60 mg/dL.[50,51]

PYROGLUTAMIC ACIDOSIS

Accumulation of 5-oxoproline (pyroglutamic acid), an organic acid intermediate of the gamma-glutamyl cycles, is a rare, but underdiagnosed, cause of severe, high AG metabolic acidosis in adults. The acidemia associated with pyroglutamic acid usually occurs in association with acetaminophen therapy and in the setting of severe sepsis, liver dysfunction, or renal dysfunction. Heterozygosity for glutathione synthase deficiency may also be an underlying risk factor for development. The etiology appears to be a drug-induced reversible inhibition of either glutathione synthetase or 5-oxoprolinase. Diagnosis is made by measuring urinary 5-oxoproline levels to demonstrate the presence of pyroglutamic acid. Treatment with methionine or *N*-acetylcysteine to replenish glutathione should be considered.[52–55]

RENAL FAILURE

Early CKD is associated with hyperchloremic normal AG metabolic acidosis, and advanced CKD is associated with elevated AG metabolic acidosis. In early CKD, acid excretion is initially maintained by increased ammonium excretion. When the GFR falls below 40–50 mL/min, tubular function decreases, leading to retention of H^+, an increase in the amount of bicarbonate excreted, and metabolic acidosis. To maintain electroneutrality, the kidneys retain chloride with each bicarbonate ion lost, causing hyperchloremic metabolic acidosis. Because glomerular function decreases at a much slower rate than the loss of tubular function, the excretion of sulfate and other organic and inorganic acid anions is not affected, as their filtration by the kidney is maintained. The AG remains in normal range because of the continued excretion of organic acids by the kidneys. In advanced CKD, when the GFR falls below 20 mL/min, the capacity of the kidneys to filter the anions of organic acids is significantly diminished, causing retention of phosphates, sulfates, urate, and hippurate anions in the plasma and development of elevated AG metabolic acidosis.[56,57]

Clinical consequences of chronic metabolic acidosis in CKD include osteopenia, worsening secondary hyperparathyroidism, CKD progression, and increased mortality. Recent clinical trials have suggested that correction or prevention of metabolic acidosis by alkali administration is able to slow the progression of CKD. As a result, to prevent CKD progression and bone loss, sodium bicarbonate supplementation (0.5–1 mEq/kg/day) is recommended for patients with CKD with plasma bicarbonate concentrations lower than 22 mEq/L.[57,58]

NON–ANION GAP (HYPERCHLOREMIC) METABOLIC ACIDOSIS

Normal or non-AG metabolic acidosis is also called *hyperchloremic metabolic acidosis* because the kidneys reabsorb chloride instead of bicarbonate, yielding no net change in the serum AG. Hyperchloremic metabolic acidosis may result from impaired renal acid excretion, increased renal or GI bicarbonate loss, H^+ gain, marked urinary excretion of organic acid anions with replacement with chloride, or administration of chloride-rich solutions during resuscitation (Box 15.4). In impaired renal acid excretion, the absence of sufficient ammonium excretion results in the acid anions being excreted with sodium and potassium. This results in a sodium deficit and avid renal retention of filtered sodium and chloride. The retained chloride replaces the lost bicarbonate. GI or urinary bicarbonate loss leads to a sodium deficit and a reduction in extracellular fluid volume. This stimulates renal retention of sodium and chloride, thereby replacing the lost bicarbonate by the retained chloride.[59]

URINARY ANION GAP

In assessing the cause of hyperchloremic metabolic acidosis, the urine AG (UAG) may be useful in differentiating renal causes from GI causes. The UAG is calculated as the difference between the measured urine cations (Na^+ and K^+) and urine Cl^-:

$$UAG = (Na^+) + (K^+) - (Cl^-)$$

In diarrhea and other nonrenal causes of hyperchloremic acidosis, the kidney should attempt to compensate by increasing net acid excretion. The major mechanism for this increase is a marked increase in urinary ammonium excretion. Because urinary ammonium measurements are not readily available, the UAG serves as a surrogate. Under normal circumstances, the sum of the excreted urine sodium and urine

Box 15.4 Differential Diagnosis of Hyperchloremic Metabolic Acidosis

Gastrointestinal Bicarbonate Loss
Diarrhea
External pancreatic or small bowel drainage
Ureterosigmoidostomy, jejunal loop

Drugs
Calcium chloride (acidifying agent)
Magnesium sulfate (diarrhea)
Cholestyramine (bile acid diarrhea)

Renal Acidosis
Hypokalemic
Proximal renal tubular acidosis (RTA) (type 2) (see Box 15.5)
Distal (classic) RTA (type 1)

Drug-Induced Hypokalemia
Acetazolamide (proximal RTA)
Amphotericin B (distal RTA)

Hyperkalemic
Generalized distal nephron dysfunction (type 4 RTA) (see Box 15.5)
Mineralocorticoid deficiency or resistance (pseudohypoaldosteronism type 1)
PHA-I, PHA-II
↓ Na^+ delivery to distal nephron
Tubulointerstitial disease
Ammonium excretion defect

Drug-Induced Hyperkalemia
Potassium-sparing diuretics (amiloride, triamterene, spironolactone)
Trimethoprim
Pentamidine
Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers
Nonsteroidal antiinflammatory drugs
Cyclosporine, tacrolimus

Normocalcemic
Early renal insufficiency

Other
Acid loads (ammonium chloride, hyperalimentation)
Loss of potential bicarbonate: ketosis with ketone excretion
Dilution acidosis (rapid saline administration)
Hippurate
Cation-exchange resins

Adapted in part from DuBose TD Jr. Acid-base disorders. In Brenner BM, ed. *Brenner and Rector's The Kidney*. 8th ed. Philadelphia: Saunders; 2008:513–546.

potassium is greater than the amount of excreted urine chloride and the UAG is positive. In patients with normal AG metabolic acidosis, the excretion of ammonium occurs with chloride, increasing the urine chloride concentration. In such settings, urine chloride usually exceeds the sum of urine sodium and urine potassium, resulting in a negative UAG; the UAG will be negative when ammonium is present and balanced by negatively charged urinary chloride. A negative UAG is consistent with increased ammonium excretion and occurs in patients who develop metabolic acidosis as a result of diarrhea. If little ammonium is present, the UAG will be zero or positive, similar to that in patients who have hyperchloremic metabolic acidosis associated with impaired ammonium excretion, as seen in renal tubular acidosis (RTA).

There are several limitations to the UAG. The UAG cannot be interpreted accurately in the setting of increased urinary excretion of unmeasured anions. Unmeasured anions may be excreted with sodium or potassium or with ammonium. Examples of unmeasured urinary anions include ketoacids, hippurate, D-lactate, and 5-oxoproline. As a result, the excretion of ammonium with these unmeasured anions will not reduce the UAG, which occurs when ammonium is excreted with chloride. In addition, the excretion of sodium or potassium with unmeasured anions leads to a positive UAG.[60] The UAG also cannot be interpreted in volume-depleted states with urine sodium levels less than 25 mEq/L because of impaired distal sodium delivery.[61]

The urine osmolal gap (UOG) can overcome some of the limitations of the UAG.[59,60] The UOG indirectly assesses urine ammonium concentration by comparing the difference of directly measured urine osmolality to the calculated urine osmolality. The formula for calculating urine osmolality is as follows:

$$\begin{aligned}&\text{Calculated urine osmolality (mOsm/kg)}\\&=(2\times[\text{Na}+\text{K}])+(\text{urea nitrogen in mg/dL})/2.8\\&\quad+(\text{glucose in mg/dL})/18\end{aligned}$$

Besides sodium, potassium, urea, and glucose (if present in the urine), the major urinary solute that contributes to urine osmolality is ammonium. Most of the UOG is therefore made up of ammonium in the form of ammonium chloride in addition to ammonium excreted with other unmeasured anions. Thus the UOG detects ammonium excretion regardless of the anion that is excreted along with it. The UOG must be divided by 2 in order to account for the anion being excreted with ammonium. In the setting of metabolic acidosis, urine ammonium levels should be higher than 200 mEq/L. An ammonium urine concentration of less than 75 mEq/L in a patient with metabolic acidosis indicates impaired renal ammonium excretion and correlates with a UOG of less than 150 mOsm/kg. In the setting of hyperchloremic metabolic acidosis from GI causes such as diarrhea, the UOG should be higher than 400 mOsm/kg.[59,60]

RENAL TUBULAR ACIDOSIS

RTA is characterized by impaired urinary acidification, resulting in retention of H^+, reduction in plasma bicarbonate levels, and hyperchloremic non-AG metabolic acidosis. RTA can be classified as proximal (type 2), distal (type 1), and hyperkalemic (type 4). The UAG is usually positive in RTA because of an inability to excrete H^+. Proximal (type 2) and distal (type 1) RTA are uncommon disorders (see Boxes 15.4 and 15.5).

Proximal Renal Tubular Acidosis (Type 2)

Proximal RTA is characterized by impaired proximal bicarbonate reabsorption with a lowered threshold for bicarbonate reclamation. This results in renal bicarbonate wasting whenever the bicarbonate concentration exceeds this lowered threshold. Below this threshold, bicarbonate is conserved and maximal urinary acidification (urine pH <5.5) occurs. Bicarbonate loss in the urine leads to increased H^+ concentration in the blood and a subsequent reduction in the arterial pH. Because of impaired proximal bicarbonate reabsorption, the distal nephrons become overwhelmed by an increase in bicarbonate delivery and cannot compensate for the loss in proximal function. However, as the plasma bicarbonate level decreases to 15–18 mEq/L, the amount of filtered bicarbonate decreases with reduced delivery of bicarbonate to the distal nephrons. At that point, the distal nephrons are able to function, leading to a reduction in bicarbonate loss and appropriate

Box 15.5 List of Select Disorders Associated With Renal Tubular Acidosis*

Renal Defect in Net Acid Excretion, Classic Distal Renal Tubular Acidosis (Type 1 RTA)

Systemic or Tubulointerstitial Disease

Medullary sponge kidney
Cryoglobulinemia
Balkan nephropathy
Nephrocalcinosis
Chronic pyelonephritis
HIV nephropathy
Renal transplant
Sjögren syndrome
Thyroiditis
Hyperparathyroidism

Drug or Toxin Induced

Ifosfamide
Amphotericin B
Foscarnet
Toluene
Mercury
Classic analgesic nephropathy

Renal Defect in HCO_3^- Reclamation, Proximal Renal Tubular Acidosis (Type 2 RTA)

Selective (Unassociated With Fanconi Syndrome)

Idiopathic

Carbonic anhydrase deficiency or inhibition
Drugs such as acetazolamide
Carbonic anhydrase II deficiency with osteopetrosis (Sly syndrome)

Generalized (Associated With Fanconi Syndrome)

Primary: inherited or sporadic
Genetically transmitted systemic diseases: cystinosis, Lowe syndrome, Wilson syndrome

Dysproteinemic States

Multiple myeloma
Monoclonal gammopathy

Secondary Hyperparathyroidism With Chronic Hypocalcemia

Vitamin D deficiency or resistance
Vitamin D dependency

Drugs or Toxins

Ifosfamide
Lead
Outdated tetracycline
Streptozotocin
Mercury
Amphotericin B (historic)

Tubulointerstitial Diseases

Sjögren syndrome
Medullary cystic disease
Renal transplantation

Generalized Defect of the Distal Nephron With Hyperkalemia (Type 4 RTA)

Mineralocorticoid Deficiency

Primary Aldosterone Deficiency

Adrenal disease (hemorrhage, destruction, infarction)
Heparin (low-molecular-weight [MW] or unfractionated)
Persistent hypotension in critically ill patient
Renin–angiotensin system modulating agents (angiotensin-converting enzyme inhibitor [ACEI], angiotensin receptor blocker [ARB])

Secondary Aldosterone Deficiency (Hyporeninemic Hypoaldosteronism)

Diabetic nephropathy
HIV disease
Tubulointerstitial nephropathy
NSAID use

Renal Tubular Dysfunction (Voltage Defect)

Drugs That Interfere With Sodium Channel or Na^+/K^+-ATPase

Amiloride
Pentamidine
Triamterene
Trimethoprim
Cyclosporine
Tacrolimus

Disorders Associated With Tubulointerstitial Disease

Renal failure
Lupus nephritis
Obstructive uropathy
Renal transplant rejection
Sickle cell disease

Adapted in part from DuBose TD Jr. Acid-base disorders. In Brenner BM, ed. *Brenner and Rector's The Kidney*. 8th ed. Philadelphia: Saunders; 2008:513–546.

* See source for complete list of disorders.

acidification of the urine to a pH less than 5.5. These patients also have hyperaldosteronism from salt wasting because of the defect in proximal reabsorption of filtered bicarbonate. Because of hyperaldosteronism, urinary potassium wasting and hypokalemia are common.[59,62]

Proximal RTA is suggested by a modestly low plasma bicarbonate level of 15–18 mEq/L with appropriate urinary acidification (urinary pH <5.5). This can be confirmed by measurement of the urine pH and fractional bicarbonate excretion during bicarbonate infusion, but this is not often done in practice. IV sodium bicarbonate is infused at a rate of 0.5–1.0 mEq/kg/hour to increase the plasma bicarbonate concentration toward normal (18–20 mEq/L). The urine pH, even if initially acidic, will rise rapidly once the reabsorptive threshold for bicarbonate is exceeded. As a result, the urine pH will increase to higher than 7.5 and the fractional excretion of bicarbonate will exceed 15%.[59,62]

In adults, proximal RTA is typically secondary to acquired proximal tubular damage such as heavy metal exposure and multiple myeloma,

whereas in children, it is associated with metabolic defects (see Box 15.5). Proximal RTA is often accompanied by other proximal tubular transport defects, including renal glycosuria, phosphate wasting, aminoaciduria, and hypouricemia (Fanconi syndrome). Medications such as carbonic anhydrase inhibitors (e.g., acetazolamide) and topiramate can cause proximal RTA by impairing proximal bicarbonate reabsorption without affecting the reabsorption of other proximal tubule solutes. The drugs tenofovir and ifosfamide can cause Fanconi syndrome.[59]

Complications include bone disease because of an increase in bone buffering of excess acid and acquired vitamin D deficiency from decreased calcitriol production. Defects in proximal transport may also result in phosphate wasting and hypophosphatemia, leading to rickets in children and osteomalacia or osteopenia in adults.[59,62]

Standard treatment is with oral alkali therapy. Because exogenous alkali is rapidly excreted in the urine, considerably higher doses of alkali are required compared with distal and type 4 RTA. About 10–15 mEq/kg/day of alkali is typically required to stay ahead of urinary excretion. Potassium citrate is the preferred form of alkali to ameliorate potassium losses. Thiazides are also sometimes used in conjunction with a low-salt diet to reduce the amount of alkali required. Thiazides induce volume contraction and enhance proximal bicarbonate reabsorption.[62]

Classic Distal Renal Tubular Acidosis (Type 1)

Classic distal RTA results from defective H^+ secretion in the distal tubule. Impaired H^+ secretion results in an inability to acidify the urine pH beyond 5.5 and reduced net acid excretion. The plasma bicarbonate may fall below 15 mEq/L. Hypokalemia occurs as a result of urinary potassium wasting from increased potassium secretion by distal tubular cells in the setting of diminished H^+ secretion. Hypercalciuria, alkaline urine, and low urinary citrate levels promote the precipitation of calcium phosphate stones and nephrocalcinosis. A diagnosis is made by the findings of hypokalemia, normal AG metabolic acidosis, inappropriately high urine pH (>5.5) regardless of the plasma bicarbonate concentration, and a positive UAG.[62]

The most common causes in adults are autoimmune disorders such as Sjögren syndrome. In children, RTA is most often a primary hereditary condition (see Box 15.5). Drugs such as ifosfamide and amphotericin cause distal RTA in adults and children. As in proximal RTA, complications include failure to thrive, rickets, and stunting of growth in children and osteomalacia or osteopenia in adults. Patients may otherwise be asymptomatic or may present with symptoms of severe acidosis or hypokalemia.[60]

Adults are generally treated with oral sodium bicarbonate or sodium citrate 1–2 mEq/kg/day. Patients with significant hypokalemia, nephrolithiasis, or nephrocalcinosis are treated with potassium citrate or Polycitra (potassium citrate plus sodium citrate).

Hyperkalemic Distal Renal Tubular Acidosis (Type 4)

Hyperkalemic distal RTA is characterized by hyperkalemia and hyperchloremic metabolic acidosis. It can occur in the setting of aldosterone deficiency or resistance or result from a voltage-dependent defect in H^+ secretion. In aldosterone deficiency or resistance, hyperkalemia is the primary disturbance, suppressing proximal tubular ammonium production and producing metabolic acidosis.[4] Urinary acidification is intact. The metabolic acidosis seen is generally mild, with the plasma bicarbonate level usually higher than 15 mEq/L. Despite impaired distal H^+ secretion, the urine pH is generally below 5.5. The ability to acidify the urine in this condition is the result of the inadequate amount of ammonia available for buffering of protons because the urinary pH falls in the absence of buffers. The findings of hyperkalemic, normal AG metabolic acidosis with an appropriately low urine pH (<5.5) and positive UAG confirm the diagnosis. The diagnosis is further supported by a bicarbonate fractional excretion of higher than 10% in the setting of bicarbonate infusion.[62]

Hyporeninemic hypoaldosteronism is the most common cause of type 4 RTA in patients with mild to moderate renal insufficiency resulting from diabetic nephropathy (see Box 15.5). Many drugs can cause type 4 RTA by affecting renin release, aldosterone production, or tubular potassium excretory capacity. Nonsteroidal antiinflammatory drugs (NSAIDs) inhibit renin release. Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), calcineurin inhibitors, and heparin can all reduce aldosterone production. Inhibitors of tubular potassium excretion include spironolactone, eplerenone, triamterene, and amiloride. The tubulointerstitial diseases commonly associated with type 4 RTA include sickle cell disease and obstructive nephropathy.[4,62]

Hyperkalemia from aldosterone deficiency or resistance can be diagnosed by measuring the transtubular potassium gradient (TTKG)[63]:

$$\text{TTKG} = (\text{urine } K^+ \times \text{plasma osmolality}) / (\text{plasma } K^+ \times \text{urine osmolality})$$

A TTKG higher than 8 indicates that aldosterone is present and that the collecting duct is responsive to it. A TTKG less than 5 in the presence of hyperkalemia indicates aldosterone deficiency or resistance. For the test to be accurate, the urine sodium concentration should be higher than 10 mEq/L and the urine osmolality should be greater than or equal to the plasma osmolality.[63]

Therapy is aimed at reducing the plasma potassium concentration and includes volume expansion, dietary potassium restriction, and potassium-wasting diuretics. Acidosis will usually improve once the hyperkalemic impedance of ammonium production is removed. Any drugs that suppress or block aldosterone should be discontinued. Mineralocorticoid replacement with fludrocortisone will improve hyperkalemia and acidosis but is not ideal in patients with uncontrolled hypertension or a history of heart failure. These patients are instead treated with a low-potassium diet and a loop diuretic.[4]

GASTROINTESTINAL TRACT LOSS

The secretions of the large and small bowel are mostly alkaline and have a bicarbonate level higher than that in the plasma. Significant loss of lower GI secretions results in non-AG metabolic acidosis (see Box 15.4). Diarrhea is the most common cause of external loss of bicarbonate, resulting in non-AG metabolic acidosis. Other causes include external drainage of pancreatic or biliary secretions, as from fistulas, ileus secondary to intestinal obstruction, and villous adenomas. Drugs that increase GI bicarbonate loss include calcium chloride, magnesium sulfate, and cholestyramine. Significant bicarbonate loss also occurs in patients who abuse laxatives. Urinary diversions, such as ureterosigmoidostomy or ureteroileostomy, can cause non-AG metabolic acidosis because of the absorption of chloride in exchange for bicarbonate across the bowel mucosa. Absorption of urinary ammonium in the sigmoid colon may also contribute to the development of acidosis, as metabolism of the ammonium in the liver results in the production of H^+.

Metabolic acidosis and hypokalemia from GI losses increase renal synthesis and ammonia excretion, thereby providing a urinary buffer that increases urine pH despite increased net acid excretion.[59] The urine pH is higher than 5.5 instead of an acid urine pH, as expected with systemic acidosis. Metabolic acidosis resulting from GI losses with a high urine pH can be differentiated from RTA by calculating the UAG.

OTHER CAUSES OF NON–ANION GAP ACIDOSIS

See Box 15.4.

Expansion of the extracellular fluid volume with non–bicarbonate-containing solutions, such as isotonic saline, causes metabolic acidosis by diluting the previous existing plasma bicarbonate (dilutional acidosis) and increasing the chloride load. This increased chloride load exceeds the renal capacity to generate equal amounts of HCO_3^-.[59,64]

Amino acids in total parenteral nutrition (TPN) are metabolized to HCl, which causes a transient non-AG metabolic acidosis. The decreased pH and decreased HCO_3^- stimulate renal reabsorption and generation of HCO_3^-. Metabolic acidosis occurs if the acid load overrides the ability of the renal tubules to secrete H^+ and generate ammonia for excretion in the urine, usually a short-lived process.[4]

In prolonged hypercapnia, renal tubules compensate for a prolonged respiratory alkalosis by decreasing reclamation and generation of HCO_3^- (which takes 12–24 hours for full effect). If the respiratory alkalosis resolves rapidly, reclamation and generation of HCO_3^- will return to normal over 1–2 days. During this period a resolving non-AG metabolic acidosis occurs.

In toluene intoxication or the treatment phase of DKA, metabolic acid production is markedly increased. Although ammonium excretion is also increased, the rate of urinary excretion of the acid anions (hippurate and keto-anions, respectively) exceeds the excretion of ammonium. The anions not excreted with ammonium are excreted with sodium and potassium, causing sodium deficits and avid retention of filtered sodium and chloride. The lost bicarbonate is replaced by the retained chloride. In addition, administration of large volumes of isotonic saline for resuscitation in patients with DKA promotes diuresis, with continued urinary loss of ketone bodies, with sodium as the cation while delivering chloride to replace the lost keto-anions.[59]

METABOLIC ALKALOSIS

Primary metabolic alkalosis is a subset of acid-base disorders characterized by an elevation in blood arterial pH, an increase in plasma HCO_3^- concentration, and a compensatory hypoventilation, resulting in a rise in $PaCO_2$. It is encountered relatively frequently in clinical practice as a result of the loss of H^+ from the GI tract or urine. This disorder is also often accompanied by hypochloremia and hypokalemia.[65]

In the presence of an increased serum bicarbonate concentration and low serum chloride (Cl^-) concentration, a patient may have either metabolic alkalosis or chronic respiratory acidosis. These disorders can be differentiated by the arterial pH, which is increased (>7.4) in metabolic alkalosis and decreased (<7.4) or normal in chronic respiratory acidosis. In primary metabolic alkalosis, the $PaCO_2$ generally increases approximately 6–7.5 mm Hg for every 10 mEq/L increase in HCO_3^- above normal.

Metabolic alkalosis may occur as a simple disorder or when associated with other disorders like respiratory acidosis, respiratory alkalosis, or metabolic acidosis, as a mixed disorder. An increase in the serum AG may be the only sign that metabolic acidosis coexists with metabolic alkalosis. Clinical examples of a mixed AG acidosis and metabolic alkalosis include patients with both DKA and vomiting or lactic acidosis with vomiting.[66]

Pathogenesis

Metabolic alkalosis can result from the loss of H^+, transcellular H^+ shift, exogenous alkali administration, or contraction alkalosis (Fig. 15.3). These factors may initiate systemic alkalosis, but under normal physiologic circumstances, alkalosis should never develop because the kidney is efficient at removing excess bicarbonate. However, in conditions where kidney function may be compromised, bicarbonate excretion may become impaired. Metabolic alkalosis is typically associated with impairment in kidney function, which is thought to maintain the alkalosis.

In effect, metabolic alkalosis results from impaired bicarbonate elimination from the kidney by its regular mechanisms (see Fig. 15.3). An increase in the plasma bicarbonate concentration results from either exogenous HCO_3^- administration or endogenous production. The kidneys will preserve rather than eliminate excess alkali and maintain alkalosis if either of the following conditions is present: (1) Cl^- deficiency (or ECV contraction), typically accompanied by potassium (K^+) depletion, which reduces effective renal perfusion and glomerular filtration and enhances bicarbonate reabsorption. Alkalosis in this setting can usually be corrected with saline infusion (saline-responsive) and K^+ repletion or (2) hypokalemia resulting from a mineralocorticoid excess, which is not responsive to ECV expansion.[67–69] This cause of alkalosis is not generally responsive to saline

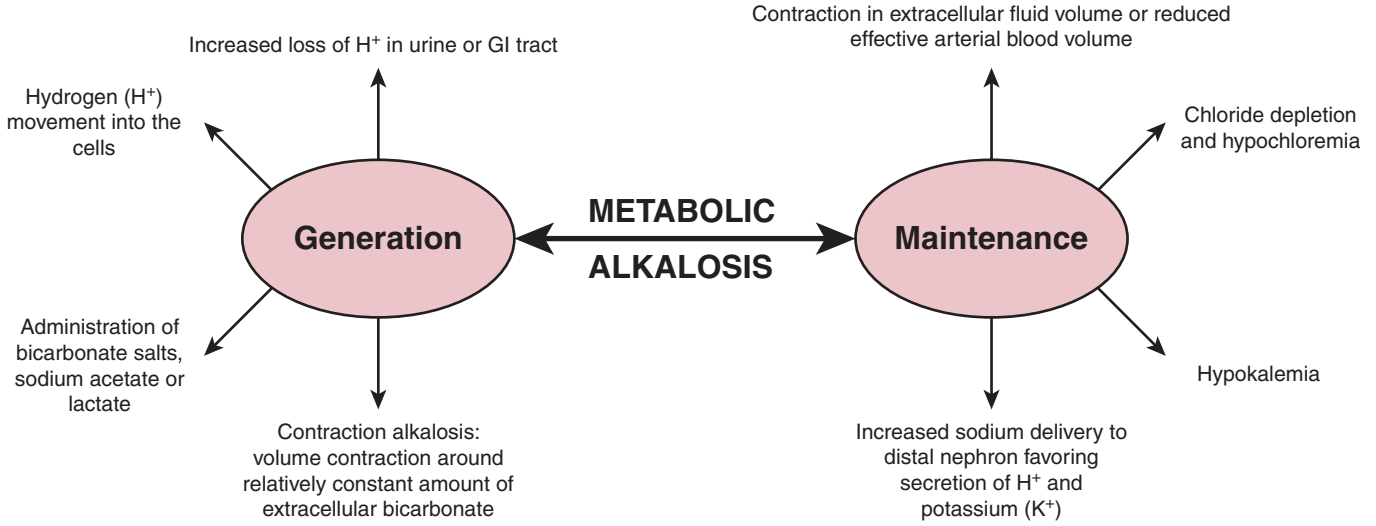


Fig. 15.3 Pathogenesis and Maintenance of Metabolic Alkalosis.

(saline-resistant), and treatment considerations include medications or surgical resection.

The most common factor maintaining metabolic alkalosis is a reduction in ECV, which leads to a reduction in GFR and a subsequent increase in sodium (Na^+), HCO_3^- reabsorption, and new bicarbonate generation.[70] Hypokalemia can both cause and maintain the presence of metabolic alkalosis. Mineralocorticoid excess is another factor that may trigger metabolic alkalosis, and, in those cases, hypokalemia is the factor that maintains the alkalosis.

Metabolic alkalosis associated with a reduction in volume responds well to repletion with normal (0.9%) saline and is known as *saline responsive.* However, mineralocorticoid or hypokalemia-induced alkalosis does not generally respond to volume administration and is said to be *saline-unresponsive.*

Symptoms of Metabolic Alkalosis

The symptoms of metabolic alkalosis vary according to the severity of the underlying acid-base abnormality. Presenting symptoms are often similar to those of hypocalcemia and may include mental confusion, decreased consciousness, seizures, muscle cramping, tetany, paresthesia, cardiac arrhythmias, and dyspnea. Common electrolyte abnormalities associated with alkalosis include hypokalemia and hypophosphatemia.[71]

Extracellular Fluid Volume Contraction, Hypokalemia, and Secondary Hyperaldosteronism

See Box 15.6.

Gastrointestinal Causes

GI hydrogen loss can result from the removal of gastric secretions (vomiting or nasogastric suction) or loss of intestinal secretions (congenital chloridorrhea, villous adenoma, laxative abuse). Loss of H^+ leading to metabolic alkalosis most commonly occurs through the GI tract by vomiting or nasogastric (NG) suction. Gastric fluid contains a high concentration of hydrochloric acid (HCl) and a lower concentration of potassium chloride (KCl). Each mEq of H^+ secreted generates 1 mEq of HCO_3^-, which is then absorbed into the plasma. Under normal physiologic conditions, the increase in plasma HCO_3^- concentration is only transient, as acid secretion into the duodenum stimulates an equal amount of pancreatic HCO_3^- secretion, which neutralizes the acid. However, if gastric fluid is removed by vomiting or NG suction, there is no stimulus for HCO_3^- secretion, because the HCl does not reach the duodenum. The net result is an increase in plasma HCO_3^- and subsequent metabolic alkalosis.

Under normal circumstances, any excess HCO_3^- generated would be excreted by the kidney in the urine, thereby correcting alkalosis.

Box 15.6 Causes of Metabolic Alkalosis

Exogenous HCO_3^- Loads
Acute alkali administration
Milk-alkali syndrome

Effective Extracellular Volume Contraction, Normotension, Hypokalemia, and Secondary Hyperreninemic Hyperaldosteronism
Gastrointestinal Origin
Vomiting
Gastric aspiration
Congenital chloridorrhea
Villous adenoma
Combined administration of sodium polystyrene sulfonate (Kayexalate and aluminum hydroxide)

Renal Origin
Diuretics (especially thiazides and loop diuretics)
Acute
Chronic
Edematous states
Posthypercapnic state
Hypercalcemia-hypoparathyroidism
Recovery from lactic acidosis or ketoacidosis
Nonreabsorbable anions such as penicillin, carbenicillin
Mg^{2+} deficiency
K^+ depletion
Bartter syndrome (loss-of-function mutation of Cl^- transport in thick ascending limb of loop of Henle)
Gitelman syndrome (loss-of-function mutation in Na^+/Cl^- cotransporter)
Carbohydrate refeeding after starvation

Other
Sweat loss in cystic fibrosis
Loss of fluid in third space

Extracellular Volume Expansion, Hypertension, K^+ Deficiency, and Hypermineralocorticoidism
Associated With High Renin
Renal artery stenosis
Accelerated hypertension
Renin-secreting tumor
Estrogen therapy

Associated With Low Renin
Primary aldosteronism
Adenoma
Hyperplasia
Carcinoma
Glucocorticoid suppressible

Adrenal Enzymatic Defects
11β-Hydroxylase deficiency
17α-Hydroxylase deficiency

Cushing Syndrome or Disease
Ectopic corticotropin
Adrenal carcinoma
Adrenal adenoma
Primary pituitary

Other
Licorice
Carbenoxolone
Chewing tobacco
Lydia Pinkham tablets

Gain-of-Function Mutation of Epithelial Sodium Channel (ENaC) With Extracellular Fluid Volume Expansion, Hypertension, K^+ Deficiency, and Hyporeninemic Hypoaldosteronism
Liddle syndrome

However, vomiting or NG suction also lowers the extracellular fluid compartment and effective circulating volume. The reduction in ECV leads to decreased GFR and less HCO_3^- filtered and also stimulates angiotensin and aldosterone production (secondary hyperaldosteronism), leading to increased Na^+ and HCO_3^- reabsorption by the proximal tubules.[72] Increased Na^+ reabsorption leads to increased HCO_3^- reabsorption because of the increase in H^+ secretion as Na^+ is exchanged for H^+ by the Na–H^+ transporter at the proximal tubule. Secreted H^+ ions combine with filtered HCO_3^-, causing reabsorption. Aldosterone primarily acts at the distal tubule to increase H^+ and K^+ secretion, resulting in greater acid and K^+ excretion. These processes lead to a hypokalemic metabolic alkalosis. Notably, the near-complete reabsorption of HCO_3^- in the setting of reduced ECV leads to the paradoxical finding of an acidic urine, despite the presence of extracellular alkalosis.

Renal Causes

See Box 15.6. Contraction alkalosis occurs when there is a relatively large loss of bodily fluid that does not contain HCO_3^-. In this setting, which is most commonly the result of diuretics, the ECV contracts around a fixed amount of HCO_3^-, resulting in a rise in HCO_3^- concentration.[73] Note that in this situation, total body bicarbonate remains the same despite the concentration change. Chronic diuretic use generates alkalosis by increasing salt delivery to the distal tubule, with resulting stimulation of H^+ and K^+ secretion. Loop and thiazide diuretics may effectively lower ECV without concomitant loss of HCO_3^-, resulting in a net increase in serum HCO_3^- and contraction alkalosis. Alkalosis is then maintained by one of several mechanisms, such as reduction of the ECV, hypokalemia, secondary hyperaldosteronism, or continued effect of the diuretic. Repletion of the extravascular fluid with 0.9% saline will typically improve the alkalosis in this setting.

Bartter syndrome is a disorder characterized by impaired Cl^- absorption, which then leads to salt wasting, volume contraction, and activation of the renin-angiotensin system. Five types of Bartter syndrome have been discovered, with four inherited in an autosomal recessive manner.[74] Bartter syndrome occurs more often in children, and the most common disorder results from a mutation of the gene encoding the bumetanide-sensitive $Na^+2Cl^-K^+$ cotransporter (*NKCC2* or *BSC1*) on the apical membrane; however, other mutations have been found involving different transporter channels. Elevated prostaglandin levels have been reported with this disorder, likely from volume contraction, hypokalemia, or high angiotensin II levels.[75] These defects lead to contraction of the ECV, hyperreninemic hyperaldosteronism, and increased Na^+ delivery to the distal nephron subsequent with K^+ wasting and alkalosis. The differential diagnosis of Bartter syndrome includes other causes of ECV contraction, such as emesis, diuretic use, or laxative abuse. Inhibition of the renin-angiotensin-aldosterone system or the prostaglandin-kinin system has been the goal of current treatment, with medications like spironolactone, prostaglandin inhibitors, propranolol, and ACE inhibitors, but the utility of such agents has been limited. K^+ and magnesium (Mg^+) repletion is also an important part of therapy.

Gitelman syndrome, like Bartter syndrome, is autosomal recessive and may manifest with hypokalemia, volume depletion with secondary hyperreninemic hyperaldosteronism, normotension, or even low blood pressure. Gitelman syndrome differs from Bartter syndrome in that it occurs more often in adulthood and is characterized by hypocalciuria, hypermagnesuria, and hypomagnesemia, similar to the effect of thiazide diuretics. Gitelman syndrome occurs as the result of missense mutations in the gene *SLC12A3,* responsible for encoding the thiazide-sensitive distal convoluted tubule Na^+/Cl^- cotransporter (NCCT).[74,76] Diminished activity of the Na^+/Cl^- cotransporter leads to calcium reabsorption and hypocalciuria. Reported symptoms include fatigue, cramping, nocturia, and salt craving. Treatment considerations include a sodium- and potassium-avid diet with magnesium supplementation. ACE inhibitors have also been advocated for this disorder.

Hypokalemia is a frequent finding in patients with metabolic alkalosis. It is an important contributor to both the development and maintenance of the alkalosis. The underlying causes of metabolic alkalosis (e.g., vomiting, mineralocorticoid excess, diuretic use) induce both H^+ and K^+ loss and thus cause hypokalemia. However, hypokalemia itself can be a primary cause of metabolic alkalosis. Hypokalemia causes metabolic alkalosis by several mechanisms. Initially, hypokalemia causes a transcellular shift, where K^+ leaves and H^+ enters cells, thereby increasing extracellular pH. Hypokalemia also causes a transcellular shift in proximal tubule cells, resulting in intracellular acidosis and ammonium (NH_4^+) production and excretion. Finally, H^+ secretion increases in the proximal and distal tubules with hypokalemia, leading to further HCO_3^- reabsorption. The net effect is an increase in acid excretion.

Magnesium deficiency promotes distal H^+ secretion and acidification of urine by stimulating renin and aldosterone secretion, which result in hypokalemic alkalosis.

Posthypercapnic alkalosis is frequently overlooked as a complication of mechanical ventilation. The normal physiologic response to respiratory acidosis is a compensatory increase in HCO_3^- reabsorption by the kidney, which increases plasma HCO_3^-. Use of mechanical ventilation for this disorder may rapidly lower the $PaCO_2$; however, plasma HCO_3^- will remain "inappropriately" elevated, resulting in development of metabolic alkalosis.[77] Additionally, spontaneous renal excretion of excess bicarbonate will be difficult if there is a concomitant presence of reduced GFR, chloride depletion, or reduced effective arterial blood volume (e.g., diuretic therapy) in critically ill patients. The duration of alkalosis in this setting, however, is unclear. Chronic respiratory acidosis is thought to be associated with urine Cl^- loss, leading to hypovolemia and hypochloremia. Repletion of Cl^- and restoration of volume (usually with 0.9% saline) typically corrects this disorder. In posthypercapnic alkalosis, the rapid fall in $PaCO_2$ may also lead to an acute increase in cerebral intracellular pH.[78,79] Complications including neurologic abnormalities and death have been reported with this effect, and as a result most experts have recommended a gradual reduction in $PaCO_2$ in patients with chronic hypercapnia.

Extracellular Volume Expansion and Mineralocorticoid Excess

The common causes of metabolic alkalosis maintain the alkalosis by hypovolemia-induced secondary hyperaldosteronism, which leads to increased acid excretion and hypokalemia. Disorders of mineralocorticoid excess, such as Conn syndrome, Cushing syndrome, and excess corticosteroid administration, produce a state of hyperaldosteronism, which also leads to hypokalemia and metabolic alkalosis (see Box 15.6).[80] In these disorders, the ECV increases, and hypertension may result. In these patients, metabolic alkalosis is perpetuated by the effects of hypokalemia, rather than hypovolemia, which leads to increased ammonium production, H^+ secretion, and HCO_3^- reabsorption.

Patients with secondary hyperaldosteronism from reduced arterial blood volume, as observed in conditions like congestive heart failure and cirrhosis, do not usually develop metabolic alkalosis unless treated with diuretics. In these patients, distal sodium delivery is reduced because of the expanded reabsorption of sodium in the proximal tubule. Without high distal sodium delivery, the effect of

aldosterone on sodium reabsorption and K^+ and H^+ excretion is diminished. High distal sodium delivery and elevated mineralocorticoid levels may occur together with primary mineralocorticoid secretory disorders or conditions like Liddle syndrome, which manifest as primary hyperaldosteronism.

Alkali Administration

In normal individuals and under most circumstances, chronic administration of sodium bicarbonate will only slightly alter the systemic pH because of the relatively rapid renal excretion of excess alkali and minimal rise in plasma bicarbonate levels. Alkalosis may occur, however, if large amounts of sodium bicarbonate or any substance metabolized to bicarbonate (like the sodium salts of citrate, acetate, or lactate) are administered more rapidly, such as in the use of sodium bicarbonate to treat lactic acidosis or administration of sodium citrate in the form of massive blood transfusions. Notably, other factors contributing to alkalosis, like hypovolemia, hypokalemia, or renal impairment, will often be present.

Citrate, the anticoagulant used in blood products, is being increasingly used as an anticoagulant for continuous renal replacement therapy (CRRT). Because 1 mmol of trisodium citrate is potentially metabolized to 3 mmol of sodium bicarbonate by the liver, metabolic alkalosis can occur from increased citrate. Metabolic alkalosis from citrate delivery in CRRT can be easily managed by decreasing the citrate infusion rate, increasing citrate and bicarbonate losses by increasing the dialysate/replacement fluid flow rate, or reducing the bicarbonate concentration in the dialysate/replacement fluid.[81]

Milk-alkali syndrome results from the ingestion of large quantities of calcium carbonate along with vitamin D and is characterized by hypercalcemia and metabolic alkalosis. Hypercalcemia causes impaired renal function through renal vasoconstriction, renal salt wasting, and volume depletion; the latter is exacerbated by vomiting. Hypovolemia and decreased renal function are responsible for maintaining systemic alkalosis. Alkalosis also increases renal reabsorption of calcium, thereby worsening hypercalcemia.

Diagnosis of Metabolic Alkalosis

When a diagnosis of metabolic alkalosis is established, the etiology can usually be determined from the patient's history. Otherwise, alkalosis is generally the result of one of three common causes: (1) emesis, (2) diuretic use, or (3) mineralocorticoid excess. Measurement of the urine chloride concentration usually helps differentiate among these conditions. When metabolic alkalosis is associated with a reduction in ECV, Na^+ and Cl^- reabsorption are enhanced to replenish ECV. In this setting, urinary Cl^- concentration should be very low, typically less than 25 mEq/L (Table 15.4 and Fig. 15.4).

Urinary Na^+ concentration is not a reliable measure of ECV status in the setting of metabolic alkalosis. If all of the filtered HCO_3^- cannot be reabsorbed, then some will be excreted with Na^+, and urinary Na^+ may be high. Thus the volume status may incorrectly appear to be euvolemic or hypervolemic.

If the urinary Cl^- is low, indicating a hypovolemic state, then 0.9% NaCl and water administration to replenish ECV should stop aldosterone production and lead to appropriate excretion of excess HCO_3^-, improvement of hypokalemia, and correction of metabolic alkalosis. These causes of metabolic alkalosis are considered saline-responsive.

Mineralocorticoid excess, by contrast, is associated with increased ECV and occasionally hypertension. Urinary Cl^- will be high, typically when higher than 40 mEq/L. Saline administration in such patients would further expand ECV and worsen hypertension. Alkalosis, which in this setting is primarily the result of hypokalemia, would not be corrected. These causes of metabolic alkalosis are considered saline-resistant.

TABLE 15.4 Diagnosis of Metabolic Alkalosis

Saline-Responsive Alkalosis	Saline-Unresponsive Alkalosis
Low Urinary [Cl^-]	High or Normal Urinary [Cl^-]
Normotensive	Hypertensive
Vomiting, nasogastric aspiration	Primary aldosteronism
Diuretics	Cushing syndrome
Posthypercapnia	Renal artery stenosis
Bicarbonate therapy of organic acidosis	Renal failure plus alkali therapy
K^+ deficiency	Normotensive
Hypertensive	Mg^{2+} deficiency
Liddle syndrome	Severe K^+ deficiency Bartter syndrome Gitelman syndrome Diuretics

The causes of saline-resistant metabolic alkalosis can be further distinguished according to whether hypertension is present. Hypertension tends to occur in mineralocorticoid excess states, whereas Bartter and Gitelman syndromes and exogenous alkali load are associated with normal blood pressure.

Treatment

The goals of the treatment of metabolic alkalosis are to reverse the cause of bicarbonate generation and address those factors that restrict secretion of excess bicarbonate from the kidneys. Diagnostic evaluation of metabolic alkalosis can be aided by measurement of the urine chloride concentration, systemic blood pressure, and estimated volume status of the patient. Other clinical findings that may assist with the evaluation include vomiting, NG suctioning, or alkali or diuretic use. Reversal of the underlying cause of alkalosis may include controlling emesis, addressing the removal of gastric secretions or lowering the gastric acid content removed, and discontinuing loop or thiazide diuretics. Medications that reduce gastric acid secretion, such as proton pump inhibitors or histamine-2 receptor blockers, have been administered to improve alkalosis in patients with persistent vomiting.[82,83] Any exogenous source of alkali, like bicarbonate, or substances that metabolize to bicarbonate (like citrate or lactate), should be discontinued if possible. Hypokalemia is common in metabolic alkalosis and should be corrected.

A reduction in renal excretion of excess bicarbonate is required to maintain metabolic alkalosis, so addressing factors that impair renal function and subsequent bicarbonate secretion will help correct alkalosis. Such conditions include reduced renal function, reduced arterial blood flow, K^+ depletion/hypokalemia, and Cl^- depletion/hypochloremia.

Treatment of metabolic alkalosis can be further divided on the basis of whether it responds to intravascular volume expansion. Patients with volume contraction as the cause of metabolic alkalosis are generally saline-responsive. On the other hand, patients with metabolic alkalosis because of mineralocorticoid excess, hypokalemia, or renal insufficiency are typically saline-resistant.

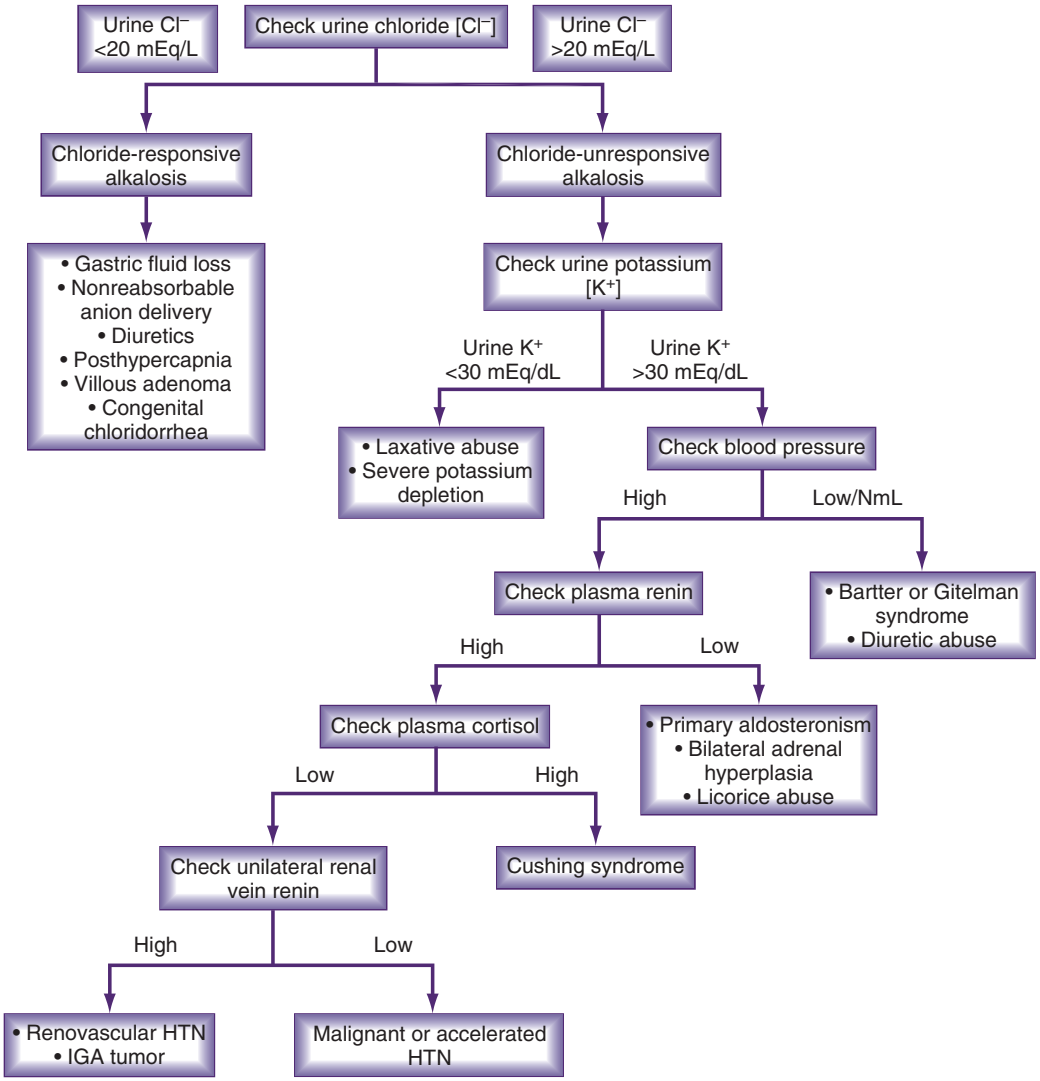


Fig. 15.4 Workup of metabolic alkalosis. (Data from DuBose TD Jr. Acid-base disorders. In Brenner BM, ed. *Brenner and Rector's The Kidney*. 8th ed. Philadelphia: Saunders; 2008:513.)

The treatment of metabolic alkalosis associated with volume contraction consists of volume expansion with 0.9% saline. Re-expansion of intravascular volume and correction of chloride deficiency lower proximal tubular bicarbonate reabsorption, enhance urine bicarbonate excretion, and lower plasma bicarbonate concentration. It is still a subject of ongoing debate whether the correction of metabolic alkalosis in response to saline infusion is from resolution of hypovolemia or secondary to repletion of the chloride deficit.[68]

Hypokalemia, if present, should be treated with potassium chloride. Metabolic alkalosis resulting from gastric acid loss, diuretics, and chloride depletion typically responds to 0.9% saline administration. Posthypercapnic metabolic alkalosis resulting from volume depletion also responds to 0.9% saline infusion.[79]

Saline-resistant metabolic alkalosis does not improve after administration of 0.9% saline. These patients are generally not volume depleted or chloride deficient, as shown by high concentrations of urinary chloride. In patients with excessive mineralocorticoid production, like in Conn syndrome, use of spironolactone to inhibit mineralocorticoid activity may be beneficial. Corticosteroid therapy may need to be discontinued, and ACE inhibitors may be helpful because of their potassium-sparing effect and control of hypertension. Surgical or chemical ablation of the adrenal glands may be necessary for definitive management.

Severe hypokalemia increases tubular H^+ excretion, ammonia production, and chloride wasting. Potassium repletion corrects this defect. As potassium wasting is a central finding in mineralocorticoid excess, Bartter syndrome, and Liddle syndrome, potassium-sparing diuretics like amiloride or triamterene are used in these patients.

Metabolic alkalosis may be observed in patients with edematous states, including heart failure, nephrotic syndrome, and cirrhosis. This often results from the use of diuretics; however, treatment with 0.9% saline is not usually helpful in these patients. Infusion of saline in this setting will increase fluid retention and edema and the alkalosis will not be corrected, as avid Na reabsorption will reduce excretion of any excess bicarbonate. These patients are often K^+ deficient, and potassium chloride administration may improve or correct the alkalosis by increasing the serum K^+ concentration. Use of potassium-sparing diuretics like amiloride and/or aldosterone antagonists like spironolactone for these patients may be indicated. Acetazolamide—a carbonic anhydrase inhibitor that inhibits proximal tubule sodium bicarbonate

reabsorption—can be administered in doses of 250–500 mg once or twice daily if additional diuresis is required in the volume-overloaded patient.[84]

Renal replacement therapy may be considered to correct metabolic alkalosis in situations where patients fail to respond to conventional therapies like volume expansion or K^+ repletion.[85] In such instances, dialysis with a lower bicarbonate bath concentration can quickly improve the alkalosis; however, even use of a standard bicarbonate bath concentration can be effective, as the patient's serum bicarbonate level is often higher than that of the standard bath concentration. CRRT can also be used to treat metabolic alkalosis, but attention to the CRRT fluid buffer composition is warranted because bases such as bicarbonate, citrate, or lactate may increase the serum bicarbonate concentration at high effluent/ultrafiltration rates.[86]

HCl for the treatment of metabolic alkalosis is usually reserved for patients with severe symptoms who do not respond to conventional therapy with IV fluids and for correction of electrolyte derangement. The arterial pH is usually higher than 7.55 and/or serum bicarbonate greater than 50 mEq/L, and there may be evidence of seizures, altered sensorium, or cardiovascular complications. Dilute HCl (0.1 *N*) should be given through a central IV catheter, and careful vigilance of catheter integrity and surrounding tissue should be maintained to avoid complications of acid extravasation, which may cause tissue necrosis.[87,88] Hemolysis can also complicate therapy with HCl. Titration of HCl can be challenging, and the goal of therapy is to lower the arterial pH to approximately 7.5, rather than to normalize the value. Alternatively, ammonium chloride (NH_4Cl), which is a precursor of HCl that is metabolized to urea and HCl, can be used in patients without severe renal insufficiency or liver failure.[89]

DIAGNOSIS OF ACID-BASE DISORDERS

A systematic approach is necessary for determining which acid-base disorder or disorders are present.[90] Accurate interpretation of acid-base balance requires simultaneous measurements of arterial pH and plasma electrolytes. The arterial blood gas (ABG) test directly measures arterial pH and $PaCO_2$. The bicarbonate concentration from the ABG test is calculated using the Henderson-Hasselbalch equation, and the bicarbonate concentration on venous chemistry panel is measured directly as "total CO_2" with an ion-selective electrode. The calculated value for HCO_3^- reported with the ABG test should be within 2 or 3 mEq/L of the measured HCO_3^- concentration obtained on the electrolyte panel. A discrepancy in the values suggests either the samples were not obtained simultaneously or that a laboratory error has occurred. The cause of acid-base disturbances is determined by examining the pH, PCO_2, and plasma electrolytes (primarily plasma bicarbonate) in the context of a given clinical situation. Analysis involves identification of the likely dominant acid-base disorder, followed by an assessment of the compensatory response. A stepwise approach to the diagnosis of acid-base disorders follows and is summarized in Box 15.7.[5,6]

The initial screening for an acid-base disorder entails obtaining a detailed history and performing a physical examination. The history and physical examination usually strongly suggest the acid-base disorder that is present. A history of diuretics or vomiting suggests metabolic alkalosis. A history of diarrhea, alcoholism, or diabetes suggests metabolic acidosis. Stigmata of liver disease on the physical examination may signify the presence of respiratory alkalosis, whereas findings of volume contraction suggest metabolic alkalosis. Kussmaul respiration is often associated with DKA and severe metabolic acidosis. Medications that can affect acid-base balance (e.g., laxatives, diuretics, topiramate, or metformin) should be considered in addition to signs of intoxication that may be associated with acid-base disturbances.

The first step in acid-base analysis is to determine whether the patient has acidemia or alkalemia by examining the arterial pH. If acidemia is present, then an acidosis must be present; similarly, if alkalemia is present, then alkalosis must be present. The second step is to determine whether the deviation in the pH (acidemia or alkalemia) is the result of a primary respiratory or metabolic derangement by examining the $PaCO_2$ and plasma bicarbonate concentration. In acidemia, a low plasma bicarbonate concentration denotes primary metabolic acidosis, whereas an elevated $PaCO_2$ points to primary respiratory acidosis. Likewise, in alkalemia, an elevated plasma bicarbonate concentration

Box 15.7 Stepwise Approach to Diagnosing Acid-Base Disorders

Initial Screening

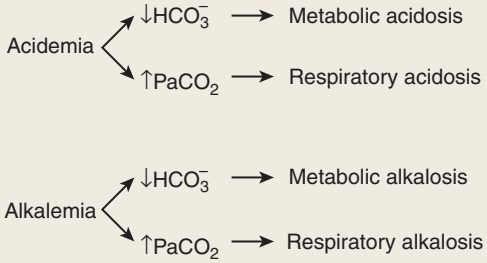
Consider the clinical setting by obtaining history and physical examination.

Obtain arterial blood gases (ABG) and electrolytes simultaneously.

Compare bicarbonate on ABG with venous electrolytes to ensure the calculated bicarbonate on ABG is within 2–3 mEq/L of measured bicarbonate on electrolyte panel.

Steps

1. Examine pH to determine if the patient has acidemia or alkalemia.
2. Look at PCO_2, HCO_3^- to determine if the primary process is metabolic or respiratory.



3. If a primary respiratory disorder is present in step 2, determine if it is acute or chronic.
4. Calculate the serum anion gap.
   a. Anion gap = $Na^+ - (Cl^- + HCO_3^-)$
5. If a metabolic disturbance is present from step 2 or high anion gap from step 4, determine if the respiratory system is adequately compensating.
   a. Expected $PaCO_2$ in acidosis: $PaCO_2 = (1.5 \times HCO_3^-) + 8 \pm 2$
   b. Expected $PaCO_2$ in alkalosis: $PaCO_2 = 40 + 0.7 \times (HCO_3^-{}_{meas.} - HCO_3^-{}_{normal}) \pm 5$
6. If anion gap is elevated, then calculate the Delta Delta Ratio (Δ/Δ) to assess for other simultaneous disorders.
   a. Δ/Δ compares the change in the anion gap with the change in bicarbonate.
   b. If ratio is between 1 and 2, then pure elevated anion gap acidosis is present.
   c. If <1, then a simultaneous normal anion gap acidosis is present.
   If >2, then a simultaneous metabolic alkalosis is present or a compensated chronic respiratory acidosis exists.

signifies primary metabolic alkalosis, whereas a low $PaCO_2$ is consistent with primary respiratory alkalosis. If a primary respiratory disturbance is present from step 2, the third step is to assess if it is acute or chronic by comparing pH and $PaCO_2$ by the formulas in Table 15.2.[6] If no primary respiratory disturbance is present, step 3 is skipped.

The fourth step is to calculate the serum AG. If primary metabolic acidosis is present from step 2, the serum AG is used to diagnose high AG metabolic acidosis. The AG should be adjusted for hypoalbuminemia. Even if metabolic acidosis is not present or the pH and $PaCO_2$ are within normal range, the serum AG should always be calculated because a **mixed acid-base** disorder can exist with a normal pH, $PaCO_2$, and plasma bicarbonate concentration, which is seen with high AG metabolic acidosis and concurrent metabolic alkalosis. If a high AG is present, ancillary tests to consider for differentiating the causes include plasma and urine ketones for ketoacidosis, plasma creatinine for renal failure, plasma L-lactate for lactic acidosis, plasma osmolality to calculate an osmolal gap and assess for toxic alcohol ingestion, and urine microscopy for crystals if ethylene glycol is suspected. If the primary metabolic acidosis is non-AG metabolic acidosis (plasma bicarbonate concentration is low without elevated AG), the UAG can help differentiate GI from renal causes.[91,92]

If a metabolic disturbance is present from step 2 or 4, the fifth step is to determine whether the respiratory system is adequately compensating. In metabolic acidosis, the Winters formula should be used to calculate the expected $PaCO_2$ for the degree of acidosis present. If the measured $PaCO_2$ is higher than the calculated expected $PaCO_2$, then concomitant respiratory acidosis is present. If the measured $PaCO_2$ is lower than the expected $PaCO_2$, then respiratory alkalosis is also present. In metabolic alkalosis, the normal respiratory response is less predictable. However, in general, the $PaCO_2$ should be between 40 and 50 mm Hg for appropriate compensation for metabolic alkalosis.[6]

If high AG metabolic acidosis is present from step 4, the last step is to determine the existence of any concurrent metabolic disturbances (such as non-AG metabolic acidosis or metabolic alkalosis) by comparing the degree of change in the serum AG with the change in the plasma bicarbonate level. This is done to assess the extent of contribution of the AG-producing process to the actual acidosis. This measurement is called Delta Delta Ratio[90]:

$$\text{Delta Delta Ratio} = \Delta AG/\Delta HCO_3^- = (AG - 12)/(24 - HCO_3^-)$$

If the metabolic disturbance is solely because of an elevated AG, the HCO_3^- should decrease by the same amount that the AG increases. A Delta Delta Ratio between 1 and 2 usually indicates uncomplicated high AG metabolic acidosis. A Delta Delta Ratio higher than 2 usually indicates a lesser fall in HCO_3^- than would be expected, given the change in the AG and the presence of concurrent metabolic alkalosis. An example of combined AG metabolic acidosis and metabolic alkalosis is volume contraction from vomiting in the setting of DKA. A Delta Delta Ratio less than 1 indicates a greater fall in HCO_3^- levels than would be expected, given the increase in the AG and therefore the presence of simultaneous non-AG metabolic acidosis. This might occur when lactic acidosis is superimposed on severe diarrhea. In this situation, the additional fall in HCO_3^- levels is the result of further buffering of an acid that does not contribute to the AG.[90]

Alternatively, an increase in anion gap can be interpreted as follows: A patient with an anion gap of 24 can be viewed as having 12 normal AG and 12 excess anions (A^-). With the assumption that the excess 12 A^- entered the body with 12 H^+ and that for every H^+, one HCO_3^- is consumed, then the expected $[HCO_3^-]$ will be 24 − 12 = 12 mEq/L. This is the expected $[HCO_3^-]$ based on the detected excess A^-. If the actual serum $[HCO_3^-]$ is equal to the expected $[HCO_3^-] \pm 2$ then there is no other acid-base disorder. If the actual serum $[HCO_3^-]$ is greater than expected $[HCO_3^-]$ then metabolic alkalosis is present. A non-AG metabolic acidosis indicating another process consuming $[HCO_3^-]$ is present if the actual serum $[HCO_3^-]$ is lesser than expected $[HCO_3^-]$.

SUMMARY

Acid-base disorders are common in the ICU and need to be anticipated in all critically ill patients. A clinician must be able to accurately monitor the acid-base status in order to promptly recognize derangements and implement appropriate interventions to prevent life-threatening complications as a result of the disturbance.

KEY POINTS

- Metabolic and mixed acid-base disorders are common in ICU patients and require early detection with a search for the underlying cause and initiation of appropriate treatment to prevent potentially fatal complications.
- Metabolic acidosis can be categorized as high or normal AG acidosis. High AG acidosis is frequently the result of lactic acidosis, ketoacidosis, toxic ingestions, or renal failure; non-AG acidosis is mostly the result of GI or renal bicarbonate loss. Diagnostic tests for differentiating causes of high AG acidosis include plasma and urine ketones, plasma creatinine, plasma L-lactate, plasma osmolality and osmolal gap, and urine microscopy for crystals. The urine AG can help differentiate causes of non-AG acidosis.
- The serum AG should always be calculated in the ICU because the presence of a significantly elevated serum AG represents metabolic acidosis, irrespective of pH or plasma bicarbonate. The serum AG must be adjusted for hypoalbuminemia.
- Compensation for primary metabolic acidosis is determined by the Winters formula. The Delta Delta gap is calculated to identify a concomitant metabolic disorder.
- Treatment for metabolic acidosis involves treating the underlying cause. Alkali therapy is often given for non-AG acidosis but is rarely indicated in high AG metabolic acidosis unless the arterial pH is less than 7.15 or for salicylate intoxication.
- Metabolic alkalosis may be initiated by acid loss or bicarbonate gain and maintained by renal mechanisms associated with bicarbonate resorption, including extracellular fluid volume contraction, chloride depletion, hypokalemia, and elevated mineralocorticoid activity.
- Metabolic alkalosis is most often caused by volume depletion with upper GI loss of hydrogen chloride (recurrent vomiting or NG suction) or by diuretic use with renal loss of H^+.
- The evaluation of metabolic alkalosis begins with measurement of the urine chloride and estimation of the ECV status. Metabolic alkalosis involving the loss or excess secretion of chloride is termed *chloride-responsive*.
- Compensation for primary metabolic alkalosis is estimated by the increase in $PaCO_2 = 0.75 \times \Delta\ HCO_3^-$.
- Treatment for metabolic alkalosis involves treating the underlying cause by administering IV 0.9% saline in chloride-responsive metabolic alkalosis and correcting mineralocorticoid excess and primary hyperaldosteronism in patients with a chloride-resistant metabolic alkalosis.

References for this chapter can be found at expertconsult.com.

ANNOTATED REFERENCES

Barski L, Eshkoli T, Brandstaetter E, et al. Euglycemic diabetic ketoacidosis. *Eur J Intern Med.* 2019;63:9–14.
This review article defines euglycemic diabetic ketoacidosis, detailing common causes, diagnosis, and management. Interest in euglycemic DKA has risen

with the more widespread use of SGLT2 inhibitors for treatment of type 2 diabetes mellitus.

Cheungpasitporn W, Zand L, Dillon JJ, et al. Lactate clearance and metabolic aspects of continuous high-volume hemofiltration. *Clin Kidney J.* 2015;8(4):374–377.
This case report presents a patient with septic shock and lactic acidosis who was treated with high-dose CRRT with a hemofiltration rate of 7 L/h. The calculated clearance of lactic acid with CRRT was quite small compared with reported rates of lactic acid overproduction in septic shock. This suggests that elevated lactic acid alone is not a sufficient indication for CRRT.

Halperin ML, Hammeke M, Jose RG, et al. Metabolic acidosis in the alcoholic: a pathophysiologic approach. *Metabolism.* 1983;32:308.
Alcoholic ketoacidosis is underdiagnosed clinically. This disorder can not only result in life-threatening acidemia but also, as a result of malnutrition, cause life-threatening hypophosphatemia. This scholarly review explains the pathophysiology and provides a basis for appreciation of the clinical syndrome.

Luke RG, Galla JH. It is chloride depletion alkalosis, not contraction alkalosis. *J Am Soc Nephrol.* 2012;23:204–207.
This article discusses chloride depletion, which is the most common cause of metabolic alkalosis. It debates the underlying pathophysiology involved in chloride depletion alkalosis with evidence from human and rat nephron segment studies. The authors conclude that chloride administration without volume expansion is necessary and sufficient to correct chloride depletion alkalosis.

Mizock BA, Belyaev S, Mecher C. Unexplained metabolic acidosis in critically ill patients: the role of pyroglutamic acid. *Intensive Care Med.* 2004;30:502–505.
This paper identifies an important and recently realized cause of high AG acidosis in the critical care setting. This is an unsuspecting yet very common setting in which metabolic acidosis because of accumulation of this compound may develop; hence, this information is critical to the clinician when formulating diagnostic and therapeutic plans for high AG acidosis.

Seddik AA, Bashier A, Alhadari AK, et al. Challenges in management of diabetic ketoacidosis in hemodialysis patients, case presentation and review of literature. *Diabetes Metab Syndr.* 2019;13(4):2481–2487.
This review article seeks to define the nuances and challenges of managing diabetic ketoacidosis in anuric patients on hemodialysis. There are currently no guidelines for managing DKA in this population, but the authors make some recommendations in this regard.

Villar J, Short JH, Lighthall G. Lactate predicts both short- and long-term mortality in patients with and without sepsis. *Infect Dis.* 2019;12:1178633719862776.
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16

Hyperkalemia and Hypokalemia

Bryan T. Romito and Anahat Dhillon

Potassium (K^+) is the most abundant intracellular cation and is maintained within narrow physiologic limits.[1] Although reported values vary, the normal serum K^+ level in humans typically ranges from 3.5 to 5.0 mEq/L.[2] Alterations in electrolyte concentrations occur frequently in critically ill patients, likely the result of malnutrition, end-organ dysfunction, comorbid diseases, and polypharmacy. Early recognition and treatment of K^+ abnormalities are essential, as both hyperkalemia and hypokalemia are associated with an increased risk of mortality in intensive care unit (ICU) patients.[3,4]

OVERVIEW OF POTASSIUM HOMEOSTASIS

The kidney is the most important organ for regulating K^+ homeostasis. It maintains total body K^+ content by matching excretion with intake.[5] Hyperkalemia is rare in healthy individuals because of the kidneys' ability to readily filter K^+. With preserved renal function, most patients can consume up to 400 mEq per day or more of K^+ without developing clinically significant hyperkalemia.[1] More than 90% of the filtered K^+ is reabsorbed in the proximal tubule and ascending limb of the loop of Henle. This reabsorption is primarily mediated by changes in sodium concentration, activity of the sodium-potassium-chloride (Na^+-K^+-$2Cl^-$) cotransporter, and activity of the sodium/potassium–adenosine triphosphatase pump (Na^+-K^+-ATPase).[5]

The mineralocorticoid aldosterone plays an important role in renal K^+ handling. It increases intracellular K^+ concentration by stimulating the Na^+-K^+-ATPase in the basolateral membrane of proximal tubule cells. In the thick ascending limb, it promotes K^+ secretion by stimulating sodium reabsorption across the luminal membrane.[5] Overall, when hyperkalemia is present, aldosterone promotes renal K^+ secretion in order to normalize serum K^+ concentration. In addition to hyperkalemia, the release of aldosterone is stimulated by activation of the renin–angiotensin–aldosterone system (RAAS). Medications and disease states that interfere with the normal functioning of this pathway can significantly alter K^+ levels.

Approximately 2% of total body K^+ is in the extracellular fluid, and 98% of K^+ is in the intracellular compartment.[6] Because the changes in renal K^+ excretion described earlier can take hours to occur, the body has developed several physiologic mechanisms to quickly shift K^+ across cell membranes in order to prevent life-threatening deviations outside of the normal range. Under normal conditions, transcellular K^+ shifts are primarily affected by insulin, catecholamines, tonicity, and acid-base disorders.[5,6]

By increasing activity of the Na^+-K^+-ATPase, insulin decreases serum K^+ by shifting it intracellularly. Increased K^+ intake causes catecholamine secretion and beta-2-receptor stimulation. Like insulin, this sympathetic stimulation results in increased activity of the Na^+-K^+-ATPase and enhanced K^+ uptake into skeletal muscle cells.[6] Extracellular hypertonicity creates an osmotic gradient that promotes K^+ efflux out of cells, increasing serum levels. Nongap metabolic acidosis causes a K^+ shift into the extracellular compartment, likely mediated by the effects of acidosis on transporters that regulate skeletal muscle cell pH.[6] The changes in K^+ dynamics in response to high anion gap metabolic acidosis and respiratory acid-base disorders are minimal.

HYPERKALEMIA

Although no consistent definition exists, *hyperkalemia* is present when serum $K^+ > 5.0$ mEq/L. The severity of hyperkalemia can be further classified as mild ($K^+ = 5.1$–5.5 mEq/L), moderate ($K^+ = 5.6$–6.0 mEq/L), or severe ($K^+ > 6.0$ mEq/L).[7] Understanding the characteristics of the laboratory sampling site is important for ensuring an accurate diagnosis. Although serum, plasma, and whole blood are generally acceptable specimens for quantifying K^+ levels, the composition of the sample site will affect the reported concentration. For example, *pseudohyperkalemia* describes an in vitro process by which measured serum K^+ is elevated relative to plasma concentrations. This typically occurs in the setting of thrombocytosis as platelets release K^+ during the clotting process, and plasma samples are devoid of platelets.[8] In *reverse pseudohyperkalemia,* the in vitro concentration of plasma K^+ exceeds that of serum. This can occur in the setting of significant leukocytosis, with cell lysis causing a release of intracellular K^+. Both entities are preanalytical phenomena and do not represent clinically significant hyperkalemia.[8]

True hyperkalemia occurs as a result of increased extracellular K^+ or decreased K^+ excretion (Table 16.1). Major risk factors for hyperkalemia include renal failure, diabetes mellitus, and the use of medications that impair renal K^+ excretion.[9,10] Hyperkalemia rarely occurs in patients with normal kidney function, and both acute and chronic renal insufficiency decrease K^+ excretion. When the glomerular filtration rate (GFR) is <15 mL/min/1.73 m^2, even small increases in K^+ intake can cause severe hyperkalemia.[11] In patients with chronic kidney disease, the risk of hyperkalemia correlates strongly with estimated GFR (eGFR). The likelihood of developing hyperkalemia approximately doubles when eGFR <15 mL/min/1.73 m^2.[12] Patients with diabetes mellitus have a higher incidence of hyperkalemia than the general population. Contributing factors include insulin deficiency and reduced tubular secretion of K^+ because of hyporeninemic hypoaldosteronism.[13]

The administration of medications that impair the RAAS is a major risk factor for elevated serum K^+. Direct renin inhibitors, angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin receptor blockers (ARBs) can all decrease renal K^+ excretion.[14,15] Beta-2-receptor blockers and nonsteroidal antiinflammatory drugs (NSAIDs) impair

TABLE 16.1 Causes of Abnormal Serum Potassium

HYPERKALEMIA	
Increased Extracellular Potassium	**Decreased Potassium Excretion**
Hypertonicity: hyperglycemia, sucrose, mannitol	Acute or chronic renal failure
Cell lysis: hemolysis, rhabdomyolysis, tumor lysis, tissue injury	Diabetes
Medications: succinylcholine, lysine, arginine, epsilon-aminocaproic acid, digoxin toxicity	Medications: beta-2-receptor blockers, NSAIDs, ACEIs, ARBs, direct renin inhibitors, potassium-sparing diuretics, ketoconazole, heparin, trimethoprim, pentamidine, calcineurin inhibitors
Hyperchloremic metabolic acidosis	Aldosterone deficiency or resistance
Hyperkalemic periodic paralysis	Type 4 renal tubular acidosis
HYPOKALEMIA	
Decreased Extracellular Potassium	**Increased Potassium Excretion**
Chronic decreased K^+ intake	Mineralocorticoid excess
Beta-2-receptor stimulation: catecholamines, stress	Bartter, Gitelman, and Liddle syndromes
Medications: insulin, toxicity from barium, thyroxine, risperidone, and quetiapine	Medications: loop diuretics, thiazide diuretics, glucocorticoids, penicillin derivatives, aminoglycosides, amphotericin B, cisplatin, tenofovir, foscarnet
Delirium tremens	GI losses: excessive diarrhea or vomiting
Hypokalemic periodic paralysis	Type 1 and type 2 renal tubular acidosis
	Magnesium deficiency

ACEI, Angiotensin-converting enzyme inhibitor; *ARB,* angiotensin receptor blocker; *GI,* gastrointestinal; *NSAID,* nonsteroidal antiinflammatory drug.

renin release.[9] Heparin and ketoconazole decrease aldosterone synthesis.[16,17] For most patients, RAAS blockade with only a single agent confers a low risk of hyperkalemia; however, the risk increases in the presence of other factors such as male sex, high baseline K^+, low eGFR, diabetes mellitus, heart failure, and coadministration of potassium-sparing diuretics.[9]

Pentamidine and trimethoprim can contribute to hyperkalemia by blocking the epithelial sodium channel (ENaC) in the distal nephron.[18] Compared with other antibiotics, trimethoprim administration is associated with an increased risk of acute kidney injury and hyperkalemia in patients aged 65 and over.[19] Calcineurin inhibitors cause downregulation of mineralocorticoid expression, leading to decreased mineralocorticoid function and aldosterone resistance.[18]

Hyperkalemia can develop as a result of transcellular K^+ dynamics, specifically the result of the release of intracellular K^+ or the prevention of extracellular-to-intracellular K^+ shifts. Given that K^+ is primarily located in the intracellular compartment, significant cell lysis from tissue injury, hemolysis, rhabdomyolysis, or tumor lysis can increase serum K^+ levels.[14] Succinylcholine is a depolarizing muscle relaxant that promotes K^+ efflux from skeletal muscle cells. The hyperkalemic response can be severe if given in the setting of burns, trauma, denervation, or prolonged immobility.[20] Administration of the positively charged amino acids L-lysine and L-arginine promote a transcellular shift of K^+ to the extracellular component to maintain electroneutrality.[21] Epsilon-aminocaproic acid is a lysine structural analogue and can produce hyperkalemia via a similar mechanism.[22] Familial hyperkalemic periodic paralysis is a rare autosomal dominant genetic disorder that results from a mutation in sodium channel function.[23]

Clinical Manifestations

Although some patients with hyperkalemia may present with paresthesias, diminished deep tendon reflexes, or weakness progressing to flaccid paralysis, most are asymptomatic. The most important effect of hyperkalemia is the impact on myocardial action potential.[14] Abnormalities in serum K^+ have electrophysiologic effects that can produce cardiac arrhythmias (Table 16.2). The electrocardiogram (ECG) abnormalities seen with hyperkalemia are often progressive and may follow a characteristic pattern. First the T wave becomes peaked, then the P wave broadens and decreases in amplitude, eventually disappearing.[24] Next the QRS complexes widen, producing a sine wave morphology as they merge with the T waves. As hyperkalemia progresses, the rhythm can degenerate into heart block, ventricular arrythmias, and asystole.[24] Although classically described, the correlation between the magnitude of K^+ elevation and ECG changes is poor. Severe hyperkalemia may present with minimal or atypical ECG findings.[14]

TABLE 16.2 Electrocardiogram Changes Caused by Abnormal Serum Potassium

Hyperkalemia	Hypokalemia
Peaked T waves	Flattened T waves
Broadening of P waves	U waves
Decrease in amplitude of P waves	ST segment depression
Loss of P waves	QT interval prolongation
Widening of QRS complexes (sine wave)	Ventricular arrhythmias
Heart block, ventricular arrhythmias, asystole	Asystole

Treatment

Treatment principles of hyperkalemia involve stabilizing the myocardial membrane, shifting K^+ to the intracellular compartment, and increasing K^+ excretion (Table 16.3). Although there is no consensus as to the level of hyperkalemia that requires intervention, it is recommended that patients with serum K^+ $\geq$6.0 mEq/L or those with ECG changes should be emergently treated.[10,14] Intravenous (IV) calcium salts (i.e., chloride and gluconate) are first-line treatment for hyperkalemia with ECG changes. Although they do not lower serum K^+, they stabilize the

TABLE 16.3 Treatment of Hyperkalemia

Treatment	Mechanism	Dose	Onset	Duration	Comments
Calcium	Stabilizes myocardial membrane	10 mL of 10% calcium chloride IV or 10-30 mL of 10% calcium gluconate IV	1–3 min	30–60 min	Dose can be repeated after 5 min if ECG changes persist
Sodium bicarbonate	Shifts K^+ into cells	50–100 mEq IV or 150 mEq IV over 3–4 h	Variable	Variable	Only effective with nongap metabolic acidosis; risk of fluid overload
Insulin	Shifts K^+ into cells	10 units IV regular insulin	15 min	4–6 h	Coadminister with 25 g of dextrose to prevent hypoglycemia
Albuterol	Shifts K^+ into cells	10 mg nebulized over 10 min	30 min	2–4 h	Risk of tachycardia
Loop diuretics	Increases renal K^+ excretion	40 mg IV furosemide or equivalent	Variable	Variable	Only administer to patients with symptomatic fluid overload
Sodium polystyrene sulfonate	Increases stool K^+ excretion	15 g 4× daily oral or 30 g 2× daily rectal	1–2 h	>4 h	Avoid in ileus or bowel obstruction; risk of intestinal necrosis
Dialysis	Removes K^+	Hemodialysis preferred over peritoneal in acute setting	Variable	Variable	Conventional hemodialysis causes most rapid fall in serum K^+

ECG, Electrocardiogram; *IV,* intravenous.

myocardial membrane and normalize ECG abnormalities. Insulin and beta-2-receptor agonists such as albuterol shift K^+ into cells, rapidly lowering serum levels. Both are effective when used as monotherapy; however, a synergistic effect occurs when they are coadministered.[25] Although efficacy data are mixed and standard dosing has not been established, sodium bicarbonate should be considered in hyperkalemic patients with a severe (pH <7.2) nongap metabolic acidosis.[14,25] Loop diuretics and cation exchange resins like sodium polystyrene sulfonate (Kayexalate) can increase K^+ excretion; however, their routine use is limited because of narrow efficacy windows, safety concerns, and delayed onset times.[26,27] Sodium zirconium cyclosilicate (ZS-9) and patiromer represent the newest generation of potassium-binding agents. Although they have been shown to be effective in treating hyperkalemia in the outpatient environment, there are limited data in the acute care setting.[27] Dialysis represents definitive treatment for hyperkalemia, but is usually reserved for cases refractory to medical management.

HYPOKALEMIA

Hypokalemia is present when serum K^+ <3.5 mEq/L.[28] Common causes of hypokalemia in critically ill patients include decreased extracellular K^+ and increased K^+ excretion. Both excessive diarrhea and vomiting can lead to hypokalemia. Large-volume emesis does not directly lower serum K^+ from gastric fluid losses; however, the reduction in hydrogen ions induces an extrarenal metabolic alkalosis that stimulates urinary K^+ wasting.[6] Although prolonged dietary restriction of K^+ can cause hypokalemia, it is more likely to exacerbate hypokalemia from other causes. Hypokalemic periodic paralysis, insulin, and beta-2-receptor stimulation from medications or stress shift K^+ into the intracellular compartment and lower serum K^+.[6,16,28] Toxicity from thyroxine, barium, risperidone, and quetiapine have all been associated with the development of hypokalemia.[16] The effect of alkalosis on lowering serum K^+ by transcellular shift is minimal.[6] There is a high prevalence of hypokalemia from increased renal K^+ excretion in patients taking loop and thiazide diuretics. Excessive mineralocorticoid activity from medications, adrenal disease, or tumor secretion will promote excessive renal K^+ losses.[28] Concomitant magnesium deficiency will exacerbate renal K^+ wasting and hypokalemia, potentially by downregulation of the sodium-chloride (Na^+-Cl^-) cotransporter in the distal tubule.[29] Other causes of hypokalemia from excessive renal losses include specific antimicrobials; antivirals; cytotoxic agents; Bartter, Liddle, and Gitelman syndromes; and some types of renal tubular acidosis (see Table 16-1).

Clinical Manifestations

Although as many as 20% of hospitalized patients develop hypokalemia, only 5% of these patients present with symptoms.[28] Common manifestations include muscle pain, cramping, and weakness of both smooth and skeletal muscle.[30] Hypokalemia is associated with an increased risk of arrhythmogenicity and potentiates the proarrhythmic effects of class III antiarrhythmics in patients with heart failure.[24] Like hyperkalemia, hypokalemia produces characteristic ECG changes (see Table 16.2). Common abnormalities include flattened T waves, prominent U waves, ST segment depression, and QT interval prolongation. Severe hypokalemia can produce malignant ventricular arrhythmias and cardiac arrest.[24,30]

Treatment

Appropriate management of hypokalemia involves treatment of underlying causes, discontinuation of offending agents, prevention of life-threatening arrhythmias, and repletion of total body K^+ stores. Every 1 mEq/L reduction in serum K^+ represents a total body deficit of 200–400 mEq.[28] In asymptomatic patients with mild to moderate hypokalemia, oral replacement with potassium chloride is recommended. Potassium bicarbonate is preferred in patients with a metabolic acidosis, and potassium phosphate is recommended in patients with hypophosphatemia.[31] Enterally administered K^+ is as effective as IV for increasing plasma concentration, and it minimizes the risk of rebound hyperkalemia.[32,33] IV repletion is recommended for patients with severe hypokalemia, those with ECG changes, or those unable to tolerate oral administration. IV correction using a peripheral route should not exceed 20 mEq/h because of the risk of phlebitis.[31] The use of infusion pumps and continuous cardiac monitoring are recommended, as inadvertent bolus administration can cause cardiac arrest. Combining IV and oral administration will result in the fastest correction of hypokalemia.[34] Treatment of coexisting hypomagnesemia is necessary to raise serum K^+ levels.[29] The use of computerized repletion protocols minimizes K^+ variability and time spent outside the physiologic range.[35]

KEY POINTS

- Hyperkalemia and hypokalemia have been associated with increased mortality in critically ill patients.
- Although classic ECG abnormalities are commonly described, severe hyperkalemia may present with minimal or atypical ECG findings.
- A synergistic hypokalemic response occurs when albuterol and insulin are coadministered.
- Severe hypokalemia can produce ventricular arrhythmias or cardiac arrest.
- IV K^+ repletion should be reserved for patients with severe hypokalemia, those with ECG changes, or those unable to tolerate oral administration.

References for this chapter can be found at expertconsult.com.

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17

Hyperphosphatemia and Hypophosphatemia

Marcus Ewert Broman

INTRODUCTION

Disturbances in the phosphate balance are common in critically ill patients, but are not always easy to relate to specific symptoms. Dysphosphatemia, however, may cause a significant increase in multiorgan failure. In a Swedish critical care cohort, more than half of the patients showed at least one serum phosphate concentration value outside the normal range (Fig. 17.1).[1] Serum phosphate levels should be measured repeatedly and at least once daily in the intensive care unit (ICU). Hypophosphatemia is multifactorial and independently associated with increased mortality, whereas hyperphosphatemia most often is secondary to renal failure. This chapter presents the etiologies, classifications of severity, clinical manifestations, and treatments of hypophosphatemia and hyperphosphatemia.

PHOSPHATE HOMEOSTASIS

Most phosphorus in the human body is complexed with oxygen as phosphate, which is a major intracellular anion. Approximately 85% of the total phosphorus amount (600 g = 20 mol) is contained in bone, where it is a constituent of crystalline hydroxyapatite. The rest (15%) is found in soft tissues, mostly intracellularly as a component of organic compounds, such as nucleic acids, cell membrane phospholipids, adenosine triphosphate, red blood cell 2,3-diphosphoglycerate, and phosphoproteins.

The normal serum phosphate concentration in adults ranges from 0.81 to 1.45 mmol/L (2.5–4.5 mg/dL). Phosphate concentration is 30% higher in children and 50% higher in infants, possibly because of an important role in growth. There is a circadian variation that is dependent on dietary intake in healthy subjects.

Serum laboratory analyses measure the free inorganic phosphate ions $H_2PO_4^-$ and HPO_4^{2-}—their ratio is pH dependent; at 7.4, the ratio is 1:4. Serum phosphate levels do not reflect total body phosphorus content. There is no common method in use to measure total body phosphorus stores. Only 55 % of the phosphate in serum is free, whereas 35% is complexed with sodium, calcium, and magnesium and 10% is bound to albumin.

The serum phosphate level may be low, although the total body phosphorus amount is normal, because of a shift into intracellular compartments or a negative intake/excretion balance. On the contrary, a total body phosphorus depletion can prevail in parallel to normal or high serum phosphate levels. Prolonged starvation and acidemia in ketoacidosis are clinical examples of situations that may deplete total body phosphorus amount.

Phosphate homeostasis relies on a complex interplay between the gastrointestinal, renal, parathyroid, and skeletal axis.

Under low serum calcium levels but also low phosphate levels, parathyroid hormone (PTH) is secreted and acts on the kidneys by enhancing hydroxylation of vitamin D to its active form, 1,25-dihydroxy vitamin D_3, which in turn augments both phosphate and calcium intestinal absorption.

Phosphate is freely filtered in the glomeruli, and up to ~90% is reabsorbed in the proximal tubules. PTH acts by reducing this tubular absorption.

A PTH release will result in a net drop in serum phosphate level. However, during steady state, the kidneys regulate phosphate homeostasis by matching urinary excretion with intake.

Tubular malfunction—for instance, because of rare genetic disorders—can lead to heavy phosphate urinary waste. The kidneys have a large capacity to excrete phosphate and thereby have a protective function against an ongoing phosphate load from nutritional intake and from metabolism.

Phosphatonins are regulatory peptides produced by osteoblasts and osteocytes in bone and secreted into the systemic circulation, where they decrease the renal tubular phosphate reabsorption, and thus increase the urinary phosphate excretion. Phosphatonins also participate in regulation of bone mineralisation. During baseline homeostasis about 200 mg of phosphate move in and out of the skeleton daily. Fibroblast growth factor-23 (FGF-23) is considered to be the key phosphatonin.[1–5]

HYPOPHOSPHATEMIA

Hypophosphatemia can be classified as moderate 0.4–0.81 mmol/L (1.25–2.5 mg/dL) or severe <0.4 mmol/L (<1.25 mg/dL).

The symptoms of hypophosphatemia are primarily a consequence of a declining 2,3-diphosphoglycerate level in erythrocytes, which increases the affinity of hemoglobin for oxygen and thereby reducing oxygen release in peripheral tissues. This in turn leads to decreased adenosine triphosphate levels in cells, slowing down all energy-dependent intracellular functions.

Critically ill patients with diabetic ketoacidosis and sepsis have a high incidence of hypophosphatemia. In particular, patients who have had cardiac surgery and major hepatic procedures tend to develop hypophosphatemia within the first week. Certain therapies instituted in the ICU, like establishing an aggressive diuresis, renal replacement therapy, and erythropoietin therapy, increase the risk of hypophosphatemia. Modern dialysis fluids contain phosphate, counteracting too high clearance. Frequently, patients present with initial hyperphosphatemia secondary to an acute kidney injury, which rapidly may turn into hypophosphatemia after renal replacement therapy has been initiated.

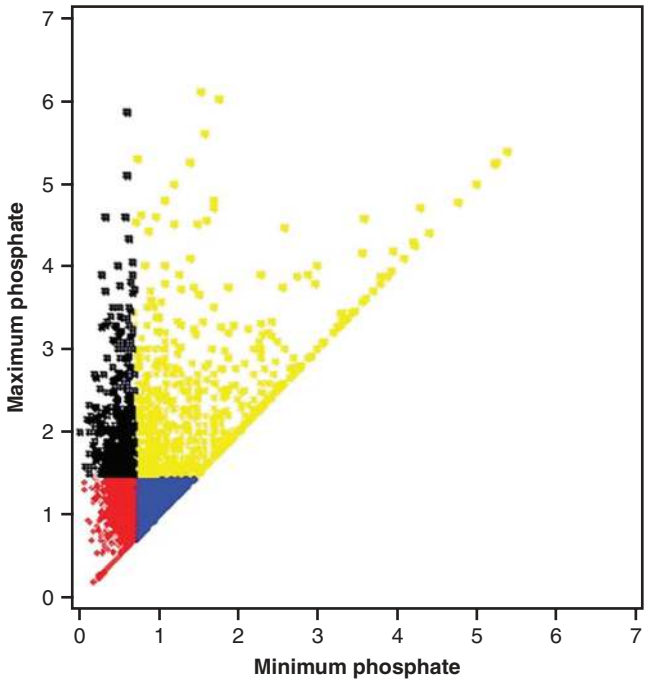

Fig. 17.1 Presentation of a large Swedish cohort consisting of 4656 patients with 19,467 phosphate measurements. Each *dot* in the plot represents the phosphate interval (defined by the lowest [x-axis] and the highest [y-axis] phosphate value) for one patient. Fifty-seven percent of the dots (*yellow,* hyper; *red,* hypo; and *black,* both hypo and hyper) are intervals with at least one value outside the normal range *(blue).* A phosphate deviation is a consequence of the critical illness itself, but also an independent parameter increasing the morbidity. The mean for all values was 1.18 mmol/L, with a standard deviation of ±0.52 mmol/L. (Modified from Broman M, Wilsson A, Hansson F, et al. Analysis of hypo- and hyperphosphatemia in an intensive care unit cohort. *Anesth Analg.* 2017;124:1897–1905.)

The phosphate homeostasis is dependent on an ongoing intestinal supply, and states with failing intestinal absorption or even losses, such as malnutrition, vomiting, diarrhea, and nasogastric suctioning, will cause hypophosphatemia (Box 17.1).

Hyperparathyroidism and proximal renal tubular disorders may impair phosphate resorption and cause hypophosphatemia. Rare genetic or acquired Fanconi syndrome results in renal tubular dysfunction and phosphaturia and subsequent hypophosphatemia.

In a fasting state the body first adapts by glycogenolysis of the liver stores, which will be depleted within 24 hours. Thereafter, insulin secretion decreases and a shift from glycogen to protein and fat catabolism takes place. Reintroduction of nutrition, especially a high-carbohydrate load, will increase insulin levels and reactivate anabolic pathways. A refeeding syndrome may follow from a combination of low phosphate supply with a sudden high anabolic demand, including an intracellular phosphate shift caused by insulin, resulting in low serum phosphate level. Identifying high-risk patients before initiating feeding and gradually increasing nutritional intake in combination with close monitoring of electrolytes and establishing timely repletion is mandatory to avoid this problem. Refeeding syndrome may appear with low levels of other electrolytes as well.

Total body phosphorus stores will be depleted in patients with ketoacidosis resulting from acidemia, which promotes phosphate shift from the cells to plasma and renal losses because of osmotic diuresis. Once insulin therapy is initiated and the acidemia is corrected, phosphate is reshifted from the serum back into the cells, resulting in severe hypophosphatemia.

Total body phosphorus depletion can also follow extreme catabolic states such as trauma, burns, and sepsis.

In hyperventilation, lowered carbon dioxide and respiratory alkalosis cause incorporation of phosphate into organic intermediates and a reduction in intracellular phosphate and a shift of phosphate from the extracellular compartment. Severe liver disease, sepsis, and salicylate intoxication can all induce hyperventilation and result in hypophosphatemia.

The severity of symptoms increases with more profound and longer-lasting hypophosphatemia.

Although moderate hypophosphatemia is often subclinical, it can be associated with significant morbidity.

Neurologic symptoms can be irritability, delirium, paresthesia, generalized seizures, and finally coma. Decreasing phosphate levels have been shown to decrease myocardial contractility and to predispose for ventricular rhythm disturbances, especially in conjunction with acute myocardial infarction. Several studies have indicated that ventilator dependence is prolonged in hypophosphatemic states and that weaning from the ventilator is more difficult. Reduced diaphragmatic strength, dysphagia, myopathy, and development of rhabdomyolysis have been reported in hypophosphatemia. Hematologic manifestations include hemolysis, thrombocytopenia, and affected phagocytosis and chemotaxis of leukocytes (Box 17.2).

In moderate or severe hypophosphatemia, 20–60 mmol phosphate (in some instances even more) can be administered intravenously over 24 hours. In addition, boluses of 20 mmol can be administered

BOX 17.1 Main Causes of Hypophosphatemia

Insufficient Intestinal Absorption
- Malnutrition
- Nasogastric suctioning
- Diarrhea
- Vomiting
- Vitamin D deficiency

Renal Excretion
- Diuretics
- Volume expansion
- Osmotic diuresis
- Primary or secondary parahyperthyroidism
- Renal tubular dysfunction
- Fanconi syndrome

Transcellular Shift
- Refeeding syndrome
- Ketoacidosis
- Insulin effect

Catabolic State
- Widely spread burns
- Multitrauma
- Sepsis

BOX 17.2 Principal Manifestations of Hypophosphatemia

Respiratory
- Worsened respiratory failure
- Dependence on ventilator

Cardiovascular
- Impaired myocardial contractility
- Cardiac rhythm disturbances

Muscular
- Muscular weakness
- Rhabdomyolysis

Neurologic
- Irritability
- Altered mental status
- Seizures

Hematologic
- Hemolysis
- Thrombocytopenia
- Affected phagocytosis and chemotaxis

BOX 17.3 Treatment of Hypophosphatemia

- Possible losses should be identified and stopped.
- Urgent correction should take place by infusing 20 mmol phosphate over 2–4 hours.
- The patient might also need a background administration of 20–60 mmol/24 hours, and in some instances even more.
- The phosphate concentration profile of the patient should be monitored with regular measurements, and the results should guide the correction.
- Phosphate content in ongoing intravenous infusions and in nutrition should be taken into account, and overcorrection should be avoided.
- If the hypophosphatemia turns out to be persistent or recurs, an evaluation of possible underlying mechanisms should take place.

over 2–4 hours (Box 17.3). Severe hypophosphatemia should be considered an emergency and corrected instantly under close surveillance and follow-up. Also, if the hypophosphatemic state is persistent or recurring, a careful evaluation of possible underlying mechanisms is mandatory.

A patient may have a disturbed phosphate regulation and be vulnerable to dysphosphatemia in both hypo- and hyper-directions. Frequent and individually well-reasoned phosphate level corrections should take place, keeping in mind that hyperphosphatemia from overcorrection might be a risk and difficult to manage in a renal failure setting.

Adverse effects of intravenous phosphate repletion are metastatic calcification, hypocalcemia, hyperkalemia associated with potassium-containing supplements, volume excess, hypernatremia associated with sodium-containing supplements, metabolic acidosis, and hyperphosphatemia. Therefore hypophosphatemia should be corrected gradually in most instances.

HYPERPHOSPHATEMIA

Hyperphosphatemia is defined as a serum phosphate level >1.45 mmol/L (>4.5 mg/dL).

Hyperphosphatemia will occur when phosphate entry into the extracellular fluid exceeds its excretion rate. There may be an endogenous or exogenous load or a shift from the intracellular compartment because of a disturbed homeostasis governing the phosphate turnover.

Patients with hyperphosphatemia are generally asymptomatic in a critical care setting, and the hyperphosphatemic state will in most cases be secondary to renal failure or to other severe multiorgan failure (Box 17.4).

Symptoms may arise from simultaneous hypocalcemia and can be life-threatening in their most severe forms. Hypotension, decreased myocardial performance, ventricular rhythm disturbances, increased vulnerability to seizures, and tetany have been described and are potentially fatal. Less severe symptoms comprise muscle cramps, perioral numbness, or tingling. Yet other symptoms may be bone and joint pain, pruritus, and rash. There can also be symptoms related to the underlying cause of hyperphosphatemia: for instance, uremic symptoms such as fatigue, shortness of breath, anorexia, nausea, vomiting, and sleep disturbances (Box 17.5).[13–17]

Diminished phosphate excretion may be caused by decreased renal excretion because of renal failure. There is a constant phosphate intake from nutrition and a phosphate burden from the metabolism. The kidneys have normally a very high capacity to excrete phosphate, and therefore the body is well protected against hyperphosphatemia. Urinary phosphate output cannot, however, match the intake anymore when glomerular filtration rate falls below ~20 mL/min/1.73 m^2.

Examples of endogenous loads are muscle breakdown in rhabdomyolysis, tumor lysis, and marked hemolysis.

BOX 17.4 Main Causes of Hyperphosphatemia

Renal
- Renal insufficiency
- Hypoparathyroidism

Cellular
- Rhabdomyolysis
- Tumor lysis

Medication Related or Iatrogenic
- Too large an ingestion
- Overcorrection with intravenous administration
- Laxatives
- Vitamin D intoxication
- Bisphosphonates
- Liposomal amphotericin B

BOX 17.5 Principal Manifestations of Hyperphosphatemia

Light Symptoms
- Can be hard to identify in a critical care setting; muscle cramps, pruritus

Severe Symptoms
- Come from simultaneous hypocalcemia; hypotension, ventricular arrhythmias, seizures

Examples of exogenous loads include ingestion of phosphate-rich compounds such as laxatives or intravenous overadministration of phosphate—for instance, too strenuous a correction of a hypophosphatemic state.

It has been shown that some critically ill patients have a tendency to vary in their phosphate concentration profile, with both hypophosphatemia and hyperphosphatemia, because of disturbed phosphate regulation during their stay in the critical care unit and are therefore prone to overcorrection. A stable phosphate concentration within the normal range should always be the goal.[1]

Other iatrogenic causes include bisphosphonate therapy in a setting of an existing renal insufficiency, use of liposomal amphotericin B in invasive fungal infections, and vitamin D toxicity.

Pathologies in the intestinal, renal, parathyroid, and bone systems may also lead to shifts that result in hyperphosphatemia.

Kidney injury over time disturbs adaptive bone mineralization processes by affecting hormonal and metabolic mechanisms. Bone hosts most of the body phosphorus as a reservoir, and bone resorption will result in increased phosphate shift to plasma and thus to hyperphosphatemia. This is defined as renal osteodystrophy.

Pseudohypoparathyroidism (renal resistance to PTH) results in increased renal phosphate reabsorption and leads to hyperphosphatemia and because of reflectory mechanisms to hypocalcemia.[18–21]

Managing hyperphosphatemia includes detecting and limiting the intake and enhancing urinary excretion. In the absence of severe renal failure or other conditions where administration of fluid is not tolerated, phosphate excretion can be optimized with saline infusion and diuretic administration enhancing a volume diuresis. Any patient with escalating, persistent, or treatment-resistant hyperphosphatemia should be considered for dialysis (Box 17.6). Oral phosphate binders do not have a role in acute dysphosphatemias in the critical care setting.

BOX 17.6 Treatment of Hyperphosphatemia

- Stop intake of phosphate
- Identify and eliminate iatrogenic causes
- Forced diuresis with saline infusion and diuretics
- Establishment of dialysis

KEY POINTS

- Phosphate has crucial functions in cell oxygen delivery, enzymatic processes, energy metabolism, and bone integrity.
- The phosphate concentration profile should be monitored and kept within the normal range 0.81–1.45 mmol/L (2.5–4.5 mg/dL).
- A moderate dysphosphatemia should be corrected without delay, and a severe dysphosphatemia should be considered an emergency.
- Hypophosphatemia is often multifactorial and may be transient without obvious symptoms and require only temporary phosphate substitution. However, should it persist, a careful evaluation of the underlying causes is compulsory for a successful resolution. Hypophosphatemia can cause significant worsening of multiorgan failure sequelae.
- Hyperphosphatemia is mostly a result of renal failure and of a multiorgan failure condition. Hyperphosphatemia in the absence of renal insufficiency is rare, because the kidney normally has a large capacity for excreting phosphate. Severe hyperphosphatemia can itself be life-threatening, and the only definitive treatment will be dialysis.

References for this chapter can be found at expertconsult.com.

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18

Hypomagnesemia

Vadim Gudzenko

Magnesium is an important ion that participates as a cofactor in over 300 enzymatic reactions, especially in those involving adenosine triphosphate (ATP). Hypomagnesemia is common in critically ill patients and is associated with increased mortality.[1,2]

CELLULAR PHYSIOLOGY AND METABOLISM OF MAGNESIUM

Magnesium is a divalent cation (Mg^{++}) that is predominantly localized to the intracellular compartment (99%). It is the second most abundant intracellular cation after potassium and plays an important role in cellular metabolism and homeostasis. At the cellular level, Mg^{++} influences membrane function by regulating ion transport; Mg^{++} is required for sodium/potassium–adenosine triphosphatase (Na^+/K^+-ATPase) activity, which maintains transmembrane gradients for Na^+ and K^+.[3,4] Mg^{++} also regulates intracellular calcium (Ca^{++}) flux by competing for Ca^{++} binding sites and influencing intracellular Ca^{++} transport.[3,4] It is also an essential cofactor for most ATP-requiring processes. Intracellular Mg^{++} is required for numerous critical biochemical processes, including DNA synthesis, activation of gene transcription, initiation of protein synthesis, and regulation of energy metabolism.[3,4]

Total body magnesium (21–28 g) is distributed in bone (53%), muscle (27%), soft tissue (19%), and blood (0.8%).[3] The normal concentration of total magnesium in serum is 1.5–2.3 mg/dL. Approximately 19% of circulating magnesium is bound to proteins, whereas 14% is complexed to plasma anions (citrate, phosphate, and bicarbonate). The majority of magnesium in plasma exists in its ionized form (67%), which represents the physiologically active species.[3] Consequently, the measurements of total serum magnesium may not accurately reflect the relative abundance of circulating Mg^{++}.[3,5]

Magnesium homeostasis is maintained by the small intestine, kidney, and bone.[3,6] Unlike calcium, there are no hormonal mechanisms for regulating Mg^{++}. Mg^{++} reabsorption in the loop of Henle is linked to sodium chloride (NaCl) transport and is inversely related to flow. Consequently, diuretic use and other conditions associated with increased tubular flow result in decreased Mg^{++} reabsorption.[3,6]

PREVALENCE AND ETIOLOGY OF HYPOMAGNESEMIA IN PATIENTS IN THE INTENSIVE CARE UNIT

The reported prevalence of hypomagnesemia in adult intensive care unit (ICU) admissions ranges from 15% to 60% of cases.[3,5] Most commonly, severe ionized hypomagnesemia in ICU settings is encountered after liver transplantation and in patients with severe sepsis,[5] but many conditions encountered in ICU patients can be associated with hypomagnesemia (Table 18.1). Hypomagnesemia is associated with an increased risk of mortality.[5]

CLINICAL SIGNS AND SYMPTOMS OF HYPOMAGNESEMIA

Hypomagnesemia is frequently asymptomatic in critically ill patients and is commonly identified through routine laboratory studies.[6,7] However, the relationship between hypomagnesemia and intracellular magnesium depletion is complex. Hypomagnesemia is most commonly seen in conjunction with hypokalemia, hypocalcemia, and/or other electrolyte abnormalities. In most instances, symptoms were attributed to Mg^{++} deficiency only after other electrolyte abnormalities had been corrected.[3,6,7] As summarized in Table 18.2, the clinical sequelae of Mg^{++} deficiency are most commonly related to the cardiovascular, metabolic, and neuromuscular systems.

Hypomagnesemia is associated with electrocardiogram (ECG) changes similar to those observed in patients with hypokalemia: flattened T waves, U waves, and a prolonged QT interval. Magnesium is a cofactor for Na^+/K^+-ATPase in cardiac tissue.[3,6,8] Hypomagnesemia is associated with a variety of dysrhythmias, including atrial fibrillation, multifocal atrial tachycardia, ventricular tachycardia, and torsades de pointes.[6,8] The administration of intravenous magnesium sulfate ($MgSO_4$) should be the initial therapy for torsades de pointes and should be considered as an adjunctive treatment for refractory ventricular dysrhythmias.[3,6,8] However, routine use of magnesium supplementation for the treatment of arrhythmia with the exception of torsades de pointes is not supported by high-quality evidence.[1] Magnesium administration during acute myocardial infarction is not recommended.[9–11]

Hypomagnesemia is commonly associated with both hypokalemia and hypocalcemia.[6] The medications and homeostatic changes that affect magnesium handling often affect K^+ handling as well. In addition, hypomagnesemia promotes the renal losses of K^+. Thus hypokalemia can be refractory to potassium supplementation unless magnesium is replaced first.[3,6] A somewhat similar condition is noted for hypocalcemia because hypomagnesemia suppresses parathyroid hormone release and activity.[12] Consequently, hypocalcemia can be refractory to Ca^{++} replacement unless Mg^{++} is replaced as well.[3,6] Hypomagnesemia has been shown to be associated with an increased incidence and degree of lactic acidosis.[13]

Magnesium produces a depressant effect on the nervous system through its ability to cause presynaptic inhibition.[3,6,8] It may also depress the seizure threshold by its ability to competitively inhibit *N*-methyl-D-aspartate receptors.[3,6,8] The neurologic and neuromuscular manifestations of hypomagnesemia include coma, seizures, weakness, and signs of muscular irritability. The supplementation of magnesium might provide neuroprotective properties in patients with traumatic brain injury and prevent cerebral vasospasm in patients with aneurysmal subarachnoid hemorrhage.[14,15] However, prehospital administration of magnesium for

TABLE 18.1 Etiology of Hypomagnesemia in the ICU[3,6,7]

Decreased GI intake	Magnesium-poor diet or total parenteral nutrition; malabsorption syndrome; short bowel syndrome
Increased GI losses	Chronic diarrhea; intestinal and biliary fistulae; nasogastric suctioning; vomiting
Intrinsic renal losses	Interstitial nephropathy; postrenal transplantation; postobstructive or postacute kidney injury diuresis
Drug-induced renal losses	Loop and thiazide diuretics; aminoglycosides; amphotericin B; cyclosporine; cisplatin; granulocyte colony-stimulating factor
Endocrine and metabolic causes	Hyperaldosteronemia; hyperparathyroidism; hyperthyroidism; SIADH; diabetic and alcoholic ketoacidosis; hypophosphatemia; hypercalcemia; hypoalbuminemia
Magnesium redistribution	Acute pancreatitis; administration of epinephrine, insulin; refeeding syndrome; massive blood transfusion
Other causes	CRRT; CPB; severe burns

CPB, Cardiopulmonary bypass; *CRRT,* continuous renal replacement therapy; *GI,* gastrointestinal; *SIADH,* syndrome of inappropriate antidiuretic hormone.

TABLE 18.2 Clinical Signs and Symptoms of Magnesium Deficiency

Cardiovascular	Metabolic	Neurologic	Neuromuscular
Atrial fibrillation, flutter	Hypokalemia	Seizures	Chvostek sign
Ventricular tachycardia, esp. torsades de pointes	Hypocalcemia	Nystagmus	Muscle cramps
Supraventricular tachycardia	Hypophosphatemia	Delirium	Carpopedal spasm
ECG changes (↑ PR, wide QRS, ↑ QT)	Insulin resistance	Coma	Muscle weakness
Hypertension	Athetoid movements	Muscle fasciculations	
Risk of digitalis toxicity			

ECG, Electrocardiogram.

patients with acute stroke did not reduce disability at 90 days.[16] In addition, the administration of Mg^{++} therapy is commonly used in pregnant patients with preeclampsia or eclampsia.[7,17]

Magnesium replacement has been used to treat bronchospasm in patients with asthma.[6] The proposed mechanism of action for the therapeutic benefit of Mg^{++} in bronchospasm involves its relaxant effects on smooth muscle and immunoregulatory actions that promote synthesis of prostacyclin and nitric oxide, leading to bronchodilation. Evidence to support the routine use of inhaled or intravenous magnesium for acute asthma attacks remains controversial; however, addition of intravenous $MgSO_4$ to nonresponders of standard therapy has been beneficial.[7]

TREATMENT OF HYPOMAGNESEMIA

The management of hypomagnesemia should include the identification and correction of underlying causes and the replacement of magnesium. The degree of hypomagnesemia, severity of clinical symptoms, associated electrolyte abnormalities, and renal function should be assessed before initiating Mg^{++} therapy.

In general, intravenous administration of Mg^{++} is preferred in symptomatic critically ill patients. Current recommendations for Mg^{++} replacement therapies are of somewhat limited value because of the lack of adequately controlled studies. Magnesium may be administered intravenously as $MgSO_4$ (1 g = 4 mmol) or $MgCl_2$ (1 g = 4.5 mmol) and orally as magnesium gluconate (500 mg = 1.2 mmol) or magnesium oxide (400 mg = 6 mmol). When intravenous Mg^{++} replacement is used, a bolus followed by continuous infusion or infusion alone is preferred, because renal filtration and excretion may limit Mg^{++} retention. For the management of torsades de pointes, 1–2 g of intravenous $MgSO_4$ over 5 minutes followed by infusion is recommended. For the urgent treatment of severe hypomagnesemia, an intravenous bolus of 4–8 mmol of Mg^{++} (1–2 g $MgSO_4$), followed by an infusion of 16–32 mmol Mg^{++} (4–8 g $MgSO_4$) over the next 6–12 hours should be considered. In cases of preeclampsia, an initial bolus of 4 g over 10–15 minutes followed by an infusion of 1 g/h should be used.[7]

KEY POINTS

- Hypomagnesemia is one of the most common electrolyte disturbances encountered in ICU patients.
- Hypomagnesemia is frequently asymptomatic; however, in ICU patients, it is associated with increased mortality.
- Hypomagnesemia in ICU patients manifests as disturbances in the cardiovascular, neuromuscular, and metabolic systems.
- Aggressive intravenous administration of magnesium is indicated in cardiac arrhythmias, including torsades de pointes, preeclampsia/eclampsia, and status asthmaticus refractory to conventional therapy.

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Hypocalcemia and Hypercalcemia

Robert N. Cooney, Joan Dolinak, and William Marx

Abnormal serum calcium concentration is a common finding in critically ill patients. The prevalence of hypocalcemia in intensive care unit (ICU) patients ranges from 70% to 90% when total serum calcium is measured and from 15% to 50% when ionized calcium is measured.[1] Hypercalcemia occurs less frequently, with a reported incidence of <15% in critically ill patients.[2] Hypocalcemia is associated with injury severity and mortality in critically ill patients.[1,3–5] However, whether low serum calcium is protective, harmful, or simply prognostic in critical illness is unclear. Therefore in most instances, the management of hypocalcemia involves treating the underlying medical condition(s), except when patients are symptomatic or hemodynamically unstable.

CALCIUM PHYSIOLOGY AND METABOLISM

Calcium is a divalent ion (Ca^{2+}) involved in critical biologic processes like muscle contraction, blood coagulation, neuronal conduction, hormone secretion, and the activity of various enzymes.[3–5] Therefore it is not surprising that intracellular and extracellular calcium levels, like pH, are tightly regulated. A normal adult contains approximately 1–2 kg of total body calcium, which is primarily located in bone (99%) as hydroxyapatite.[1,3,5] Skeletal stores of calcium represent an unlimited reservoir that is predominantly regulated by extracellular Ca^{2+}, parathyroid hormone (PTH), and calcitonin. Extracellular concentrations of Ca^{2+} are typically 1–10,000 times greater than cytoplasmic Ca^{2+} levels.[1,3] Similarly, the majority of intracellular calcium (>90%) is found in subcellular organelles (e.g., mitochondria, microsomes, and endoplasmic or sarcoplasmic reticulum [ER/SR]) as opposed to in the cytoplasmic compartment. Ca^{2+}-mediated cell signaling involves rapid changes in cytoplasmic Ca^{2+} from both internal and external stores.[6,7] Cytoplasmic Ca^{2+} influx occurs through cell membranes by receptor-activated, G-protein–linked channels and the release of internal Ca^{2+} from ER/SR by second messengers.[6] The efflux of cytoplasmic Ca^{2+} involves the transport of Ca^{2+} across the cell membrane and into the ER/SR via specific transporters.[6–8] These tightly controlled pulsations of cytoplasmic Ca^{2+} thus regulate signal strength and frequency for calcium-mediated cellular functions. Alterations in Ca^{2+} signaling have been identified in myocytes, hepatocytes, neutrophils, and T lymphocytes during sepsis and may contribute to the development of organ dysfunction during catabolic illness (for a review see Ref. 7).

Extracellular calcium homeostasis is maintained by the coordinated actions of the gastrointestinal tract, kidneys, and bone.[1,3] Levels of extracellular Ca^{2+} are detected by calcium-sensing receptors on parathyroid cells.[8] In response to low serum Ca^{2+}, the parathyroid glands secrete PTH, which reduces the renal reabsorption of phosphate, increases renal calcium reabsorption, and stimulates renal hydroxylation of vitamin D.[1,3] PTH and 1,25-dihydroxy vitamin D (calcitriol) promote the release of calcium from bone by activating osteoclasts.[1,3] Calcitriol also stimulates intestinal absorption of dietary calcium and regulates PTH secretion by inhibiting PTH gene transcription. PTH secretion is also influenced by serum phosphate concentration. High circulating phosphate levels stimulate PTH secretion by lowering extracellular Ca^{2+}. Magnesium is required for the release of PTH from parathyroid cells and may explain the occurrence of hypocalcemia in patients with magnesium deficiency. Calcitonin is a calcium-regulating hormone secreted by the parafollicular C cells of the parathyroid gland during hypercalcemia. Although calcitonin inhibits bone resorption and stimulates the urinary excretion of calcium, this hormone does not appear to play a major role in calcium homeostasis in humans.[1,3]

The normal concentration of ionized calcium in the extracellular space (plasma and interstitium) is 1.2 mmol/L and represents 50% of the total extracellular calcium. The remaining 40% is bound to plasma proteins, and 10% is combined with citrate, phosphate, or other anions. Total serum calcium normally ranges from 9.4 to 10.0 mg/dL (2.4 mmol/L). The distribution of ionized and bound calcium may be altered in critically ill patients. Chelating substances like citrate and phosphate may influence the abundance of ionized Ca^{2+}. Increased free fatty acid levels caused by lipolysis or parenteral nutrition result in increased binding of calcium to albumin.[9] Protein-bound calcium is also increased during alkalosis and reduced during acidosis.[1,3] Correcting total serum calcium for albumin and pH does not accurately estimate ionized Ca^{2+}.[10,11] Therefore a direct measurement of ionized serum calcium has been found to be the most accurate way to determine the concentration of this cation, and hence this approach is indicated in critically ill patients.[12]

HYPOCALCEMIA IN CRITICALLY ILL PATIENTS

Ionized hypocalcemia is frequently seen in critically ill patients with sepsis, pancreatitis, severe traumatic injuries, or after major surgery. The incidence of hypocalcemia ranges from 15% to 50%.[3] The degree of hypocalcemia correlates with illness severity as measured by the Acute Physiology and Chronic Health Evaluation (APACHE) II score and is associated with increased mortality in critically ill patients.[4] In particular, the degree of systemic inflammation, as measured by cytokine, tumor necrosis factor (TNF)-alpha, and pro-calcitonin levels, appears to correlate with hypocalcemia in ICU patients.[11] Potential etiologies for the hypocalcemia of critical illness include impaired PTH secretion or action, vitamin D deficiency or resistance, calcium sequestration or chelation, or impaired mobilization of Ca^{2+} from bone (Table 19.1).

Hypocalcemia in the ICU is rarely caused by primary hypoparathyroidism. However, sepsis and systemic inflammatory response syndrome (SIRS) is commonly associated with hypocalcemia, which is caused in part by the impaired secretion and action of PTH and the failure to synthesize calcitriol.[1,3,11] Hypomagnesemia may contribute

TABLE 19.1 Causes of Hypocalcemia

Impaired Parathyroid Hormone Secretion or Action
Primary hypoparathyroidism
Secondary hypoparathyroidism
Impaired Vitamin D Synthesis or Action
Poor intake
Malabsorption
Liver disease
Renal disease
Hypomagnesemia
Sepsis
Calcium Chelation/Precipitation
Hyperphosphatemia
Citrate
Pancreatitis
Rhabdomyolysis
Ethylene glycol
Decreased Bone Turnover
Hypothyroidism
Calcitonin
Cis-platinum
Diphosphonates
Mithramycin
Phosphates

From Zaloga GP. Hypocalcemia in critically ill patients. *Crit Care Med.* 1992;20(2):251–261.

to hypocalcemia during critical illness via inhibitory effects on PTH secretion and target organ responsiveness.[1,3,5] However, the presence of hypomagnesemia only weakly correlates with hypocalcemia in ICU patients.[4]

In many instances, the hypocalcemia of critical illness is multifactorial in etiology. Elderly patients are at an increased risk for vitamin D deficiency because of malnutrition, poor intestinal absorption, and hepatic or renal dysfunction.[3] In obese patients with previous gastric bypass, the intestinal absorption of calcium dramatically decreases despite reasonable vitamin D levels and recommended calcium intake.[13] Renal failure may precipitate hypocalcemia via the decreased formation of calcitriol and hyperphosphatemia and the chelation of ionized calcium.[1,3] The use of continuous renal replacement therapy in critically ill patients is associated with significant magnesium and calcium losses. This results in electrolyte replacement requirements that often exceed the calcium and magnesium supplementation provided in standard parenteral nutrition formulas.[14] Other potential causes of ionized hypocalcemia in critically ill patients include alkalosis (increased binding of Ca^{2+} to albumin), medications (anticonvulsants, antibiotics, diphosphonates, and radiocontrast agents), massive blood transfusion, sepsis, and pancreatitis.[1,3–5] More recently, the infusion of high doses of propofol have been shown to reduce circulating calcium concentrations by elevating serum PTH levels, but the physiologic significance of this phenomenon is unclear.[15] Ionized hypocalcemia (<1.0 mmol/L) is associated with prehospital hypotension and represents a better predictor of mortality in severely injured patients than does base deficit.[16] The exact reasons for this observation are unclear but potentially relate to head injury and/or the presence of hemorrhagic shock. Injured patients receiving blood transfusions may develop hypocalcemia as a consequence of Ca^{2+} chelation by citrate, which is used as an anticoagulant in banked blood.[17–19] The incidence of transfusion-related hypocalcemia is related to both the rate and volume of blood transfusion.[17,18] When blood transfusions are administered at a rate of 30 mL/kg/h (e.g., 2 L/h in a 70-kg patient) and hemodynamic stability is maintained, ionized Ca^{2+} levels are preserved by physiologic compensatory mechanisms.[19] Transient hypocalcemia may be observed with rapid transfusion and can be prolonged or exacerbated by hypothermia, renal failure, or hepatic failure.[17–19] Consequently, ionized calcium should be monitored and replaced when clinically indicated during massive transfusion. However, hypocalcemia tends to normalize within 4 days after ICU admission, and failure to normalize in severely hypocalcemic patients may be associated with increased mortality. Calcium replacement does not typically improve normalization or reduce mortality.[20]

HYPOCALCEMIA IN SEPSIS AND PANCREATITIS

Hypocalcemia is especially common in critically ill patients with systemic infection or pancreatitis.[1,3,4,7,11] In animal models, serum calcium concentrations decrease after endotoxin infusion.[7,11,21,22] When septic patients with hypocalcemia were compared with nonseptic controls, increased TNF-alpha and interleukin-6 levels correlated with ionized hypocalcemia.[23] Septic patients with hypocalcemia may demonstrate increased or decreased PTH levels; however, urinary excretion of calcium and bone resorption appear to be preserved when compared with controls.[11,21] Procalcitonin levels are increased during sepsis-induced hypocalcemia, but mature calcitonin only exerts a weak and transient effect on circulating calcium level.[23,24] Collectively, the results suggest that hypocalcemia during severe infection has a multifactorial etiology but that inflammatory cytokines, impaired activation of vitamin D, and elevated procalcitonin are contributory.

It remains unclear whether sepsis-induced hypocalcemia is pathologic or protective. Calcium administration in experimental sepsis has been shown to increase or have no effect on mortality.[21,22] Similarly, investigations on the effects of Ca^{2+} blockade on septic mortality demonstrate conflicting results.[23–25] Therefore although sepsis-induced hypocalcemia is commonly seen in critically ill patients, neither routine replacement of calcium nor the use of calcium channel blockers is supported by the existing literature. As with most situations, sepsis-induced hypocalcemia should be treated if patients are symptomatic.

Pancreatitis represents another inflammatory condition that is associated with hypocalcemia in critically ill patients.[1,3,25,26] Saponification of retroperitoneal fat contributes to the development of hypocalcemia in patients with pancreatitis.[3,25,26] In rats with experimental pancreatitis, injection of free fatty acids into the peritoneum induces hypocalcemia.[25] However, the amount of calcium chelated is relatively small compared with the calcium stores in the bone reservoir available for exchange. Interestingly, elevated levels of PTH seen in pancreatitis, like sepsis, do not result in normalized ionized calcium levels.[25–27] Although the resistance of bone and kidney to PTH may be a factor, it is likely that inflammatory pathways identical to those in sepsis are responsible. In pancreatitis, like sepsis, hypocalcemia is an indicator of disease severity. As with most clinical conditions, calcium replacement during pancreatitis should be reserved for the symptomatic or hemodynamically unstable patient.

HYPOCALCEMIA AND MASSIVE TRANSFUSION PROTOCOLS

Massive transfusion (more than 10 units of packed red blood cells [PRBCs] in a 24-hour period) is a commonly used technique in the resuscitation of trauma patients. Fresh frozen plasma (FFP) and PRBCs are stored with citrate as the preservative. Ca is a cofactor for

factors II, VII, IX, and X. Hypocalcemia occurs because of calcium chelation by citrate.[28] Low ionized calcium levels are associated with hypotension and poor outcome. Ionized calcium (iCa) levels (iCa <1) has been shown to be an independent predictor for the need for massive transfusion and mortality.[29] Monitoring serum calcium levels during massive transfusion protocols is a prudent practice.

SIGNS AND SYMPTOMS OF HYPOCALCEMIA

Hypocalcemia is frequently asymptomatic, and attributable signs or symptoms may be difficult to elucidate in critically ill patients. In general, the signs and symptoms of hypocalcemia correlate with both the magnitude and rapidity of onset of the condition. Neurologic (paresthesias, seizures, dementia) and cardiovascular (hypotension, impaired cardiac contractility, dysrhythmias) signs may be seen with ionized hypocalcemia Ca^{2+} <1.0 mmol/L.[3,5] Neuromuscular symptoms of profound hypocalcemia include muscle spasms and tetany. Psychiatric disturbances (dementia, psychosis, depression) also may be attributable to hypocalcemia.[3,5]

Classic signs of hypocalcemia include the Chvostek and Trousseau signs, which test for latent tetany. The Chvostek sign is an involuntary twitching of facial muscles in response to light tapping of the facial nerve. It is nonspecific and is present in 10% to 25% of normal adults and may be completely absent in chronic hypocalcemia. The Trousseau sign is a carpopedal spasm induced by reduced blood flow to the hand in the presence of hypocalcemia when a blood pressure cuff is inflated to 20 mm Hg for 3 minutes. The Trousseau sign is also nonspecific and may be absent in one-third of patients with hypocalcemia.

Cardiac dysrhythmias, such as ventricular tachycardia, prolonged QT interval, and heart block, are more serious complications of hypocalcemia.[3,5] In addition, decreased cardiac output and hypotension, especially where refractory to vasopressors and volume, should prompt calcium replacement when hypocalcemia is present.[3,5]

TREATMENT OF HYPOCALCEMIA

Critical thresholds for calcium replacement vary, but severe ionized hypocalcemia <0.8 mmol/L and symptomatic hypocalcemia should be replaced in critically ill patients.[1,3,5] Treatment of asymptomatic ionized hypocalcemia >0.8 mmol/L is usually unnecessary and may be harmful in conditions such as sepsis and cellular hypoxia.[1,3,5,27]

Treatment of hypocalcemia requires intravenous calcium replacement. The two solutions most commonly used are 10% calcium chloride and 10% calcium gluconate. Each solution contains 100 mg/mL of calcium salt and is provided in 10-mL ampules. Ten percent calcium chloride contains 27 mg/mL of elemental calcium (1.36 mEq/mL); 10% calcium gluconate contains 9 mg/mL (0.46 mEq/mL). Typically, 10 mL of 10% calcium gluconate solution is infused over 10 minutes. A total of 200 mg of elemental calcium may be necessary to raise the total serum calcium by 1 mg/dL. Because the effect of calcium infusion is usually brief, a continuous infusion may be necessary. Calcium chloride should not be infused peripherally if calcium gluconate is available, because the former can produce tissue necrosis and thrombophlebitis if extravasation occurs.

Hemodynamically unstable patients in the ICU who are hypocalcemic may show a transient increase in blood pressure and/or cardiac output with calcium administration. This is probably the result of increased cardiac performance.[27] However, in the presence of tissue hypoxia, calcium administration may aggravate the cellular injury.[9,24] Nonetheless, calcium administration is probably warranted in the hypocalcemic, hemodynamically unstable patient, especially those requiring adrenergic support.

Despite the prevalence of hypocalcemia in critically ill patients, there is a paucity of evidence on the benefit of calcium supplementation in this population. Other than elevating systemic ionized calcium, there is no clear evidence that calcium supplementation affects the outcome in critically ill ICU patients.[28] Collectively, these data suggest that hypocalcemia is a metabolic derangement associated with severe illness as opposed to a correctable condition resulting in a poor outcome.

HYPERCALCEMIA

Hypercalcemia is rare in critically ill patients, estimated to be present in between 1% and 15% of ICU patients.[2] Defined as an increase in serum calcium above 10.4 mg/dL (2.60 mmol/L), hypercalcemia usually is caused by excessive bone resorption. Hyperparathyroidism and humoral hypercalcemia of malignancy are the most common causes of hypercalcemia in hospitalized patients.[2,5,29] Less common causes of hypercalcemia include granulomatous disease, prolonged immobilization, and medications (e.g., thiazide diuretics or lithium) (Table 19.2).[35-43]

TABLE 19.2 Causes of Hypercalcemia

Parathyroid Hormone Mediated
Sporadic (adenoma, hyperplasia, or carcinoma)
Familial (MEN neoplasia 1, 2a, or 4; hyperparathyroid jaw tumor syndrome; familial isolated hyperparathyroidism)
Ectopic parathyroid hormone in malignancy
Tertiary hyperparathyroidism
Malignancy
Hypercalcemia of malignancy (PTHrP)
Local osteolysis
Ectopic parathyroid hormone
Calcitriol-related hypercalcemia
Vitamin D Related
Granulomatous disease (i.e., sarcoidosis, tuberculosis, berylliosis, coccidiomycosis, histoplasmosis, leprosy, inflammatory bowel disease, foreign body granuloma)
Vitamin D intoxication
Endocrine Disorders
Thyrotoxicosis
Adrenal insufficiency
Pheochromocytoma
VIPoma (Verner Morrison) syndrome
Drugs
Thiazide diuretics
Lithium
Milk-alkali syndrome
Hypervitaminosis A
Other
Immobilization in major burns with renal failure
Acute renal failure with rhabdomyolysis
Chronic renal failure treated with calcium and calcitriol or a vitamin D analogue
Renal transplant
Candidiasis in the setting of acute leukemia or immunosuppression
Genetic mutation of the *CYP24A1* gene

MEN, Multiple endocrine neoplasia; *PTHrP,* parathyroid-related protein.

Mild hypercalcemia is usually asymptomatic. However, patients with circulating Ca^{2+} above 12 mg/dL may manifest symptoms of confusion, delirium, psychosis, and coma.[2,5,29] Patients with hypercalcemia also may experience nausea, vomiting, constipation, abdominal pain, and ileus. Cardiovascular effects of hypercalcemia include hypotension, hypovolemia, and shortened QT interval. Profound skeletal muscle weakness may result. Seizures, however, are rare.

The treatment of hypercalcemia should be directed at the underlying medical condition. Saline infusion and diuresis are indicated in symptomatic patients and when the serum calcium level rises above 14 mg/dL (3.5 mmol/L). For patients with underlying malignancy, treatment with salmon calcitonin, pamidronate, or plicamycin may be necessary. These agents act to inhibit bone resorption. Hydrocortisone can also be used in combination with calcitonin to treat hypercalcemia associated with multiple myeloma.

Steroids are a principal therapeutic option produced by excessive production of calcitriol from calcidiol, independent of PTH, by the macrophages present in granulomas.[30] In foreign body granulomas with hypercalcemia, initial treatment may also include locally injecting steroids near the foreign body. The imidazole antifungals, primarily ketoconazole, inhibit the 1-alpha-hydroxylase from the macrophage and have been used to treat hypercalcemia in which steroids are not effective or their side effects cannot be tolerated.[31,32] Imidazoles can reduce calcium levels in other causes of hypercalcemia, though hepatic toxicity will limit their use.[33]

KEY POINTS

- Massive transfusion can cause hypocalcemia, in part because of the citrate used to store blood and chelation. Replacement is often necessary.
- The best test for hypocalcemia is an ionized calcium level, with replacement when values are <1.0 mmol/L.
- Hypocalcemia is frequently seen in ICU patients with sepsis or SIRS, pancreatitis, massive transfusions, and/or solid organ failure. It is often multifactorial and can be caused by vitamin D deficiency, inflammatory cytokines TNF-alpha and interleukin-6, and sequestering in the case of pancreatitis.
- Hypercalcemia is less likely to be encountered in the ICU. Most commonly, this is from an elevated PTH, but could be paraneoplastic, lytic, or caused by an infectious or granulomatous process.
- Initial treatment of hypercalcemia should be saline infusion and diuresis. Treatment should then be tailored to the cause and the patient's tolerance.

References for this chapter can be found at expertconsult.com.

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Disorders of Glucose Control or Blood Glucose Disorders

Roshni Sreedharan and Basem B. Abdelmalak

INTRODUCTION

Alterations in glucose metabolism are common in the intensive care unit (ICU). The adverse effects of uncontrolled hyperglycemia, especially in a critically ill patient, are fairly well described.[1–3] Management strategies for hyperglycemia in the critically ill patient have gone through substantial changes over the past two decades. Although hyperglycemia is associated with adverse clinical outcomes, trying to achieve euglycemia in all patients has not proven to be the solution. Although the initial landmark randomized controlled trial showed remarkable benefits to tight glycemic management in the ICU,[1] attempts by other investigators to replicate those findings were futile. On the contrary, it resulted in an increase in hypoglycemic episodes and consequently mortality, as evidenced by the largest multicenter randomized controlled trial to date.[4,5] It is worth noting that there is an exceedingly large body of evidence from observational and retrospective studies shedding light on the various glycemic domains that clinicians should keep in mind while managing hyperglycemia in both patients with and without diabetes.[6–8] The presence of a history of diabetes and the extent of a patient's chronic glycemic state would probably play a role in determining the glycemic target.[9,10] Furthermore, glycemic variability, regardless of the chosen target, may also have an impact on glycemic management outcomes.[11]

Hyperglycemia is associated with harm in the ICU, as is hypoglycemia, which is equally, if not even more, serious than hyperglycemia in its detrimental impact.[12,13] Hypoglycemia thus deserves much attention concerning its etiology, risk factors, and interventions aimed at prevention and timely treatment.

This chapter gives an overview of hyperglycemia, hypoglycemia, and their management strategies in the critically ill patient.

HYPERGLYCEMIA

Definition of Hyperglycemia

When a critically ill patient is hyperglycemic, it is important to delineate the clinical group to which the patient belongs. These include the following:

- A known diabetic
- Undiagnosed diabetic
- Nondiabetic with new-onset hyperglycemia (stress-induced)

The American Diabetes Association (ADA) has published criteria for the diagnosis of diabetes mellitus.[14] A diagnosis of diabetes is established when any one of the following criteria is met:

- Fasting plasma glucose >126 mg/dL (7 mmol/L)
- Postprandial plasma glucose >200 mg/dL (11.1 mmol/L) after 2 hours of a 75-g oral glucose tolerance test
- HbA_{1c} >6.5%
- Classic symptoms of hyperglycemic crisis with a random glucose >200 mg/dL (11.1 mmol/L)

Unfortunately, there is no set definition for hyperglycemia in the critically ill patient, as it is confounded by the presence of multiple variables, including the severity of illness, concurrent administration of glucose-containing medications such as antibiotics, feeding, and hyperglycemia-inducing medication, such as catecholamine infusions or glucocorticoids. When a patient presents with new-onset hyperglycemia (NOH), whether critically ill or not, it is prudent to rule out the presence of undiagnosed diabetes mellitus. The presence of an HbA_{1c} >6.5% might aid in making this diagnosis. The ADA/American Association of Clinical Endocrinologists (ACCE) in their consensus statement recommend that any blood glucose >180 mg/dL (10 mmol/L) be treated in patients who are critically ill in an attempt to reduce the adverse outcomes associated with hyperglycemia.[15]

Stress-Induced Hyperglycemia

Hyperglycemia was initially considered to be a normal adaptive response in a critically ill patient to survive a period of acute stress. An increase in the levels of catecholamines, growth hormone, exogenous and endogenous glucocorticoids, and glucagon, along with an increase in circulating cytokines and peripheral insulin resistance, may play an important role in the genesis of stress-induced hyperglycemia.[16,17] However, stress hyperglycemia in patients with previously normal glucose homeostasis has been associated with an increase in adverse outcomes in patients who are critically ill. These adverse outcomes were attributed to either hyperglycemia per se or free radical injury and its related adverse coronary and intracranial events.[18] Although hyperglycemia by itself during acute illness may not be the actual cause of the increase in mortality, it may indicate and correlate with the degree of underlying disease severity.

Diabetic versus Nondiabetic Blood Glucose Management in the ICU

Recent evidence indicates that glycemic targets in the ICU should probably vary based on the presence of a history of diabetes and the chronic glycemic state before ICU admission.[6,9,10,19,20] Furthermore, Abdelmalak and colleagues reported that 11% of patients presenting for noncardiac surgery have undiagnosed diabetes,[21] and there is no reason not to believe that many patients are probably admitted to ICU who are also undiagnosed diabetics. Diabetic patients who are chronically hyperglycemic can probably tolerate, or might even do better with, a higher-than-normal glycemic target and reduced glycemic variability. A retrospective study of 450 critically ill diabetic patients with a total of 9946 glucose measurements in the study cohort found that patients who had higher (>7%) preadmission HbA_{1c} levels had a lower mortality when the ICU time-weighted glucose concentration was higher (>180 mg/dL [10 mmol/L]), as compared with patients who had lower HbA_{1c} (<7%).[22] Similar findings were reported in

larger patient cohorts.[9,23,24] A meta-analysis of nine studies was conducted in 2012 with regard to hyperglycemia and in-hospital mortality associated with sepsis, measuring unadjusted ICU mortality in five of the nine studies. They observed an increase in ICU mortality and a 2.7-fold increase in hospital mortality in patients with NOH as opposed to diabetic patients with hyperglycemia.[25] This difference may be the result of the fact that in a previously chronically hyperglycemic diabetic, the organs and immune system may have been accustomed to higher blood glucose concentrations, and an acute attempt at euglycemia presents a state of relative hypoglycemia for them. Furthermore, if such an attempt at euglycemia is associated with moderate or severe hypoglycemia, as is the case with many tight glycemic control algorithms, such dangerously low concentrations are harmful by themselves[5,12] and contribute to a significant increase in glycemic variability.[11] One of the largest database studies evaluating the effect of diabetes on outcomes in critically ill patients found that hyperglycemia was more detrimental in nondiabetics and was potentially protective in diabetics. There was an increased risk of mortality exclusively in diabetic patients in the normoglycemic/hypoglycemic range, suggesting a relative intolerance to relative and absolute hypoglycemia in this subset of patients.[26] In light of these findings, we probably should seek different glycemic targets (and more robust insulin protocols to achieve such targets) that vary based on the presence of a diagnosis of diabetes and previous chronic glycemic states. Marik and Egi have proposed an example of such variable glycemic targets based on the patient's clinical condition, history of diabetes, and HbA_{1c}, signifying the extent of the long-term status of glycemic control.[27]

THE GLYCEMIC DOMAINS AND THE INFLUENCE OF PREEXISTING DIABETES DIAGNOSIS ON OUTCOMES IN THE ICU

The three domains of glycemic control are hyperglycemia, hypoglycemia, and glucose variability. Each of these has independently been shown to increase mortality in critically ill patients.[7,11,13,28,29] Two large studies evaluated these three domains and the approach to glycemic management in the ICU, in addition to the role of diabetes in this complex milieu. The results of both studies are strikingly similar. Hyperglycemia and an increase in glucose variability were associated with an increase in mortality in nondiabetic but not in diabetic patients. On the other hand, hypoglycemia was associated with an increase in mortality in both groups. Furthermore, in diabetic patients, premorbid glycemic control has been shown to play an important role in outcomes based on the glycemic goals. In patients with poor preadmission glycemic control, mortality was higher with lower ICU blood glucose levels than their own "normal" (i.e., relative hypoglycemia). Conversely, in patients with good preadmission glycemic control, survival was higher when ICU blood glucose levels were maintained closer to the normal range (which is also their own normal as well). In 2014 Plummer and colleagues[30] further substantiated previous observations by Egi and colleagues,[22] who observed an 18% increase in the risk of mortality for every 20 mg/dL (1.1 mmol/L) increase in maximum blood glucose in nondiabetic and diabetic patients with good preadmission glycemic control. The data from these studies further emphasize that having one glycemic goal for all critically ill patients is probably suboptimal.[8,20,22,30]

GLYCEMIC GOAL IN THE ICU

Based on the NICE-SUGAR trial, most centers target a blood glucose level of <180 mg/dL (10 mmol/L) for critically ill patients in an attempt to treat hyperglycemia while reducing the incidence of hypoglycemia[4] noticed with the application of tight glycemic control. The ADA also recommends a goal of 140–180 mg/dL (7.7–10 mmol/L) in ICU patients.[31]

GLUCOSE MONITORING IN THE ICU

In current-day practice, most ICUs use bedside glucometers for monitoring, reporting, and managing blood glucose in critically ill patients. Bedside glucometers were introduced in an attempt to improve outpatient diabetes control (i.e., for patient self-monitoring of blood glucose) and are probably not accurate for intensive monitoring and treatment of hyperglycemia in critically ill patients.[32–35] Several variables can affect the accuracy of a bedside glucometer, such as rapidly changing hematocrit, hypoxia, acidosis, use of vasopressors, and peripheral edema. This makes measuring capillary blood glucose using a bedside glucometer less than ideal in the monitoring of patients who need titration of insulin infusions. The Central Laboratory and Standards Institute (CLSI), and the Food and Drug Administration (FDA) require that 95% of the meter readings are within 20% of the reference value. Although such monitors may meet this standard, the issue remains that allowing even that much of a variation in a critically ill patient on an infusion can make insulin therapy risky.[35] Laboratory whole-blood glucose measurement is the gold standard in blood glucose measurement but is labor intensive and not very practical when hourly glucose measurements are required. Another option is to monitor blood glucose using a blood gas analyzer (BGA), which is close to laboratory standards.[34] Blood glucose measurement from arterial whole-blood samples drawn via an arterial line using a BGA is associated with fewer errors (1% outside the permitted 20% error zone) when compared with capillary samples (27% outside the 20% error zone) or arterial samples (12% outside the 20% error zone) using a glucometer.[36] Arterial blood samples have been recommended for the measurement of blood glucose using a BGA, and this has also been extended to point-of-care (POC) testing when used, as opposed to capillary blood samples. In critically ill patients who are dysglycemic, hourly blood glucose measurements are recommended.[29] Although POC testing has been largely used for this purpose, continuous glucose monitoring (CGM) techniques are being developed to consistently recognize dysglycemic episodes.[37] CGM techniques could be either subcutaneous or intravenous. Subcutaneous CGM devices have been studied extensively. The accuracy and reliability of these subcutaneous devices have been demonstrated in critically ill patients in circulatory shock and on vasopressor infusions.[38] In a randomized trial evaluating the impact of CGM on glycemic control and the occurrence of hypoglycemia in critically ill patients, CGM did not improve overall glycemic control but did reduce the occurrence of hypoglycemic events.[39] Another interesting extension of CGM is in the implementation of fully automated closed-loop glucose control. This system automatically modulates insulin (or dextrose) delivery based on glucose measurements using a CGM device without human input. An evaluation of the feasibility of an automated closed-loop glucose control system using continuous subcutaneous glucose measurements in critically ill patients demonstrated an increased duration of blood glucose within the target range without the occurrence of hypoglycemia.[40] CGM techniques are probably as effective and safe as POC testing. In addition, they reduce nursing burden and detect more dysglycemic/hypoglycemic episodes, especially during the night.[39,41,42] Although the technology seems very promising, routine use of CGM techniques in ICUs would need more trials demonstrating their safety and efficacy.[31]

The practical option of using a bedside glucometer might be an acceptable one in many situations when the gold standard is not available or feasible or poses much delay, provided that blood samples are

whole blood—either arterial or central venous vs. capillary samples—when feasible. When the glucometer-rendered glucose value is near the extremes, especially hypoglycemia, and/or showing a major difference compared with the prior value, a central laboratory confirmation might be in order.

Irrespective of the method of blood glucose monitoring or target blood glucose used, there is a requirement to implement a systematic algorithm for insulin infusion titration in the critically ill patient to reduce the occurrence of adverse incidents, primarily hypoglycemia and glucose variability.[43,44] Although Preiser and Devos made this suggestion at a time when tight glucose control was still in vogue, it still holds true when we target a more moderate blood glucose target as well. They suggested that ICUs should develop protocols in collaboration with nursing and medical staff, which are locally applicable. These systematic algorithms should suggest adaptation of the rate of insulin using a dynamic rather than a sliding scale (e.g., adapting the rate of infusion to nutritional support and to the delta change from the prior value vs. the absolute glucose value), the time for next glucose check, types of devices to be used for sampling, and sites of sampling. Once a protocol has been developed, all ICU healthcare providers should be educated on it. On implementation, the quality of this protocol can be evaluated by the incidence of hypoglycemia divided by the frequency of blood glucose checks, time to achieve target glucose, proportion of time in the target range, and blood glucose variability.[45] By implementing such robust algorithms and protocols, we can strive to achieve better glycemic control in critically ill patients and at the same time reduce glucose variability and the occurrence of hypoglycemia.

These issues led to the consensus recommendations on measurement of blood glucose and reporting glycemic control in critically ill adults[35] that has taken a more conservative approach. Here are a few excerpts from the Consensus Recommendations on Measurement of Blood Glucose and Reporting Glycemic Control in Critically Ill Patients:

- All patients whose severity of illness warrants an invasive vascular monitor should have blood glucose samples drawn from an arterial line. If not available, as a second option, samples can be drawn from a central venous line. Only when severity of illness does not warrant an invasive line should capillary blood be used for sampling.
- Samples taken from arterial or central lines should be analyzed either in the central laboratory or using a blood gas analyzer. If delay with the central laboratory is unacceptable, blood gas analyzers should be the default analyzer. A glucometer is acceptable only when a capillary sample is taken from a patient considered to be too well to need invasive vascular access.

ADA Recommendations for Management of Blood Glucose in Hospitalized Patients

In 2020 the ADA issued recommendations for the management of blood glucose in a critically ill adult based on the evidence available thus far[31]:

- Continuous intravenous insulin infusion is the best method for achieving glycemic targets in the critical care setting.
- Insulin therapy should be initiated for persistent hyperglycemia starting at a threshold greater than 180 mg/dL (10 mmol/L). Once insulin therapy is started, a target glucose range of 140–180 mg/dL (7.8–10.0 mmol/L) is recommended for the majority of critically ill and noncritically ill patients.
- More stringent goals such as 110–140 mg/dL (6.1–7.8 mmol/L) may be appropriate for selected critically ill patients, as long as this can be achieved without significant hypoglycemia.
- Intravenous insulin should be administered based on validated written or computerized protocols that allow for predefined adjustments in the infusion rate, accounting for glycemic fluctuations and insulin dose.
- A hypoglycemia management protocol should be adopted and implemented by each hospital. A plan for preventing and treating hypoglycemia should be established for every patient. Episodes of hypoglycemia in the hospital should be documented and tracked.
- The treatment regimen should be reviewed and changed if necessary to prevent further hypoglycemia when the blood glucose value is less than 70 mg/dL (3.9 mmol/L).

HYPOGLYCEMIA

Definition of Hypoglycemia

In 2013 the ADA and the Endocrine Society Workgroup defined hypoglycemia in five categories[46,47]:

- Severe hypoglycemia (symptoms requiring assistance from another person, neuroglycopenic symptoms, seizures or coma, and reversal of these symptoms with the administration of glucose). Glucose measurements may not be available, but neurologic recovery after glucose administration is diagnostic.
- Documented symptomatic hypoglycemia (with a measured plasma glucose of <70 mg/dL [3.9 mmol/L]).
- Asymptomatic hypoglycemia (no symptoms of hypoglycemia but measured plasma glucose is <70 mg/dL [3.9 mmol/L]).
- Probable symptomatic hypoglycemia (symptoms of hypoglycemia not accompanied by a plasma glucose measurement but are presumed to be caused by a plasma glucose concentration <70 mg/dL [3.9 mmol/L]).
- Pseudo-hypoglycemia (symptoms of hypoglycemia in a person with diabetes but with a measured plasma glucose concentration >70 mg/dL [3.9 mmol/L]).

The definition of hypoglycemia in a critically ill patient is challenging because of a lack of symptom reporting in sedated or critically ill patients. The definition and recognition of hypoglycemia in this group of patients are dependent on close monitoring of measured blood glucose. Landmark studies, which have resulted in current glucose management strategies in the ICU, have repeatedly used previously defined severe hypoglycemia values (blood glucose <40 mg/dL [2.2 mmol/L]) for the diagnosis of hypoglycemia in the ICU.[1,2,4]

In 2020 the ADA defined the levels of hypoglycemia severity as follows[48]:

Level 1: measurable glucose concentration <70 mg/dL (3.9 mmol/L) but ≥54 mg/dL (3.0 mmol/L)

Level 2: blood glucose concentration <54 mg/dL (3.0 mmol/L)

Level 3: severe event characterized by altered mental or physical functioning requiring assistance from another person for recovery

INCIDENCE OF HYPOGLYCEMIA IN THE CRITICALLY ILL

The reported incidence of hypoglycemia is variable and depends on the definition used, the glycemic target, and the admission diagnosis. In a retrospective study from the Australia and New Zealand Intensive Care Society adult patient database, the incidence of hypoglycemia (lowest blood sugar observed during the first 24 hours of ICU stay) ranged from 1.5% to 13.8% depending on the definition used (<44 mg/dL [2.4 mmol/L] versus <82 mg/dL [4.5 mmol/L]).[49]

An interesting study by Niven and colleagues examined the impact of two major landmark trials (Leuven 1 and NICE-SUGAR) on glycemic management in 195 adult ICUs over 80 hospitals from January 1, 2001, to December 31, 2012, using the APACHE database. At the start

of the study, the incidence of hypoglycemia was 3%. This increased to 5.8% after the Leuven study, which advocated tight glycemic control, was published and then slightly dropped to 5.2% after the NICE-SUGAR investigators published their results recommending a more liberal target.[50]

RISK FACTORS AND BARRIERS TO RECOGNITION OF HYPOGLYCEMIA IN THE ICU

Identified predictors of hypoglycemia in the ICU include female gender, APACHE 2 score, continuous venovenous hemodialysis (CVVHD), use of bicarbonate substitution solutions, diagnosis of sepsis, use of vasopressors/inotropes, prior diagnosis of diabetes mellitus, serum creatinine >3 mg/dL, insulin therapy, discontinuation of nutrition therapy without an adjustment in insulin therapy, mechanical ventilation, and ICU length of stay.[12,51,52] There are several barriers and risk factors to recognizing hypoglycemia in a critically ill patient—sedation, absence of symptoms, reduced oral intake, frequent change in rate of enteral or parenteral nutrition, and inappropriate timing of insulin. Even a single episode of severe hypoglycemia (<45 mg/dL [2.5 mmol/L]) has been associated with increased mortality.[12] Increased vigilance and relaxation of the glycemic target are warranted in patients with risk factors so as to reduce the incidence of hypoglycemia.

OUTCOMES OF HYPOGLYCEMIA IN THE CRITICALLY ILL

In a post hoc analysis of the NICE-SUGAR trial, severe hypoglycemia (<40 mg/dL [2.2 mmol/L]) and moderate hypoglycemia (41–70 mg/dL [2.3–3.9 mmol/L]) occurred in 3.7% and 45% of the studied patients, respectively. Although hypoglycemia was more common in the intensive insulin therapy group (93.3% severe hypoglycemia; 82.4% moderate hypoglycemia), the association of hypoglycemia with death was similar in both groups. Moderate hypoglycemia was associated with a 40% increase in the risk of death, and severe hypoglycemia doubled this risk. For both groups, the strongest association with death was from distributive shock. This was probably related to the impairment of autonomic function, white blood cell activation, and release of inflammatory mediators.[5] In a recent systematic review and meta-analysis of longitudinal follow-up cohort studies investigating the association between hypoglycemia and adverse outcomes, a dose-dependent relationship between the severity of hypoglycemia and adverse vascular events and mortality was recognized.[53] In some circumstances, hypoglycemia is a consequence of severe underlying disease and serves as a predictor of death and not necessarily the cause. From prospectively collected data from two observational cohorts, patients with hypoglycemia had a higher mortality in comparison with those without hypoglycemia, even after stratification by severity of illness, diagnostic category, diabetic status, mean blood glucose during ICU admission, and coefficient of variation as an index of glycemic variability.[13] In a retrospective cohort study from the Netherlands, despite adjustment for disease severity, the incidence of death in patients exposed to hypoglycemia (<45 mg/dL [2.5 mmol/L]) was 40 per 1000 ICU days compared with 17 per 1000 ICU days in patients without an exposure to hypoglycemia, indicating a possible causal relationship.[54]

PHYSIOLOGY AND SYMPTOMATOLOGY OF HYPOGLYCEMIA

During an episode of hypoglycemia, below a blood glucose concentration of 65 mg/dL (3.6 mmol/L), the secretion of counterregulatory hormones glucagon and epinephrine increases. Both glucagon and epinephrine increase blood glucose concentrations by increasing gluconeogenesis and glycogenolysis—glucagon to a much greater degree than epinephrine. Free fatty acids are mobilized from the adipose tissue and converted to ketone bodies to be used as an energy source when there is a decrease both in insulin and in the ratio of insulin to glucagon.[55] The brain and heart are two organs that are dependent on glucose for energy utilization and function. Consequently, most of the symptoms of hypoglycemia are related to these two organ systems.

The brain uses glucose and ketone bodies as fuel, especially during starvation.[56] Brain glucose concentrations drop close to zero when blood glucose concentration falls below 36 mg/dL (2 mmol/L).[57] This can result in irreversible brain injury in cases of severe and prolonged hypoglycemia. Patients experiencing hypoglycemia present with either adrenergic (tremors, palpitations, anxiety), cholinergic (sweating, paresthesias), or neuroglycopenic symptoms (cognitive, behavioral, psychomotor changes, seizures, coma).[58–60] Hypoglycemic coma may occur when glucose levels are below 40–50 mg/dL (2.2–2.3 mmol/L).[60] The neurons most sensitive to hypoglycemia are located in the superficial layers of the cortex, the hippocampus, the caudate nucleus, and the subiculum.[55,61,62] Even in the absence of cell death, mild recurrent hypoglycemia can cause dysfunction in the hippocampus.[63]

The myocardial cells can use either fatty acids or glucose as fuel. During episodes of hypoxia or ischemia, myocardial cells preferentially use glucose as a substrate for adenosine triphosphate (ATP) generation.[64] Hypoglycemic episodes stimulate the sympathoadrenal system, which can be proarrythmogenic.[65] Various rate and rhythm disturbances, including sinus tachycardia, sinus bradycardia, atrial and ventricular ectopies, and ventricular repolarization abnormalities, have been observed during acute hypoglycemic episodes.[66–68]

MANAGEMENT OF HYPOGLYCEMIA

The management of hypoglycemia involves recognition, immediate treatment, development of a differential diagnosis, evaluation, and long-term management.

Recognition of Hypoglycemia (Fig. 20.1)

Hypoglycemia is usually recognized using the Whipple triad:

- Symptoms of hypoglycemia
- Documented low blood glucose concentration
- Resolution of symptoms when plasma glucose is raised

This is not always possible in critically ill patients. The diagnosis of hypoglycemia is established when the measured plasma glucose is less than 70 mg/dL (3.9 mmol/L).

Treatment

- Depending on the extent of neurologic or neuroglycopenic symptoms, make sure that airway protection is ensured.
- Supplementing glucose is crucial once a diagnosis of hypoglycemia is established. Patients with mild to moderate symptoms of hypoglycemia are effectively treated with oral glucose tablets or carbohydrate-rich food supplements. A response is usually seen in 15–20 minutes. Continued monitoring and supplementation with glucose (as needed) is recommended, as the response to oral glucose may be transient.[69]
- In patients who have severe symptoms or are unable to take glucose orally, intravenous dextrose is supplemented. An initial dose of 25 g of 50% dextrose (50 mL) or a fraction of it is given. For example, if mild to moderate hypoglycemia is encountered, 6.25 g (12.5 mL) or 12.5 g (25 mL), respectively, is given and that can be repeated as needed. The rationale behind giving a smaller amount vs. the full dose in mild to moderate hypoglycemia is to avoid converting a

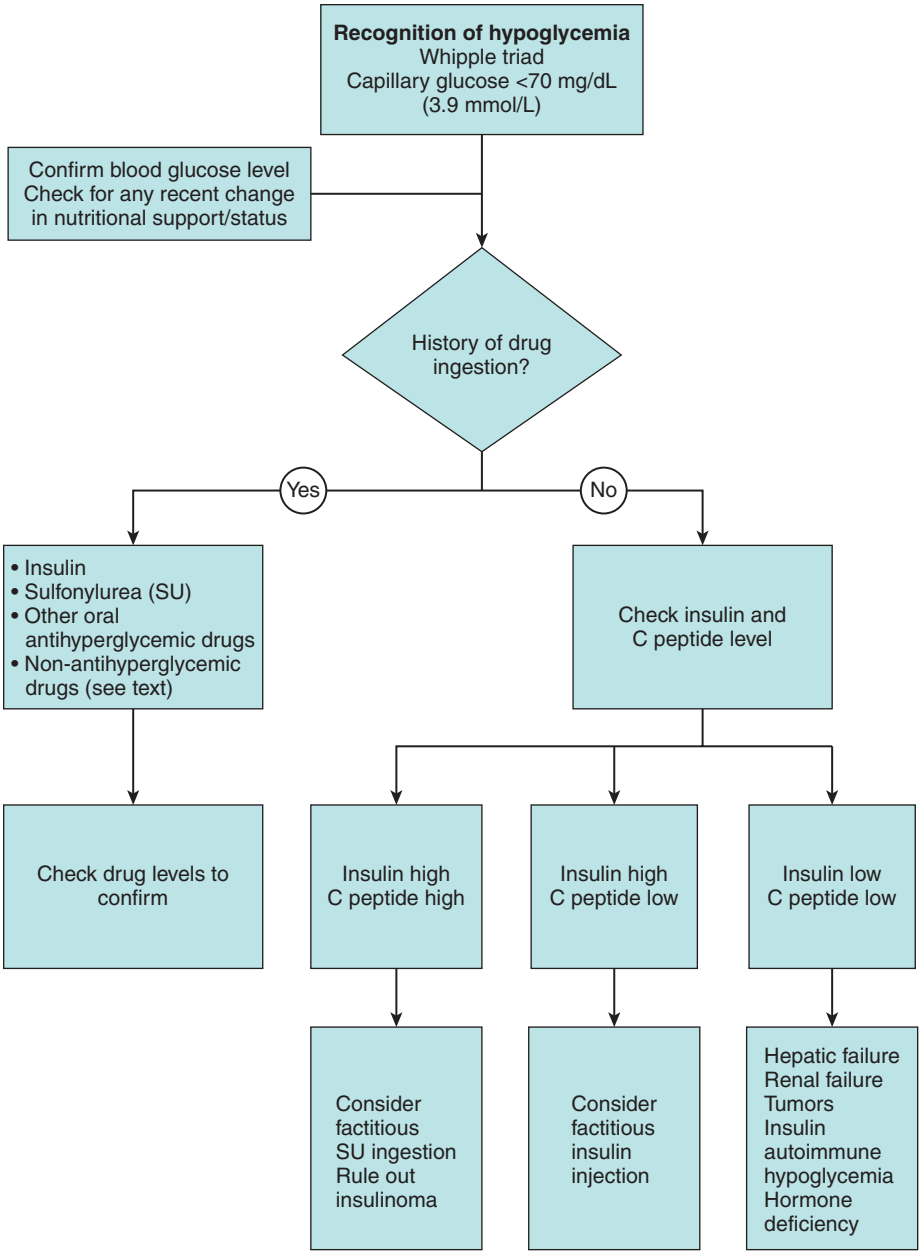

Fig. 20.1 Recognition and Evaluation of Hypoglycemia.

hypoglycemic episode to a hyperglycemic one. The full ampule of 25 g is usually needed to treat severe hypoglycemia (50 mL). A recheck of the blood glucose level would be indicated immediately in 5 minutes or so, after injecting the D50 intravenously. Similar to oral glucose, the effect is transient and may need a continuous dextrose infusion.

- Glucagon can either be given intravenously or subcutaneously at a dose of 1 mg in adults when hypoglycemia is severe or refractory. This can cause transient hyperglycemia.[70]

Differential Diagnosis

- In a critically ill patient, hypoglycemia may be a consequence of therapy with insulin for the management of hyperglycemia, especially when there is a change in nutritional support. Other insulin secretagogues, oral hypoglycemic agents, and several other non-antihyperglycemic agents[71] are frequent culprits as well. The commonly cited non-antihyperglycemic drugs responsible for inducing hypoglycemia include quinolones, pentamidine, quinine, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, and insulin-like growth factor (IGF).[71] Critical illness or sepsis leading to hepatic, renal, and cardiac dysfunction in and of itself can cause hypoglycemia. Rarely, tumors (islet and nonislet cell), hormonal deficiencies, and development of antibodies to either insulin or the insulin receptor may be the cause of hypoglycemia in critically ill patients.[69]

Evaluation

- When blood glucose concentration is indicative of hypoglycemia, it should be corrected immediately and the cause should be investigated.
- If there is no obvious medication-related cause, measurement of insulin and C peptide levels can be helpful.

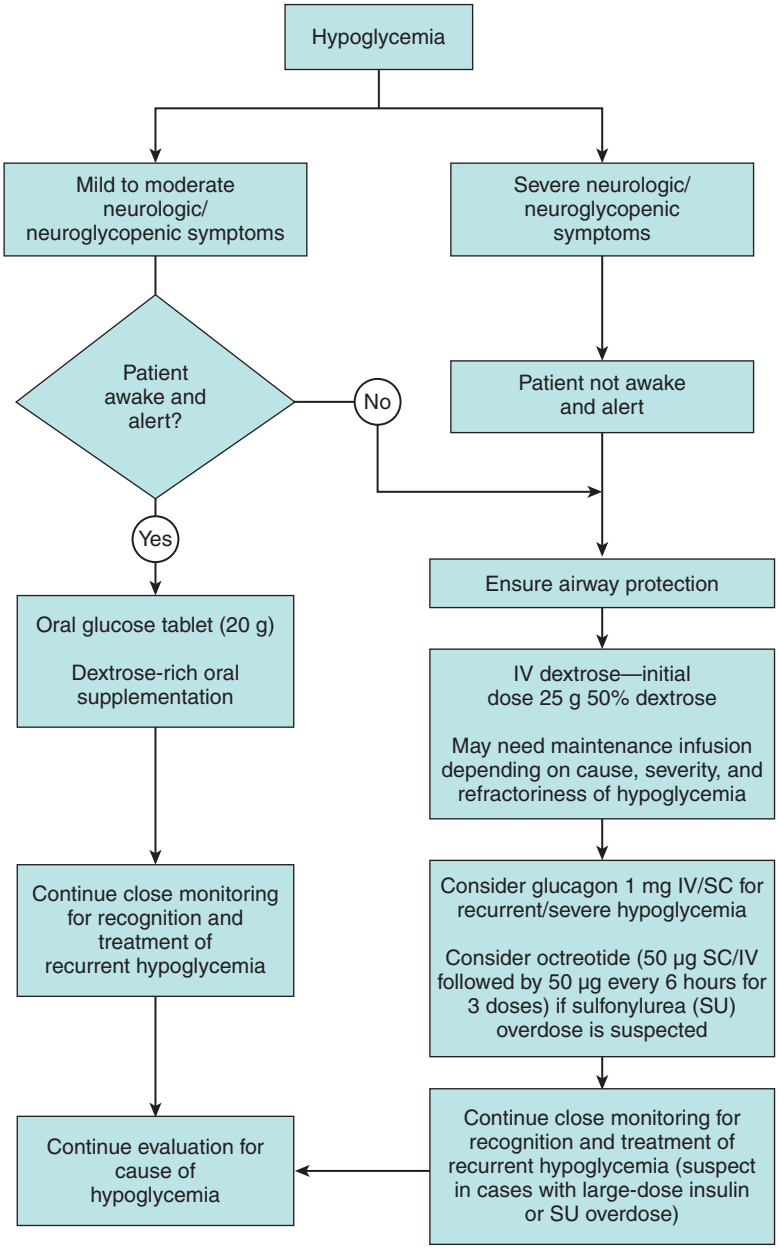

Fig. 20.2 Management of Hypoglycemia. *IV*, Intravenous; *SC*, subcutaneous.

- Make sure that no sudden change in nutritional status (nil per oral [NPO] status/change in rate of enteral/parenteral feed) and/or the insulin content in the feeding solution has been made.
- If sulfonylurea is suspected as the cause, radioimmunoassay can detect sulfonylurea levels.
- Check all medications to look for medication-induced hypoglycemia (non-antihyperglycemic).
- Evaluate for deterioration in renal or hepatic function.
- Evaluate for hormonal deficiencies: thyroid hormone, cortisol.
- Rule out medication error, wrong dose, or concentration of insulin (a common offending agent in medication error).

Management (Fig. 20.2)

- Treat the cause.
- Depending on the cause, an extended period of treatment may be necessary, such as in the case of sulfonylurea-induced hypoglycemia or inadvertent administration of a large dose of insulin.
- In cases of sulfonylurea-induced hypoglycemia, octreotide may be used.[72–74]

CONCLUSION

Several investigators have substantiated the existence of three domains that clinicians need to consider when managing hyperglycemia and setting glucose control targets in the ICU. In attempting to achieve a safe glycemic target, clinicians should consider the treatment of hyperglycemia, prevention of hypoglycemia, and reduction of glycemic variability.[6,9,10,24] Each one of these factors weighs in on improving outcomes in these patients. It is of paramount importance that we tailor insulin protocols based on the clinical picture of the patient to achieve an appropriate target glycemic control. Further research should be directed toward developing such protocols. Although labor intensive, this, coupled with a standardized method for glucose measurement in the ICU, could provide us with data for further clinical

research on the impact of glycemic control on outcomes in critically ill patients. Glycemic control and avoidance of hyperglycemia are important in critically ill patients, but close attention should be paid to prevent hypoglycemia and its related adverse outcomes. Even mild hypoglycemia in the critically ill is associated with increased mortality. Current evidence suggests moving toward more moderate targets that are associated with improved outcomes and fewer hypoglycemic episodes until further evidence emerges.

KEY POINTS

- An increase in the levels of catecholamines, growth hormone, exogenous and endogenous glucocorticoids, and glucagon, along with an increase in circulating cytokines and peripheral insulin resistance, may play an important role in the genesis of stress-induced hyperglycemia.
- In their consensus statement the ADA/ACCE recommend that any blood glucose >180 mg/dL (10 mmol/L) be treated in patients who are critically ill in an attempt to reduce the adverse outcomes associated with hyperglycemia.
- Continuous intravenous insulin infusion has been shown to be the best method for achieving glycemic targets in the critical care setting.
- Once insulin therapy is started, a target glucose range of 140–180 mg/dL (7.8–10.0 mmol/L) is recommended for the majority of the critically ill and non–critically ill patients.
- Just as "one size does not fit all," one glycemic target does not suit all ICU patients. We probably should seek different glycemic targets (and more robust insulin protocols to achieve such targets) that vary based on the presence of a diagnosis of diabetes and previous chronic glycemic state.
- There is a requirement to implement a systematic algorithm for insulin infusion titration in critically ill patients to reduce the occurrence of adverse incidents, primarily hypoglycemia and glucose variability. These systematic algorithms should suggest adaptation of the rate of insulin using a dynamic rather than a sliding scale, the time for next glucose check, type of devices to be used for sampling, and sites of sampling.
- Although laboratory blood glucose measurement is the gold standard, it is labor intensive and not practical for hourly blood glucose measurements. Blood glucose measurement from arterial whole-blood samples drawn via the arterial line using a BGA is associated with fewer errors when compared with capillary samples or arterial samples using a glucometer and hence recommended for POC testing in the ICU.
- The single largest factor limiting achievement of glycemic control in the ICU is the occurrence of hypoglycemia and subsequent increase in mortality.
- The ADA defines moderate hypoglycemia as a blood glucose level of 40–70 mg/dL (2.2–3.9 mmol/L) and severe hypoglycemia as a blood glucose <40 mg/dL (2.2 mmol/L). Mild, moderate, and severe hypoglycemia are associated with increased mortality in the critically ill, and any blood sugar less than 70 mg/dL (3.9 mmol/L) warrants aggressive evaluation and management.
- The ADA Standards of Medical Practice 2016 recommends a goal of 140–180 mg/dL (7.7 mmol/L) in critically ill patients, although the goal may vary from patient to patient based on the admission diagnosis, preadmission diagnosis of diabetes, and chronic glycemic state before admission to the ICU.
- Although laboratory whole-blood glucose is the gold standard for blood glucose measurement, it is time consuming, labor intensive, and not practical when hourly blood glucose measurements are required. Hence arterial blood samples are recommended for blood glucose measurement using a BGA as opposed to capillary samples or arterial samples using a glucometer.
- Identified predictors of hypoglycemia in the ICU include female gender, APACHE 2 score, CVVHD, use of bicarbonate substitution solutions, diagnosis of sepsis, use of vasopressors/inotropes, prior diagnosis of diabetes mellitus, serum creatinine >3 mg/dL, insulin therapy, discontinuation of nutrition therapy without an adjustment in insulin therapy, mechanical ventilation, and ICU length of stay.
- Patients experiencing hypoglycemia present with either adrenergic (tremors, palpitations, anxiety), cholinergic (sweating, paresthesias), or neuroglycopenic symptoms (cognitive, behavioral, psychomotor changes, seizures, coma). Hypoglycemic coma may occur when glucose levels are below 40–50 mg/dL (2.2–2.3 mmol/L). Various rate and rhythm disturbances, including sinus tachycardia, sinus bradycardia, atrial and ventricular ectopies, and ventricular repolarization abnormalities, have been observed during acute hypoglycemic episodes.
- Once hypoglycemia is recognized, various possible causes should be evaluated and management initiated. Depending on the severity of neurologic symptoms, treatment is initiated with oral or intravenous dextrose and glucagon. Depending on the cause, an extended duration of treatment may be required.

References for this chapter can be found at expertconsult.com.

ANNOTATED REFERENCES

American Diabetes Association. 2. Classification and diagnosis of diabetes: Standards of Medical Care in Diabetes 2020. *Diabetes Care.* 2020;43(Suppl. 1):S14–S31.
This paper is the statement of the American Diabetes Association on the standards for managing blood glucose and diabetes in the hospital, focusing on critically ill patients.

Krinsley JS. Glycemic control in the critically ill: What have we learned since NICE-SUGAR? *Hosp Pract. (1995).* 2015;43:191–197.
This paper is a review of the recent research on glucose control in critically ill patients. It goes over understanding the domains of glycemic control, the role of diabetic status on these domains, their effect on mortality, and the importance of premorbid glucose control in critically ill patients with diabetes.

Krinsley JS, Egi M, Kiss A, et al. Diabetic status and the relation of the three domains of glycemic control to mortality in critically ill patients: an international multicenter cohort study. *Crit Care.* 2013;17:R37.
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This study done by the NICE- SUGAR investigators is a post hoc analysis of the original study done in 2009, which showed that intensive glucose therapy in critically ill patients posed an increased risk of death in addition to an increased incidence of hypoglycemia. With this analysis they demonstrated that although not causal, both moderate and severe hypoglycemia were associated with an increased risk of death.

Niven DJ, Rubenfeld GD, Kramer AA, et al. Effect of published scientific evidence on glycemic control in adult intensive care units. *JAMA Intern Med.* 2015;175:801–809.
This paper talks about the rapid adoption of tight glucose control when positive scientific evidence was published but it was not effectively deadopted when evidence to the contrary was brought to light. It reinforces the need to promote the deadoption of ineffective clinical practices.

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Anemia

Fahim Habib, Carl Schulman, and Alessia C. Cioci

INTRODUCTION

Anemia is defined as a reduction in the circulating red cell mass, the hemoglobin concentration, or both with an associated decrease in the oxygen-carrying capacity of blood.[1] It is among the most common clinical problems encountered among critically ill patients in the intensive care unit (ICU). Although a proportion are anemic on admission, the majority of the remainder become anemic during their ICU stay, and over 90% of ICU patients are anemic by day 3.[2] The likelihood of becoming anemic increases with each additional day in the ICU. Because of the association of anemia with worse clinical outcomes,[3] the traditional approach had been to transfuse packed red blood cells (PRBCs) in response to low hemoglobin (Hb) levels, with a Hb level of <10 g/dL being the most commonly used trigger for transfusion. As a result, 30%–50% of ICU patients were transfused an average of 5 units of PRBCs in response to a mean Hb concentration of 8.5 g/dL.[4] The Transfusion Requirements in Critical Care (TRICC) study was seminal in establishing the safety of a restrictive transfusion strategy.[5] Additionally, the increased recognition of transfusion-related complications, growing concerns about the scarcity of blood, and the economic impact of transfusion (approximately $270 per unit transfused in the United States) have prompted a major paradigm shift in the approach to the management of anemia in the ICU.[6,7] Current approaches include preventing blood loss, conserving blood, minimizing hemodilution resulting from the use of excess volumes of crystalloid for resuscitation, avoiding transfusions based on "transfusion triggers" alone, and accepting a lower Hb threshold in the majority of critically ill patients. Future efforts focus on improved conservation of blood, transfusion alternatives, and further advancements in blood substitutes.

EPIDEMIOLOGY

Clinically, anemia is defined by the hemoglobin concentration of blood. The World Health Organization defined anemia as a hemoglobin concentration of <14 g/dL for men and <12 g/dL for nonpregnant adult females.[8] Others have described the limits of a normal hemoglobin to range from 13.0 to 14.2 g/dL for men and from 11.6 to 12.3 g/dL for nonpregnant adult females.[9] Using these definitions, more than 60% of all critically ill patients are anemic at admission, and the majority of those with normal hemoglobin levels at admission will become anemic while in the ICU.[3,10] Over 90% will be anemic within 72 hours of ICU admission, and up to 25% of critically ill patients will have a hemoglobin concentration of <9 g/dL at some point in their ICU stay, especially when the ICU length of stay exceeds 7 days. Among patients who are not admitted for bleeding, have not been transfused, and do not have acute or chronic renal failure, there is an initial rapid decline in hemoglobin levels over the first 3 days by about 5 g/dL, followed by a slower rate of subsequent decline in hemoglobin concentration.[10,11] Each day spent in the ICU increases the chance of receiving a transfusion by 7%,[12] and 25%–53% of ICU patients will be transfused an average of 5 units of PRBCs per patient.[3,9,10,13–15] Among subgroups, patients admitted to the ICU for emergency surgery and trauma are transfused more often than medical ICU patients (57% and 48% vs. 32%). Patients with malignancies also have a higher prevalence of anemia at admission (68%), develop it during the ICU stay (47%), and have a need for transfusions.[16]

ETIOLOGY

The cause of anemia in critically ill ICU patients is often multifactorial.[17] The relative contribution of a particular etiologic factor varies from patient to patient and in the same patient from one time point to another. Key among these are (1) hemodilution, (2) blood loss, (3) impaired erythropoiesis, and (4) altered iron metabolism. Together the impairment in the development of mature red blood cells and alteration in metabolism of iron contribute to the development of the anemia of critical illness. Other concurrent derangements secondary to sepsis, hemolysis, use of antibiotics and chemotherapeutic agents, underlying hepatic or renal dysfunction, bone marrow suppression, and nutritional deficiencies further exacerbate anemia in the critically ill (Fig. 21.1).

Hemodilution

In the absence of bleeding, hemodilution is mostly responsible for the initial decrease in hemoglobin levels observed in the first 72 hours after admission to the ICU and results from the liberal use of crystalloids and, on occasion, colloids for the initial resuscitation of critically ill patients.[18,19] Limiting crystalloid use, earlier use of vasopressor therapy in patients who fail to respond to fluid resuscitation, and close monitoring of volume status are key to prevention of anemia caused by hemodilution.

Blood Loss

Blood loss can occur as a consequence of pathologic bleeding caused by the underlying disease process necessitating admission to the ICU, especially trauma and gastrointestinal (GI) hemorrhage, or from surgical interventions to treat the underlying or associated disorders. Stress gastritis, although rare since the advent of effective acid suppression therapy, remains a serious problem. The overwhelming majority of critically ill patients demonstrate some evidence of mucosal damage within the first 24 hours of admission. Overt anemia occurs in 5% of patients with stress-related GI bleeding, and clinically important bleeding necessitating transfusion is observed in 1%–4% of critically ill patients.[20] The risk for bleeding secondary to erosive gastritis is greatest in those on mechanical ventilation, those with coagulopathy, those with head injury, and those receiving corticosteroids.[21] Phlebotomy is an

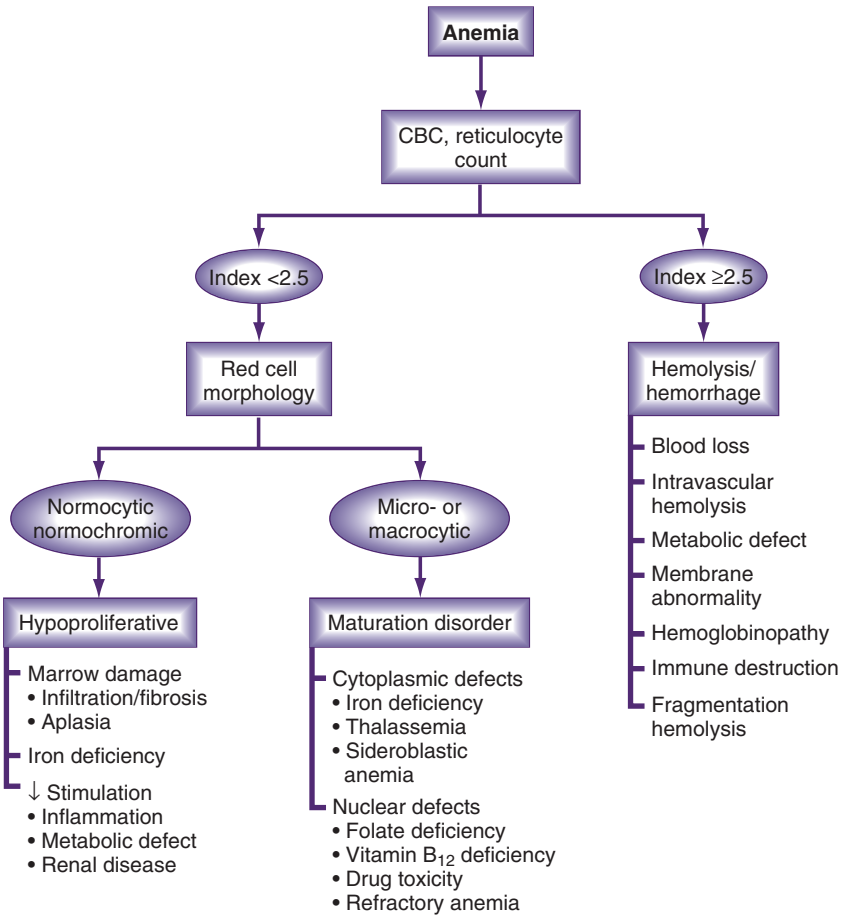

Fig. 21.1 Physiologic classification of anemia. *CBC,* Complete blood count. (From Adamson JW, Longo DL. Anemia and polycythemia. In Kasper DL, Hauser SL, Jameson JL, et al., eds. *Harrison's Principles of Internal Medicine,* 19th ed. New York, NY: McGraw-Hill; 2015: Fig. 77-17.)

TABLE 21.1 Average Volumes of Blood Drawn for Diagnostic Testing

Arterial blood gas	2 mL
Chemistry	5 mL
Coagulation studies	4.5 mL
Complete blood counts	5 mL
Blood culture	10 mL
Drug levels	5 mL
Standard discard amount	2 mL

often unrecognized yet significant cause of hospital-acquired anemia in the ICU. Patients are on average phlebotomized 4.6 times a day with the removal of 40–60 mL of blood daily.[3,10] For every 50 mL of blood drawn, the risk of moderate to severe anemia increases by up to 18%.[22] The volume of blood required to be drawn varies with the test being ordered, but typical volumes required for the various common tests are presented in Table 21.1. Increasing severity of illness correlates with an increased number of laboratory studies ordered and thereby the blood volume drawn. The presence of an arterial line further increases the phlebotomized blood volume because of the need to "waste" before an appropriate sample can be obtained. Approximately half of all patients are transfused as a direct result of phlebotomy.[23]

Impaired Erythropoiesis

Under normal circumstances, in response to low arterial oxygen tension, the peritubular capillary endothelium of the kidney produces a glycoprotein hormone erythropoietin (EPO), which acts on bone marrow to stimulate the production of red blood cells. In critically ill patients, this erythropoietic response is blunted. It is believed to result from inappropriately low EPO levels compared with the degree of anemia.[24,25] EPO levels were reduced by up to 75% when compared with patients with iron-deficiency anemia not related to critical illness.[26] The blunted EPO production is likely mediated by proinflammatory cytokines such as interleukin (IL)-1, and IL-6, which downregulate the expression of the gene encoding EPO.[27] IL-6 also inhibits the renal production of EPO.[28] Subsequent studies, however, have questioned reduced EPO levels as the basis for impaired erythropoiesis.[28] A resistance to the effects of EPO, rather than its absolute level, may be the dominant mechanism behind the impaired erythropoiesis.

Altered Iron Metabolism

Under physiologic conditions, iron metabolism is tightly controlled. Approximately 10% of the 10–20 mg of iron contained in the diet is absorbed, primarily in the proximal duodenum (Fig. 21.2). The dietary iron may be in the heme or nonheme form. The heme form is absorbed via a heme carrier protein (HCP1), and the nonheme form is first converted from the ferric to the ferrous form by the enzyme

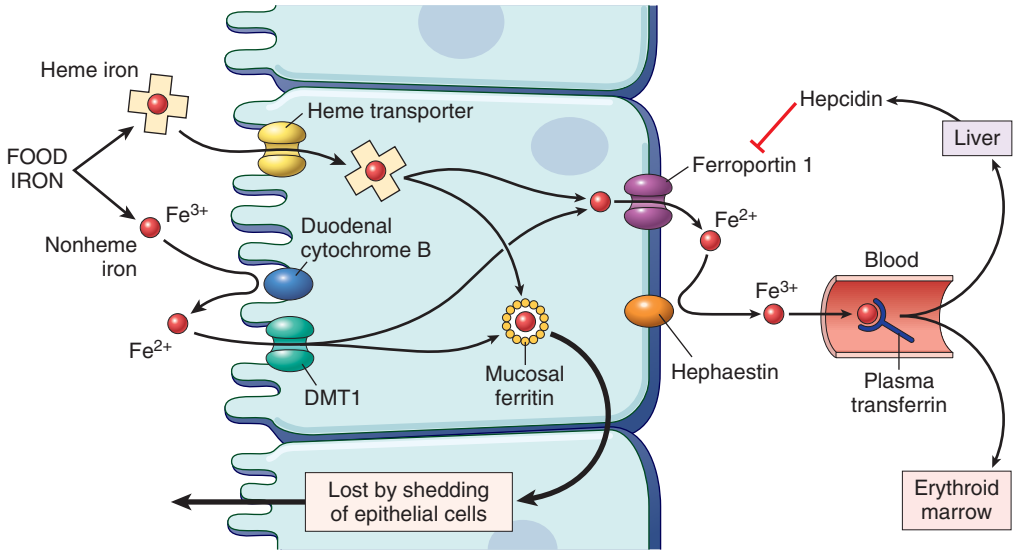

Fig. 21.2 Iron absorption in the duodenum. When the storage sites of the body are replete with iron and erythropoietic activity is normal, plasma hepcidin balances iron uptake and loss to and maintains iron homeostasis by downregulating ferroportin and limiting iron uptake. *DMT1,* Divalent metal iron transporter 1. (From Kumar V, Abbas AK, Aster JC, eds. *Robbins & Cotran Pathologic Basis of Disease,* 9th ed. Philadelphia, PA: Elsevier; 2015.)

duodenal cytochrome B (DcytB) and then transported across the apical membrane by the divalent metal iron transporter 1 (DMT1). The next step is determined by the iron needs of the body. If the iron stores are adequate and no additional iron is needed, the absorbed iron is stored in the enterocyte bound to ferritin and discarded when the enterocyte is shed. If there is a need for iron, the iron export protein ferroportin transports the iron across the basolateral membrane and into circulation, where it is transported bound to the glycoprotein transferrin, which maintains the iron in a soluble nontoxic form. At the cellular level it binds to the transferrin receptor (TfR1) facilitating the internalization of iron into cells. The principal determinant of whether the iron will be shed or absorbed is a 25-amino-acid peptide hepcidin, secreted by hepatocytes.[29] In conditions of adequate iron stores, there is an increase in hepcidin synthesis and release. It then circulates in plasma bound to an alpha-2-macroglobulin, ultimately binding to the iron export protein ferroportin on duodenal enterocytes, causing their internalization and degradation and preventing export of iron out of the cell. In conditions of iron need, increased erythropoietic demand, or hypoxia, hepcidin secretion decreases, allowing ferroportin to actively export iron from the enterocyte into circulation. In critical illness the associated inflammation results in the release of IL-6, which induces the synthesis of hepcidin, with resultant decreases in levels of serum iron and transferrin and decreased transferrin saturation despite adequate iron stores and results in the anemia observed in ICU patients. Additionally, the amount of iron lost as a result of blood loss from a variety of causes can reach up to 64 mg per day. This cannot be adequately compensated for by the 1–2 mg of iron absorbed daily, and a superimposed iron-deficiency anemia develops.[30]

Miscellaneous

Many of the drugs commonly used in the ICU have been implicated in the development of anemia, including antibiotics, angiotensin-converting enzyme inhibitors, calcium channel blockers, and beta-blockers. These medications may further suppress bone marrow function or lead to immunologically mediated hemolysis.[31]

LABORATORY EVALUATION OF ANEMIA IN THE ICU

The *complete blood count* (CBC) is the initial laboratory test performed in the evaluation of anemia. The hemoglobin, hematocrit, and red blood cell count are needed to establish the diagnosis and severity of the anemia. The absence of a uniform definition of anemia and the lack of a grading scale must, however, be recognized. The CBC also provides the red blood cell indices, including the mean cell volume (MCV), the mean cell hemoglobin, and the mean cell hemoglobin concentration (MCHC). Based on the MCV, the anemia can be classified into microcytic (MCV <80 fL), normocytic (MCV 80–100 fL), and macrocytic (MCV >100 fL).[32] The red blood cell distribution width (RDW), a measure of the variation in red blood cell size, is another parameter reported as part of the CBC and further aids in elucidating the cause. The various common causes of anemia based on these two indices are presented in Table 21.2.

The *reticulocyte count* is a measure of immature red blood cells present in circulation and is a marker of red blood cell production. It may be reported either as an absolute number or as a percentage. The normal absolute number of reticulocytes in the absence of anemia ranges from 25,000/μL to 75,000/μL. In the presence of anemia, a value of greater than 100,000 μL represents an appropriate response, whereas counts of less than 75,000 μL suggest a hypoproliferative process. When expressed as a percentage, normal values range from 1% to 2%. Values of 1.5% in men and 2.5% in women are considered elevated. In the anemic patient marrow response ramps up within 10 days of onset, increasing up to two to three times normal in order to combat the anemia. To account for these changes, the reticulocyte index is used, which estimates marrow production relative to normal. It is calculated using the formula:

$$\text{Reticulocyte index} = \text{Reticulocyte count (\%)} \times [\text{patient's hematocrit/normal hematocrit for age and gender}]/2.$$

A value of <2 denotes a hypoproliferation or maturation defect. For critically ill patients, there are several factors that may damage marrow response or lead to defects in erythrocyte maturation, including trauma,

TABLE 21.2 Diagnosis of Anemia Based on the Mean Corpuscular Volume and Red Blood Cell Distribution Width

	Low MCV (<80 fL)	Normal MCV (80–99 fL)	High MCV (≥100 fL)
Normal RDW	Anemia of chronic disease alpha- or beta-thalassemia trait	Acute blood loss Anemia of chronic disease	Aplastic anemia Chronic liver disease
	Hemoglobin E trait	Anemia of renal disease	Chemotherapy, antivirals, or alcohol
Elevated RDW	Iron deficiency Sickle cell beta-thalassemia	Early iron, folate, or vitamin B_{12} deficiency Dimorphic anemia (for example, iron + folate deficiency)	Folate or vitamin B_{12} deficiency Immune hemolytic anemia
		Sickle cell anemia	Cytotoxic chemotherapy
		Sickle cell disease	Chronic liver disease
		Chronic liver disease	Myelodysplasia
		Myelodysplasia	Hereditary spherocytosis, hereditary elliptocytosis, congenital hemoglobinopathies and RBC enzymopathies

From Lin JC. Approach to anemia in the adult and child. In Hoffman R, Benz EJ, Silberstein LE, et al., eds. *Hematology: Basic Principles and Practice,* 7th ed. Philadelphia, PA: Elsevier; 2018.
MCV, Mean corpuscular value; *RBC,* red blood cell; *RDW,* red blood cell distribution width.

inflammation, drugs/toxins, metabolic derangements, and sepsis, resulting in a low index value.[33]

Iron studies are needed to confirm the diagnosis of iron deficiency as a cause of microcytic anemia. These include the serum iron, ferritin, transferrin, and total iron-binding capacity. Given that both iron-deficiency anemia and anemia of critical illness frequently coexist in ICU patients, the characteristic pattern of iron studies reveals a low serum iron, low total iron-binding capacity, and low transferrin saturation. As ferritin is an acute-phase reactant, it is often normal or elevated.[2] However, in contrast to iron-deficiency anemia, in anemia of critical illness, EPO levels are only mildly elevated,[34] reticulocyte counts are disproportionately low, and hepcidin levels are elevated. There is, however, no commercial assay available to measure hepcidin levels.

Macrocytic anemias (MCV >100 fL) most commonly result from deficiencies of vitamin B_{12} or folate. Serum levels of both micronutrients are significantly affected by dietary modifications and are not reliable alone in making a diagnosis. *Methylmalonic acid and homocysteine levels* need to be obtained. Levels of both will be elevated in vitamin B_{12} deficiency, whereas in folate deficiency, methylmalonic acid levels are elevated and homocysteine levels are not. Other causes of macrocytic anemia include drugs and toxins, particularly chemotherapy agents, zidovudine, and alcohol. Rarely, especially in patients who have undergone significant gastric resections, pernicious anemia caused by deficiency of intrinsic factor can occur.

Elevated *lactate dehydrogenase* levels occur as a result of release from destruction of red blood cells in hemolytic anemias. Haptoglobin, an acute-phase reactant, binds the released free hemoglobin, and the complex is rapidly cleared from serum with a resultant decrease in serum *haptoglobin* levels. Elevated indirect *bilirubin* levels are also characteristic. In the presence of hemolysis, a positive *Coombs test* is suggestive of an autoimmune hemolytic anemia. A negative Coombs test should prompt evaluation for sickle cell diseases, thalassemia, glucose-6-phospahte dehydrogenase (G6PD) deficiency, hereditary spherocytosis, hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, and disseminated intravascular coagulation. A *peripheral smear* in addition to other clinical characteristics may help make the diagnosis.

PREVENTION OF ANEMIA IN THE ICU

The single most efficacious preventive measure is to avoid ordering daily screening laboratory tests, particularly CBCs and electrolyte/renal panels.[35] The average blood volumes needed for the more common tests are presented in Table 21.2. The absence of evidence in support for routine blood tests along with the potential for harm caused by such an approach has prompted several societies, including the Society of Critical Care Medicine (SCCM), to promote a philosophy of "Choosing Wisely," recommending against reflex routine testing.[36] The use of pediatric-sized blood collection tubes[37] and use of a blood-conserving arterial line system are other preventive approaches to blood loss.[38,39] Effective stress ulcer prophylaxis to reduce blood loss from the GI tract, correction of coagulopathy, and correction of nutritional deficiencies are other useful preventive measures.

MANAGEMENT OF ANEMIA IN THE ICU

Red Blood Cell Transfusion

Transfusion of PRBCs remains the standard approach for the management of anemia in critically ill patients. Approximately 40% of ICU patients receive blood transfusions.[40] Historically, transfusion was indicated for Hb concentrations below 10 g/dL. However, recent scientific evidence suggests that most critically ill patients safely tolerate lower Hb levels.[41] Additionally, PRBC transfusions are associated with numerous potential complications and are linked to worse outcomes. Finally, blood is a scarce and costly resource that may not always be available.[42] These considerations have led to a shift in transfusion guidelines, with recommendations that PRBCs be used for physiologic indications rather than an Hb-based transfusion trigger.

Liberal transfusion for Hb values less than 10 g/dL was based on historical observations that anemia was poorly tolerated in surgical patients.[43] However, subsequent studies have failed to validate this notion, and anemia below this threshold appears to be well tolerated. Clinical evidence to support this comes from studies in Jehovah's Witness patients who refuse to accept PRBC transfusions on religious grounds. In conscious healthy volunteers, isovolemic dilution can be tolerated until the Hb concentration decreases to 5 g/dL, without an increase in lactate concentration; however, significant cognitive changes were noted.[41,44] However, mortality increases significantly at Hb values below 5 g/dL, more so in individuals older than 50 years.[45]

Several studies have shown no benefit to liberal transfusion of PRBCs, while routinely showing an association with more ICU days and increased mortality. The ABC trial, a prospective observational study of 3534 patients from 146 Western European ICUs, found that mortality was significantly higher in the transfused than in the non-transfused group. The differences persisted even after the patients

were matched for the degree of organ dysfunction.[3] The CRIT study, a prospective, multicenter, observational study of 284 ICUs in 213 hospitals in the United States, found that transfusion was independently associated with longer ICU and hospital stays, in addition to increased mortality.[10] The multicenter trials group of the American Burn Association studied patients with more than or equal to 20% total body surface area burns at 21 burn centers in the United States and Canada. Overall, they found that nearly 75% of patients were transfused during their hospital stay, receiving a mean of 14 units. The number of units transfused correlated significantly with the number of infections and mortality.[46] In a prospective observational study by the North Thames Blood Interest Group, 53% of patients were transfused for a mean pretransfusion Hb level of 8.5 g/dL. About two-thirds were transfused for low Hb levels and only 25% for hemorrhage. ICU mortality in the transfused patients was significantly higher than that in the nontransfused patients.[13] Finally, Marik and Corwin analyzed outcomes in 272,596 patients, as reported in 45 studies. Blood transfusion was associated with an increased risk of death, infectious complications, and development of acute respiratory distress syndrome (ARDS).[47]

Most transfusions in the ICU are performed for the treatment of hemodynamically stable anemia. In the CRIT trial, over 90% of transfusions were given for this reason.[10] Perceived benefits of transfusion include increase in oxygen delivery to the tissues; increase in cell mass and blood volume; alleviation of symptoms of anemia, including dyspnea, fatigue, and diminished exercise tolerance; and relief of cardiac effects. The optimal Hb concentration can be influenced by the premorbid health status, disease process, and other factors.

The historical transfusion trigger of 10 g/dL was directly challenged in the TRICC trial.[48] Patients enrolled were randomized to either a restrictive transfusion strategy (transfusion for Hb below 7 g/dL, with a goal of maintaining circulating Hb between 7 and 9 g/dL) or a liberal transfusion strategy (transfusion for Hb levels less than 10 g/dL, with a goal of maintaining Hb between 10 and 12 g/dL). The restrictive transfusion strategy resulted in a 54% decrease in the average number of units transfused and avoidance of transfusion in 33% of patients, with no difference in 30-day mortality between the groups.

The use of a lower transfusion trigger of 7 g/dL is considered safe in critically ill patients, except in those with acute myocardial ischemia, who may benefit from a higher threshold of 8 g/dL. These guidelines have been adopted in most societal recommendations, although transfusions for Hb level alone are discouraged.[4,49] Additional indications for transfusion include hemorrhagic shock or evidence of inadequate tissue oxygenation.

Adverse Effects of Transfusion

A large proportion of ICU patients continue to receive PRBC transfusions for anemia, exposing them to serious risks, including transmission of infectious diseases, immune-mediated reactions (acute or delayed hemolytic reactions, febrile allergic reactions, anaphylaxis, and graft-versus-host disease), and non–immune-related complications (fluid overload, electrolyte toxicity, and iron overload). Transfusion-related complications are encountered in up to 4% of PRBC transfusions.[10] The risk of adverse outcomes increases incrementally with each unit of PRBC transfused.[50,51] In an observational cohort study of 5814 patients undergoing coronary artery bypass grafting, each unit of PRBC transfused resulted in more complications. Overall, there was a 73% increase in the odds of a major morbidity for each unit transfused (Table 21.3).[50]

With advances in screening and improvements in blood banking technology, transmission of infectious agents is less common. Current estimates of the risk of infection per unit of blood are approximately 1 in 2 million for human immunodeficiency virus, 1 in 1 million for hepatitis C virus, and 1 in 100,000 for hepatitis B virus.[52] The most common transfusion-related infections are secondary to bacterial contamination, which has an incidence of 12.6 events per 1 million units of allogeneic blood components transfused.[53] The risk of bacterial contamination is higher for PRBCs than for whole blood. Transfusion-related bacterial infections are most often caused by gram-positive organisms (e.g., staphylococcal spp., streptococcal spp., 58%) but may also be caused by gram-negative organisms (e.g., *Yersinia enterocolitica*, 32%). About 10% of these infections will result in a fatal outcome.[53] Increasing global travel has led to the emergence of infectious diseases not usually seen in the United States. Chagas disease, caused by the parasitic protozoan *Trypanosoma cruzi,* is endemic in much of South and Central America. Immigrants from these endemic areas now form an increasing proportion of the blood donor pool. This issue is especially relevant in regions with high immigrant populations. In two such cities, Los Angeles and Miami, seropositive rates among donors were 1 in 7500 and 1 in 9000, respectively, and have been increasing.[54] Once acquired, the parasitemia persists long after acquisition of the infection.[55] Novel therapies are being developed to mitigate the risk of transfusion contamination and infection. These include INTERCEPT, a photochemical treatment process that uses amotosalen and ultraviolet A (UVA) light to inactivate viruses, bacteria, parasites, and leukocytes that contaminate transfusion-ready blood products.[56]

The most common of all transfusion reactions are febrile nonhemolytic transfusion reactions (FNHTRs). These reactions are caused

TABLE 21.3 Potential Adverse Consequences Associated With Red Cell Transfusion

Infectious Complications	
Human immunodeficiency virus infection	1 in 2.3 million
Human T-lymphotropic virus infection	1 in 2 million
Hepatitis C virus infection	1 in 1.8 million
Hepatitis B virus infection	1 in 350,000
Parvovirus B19 virus infection	1 in 10,000
Bacterial infections (*Staphylococcus,* streptococci, *Yersinia enterocolitica,* etc.)	1 in 250,000
Parasitic infections (Chagas disease)	1 in 29,000 donors seropositive
Noninfectious Complications	
Hemolytic transfusion reactions	1 in 10,000 to 1 in 50,000
Delayed hemolytic transfusion reaction	1 in 1500
Febrile nonhemolytic transfusion reactions	1 in 100 to 35 in 100
Major allergic reactions	1 in 20,000 to 1 in 50,000
ABO mismatching	1 in 14,000 to 1 in 38,000
Transfusion-related acute lung injury (TRALI)	1 in 5000
Transfusion-related immunomodulation (TRIM)	1 in 100
Transfusion-associated circulatory overload (TACO)	Observed once two blood volumes replaced
Coagulopathy	Observed after transfusion of 10–15 units
Iron overload	
Hypothermia	
Hyperkalemia	
Thrombocytopenia	
Pulmonary hypertension	

by the accumulation of cytokines in stored blood components.[57–59] FNHTRs present within 1–6 hours after transfusion with fever, chills, occasionally severe rigors, and possibly mild dyspnea. Risk factors include young age, blood product type (highest with red blood cells and platelets), and whether the blood was leukoreduced or not.[60–62] Management includes termination of the transfusion and administration of antipyretics if necessary. Prevention is centered on prestorage leukoreduction, which involves removing white blood cells by passing the blood products through a specialized filter soon after it is collected.[63]

Major ABO blood type mismatching is estimated to occur in 1 of 138,673 PRBC units transfused and results in 1 death per 2 million units transfused.[53] Incompatibility may also result from antigens not routinely detected by current antibody assays. As a consequence, fatal acute hemolytic reactions still occur in 1 of every 250,000–1 million transfusions, and 1 patient per 1000 demonstrates the clinical manifestations of a delayed hemolytic transfusion reaction.[64,65]

Transfusion-related acute lung injury (TRALI) is a potentially serious pulmonary complication of transfusion. In severe cases, its clinical presentation is similar to that of ARDS.[66] Although initially described by Barnard in 1951 as noncardiogenic pulmonary edema related to transfusion, the term *TRALI* was coined by Popovsky and colleagues.[67,68] TRALI presents as hypoxic respiratory insufficiency of sudden onset within 6 hours of a transfusion, but usually starting within the first hours after transfusion.[69–71] Hypoxemia, fever, hypotension, tachycardia, and cyanosis may also occur. In 2019 the Delphi panel introduced new TRALI classification terminology. TRALI type I occurs in patients with no other risk factors for ARDS. TRALI type II occurs in patients who have risk factors for or have mild ARDS with marked respiratory deterioration after the transfusion event.[72] In these patients with risk factors for ARDS, recent studies have proposed a change of nomenclature from "possible TRALI" to "transfused ARDS."[73] Chest x-ray shows bilateral infiltrates, which may progress and cause whiteout of the entire lung field. Differential diagnosis includes transfusion-associated circulatory overload (TACO), cardiac diseases, allergic and anaphylactic transfusion reactions, and bacterial contamination of the blood. Although the exact incidence is unknown, TRALI is estimated to occur in 1 of every 5000 transfusions.[74] TRALI had been the leading cause of transfusion- related mortality in the United States until 2016, when it was surpassed by TACO.[75] Current evidence suggests two etiologies of TRALI: immune and nonimmune. Potential mediators include antileukocytic antibodies, lipid peroxidation products, and other as-yet unrecognized agents. Neutrophils are the key effector cells. Transfusions from multiparous female donors owing to exposure to paternal leukocytes are associated with the highest risk of the development of TRALI in the recipient.[76] Upon diagnosis or suspicion of TRALI, transfusions should be terminated and the blood bank notified. Treatment is centered on the correction of hypoxemia, with endotracheal intubation and mechanical ventilation being required in as many 80% of cases.[77–79]

Transfusion-related immunomodulation (TRIM) results in an increased incidence of bacterial infections, cancer recurrence, and organ dysfunction.[80,81] Opelz and colleagues first suggested clinical evidence of TRIM in 1973, when improved renal allograft survival was observed in patients transfused before transplantation.[82] Current evidence implicates transfusions in the development of nosocomial infections, including wound infections, pneumonia, and sepsis. In a prospective observational study, Taylor and colleagues found a significant association between transfusion and development of nosocomial infections (14.3% vs. 5.3%, $P <$,0001). In addition, mortality and length of stay were increased in the transfused group. The risk of infection increases 9.7% for each unit of PRBC transfused.[83] Development of these infectious complications results not only in increased length of stay but also in increased in-hospital deaths and increased costs as well.[84] These effects may be reduced by the use of prestorage leukocyte depletion.[85]

Other complications include TACO with the development of fluid overload and pulmonary edema and pulmonary hypertension with a decreased right ventricular ejection fraction.[85–87] The risk of TACO increases with the volume transfused—a transfusion of just two to four units carries an odds ratio (OR) of 2.00 for developing the complication.[88] The incidence of TACO is estimated to occur in 1%–4% of all transfusions given.[89,90] Management is centered around ventilatory support if needed and fluid mobilization.

Finally, the transfusion of PRBCs may not augment the oxygen-carrying capacity of blood. This results from development of the "storage lesion" caused by changes in red blood cells that occur during ex vivo storage. These changes are both structural and functional and include reduced deformability impeding microvascular flow, altered adhesiveness and aggregation, reduced intracellular levels of 2,3-diphosphoglycerate (which shifts the oxyhemoglobin dissociation curve to the left and reduces oxygen delivery to the tissues), reduced levels of nitric oxide and adenosine triphosphate, and accumulated bioactive compounds with proinflammatory activity.[91–96] The risk of complications increases with the duration of storage.[97,98] Koch and colleagues examined data from 6002 patients undergoing cardiac surgery. Patients given older blood had higher rates of in-hospital mortality and more complications.[99] Other recent studies have not found such an effect of storage.

The Role of Erythropoietin

Many factors contribute to the development of anemia in critically ill patients, but inappropriately low endogenous levels of EPO in response to anemia is a demonstrated phenomenon in critically ill patients.[24] Furthermore, there is a failure of circulating EPO to induce a response commensurate with the degree of anemia.[24] Recognition of these considerations has prompted the use of pharmacologic doses of EPO in an effort to reduce the need for and/or the amount of red blood cells transfused, but this approach has not been validated by scientific evidence. Corwin and colleagues conducted a prospective randomized, placebo-controlled trial (EPO3) on 1460 patients and found that epoetin alfa therapy did not decrease the number of PRBC units transfused and did not improve outcomes. Furthermore, a significant increase in thrombotic events was noted (hazard ratio, 1.41; 95% confidence interval [CI], 1.06–1.86).[100] Accordingly, routine use of EPO cannot be recommended. At our institutions, EPO use is limited to patients with chronic renal failure and Jehovah's Witnesses.

Current Recommendations

The decision to transfuse should be based on a patient's overall clinical picture and his or her individual demographics. Recommendations are summarized in Box 21.1.

Hemorrhage. Transfusion is indicated for patients with acute bleeding and hemodynamic instability or evidence of inadequate oxygen delivery, as demonstrated by elevated lactic acid or base deficit. Transfusion should be initiated without delay for laboratory analysis and should continue until bleeding is controlled and physiologic parameters have normalized.[107]

Critically ill. In hemodynamically stable patients with anemia, a restrictive strategy of transfusion should be employed. Transfusion with PRBCs should be instituted when the Hb level falls to less than 7 g/dL; however, the decision to transfuse should not be based on Hb level alone. Consideration should be given to the patient's intravascular volume status, evidence of shock, duration and extent of anemia, and cardiopulmonary physiologic parameters.[4]

BOX 21.1 Summary of Current Recommendations[4]

1. Packed red blood cell (PRBC) transfusion is indicated in patients with hemorrhagic shock (level 1).[19]
2. PRBC transfusion may be recommended for patients with acute hemorrhage after adequate fluid resuscitation if they have evidence of hemodynamic instability or evidence of inadequate systemic perfusion as demonstrated by elevated serum lactate or presence of a base deficit (level 1).[81]
3. A restrictive strategy of transfusion for hemoglobin (Hb) levels <7 g/dL is recommended for hemodynamically stable, critically ill patients, except for those with myocardial infarction or unstable angina.[101] This restrictive strategy is also recommended in critically ill trauma patients[102] and in those with stable cardiac disease (level 1).[101]
4. Transfuse patients with acute coronary syndromes who have admission Hb levels of <8 g/dL. Achieve posttransfusion hematocrit (Hct) of 30%–33% (level 3).[82,83,103]
5. Do not transfuse based on a transfusion trigger alone. Instead, individualize the decision based on the patient's intravascular volume status, evidence of shock, duration and extent of anemia, and cardiopulmonary status.
6. Transfuse as single units (level 5).[4]
7. Do not use transfusion as a means to wean patients off mechanical ventilation (level 2).[10]
8. Do not use transfusion as a stand-alone strategy to improve tissue oxygen delivery (level 2).[104]
9. In sepsis, transfusions can be recommended as part of a strategy of early goal-directed therapy during the initial resuscitation[86,105] (level 2).
10. Evidence for transfusion in patients with subarachnoid hemorrhage and traumatic brain injury should be individualized.[106]

Except in hemorrhage, patients should be re-evaluated after each unit of PRBCs to determine the need for additional transfusion.

Myocardial ischemia. Patients at risk of myocardial ischemia may benefit from a higher transfusion trigger of 8 g/dL. For patients with cardiac disease undergoing coronary artery bypass graft surgery, increased mortality is observed in patients with Hb levels below 8 g/dL on admission. Reduction in mortality can be achieved by transfusing to a hematocrit of 30%–33%. No mortality benefit is seen with hematocrits above 33%, and increased mortality is observed when hematocrits above 36% are achieved.[108–110]

Sepsis. There is no evidence to support routine transfusion of PRBCs in sepsis. Increased Hb has not been shown to yield improved tissue oxygenation.[111] Transfusion may be indicated for failure to achieve an adequate mixed venous saturation after adequate fluid resuscitation.[19]

Mechanical ventilation. No benefit in the weaning process or difference in duration of mechanical ventilation has been observed.[110]

NOVEL STRATEGIES

It is evident that hemodynamically stable patients can tolerate marked degrees of anemia. The understanding of the risks of receiving transfusions and the growing number of patients who do not accept blood products for personal or religious purposes has led to the recent shift to "bloodless medicine" at certain institutions. These "bloodless centers," particularly in surgical patients, are implementing strategies such as treating preoperative anemia, using erythropoiesis-stimulating agents, minimizing operative blood loss with hemostatic agents, and using autologous blood salvage during procedures in order to decrease the need for transfusions.[101,102] Other strategies include using low-volume adult or pediatric sampling tubes in the laboratory, reducing the number of laboratory tests ordered, and point-of-care microanalysis.[103,104] Additional approaches may include the development of newer methods of blood storage, use of advanced computing technologies to optimize the use of blood inventories, and development of blood substitutes.[105,112]

Blood substitutes are a novel strategy largely in response to concerns regarding the potential transmission of infectious agents and the impending shortage of blood in the face of increasing demands, and are also being implemented in bloodless centers across the country.[113] These innovations are specifically targeted as oxygen carriers (OCs) for delivery in the body, with huge strides being achieved over the last decade. They offer the distinct advantages of better shelf life without requirement of refrigeration, universal compatibility, clinically useful intravascular half-life (18–24 hours), and have freedom from the risk of infectious disease transmission (possibly with the exception of prion-mediated diseases). The two major types of OCs have been the Hb-based oxygen carriers (HBOCs) and perfluorocarbons (PFCs). Research of PFCs is mostly targeted toward diagnostic rather than clinical applications. HBOCs are derived from bovine and human blood and have initially showed promising results. HBOCs were not without complications, with one study of trauma patients having increased mortality over patients receiving saline infusion.[114] This increased mortality may have been a result of its nitric oxide scavenging properties leading to increased vasoconstriction effects.

To combat this, there was the creation of Sanguinate, a bovine pegylated carboxyhemoglobin that inhibits the previous vasoconstricting effects of HBOCs. It has shown promising results in Food and Drug Administration (FDA)–approved trials, even proving lifesaving in one case report, with no adverse events reported.[115,116] Another polymerized bovine hemoglobin, known as *Hemopure,* has had success in further case reports of Jehovah's Witnesses with hemolytic and sickle cell anemias.[117,118]

MacKenzie and colleagues recently described the outcome in 54 patients with severe life-threatening anemia (median Hb level, 4 g/dL) treated with the blood substitute HBOC-201; 23 (41.8%) of 54 patients survived to discharge. Survival was significantly more likely when the blood substitute was administered earlier (3.2 days in survivors vs. 4.4 days in nonsurvivors, $P = .027$).[119] Currently, most research is in its potential use for hemorrhagic shock and clinical situations where blood transfusion is not an option. Results so far have mostly been from small individual studies. Although promising, available data do not support the use of blood substitutes in their current form, and research is still ongoing.

KEY POINTS

- Anemia is exceedingly common in patients admitted to the ICU. Over 60% are anemic on admission, and more than 80% become anemic by day 3 of their ICU stay.
- Anemia in the critically ill patient is multifactorial in etiology. Iron-deficiency anemia and anemia of critical illness are the most frequent causes.
- Anemia of critical illness is cytokine mediated and results from decreased production of EPO, reduced response to EPO, and altered iron metabolism.
- Transfusion is clearly indicated for hemorrhagic shock and hemodynamic instability associated with blood loss after adequate fluid resuscitation.
- Transfusion of packed red blood cells is still employed by the majority of clinicians as the mainstay of therapy for anemia in critical illness. However, the optimal Hb concentration essential to maintain ideal tissue oxygen delivery remains unknown.
- A restrictive transfusion strategy is recommended for critically ill, hemodynamically stable patients without evidence of cardiac ischemia. Transfusion in these patients can often be avoided when the circulating Hb level is above 7 g/dL.
- Treatment with recombinant human EPO initially showed promise as a strategy for reducing exposure to allogeneic blood. More recent evidence, however, refutes these findings and points instead to an increase in thrombotic complications.
- Novel strategies to avoid the need for blood transfusion include use of blood conservation techniques, improved blood storage techniques, advanced inventory control, and evaluation of the efficacy of blood substitutes.

References for this chapter can be found at expertconsult.com.

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ANNOTATED REFERENCES

Corwin HL, Gettinger A, Fabian TC, et al. Efficacy and safety of epoetin alfa in critically ill patients. *N Engl J Med.* 2007;357:965–976.
In this prospective, randomized, placebo-controlled trial, 1460 anemic ICU patients received weekly recombinant human erythropoietin or placebo without benefit regarding 140-day mortality or transfusion requirements. EPO was associated with a significant increase in the incidence of thrombotic events. The purported benefits of EPO in the critically ill were clearly dispelled by this large multicenter trial.

Corwin HL, Gettinger A, Pearl RG, et al. The CRIT Study: anemia and blood transfusion in the critically ill—current clinical practice in the United States. *Crit Care Med.* 2004;32:39–52.
This prospective, multicenter, observational study described the transfusion experiences of ICU patients at 284 ICUs over a short period in the United States. Among subjects enrolled, 44% were transfused a mean of 4.6 ± 4.9 units; average ICU stay was 21 days. This study examined red blood cell transfusion practices in the critically ill in the United States.

Hébert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. *N Engl J Med.* 1999;340:409–417.
This Canadian study found no benefit of a liberal transfusion strategy when compared with a restrictive one when 838 anemic critically ill patients were compared for 30-day mortality or severity of organ dysfunction. This landmark trial demonstrated that a hemoglobin transfusion threshold of 7 g/dL was appropriate in critically ill patients without ongoing cardiac ischemia or GI bleeding.

Koch CG, Li L, Duncan AI, et al. Morbidity and mortality risk associated with red blood cell and blood-component transfusion in isolated coronary artery bypass grafting. *Crit Care Med.* 2006;34:1608–1616.
This study established the morbidity of transfusion in 11,963 patients who underwent isolated coronary artery bypass from 1995 through 2002, 5814 (48.6%) of whom were transfused. Transfusion of red blood cells was associated with a risk-adjusted increased risk of every postoperative morbid event: mortality, renal failure, prolonged ventilatory support, serious infection, cardiac complications, and neurologic events.

Koch CG, Li L, Sessler DI, et al. Duration of red-cell storage and complications after cardiac surgery. *N Engl J Med.* 2008;358:1229–1239.
This study examined the relationship between serious complications and mortality after cardiac surgery and transfusions of "older blood." Transfusion of red blood cells stored for more than 2 weeks was associated with a significantly increased risk of postoperative complications and reduced survival. Findings supported the notion that blood stored for prolonged periods may be deleterious.

Napolitano LM, Kurek S, Luchette FA, et al. Clinical practice guideline: red cell transfusion in adult trauma and critical care. *J Trauma.* 2009;67(6):1439–1442.
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Natanson C, Kern SJ, Lurie P, et al. Cell-free hemoglobin-based blood substitutes and risk of myocardial infarction and death: a meta-analysis. *JAMA.* 2008;299(19):2304–2312.
Definitive review of 16 trials involving five different oxygen therapeutic agents and 3711 patients in varied patient populations. Use of these blood substitutes was associated with a significantly increased risk of death and myocardial infarction.

Weiskopf RB, Viele MK, Feiner J, et al. Human cardiovascular and metabolic response to acute, severe isovolemic anemia. *JAMA.* 1998;279:217–221.
Acute isovolemic reduction of blood Hb concentration to 50 g/L in conscious, healthy, resting humans does not produce evidence of inadequate systemic oxygen delivery, as assessed by lack of change of VO_2 and plasma lactate concentration. This important investigation established that significant anemia could be tolerated in healthy individuals.

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22

Coagulopathy in the Intensive Care Unit

Hunter B. Moore, Peter K. Moore, and Ernest E. Moore

DIVERGENT PATIENT POPULATIONS: TRAUMA VERSUS SEPSIS

Noncardiac intensive care units (ICUs) predominantly manage coagulopathy in patients with trauma or sepsis. Although trauma is known as the third most frequent cause of death in the United States,[1] sepsis, which is not as well categorized, is believed to be the leading cause of death in hospitalized patients.[2] Both patient populations are at risk of developing coagulation abnormalities.[3] However, the drivers of pathology and timing are divergent. Trauma-induced coagulopathy (TIC) occurs within minutes to hours after injury,[4] whereas sepsis-induced coagulopathy (SIC) represents a spectrum of patients who have been ill days to weeks before progressing to coagulopathy associated with adverse outcomes[5] (Fig. 22.1). Attempting to assimilate the early drivers of coagulation changes between sepsis and trauma have highlighted discordances during the early phases of each disease process.[6] Therefore the approaches to the initial management of coagulopathy in trauma and sepsis are divergent. Whereas trauma research has focused on promoting coagulation, sepsis investigation has tested antithrombotic therapy such as activated protein C and antithrombin. However, the crosstalk between TIC and SIC shares a common historical origin with the term *disseminated intravascular coagulation (DIC).*

ORIGINS OF THE TERMINOLOGY OF DISSEMINATED INTRAVASCULAR COAGULATION

The early descriptions of coagulation changes during hemorrhagic shock date back to the 1770s. Hewson observed that the last blood drawn in sheep clotted first.[7] Almost 150 years later Cannon and Mendenhall validated this finding in which he observed clotting time in dogs was decreased with progressive hemorrhage.[8] This early onset of hypercoagulability led numerous investigators to attribute hypercoagulability as the driving mechanism for irreversible shock after hemorrhage.[9,10] Histologic evaluation of these animals demonstrated microvascular thrombi, and the term DIC was introduced to the literature.[11] Hardaway and colleagues had a long-term interest in DIC driving irreversible shock and demonstrated that pretreating animals with heparin before hemorrhage could effectively reverse DIC-attributable death.[12] They also demonstrated that a fibrinolytic agent could have the same effect of reversing lethal shock when delivered during resuscitation.[13] Hardaway's group later documented intravascular clots in patients with organ failure in 1965.[14]

In 1969 Cafferata and colleagues[15] provided the most compelling evidence of DIC in humans, with a observational postmortem examination of 12 patients who failed to resuscitate several days after injury, despite gaining surgical hemostasis. All 12 patients had clinical evidence of oozing and low-grade bleeding during the perimortem period; however, 8 of these patients had thrombi in their lungs. In the 1970s it was shown that endotoxin infusion could also drive organ failure associated with microvascular clots in animal models.[16] This was then appreciated in patients with cancer,[17] in which it was observed that treating patients with heparin had no effect on outcomes, as the underlying malignancy drove microthrombosis. These early studies set the foundation for decades of research in DIC driving coagulopathy in the critically ill. The laboratory diagnosis of DIC can be misleading, as intravascular microthrombi in a large autopsy series were evident in only 60%.[18]

A review of the interconnectivity of the inflammation and coagulation leading to excessive fibrin deposition and organ failure was published in the *New England Journal of Medicine* in 1999.[3] Twenty years later, as the COVID-19 pandemic overwhelms the healthcare system worldwide with concerns for a lethal cytokine storm, autopsy reports from these patients demonstrate thrombi deposition in multiple organ systems.[19] The most worrisome aspect of DIC is that it heralds the initiation of end-stage organ failure,[20] with no effective treatment, and remains a cause of irreversible shock, as reported by Hardaway and colleagues a half-century earlier.[12] Therefore the objective of ICU treatment is to address the critically ill patient's coagulopathy while treating the underlying clinical disease process to prevent progression to DIC.

IDENTIFICATION OF EARLY TRAUMA-INDUCED COAGULOPATHY

Coagulation changes after trauma are proposed to be broken down into early versus late changes.[21] Early coagulopathy in trauma is driven by shock and tissue injury[22] (Fig. 22.2) There is a spectrum of coagulation early after injury that appears to have divergent drivers.[23,24] These coagulation changes can range from hypocoagulable to hypercoagulable, including a mixed phenotype of one component of coagulation upregulated, whereas the other is inhibited[25] (Fig. 22.3). The majority of early deaths in trauma are related to bleeding and occur a median of 3 hours postinjury.[26] Most of these patients will not reach the ICU because of failure to obtain hemorrhage control in the prehospital setting, emergency department (ED), or operating room. This is often attributable to noncompressible truncal injuries in which the patient has bled to death because of structural problems[27] rather than coagulopathy. Of those patients who fail to generate a hemostatic response after injury and initial resuscitation, the question has been proposed if they are bleeding (coagulopathic) because they are dying or dying because they are bleeding.[28] Therefore attribution to death from coagulopathy becomes a challenge to decipher in critically injured patients. Regardless of the cause or effect, coagulation assessment is an important initial prognostic marker on trauma patients.

The fibrinolytic system appears to be the first component of coagulation activated after severe injury.[29] However, by hospital arrival, the

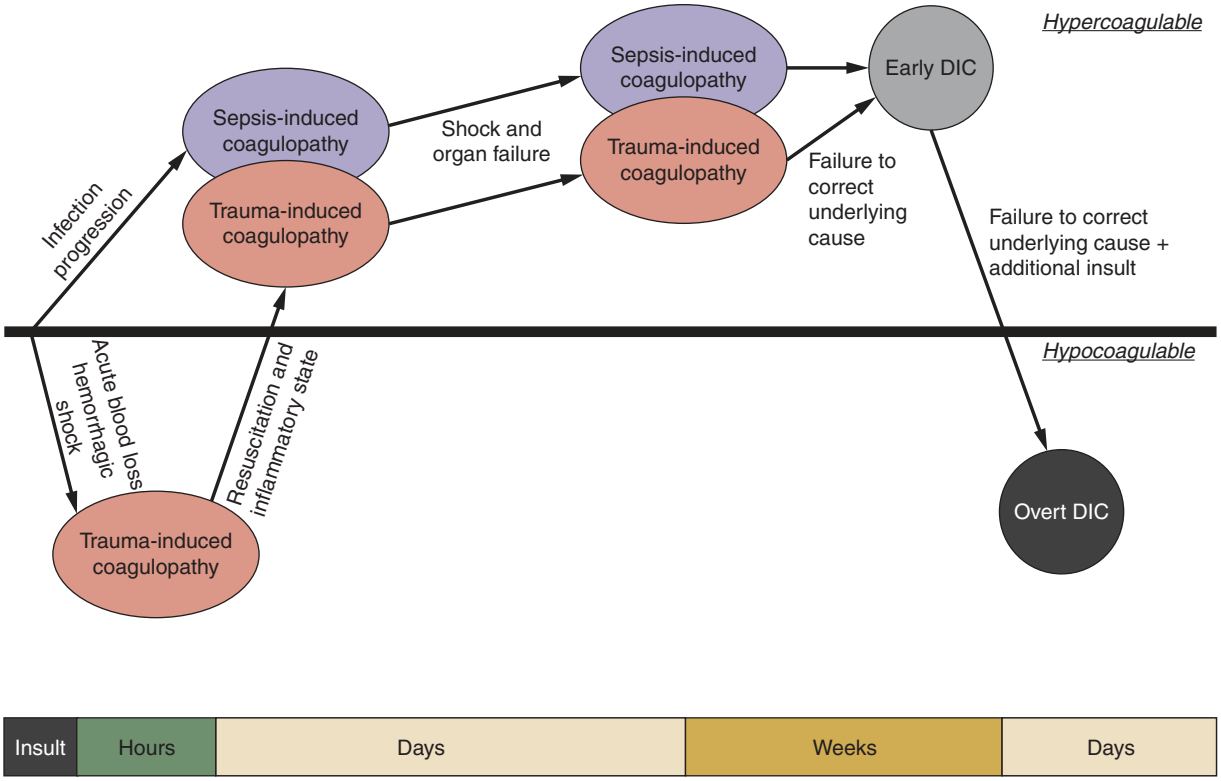

Fig. 22.1 Early trauma-induced coagulopathy (TIC) is distinct in mechanisms and clinical manifestations from disseminated intravascular coagulation (*DIC*), but later TIC and DIC have similar mechanisms and clinical consequences.

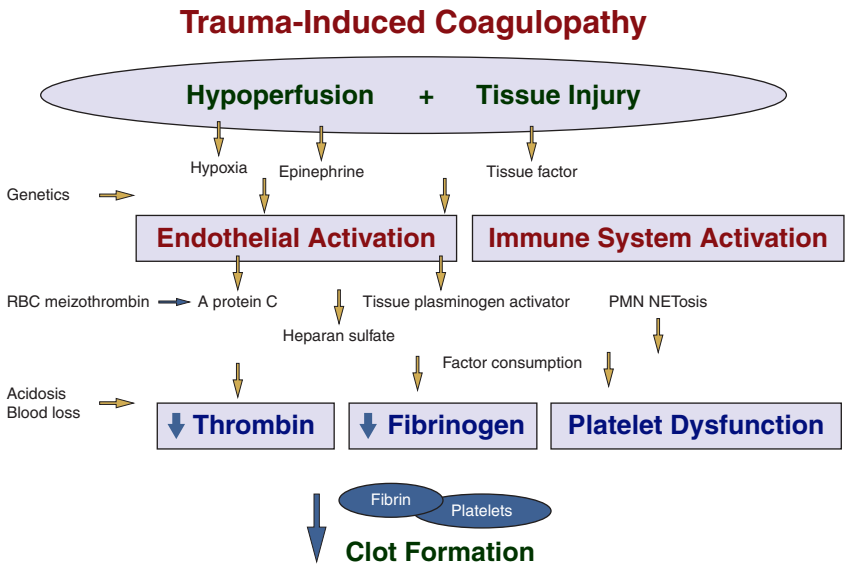

Fig. 22.2 Early trauma-induced coagulopathy (TIC) is driven by hypoperfusion and tissue injury, resulting in inadequate thrombin generation, fibrinogen depletion, and platelet dysfunction.

majority of patients have shut down fibrinolysis.[30,31] Typically, coagulopathic-injured patients have a prolonged international normalized ratio (INR) with elevated D-dimer levels in the ED.[4] There have been multiple proposed thresholds for INR levels to define patients as coagulopathic in trauma.[4,32,33] Although >1.2 has been proposed, an INR >1.5 is superior in predicting mortality and morbidity after trauma.[34] INR-defined coagulopathy in the acute setting has applicability to the patient who is resuscitated and transferred to the ICU, as this early coagulation change is also associated with organ failure and later thrombotic complications.[34,35] However, INR only represents the plasma contribution to clotting, ignoring the critical role of platelets. Moreover, INR does not reflect deficiency of clotting factors of the extrinsic system, which is what is presumed to account for a prolonged INR.[35]

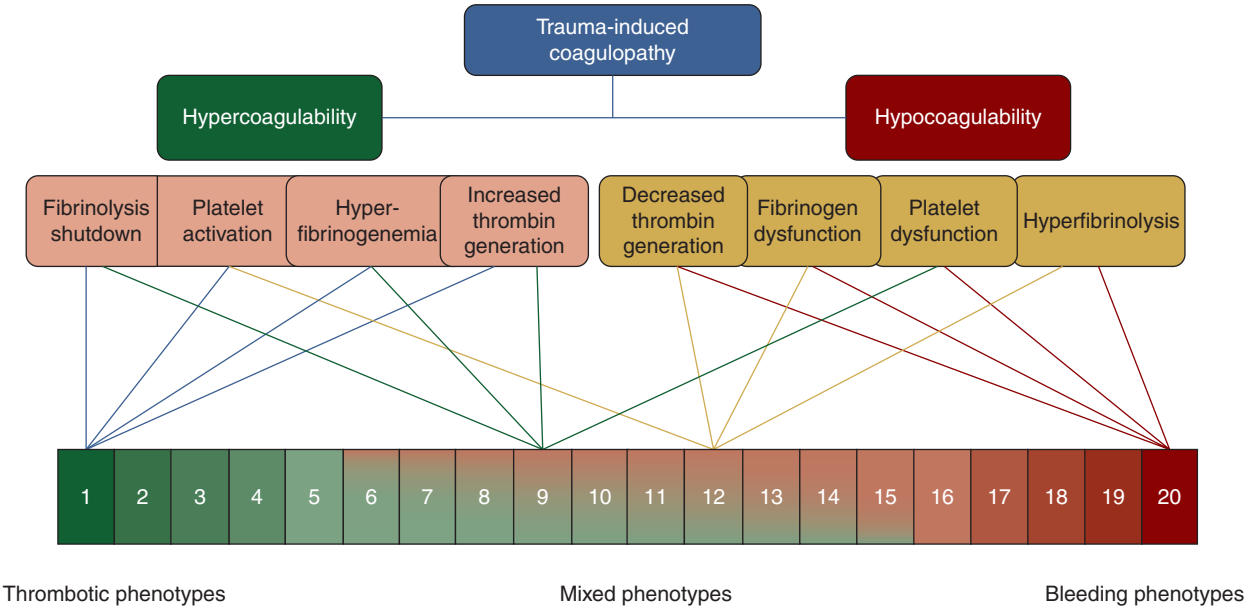

Fig. 22.3 Severe injury can provoke a myriad of trauma-induced coagulopathy (TIC) phenotypes that generally begin with uncontrolled bleeding and progress to thrombotic complications.

The more recent approach to identifying patients with early TIC is with viscoelastic hemostatic assays (VHAs).[36] This approach is able to replace a battery of conventional coagulation assays,[37] and transfusions based on the different coagulation measurements from VHA compared with conventional laboratory assessment have been demonstrated to reduce mortality.[38] Although there are multiple components of coagulation that may be deranged in VHA, a decrease in clot strength has repeatedly been associated with increased mortality.[39–42]

MECHANISMS OF EARLY TIC

The mechanisms driving early TIC are complex (see Fig. 22.2). The major components include impaired thrombin generation, fibrinogen dysfunction, platelet dysfunction, and alterations of the fibrinolytic system.[43] Although the exact mechanisms of each component are not clearly understood, some prevailing hypotheses have been generated. Decreased thrombin generation has been proposed to occur through activation of protein C[44] and shedding of the glycocalyx,[45] but the role of these mechanisms remains controversial. Fibrinogen dysfunction is believed to be related to metabolic abnormalities[46] and consumption at the site of injury.[47] Platelet dysfunction has been associated with damage-associated molecular pattern proteins such as histones[48] through binding Toll-like receptors.[49] Fibrinolysis activation is proposed to occur via tissue plasminogen activator (tPA) release from hemorrhagic shock,[50] whereas fibrinolysis suppression (shutdown) is associated with tissue injury.[51] There are numerous review articles on the topic of early TIC that describe the details of these hypotheses and others.[43,52–55]

Regardless of the underlying pathobiology, few early adjuncts in trauma resuscitation have been demonstrated to reduce mortality in trauma patients at risk of bleeding. The following are the three adjuncts in which clinical trials have resulted in positive outcomes: (1) tranexamic acid (TXA), which reduced bleeding mortality by 0.6% in a large multinational trial[56]; (2) prehospital plasma resuscitation in patients requiring helicopter transportation (9.8% reduction mortality)[57]; and (3) VHA-based resuscitation in patients in which the massive transfusion protocol (MTP) was activated (15.8% reduction mortality).[38] In each of these trials, total red blood cell transfusions were not reduced. The mechanisms by which these hemostatic adjuncts improve mortality remain unclear. Most trauma centers with adequate blood banks will use MTPs with an empiric ratio of red blood cell, plasma, and platelets to guide early resuscitation before coagulation test results become available. Many MTPs use a ratio of 1:1:1 despite lower ratios (2:1:1) having comparable outcomes.[58] The threshold for adding empiric blood components such as cryoprecipitate should start when patients have received more than 4 units of red blood cells.[59] In the future whole-blood resuscitation may become an alternative option for early hemostatic resuscitation in patients who are massively bleeding.[60] With these empiric transfusion strategies becoming more popular, the intensivist will take on a more important role in the de-escalation of hemostatic resuscitation, which will be discussed in the later section discussing late TIC.

IDENTIFICATION OF SEPSIS-INDUCED COAGULOPATHY

The onset of coagulation changes after sepsis is less well defined. A nonhuman primate model suggests this process begins to occur early[61–63] and appears to be variable based on the pathogen. The hallmark of sepsis driving coagulation changes includes a drop in platelet count, prolonged INR, and increase in fibrin degradation products.[64] When the International Society of Thrombosis and Hemostasis (ISTH) developed a DIC score, it was acknowledged that coagulation abnormalities in sepsis and other causes of DIC proceeded overtly apparent DIC.[65] This nonovert DIC group of patients was later simplified into a score to diagnosis SIC based on platelet count, INR, and Sequential Organ Failure Assessment (SOFA) score.[5] Prospective evaluation of the SIC score identified that this definition of coagulopathy in sepsis represented a broader spectrum of patients, some of whom were at risk of progression to overt DIC.[66] The prevalence of SIC appears to be comparable to TIC,[67] in which roughly a quarter of patients with sepsis meet this definition.[68] However, incorporation

of a SOFA score requires six variables that are calculated based on variables measured in the first 24 hours in the ICU. Unlike TIC, which can be determined within an hour of admission to the ED,[69] SIC is more challenging to diagnose and requires an ICU setting. Specifically, platelet counts and INR in the ED have not been found to predict mortality in sepsis.[70]

VHA testing in sepsis has gained popularity.[71–73] Several studies have demonstrated that a decreased angle,[71,72] decreased clot strength,[72] and lack of fibrinolysis[74] are associated with DIC and poor outcomes. However, septic patients without evidence of DIC have a tendency for hypercoagulability.[72] From the existing VHA data, it appears that patients with sepsis have a tendency towards hypercoagulability with fibrinolysis resistance,[72,75] and the reduction in clot strength/fibrinogen appears to be a later event in which patients have transitioned to DIC and organ failure.[72,73] Unlike early TIC, when there is clear evidence of pathology with ongoing bleeding from injured tissue caused by mechanical disruption and coagulation abnormalities, pathologic sequelae from early SIC are not clinically apparent, as these patients are not bleeding, and the progression to organ failure manifests in a time course measured by days rather than bleeding to death in minutes.

MECHANISM OF SIC/DIC AND TREATMENT

The drivers of DIC have been studied for decades without differentiation of the earlier stage of the disease process through SIC. Inflammation-provoked cytokine release is believed to be the initiator of coagulation changes in sepsis caused by endotoxin.[20] Cytokine production is believed to stimulate tissue factor production, resulting in systemic activation of coagulation.[76] Tissue factor expression is upregulated on macrophages and endothelial cells in response to elevated tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6, and IL-1.[77] At the same time the cytokine storm damages the endothelium, reducing the antithrombic capacity of the systemic circulation via suppression of protein C, protein S, antithrombin, and tissue factor pathway inhibitor (TFPI).[78] VHA testing in healthy humans with endotoxin infusion has demonstrated activation of the fibrinolytic system within 2 hours after infusion, followed by a shutdown of fibrinolysis within an hour because of elevated plasminogen activator inhibitor-1 (PAI-1) levels.[79] Fibrinolysis activation with subsequent rapid suppression by PAI-1 was documented with endotoxin infusion in nonhuman primates, with concurrent increases in thrombin generation.[80] Pentoxifylline attenuates these fibrinolytic changes in this animal model, whereas IL-6 and TNF-α inhibitors have no effect.[81] These experiments were followed up with the hypothesis that an antifibrinolytic would prevent progression to DIC by blocking plasmin activation; however, TXA had no impact on the prothrombin component of endotoxin infusion in healthy subjects and did not alter cytokine production.[82] Regardless, the overwhelming majority of patients will have long passed the initial fibrinolytic activation phase of endotoxemia by the time sepsis is diagnosed.

An important component of DIC/SIC coagulopathy is thrombocytopenia. Declining platelet counts in DIC have been proposed to be largely attributable to consumption of platelets via fibrin accumulation in the intravascular space.[76] More recent animal data support that platelets bind lipopolysaccharide (LPS) via the Toll-like receptors and become activated, resulting in deposition in the lungs and increasing levels of TNF-α.[83] Inhibition of platelets has been proposed to be a potential therapy to attenuate the progression to DIC and organ failure.[84] Other causes of decreased platelet counts in the ICU associated with organ failure include thrombotic microangiopathy (TMA). TMA processes include hemolytic uremia syndrome (HUS), thrombotic thrombocytopenic purpura (TTP), and Shiga toxin–producing *Escherichia coli*. However, these occur at a much lower frequency (~150 times less frequent) than DIC-associated thrombocytopenia.[85]

Management of SIC/DIC has been focused on enhancement of the anticoagulation system. There are no randomized controlled trials treating septic patients with presumed SIC/DIC with heparin, antithrombin, protein C, thrombomodulin, or TFPI that have improved mortality. A summary of the clinical trials can be found at references that are predominantly targeted to patients with overt DIC.[86-88] The current management of SIC is to treat the underlying cause. This is most appropriately addressed by implementing the Surviving Sepsis Campaign recommendations of early sepsis diagnosis, administration of empiric broad-spectrum antibiotics (within 1 hour based on the presumed site of infection), 30 mL/kg crystalloid resuscitation in patients in shock or with high lactate levels (to be completed within 3 hours), addition of vasopressors in those whose blood pressure is not responding to initial crystalloid resuscitation (within 1 hour), and source control as soon as feasible (but within 6 hours).[89]

THE TRANSITION FROM EARLY TO LATE TIC: HYPOCOAGULABLE TO HYPERCOAGULABLE STATE

While the focus of early TIC is dominated by concerns for correcting underlying hypercoagulability to reduce bleeding, the focus of late TIC is transitions to treatment strategies to prevent thrombotic complications and organ failure.[21] Upon arrival in the ICU, severely injured trauma (with potential ongoing bleeding) requires a multimodality approach. Resuscitation should be optimized resuscitation while coagulopathy is corrected. Neglecting hypothermia and acidosis will exacerbate ongoing hemostatic dysfunction[90] and risk the patient getting stuck in the lethal triad of trauma. Obtaining baseline laboratory assessment of the patient's acid-base status and degree of anaerobic metabolism is an important first step in the management of a coagulopathic trauma patient. Hypocalcemia is another risk factor for ongoing coagulopathy. Patients receiving massive transfusions are at risk of hypocalcemia because of calcium binding to the citrate in the transfused blood.[91] Empiric calcium administration can be considered in patients with evidence of ongoing bleeding.

The timing from injury is also an important consideration in patient management. As previously mentioned, fibrinolysis activation is one of the earliest changes in coagulation after severe injury, and commonly is suppressed soon after.[29] This reperfusion fibrinolysis shutdown is associated with a massive increase in PAI-1 levels.[92] The timing of peak reperfusion fibrinolysis shutdown is between 2 and 4 hours after injury.[52] This has a similar time course to fibrinolysis shutdown induced by endotoxin in animal models.[80] Most severely bleeding trauma patients who survive to be admitted to the ICU will be in fibrinolysis shutdown[93] because those who have failed to correct hyperfibrinolysis (excessive systemic fibrinolysis) will have bled to death in the ED or in the operating room.[94] Therefore the use of antifibrinolytics upon ICU arrival of these patients is unlikely to have a benefit, and most will be past the 3-hour time from injury when TXA loses its survival benefit.[95]

Despite fibrinolysis shutdown being highly prevalent in this patient population, it does not equate to hemostasis. Patients in fibrinolysis shutdown who are undergoing massive transfusion will frequently have a prolonged INR, low fibrinogen, and platelet dysfunction.[96] TXA in this cohort does not improve fibrin clot strength (when assessed ex vivo) and has been associated with increased mortality.[97] Therefore all trauma patients on arrival to the ICU should have a global coagulation

assessment. By the time the patient arrives, initial coagulation laboratory values should have been obtained, which will also provide clinically relevant information. As previously mentioned, initial coagulation laboratory studies not only predict early mortality from bleeding but also are biomarkers for injury severity, the development of thrombotic complications, and organ failure.[34]

The hemostatic resuscitation of trauma patients in the ICU should be transitioned to goal-directed blood component administration. We have implemented a thromboelastography (TEG)-directed resuscitation approach based on an ongoing evaluation of blood product utilization at the Ernest E. Moore Shock Trauma Center.[98] The specific cutoffs for blood product transfusions based on VHA assessment are center-dependent. Manufacture normal limits do not necessarily reflect the hemostatic needs of actively bleeding trauma patients. We have used a rapid TEG-activated clotting time greater than 128 seconds as an indication for a plasma transfusion, a TEG angle of less than 65 degrees as an indication for cryoprecipitate transfusion, a TEG maximum amplitude (MA) less than 55 mm for a platelet transfusion, and LY30>5% for the antifibrinolytics (which is exceedingly rare in the ICU).

Rotational thromboelastometry (ROTEM) also provides comparable results to TEG in hemostatic resuscitation.[99] One advantage with the current ROTEM platform over TEG is the amplitude at 5 and 10 minutes. These results provide information to guide platelet- and fibrinogen-based products 20 minutes earlier than the current TEG parameters.[41] Without VHA testing, goal-directed resuscitation is based on standard laboratory assessment with a complete blood count, INR, and Clauss fibrinogen. Inflection points for transfusions with these assays require more estimating of what clotting parameter is dysfunctional. Regardless of coagulation assessment, the active bleeding patients should have a hemoglobin target of 10 to optimize platelet function.[100]

After the initial assessment of coagulation function and physiologic parameters of the ICU patient, the decision to transfuse should be based on clinical evidence of ongoing bleeding. Patients who are hemodynamically stable, have corrected their acidosis, and have stable hemoglobin levels do not necessarily warrant correction of an ongoing laboratory-detected coagulopathy. Each transfusion of blood incurs some risk to the patient. A high ratio of plasma to red blood cells has not been associated with an increased risk of acute respiratory distress syndrome (ARDS) in a patient undergoing a massive transfusion.[101] However, in patients requiring less blood products, high plasma utilization (>6 units) was significantly associated with ARDS,[102] particularly when a concomitant chest injury was present.[103] The same association has been appreciated with platelet transfusions.[104] Cryoprecipitate in trauma has not been associated with these adverse outcomes, but could be because of lower utilization. The combination of cryoprecipitate and TXA, however, has been associated with an increased risk of thrombotic complications.[105]

The transition to pathologic hypercoagulability resulting in thrombotic complications in trauma appears to become relevant with fibrinolysis resistance at 12 hours from injury[106] and with increased clot strength at 24–48 hours.[106,107] The inflection-point, VHA-detected risk of hypercoagulability appears to be a clot strength with an MA in the 70-mm range with TEG.[108–110] Management of late TIC hypercoagulability will be addressed in a later section. During this transition time from early to late TIC, patients will require ongoing evaluation for surgical bleeding. Patients who have a corrected coagulation profile and continue to be hypotensive or have surgical drains/chest tubes with high output should warrant consideration for taking the patient to the operating room.

Late TIC and SIC

Early TIC and SIC have completely different pathobiology. Trauma patients with early TIC are at high risk of bleeding to death, often present to the hospital in hemorrhagic shock, frequently undergo blood product resuscitation, and definitive care may require an operative intervention to control bleeding, whereas SIC patients present with distributive shock, undergo crystalloid resuscitation, are dependent on antibiotics to treat the underlying disease process, and may require an operative intervention to get source control of the infection. Assimilating these pathologies begins to occur after these patients have been resuscitated and are in the ICU. These critically ill patients begin to share similar coagulation features.

The proinflammatory immune response after trauma and sepsis resuscitation is referred to as the systemic inflammatory response (SIRS). When SIRS is severe and remitting, it can cause early multiple organ failure (MOF) and death.[111] The immune counterbalance to SIRS is called *compensatory antiinflammatory response syndrome (CARS)*.[112] CARS is associated with increased secondary infections, which can contribute to the development of late MOF and death.[113] Fortunately, with improved ICU care, both early and late MOF deaths have largely disappeared over the past decade. However, failure of SIRS and CARS to return to an immune homeostatic state can result in what has recently been coined persistent inflammation, immunosuppression, and catabolism syndrome, which is associated with chronic critical illness (CCI) with prolonged ICU stays and dismal long-term outcomes.[114] Similarity between trauma and sepsis coagulopathy during SIRS and CARS may persist and contribute to the underlying pathobiology of CCI. This is an unexplored area of research.

The transition to terminal coagulopathy represented as DIC is appreciated by a progressive decline in platelets and fibrinogen, which is presumed to occur from a consumption of these clotting components at the microvascular level.[76] Patients manifest an oozing coagulopathy but retain components of hypercoagulability via inhibited fibrinolysis.[115] Several scores are used to calculate the risk of DIC, with the International Society of Thrombosis and Haemostasis (ISTH) and Japanese Association for Acute Medicine (JAAM) having comparable performance.[116] Unfortunately, calculating DIC does not improve outcomes, and the treatment of these patients is supportive with the objective to treat the underlying pathology. A new definition of DIC based on quantifying thrombin generation to plasmin (fibrinolysis) ratios suggests that the majority of these patients have a disbalance of excessive thrombin generation and lack of plasmin generation driving coagulopathy.[117]

Trauma and sepsis drive a more rapid onset of DIC with a worse prognosis,[118] whereas malignancy-associated DIC tends to be more indolent and responsive to hemostatic adjuncts to address specific coagulation abnormalities.[119] This is an important patient management concept, as those patients with trauma and sepsis require vigilant efforts to determine if there is appropriate antibiotic coverage, source control, or need for procedure or operative intervention to prevent a vicious cycle of ongoing coagulopathy. Clinical trials are assessing if adjuncts to balance thrombin generation, such as soluble thrombomodulin[120–122] and antithrombin[123,124] or in combination,[123] are effective, but there is no definitive evidence for improvement in mortality with these treatment strategies at this time.[125] Additionally, prior work with activated protein C did not improve survival in DIC[126] despite promising early clinical observational studies. Ultimately the goal of management of DIC is treating the patient's underlying cause before they reach this level of critical illness.

KEY POINTS

- Early TIC is a distinct entity from DIC, but later TIC and DIC may share common features.
- Early TIC typically manifests as the inability to achieve hemostasis and is driven by a combination of inadequate thrombin generation, fibrinogen depletion, and platelet dysfunction.
- DIC is the result of inflammation-provoked hypercoagulability, resulting in increased tissue factor expression and widespread clot formation.
- Fibrinolysis shutdown can occur in both TIC and DIC, inhibiting the physiologic process of clot degradation.
- Viscoelastic hemostatic assays (TEG and ROTEM) provide the best assessment of the coagulation system.
- SIC is a new terminology based on platelet count, INR, and organ dysfunction and may progress to DIC.

References for this chapter can be found at expertconsult.com.

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23

Jaundice

Ryan Rodriguez and Marie Crandall

Bilirubin is a by-product of heme metabolism. Heme is largely derived from the hemoglobin in senescent red blood cells and is oxidized in the spleen, liver, and other organs by two isoforms of the enzyme heme oxygenase, in the presence of nicotinamide adenine dinucleotide phosphate (NADPH) and molecular oxygen, to form biliverdin, carbon monoxide, and iron.[1] Subsequently, biliverdin is converted into bilirubin by the phosphoprotein biliverdin reductase, which also uses NADPH as a cofactor. A visual representation of this pathway is shown in Fig. 23.1. Bilirubin is a lipophilic molecule. To be excreted, bilirubin that is produced in extrahepatic organs is bound to albumin and transported to the liver. The liver takes up the bilirubin – albumin complex through an albumin receptor. Bilirubin, but not albumin, is transferred across the hepatocyte membrane and transported through the cytoplasm to the smooth endoplasmic reticulum bound primarily to ligandin or Y protein, a member of the glutathione *S*-transferase gene family of proteins. Within hepatocytes, bilirubin is converted to water-soluble derivatives, bilirubin monoglucuronide and bilirubin diglucuronide, by the enzyme uridine diphosphate-glucuronosyl transferase. These conjugated forms of bilirubin are secreted across the canalicular membrane into the bile via an energy-dependent process. Conjugated bilirubin is excreted in the bile into the intestine, where it is broken down by the gut microflora into urobilinogen and stercobilin.

Total serum bilirubin consists of an unconjugated fraction and a conjugated fraction. The conjugated forms of bilirubin exist both freely in the serum and bound covalently to albumin. Conjugated bilirubin is water soluble and reacts directly to certain dyes added to the serum specimen. The unconjugated bilirubin does not react with the colorimetric reagents until a solvent is added. Accordingly, the conjugated and unconjugated forms of bilirubin are sometimes referred to as "direct" and "indirect" bilirubin. The sum of these two measurements is the "total" bilirubin. The normal total bilirubin concentration in adults is less than 18 μmol/L (1.0 mg/dL). Although any total bilirubin concentration higher than the upper limit of normal constitutes hyperbilirubinemia, jaundice (i.e., yellow discoloration of the sclerae, mucous membranes, and skin) is usually not clinically apparent unless the serum total bilirubin level is greater than 50 μmol/L (2.8 mg/dL). Unconjugated or indirect hyperbilirubinemia is present when the total serum bilirubin concentration is above the upper limit of normal and less than 15% of the total is in the direct or conjugated form.

DIFFERENTIAL DIAGNOSIS

The multitude of diagnoses depicted in Box 23.1 divides the causes of hyperbilirubinemia into two large groups according to whether the predominant abnormality is an increase in the circulating concentration of unconjugated (indirect) bilirubin or an increase in the concentration of conjugated (direct) bilirubin. Although this classification scheme is useful under some circumstances, many of the diagnoses listed in Box 23.1 are extremely rare and highly unlikely to be encountered by the intensivist caring for critically ill (adult) patients. A more useful classification scheme is depicted in Box 23.2. In this scheme, the causes of jaundice are grouped into three primary categories: extrahepatic obstruction to bile flow, increased bilirubin production, and impaired excretion secondary to hepatocellular necrosis and/or intrahepatic cholestasis and hepatitis. It is common for multiple mechanisms to be involved simultaneously.

Hyperbilirubinemia occurs frequently in critically ill patients and is an independent risk factor for an unfavorable outcome.[2,3] In a retrospective study of adult patients admitted to an intensive care unit (ICU) with severe sepsis or septic shock, the mortality rate was 12%, 24%, and 42% for individuals with a peak serum bilirubin concentration during the first 72 hours that was ≤1, 1.1–2, or >2 mg/dL, respectively.[4] In another retrospective study, hyperbilirubinemia was a significant risk factor for the development of acute respiratory distress syndrome (ARDS) among patients admitted to an ICU with sepsis.[5] In one widely cited study, hyperbilirubinemia occurred in 217 of 2857 trauma patients who had an Injury Severity Score greater than 14 and survived for longer than 48 hours after admission to the hospital.[6] In this study, hyperbilirubinemia was significantly associated with an increased length of stay in the ICU and death. Hyperbilirubinemia is also common in ICU patients who are recovering from cardiac surgery.[7,8] In this category of ICU patients, risk factors for the development of hyperbilirubinemia include prolonged cardiopulmonary bypass time, prolonged aortic cross-clamp time, and use of an intraaortic balloon pump.[8]

Determining the cause of new-onset hyperbilirubinemia is important when managing ICU patients because some problems can be corrected. Exclusion of a mechanical cause for jaundice (e.g., obstruction of the common bile duct because of choledocholithiasis or stricture) assumes the highest priority because failure to correct this type of problem in a timely fashion can lead to serious morbidity or even mortality. Fig. 23.2 shows an approach to handling new-onset hyperbilirubinemia in an adult patient. Hyperbilirubinemia is multifactorial, and although laboratory values evaluating the production and excretion of bilirubin can guide the workup, a liver biopsy or cholangiography is necessary when no other diagnosis can be confirmed.

Iatrogenic injuries to the common bile duct are fortunately quite rare. Damage to the biliary tree, stricture of biliary anastomoses, and retained stones after cholecystectomy or common bile duct exploration present as hyperbilirubinemia and elevated circulating levels of alkaline phosphatase or gamma-glutamyltransferase. Most often the diagnosis is made by detecting the dilation of intrahepatic and extrahepatic bile ducts using ultrasonography.

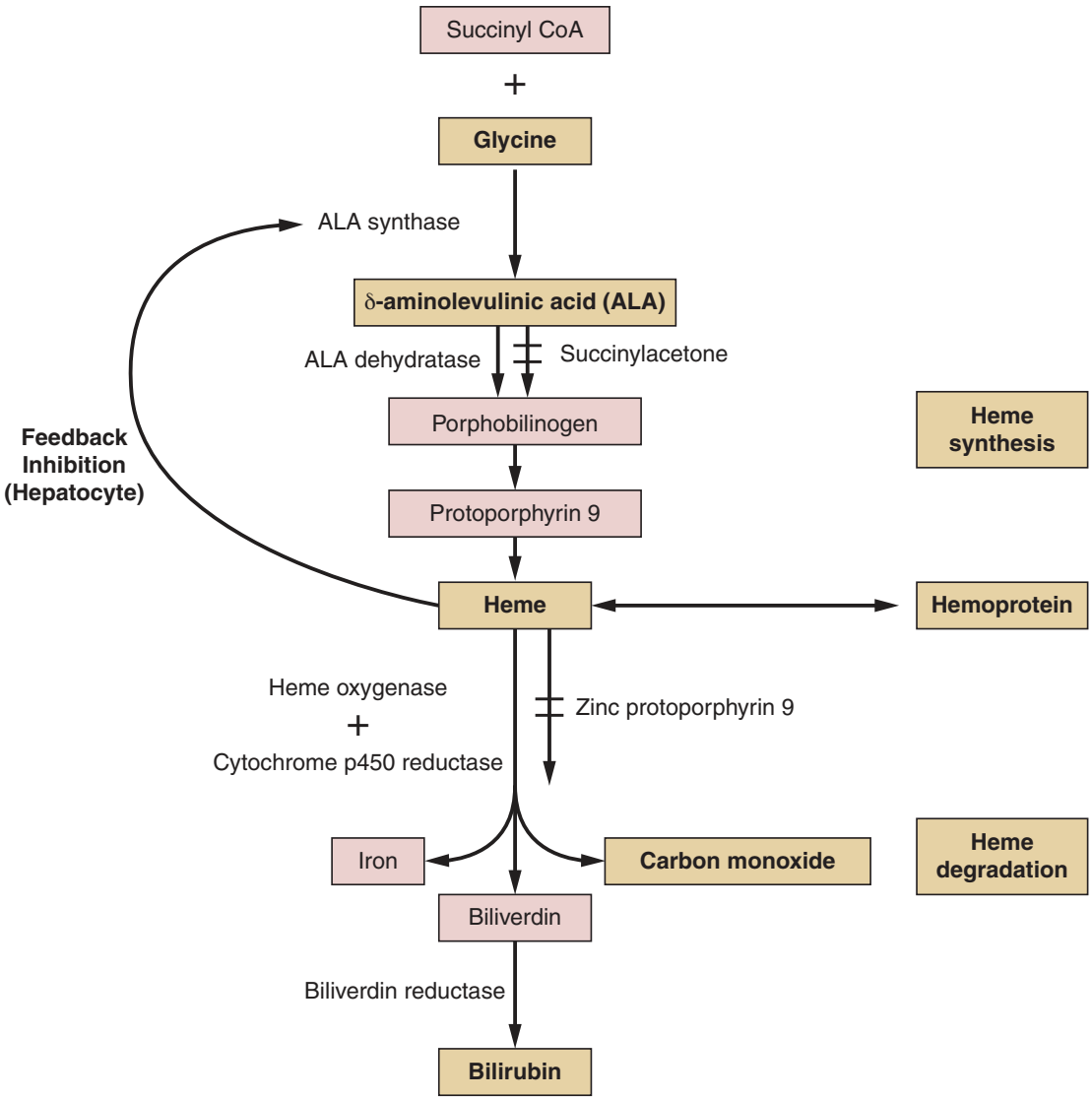

Fig. 23.1 Pathway, Regulation, and Inhibitors of Heme Metabolism. The first enzyme of the heme biosynthetic pathway, aminolevulinate (*ALA*) synthase (*ALAS*), is the rate-controlling enzyme of this pathway. Heme formation is subject to end-product regulation by negative feedback, but the exact point of metabolic control differs between hepatocytes and erythroid cells. In the liver, ALAS is regulated negatively by heme, the end product of the pathway. In contrast, in erythroid cells, ALAS is not under the same regulatory mechanism. Heme oxygenase (HO) is the rate-controlling enzyme of the heme degradation pathway. Succinylacetone (SA) is a potent inhibitor of ALA dehydratase activity. ZnPP9 is a potent inhibitor of HO activity. (From Tatsuya I, Chiang G, Ronnett GV. The regulation of heme turnover and carbon monoxide biosynthesis in cultured primary rat olfactory receptor neurons. *J Neurosci*. 1996;16:5621–5628, Fig. 3.)

By exceeding the capacity of the liver to conjugate and excrete bilirubin into the bile, hemolysis can result in jaundice. However, the liver can excrete approximately 300 mg/day of bilirubin,[9] and therefore clinically significant hyperbilirubinemia is only apparent if the rate of hemolysis (i.e., the number of red blood cells lysed per unit time) is fairly rapid. Approximately 10% of the erythrocytes in an appropriately cross-matched unit of packed red blood cells undergo rapid hemolysis, yielding about 250 mg of bilirubin.[10] Accordingly, transfusion of a single unit of packed red blood cells is not likely to increase the total serum bilirubin concentration. However, transfusion of multiple units of blood over a short period almost inevitably leads to some degree of hyperbilirubinemia, particularly if hepatic functionality is already impaired. Other common causes of acute hemolysis in ICU patients include sickle cell disease, immune-mediated hemolytic anemia, and disseminated intravascular coagulation.

Any condition that leads to extensive hepatocellular damage will increase the circulating total bilirubin concentration. Conditions in this category that are commonly encountered in ICU patients include viral hepatitis, "shock liver," alcoholic hepatitis, and hepatocellular injury induced by drugs, especially acetaminophen.[11] In most forms of jaundice resulting from hepatic inflammation or hepatocellular damage, circulating levels of transaminases are elevated to a greater extent than the total bilirubin concentration. Making a diagnosis of acetaminophen overdose early is extremely important because specific therapy using *N*-acetylcysteine can be lifesaving.[11]

BOX 23.1 Differential Diagnosis of Hyperbilirubinemia

A. Unconjugated hyperbilirubinemia
  1. Overproduction of bilirubin
    a. Hemolysis, intravascular: disseminated intravascular coagulation
    b. Hemolysis, extravascular
      i. Hemoglobinopathies
      ii. Enzyme deficiencies (e.g., glucose-6-phosphate dehydrogenase deficiency)
      iii. Autoimmune hemolytic anemias
    c. Ineffective erythropoiesis
    d. Resorption of hematoma
    e. Massive transfusion
  2. Hereditary unconjugated hyperbilirubinemia
    a. Gilbert syndrome (autosomal dominant)
    b. Crigler-Najjar syndrome type I (autosomal recessive)
    c. Crigler-Najjar syndrome type II (autosomal dominant)
  3. Drugs
    a. Chloramphenicol: neonatal hyperbilirubinemia
    b. Vitamin K: neonatal hyperbilirubinemia
    c. 5-Beta-pregnane-3 alpha, 20-alpha-diol: cause of breast milk jaundice
B. Conjugated hyperbilirubinemia
  1. Inherited disorders
    a. Dubin-Johnson syndrome (autosomal recessive)
    b. Rotor syndrome (autosomal recessive)
  2. Hepatocellular diseases and intrahepatic causes
    a. Viral hepatitis
    b. Alcoholic hepatitis
    c. Drug-induced hepatitis (e.g., because of isoniazid, nonsteroidal antiinflammatory drugs, and zidovudine)
    d. Cirrhosis
    e. Drug-induced cholestasis (e.g., because of prochlorperazine, haloperidol [Haldol], and estrogens)
    f. Sepsis
    g. Postoperative jaundice
    h. Infiltrative liver disease: tumors, abscesses (pyogenic, amebic), tuberculosis, parasites (e.g., *Toxoplasma*), *Pneumocystis jirovecii* pneumonia, *Echinococcus*
    i. Primary biliary cirrhosis
    j. Primary sclerosing cholangitis
  3. Extrahepatic causes
    a. Gallstone disease
    b. Pancreatitis-related stricture
    c. Pancreatic head tumor
    d. Cholangiocarcinoma
    e. Primary sclerosing cholangitis

Adapted from Bernstein MD. Hyperbilirubinemia. In Rakel RE, ed. *Saunders Manual of Medical Practice*. Philadelphia: Saunders; 1996:371–373, with permission.

BOX 23.2 Classification for Acute Jaundice Associated With Critical Illness

I. Extrahepatic bile duct obstruction
  A. Choledocholithiasis
  B. Common bile duct stricture
  C. Traumatic or iatrogenic common bile duct injury
  D. Acute pancreatitis
  E. Malignancy (e.g., ampullary carcinoma)
II. Increased bilirubin production
  A. Massive transfusion
  B. Resorption of blood collections (e.g., hematomas, hemoperitoneum)
  C. Acute hemolysis
    1. Disseminated intravascular coagulation
    2. Immune-mediated
III. Impaired excretion because of hepatocellular dysfunction, hepatitis, or intrahepatic cholestasis
  A. Drug- or alcohol-induced hepatitis
  B. Drug-induced intrahepatic cholestasis
  C. Drug-induced hepatocellular necrosis
  D. Gilbert syndrome
  E. Sepsis and other causes of systemic inflammation
  F. Total parenteral nutrition
  G. Viral hepatitis

Efforts to understand the pathophysiologic mechanisms responsible for cholestatic jaundice resulting from sepsis have largely focused on lipopolysaccharide (LPS)-induced alterations in the function and expression of various bile acid transporters.[12–14] Nevertheless, another factor that likely contributes to the development of intrahepatic cholestasis is the back-leakage of bile from the canalicular spaces into the sinusoids.[15]

SIDE EFFECTS OF TPN USAGE IN THE CRITICAL CARE SETTING

Malnutrition among hospitalized patients has been associated with increased morbidity, prolonged hospital stay, and increased costs to the healthcare system, but at times, an extended period of "nil per os (NPO)" status is one of the factors in current treatment algorithms for an extensive list of disease processes. Several studies have documented that "bowel rest" is associated with a disruption of the mucosal barrier structure and function, augmenting the inflammatory response to illness and resulting in greater infectious morbidity. Although this has been seen in some patient studies, total parenteral nutrition (TPN) as a temporary measure during these NPO periods has been shown to possibly reduce the complication rate in malnourished patients. As a consequence, nutritional support, most notably TPN, has become a standard of care for malnourished hospitalized patients.[16]

TPN has been shown to be associated with the development of hyperbilirubinemia.[17] The basis for TPN-induced cholestasis is thought to be multifactorial. Prolonged bowel rest and ileus may promote bacterial overgrowth and increased translocation of LPS into the portal vein on this basis. Phytosterols are present in the lipid emulsions used for TPN and have been associated with cholestasis, especially in premature infants.[18] Results from two retrospective studies suggest that the administration of more than 1 g/kg/day of lipid emulsion is associated with an increased incidence of hepatocellular dysfunction.[19,20] However, these data were derived from

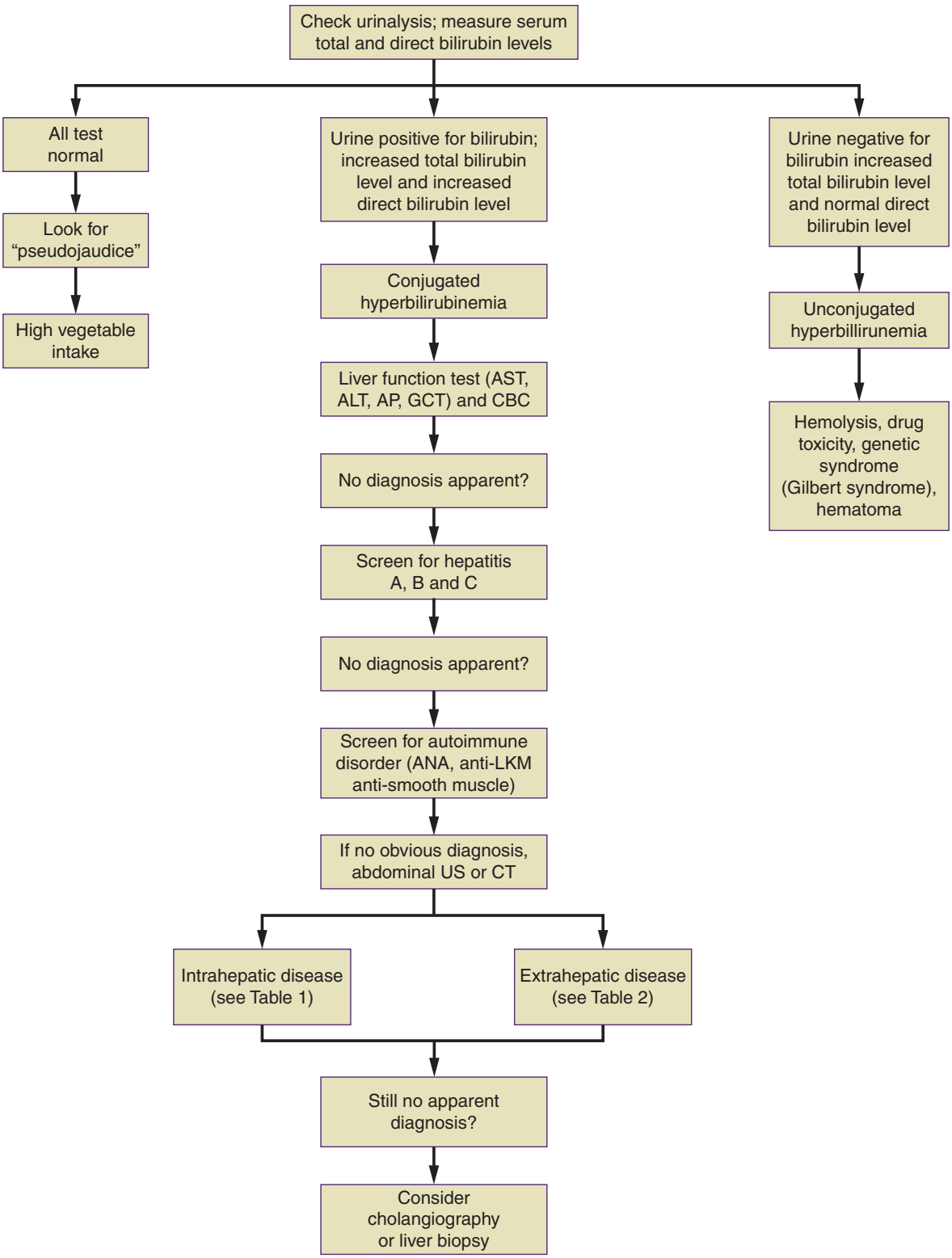

Fig. 23.2 Algorithm for a Systematic Approach to the Adult Patient with Jaundice. *ALT,* Alanine transaminase; *ANA,* antinuclear antibodies; *anti-LKM,* liver-kidney microsomal antibodies; *AP,* alkaline phosphatase; *AST,* aspartate transaminase; *CBC,* complete blood count; *CT,* computed tomography; *GGT,* gamma-glutamyltransferase; *US,* ultrasonography. (From Roche S, Kobos R. Jaundice in the adult patient. *Am Fam Physician*. 2004;69[2]:299–304, Fig. 1.)

studying patients receiving TPN at home for prolonged periods and may not apply to ICU patients. In any case, TPN is associated with the development of jaundice and hepatocellular damage. Accordingly, except in rare cases, the majority of ICU patients are better served by receiving enteral rather than parenteral nutrition.

KEY POINTS

- Heme is largely derived from the hemoglobin in aged red blood cells and oxidized in the spleen, liver, and other organs to produce bilirubin as a by-product.
- Total serum bilirubin consists of an unconjugated fraction and a conjugated fraction.
- Hyperbilirubinemia can be divided into unconjugated (hemoglobinopathies, enzyme deficiencies, autoimmune, certain drugs) vs. conjugated (viral hepatitis, alcoholic hepatitis, sepsis, postoperative, infiltrative liver disease).
- The normal total bilirubin concentration in adults is less than 18 mmol/L (1.0 mg/dL).
- Hyperbilirubinemia occurs frequently in critically ill patients and is an independent risk factor for an unfavorable outcome.
- The liver can excrete approximately 300 mg/day of bilirubin.
- TPN is associated with the development of hyperbilirubinemia.

References for this chapter can be found at expertconsult.com.

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Chan S, McCowen KC, Bistrian BR, et al. Incidence, prognosis, and etiology of end-stage liver disease in patients receiving home total parenteral nutrition. *Surgery*. 1999;126:28–34.
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24

Ascites

Zarah D. Antongiorgi and Jennifer Nguyen-Lee

DEFINITION AND DIAGNOSIS

Whereas a normal peritoneal cavity contains only 25 mL of fluid, the peritoneum has the capacity to absorb 900 mL/day.[1] Ascites is the pathologic accumulation of peritoneal fluid, occurring most commonly in decompensated liver cirrhosis (85%), with malignancy, tuberculosis, heart failure, and pancreatitis accounting for the remainder.[2,3] The International Club of Ascites classifies ascites severity, with fluid detectable only on imaging (<100 mL) as grade 1, moderate symmetric abdominal distention with up to 1 L of fluid as grade 2, and tense distention associated with a large volume of fluid as grade 3.[4] Cirrhotic ascites can be uncomplicated or complicated, the latter involving concomitant development of spontaneous bacterial peritonitis (SBP), hepatorenal syndrome, or hepatic hydrothorax. Refractory ascites (5%–10% of cases) is persistent or rapidly recurring ascites despite maximal medical therapy.[4]

Symptoms of ascites include weight gain, abdominal pain, fullness, early satiety, and shortness of breath. History and physical examination looking for signs of liver disease or other underlying cause form the foundation of diagnostic evaluation. Detecting ascites on examination can prove difficult if <1500 mL is present. If flank dullness on percussion is not appreciated, there is a 90% chance no ascites is present.[5] Although computed tomography (CT) will identify ascites, ultrasound is the preferred imaging modality. It is a highly sensitive, low-cost, nonradiation-producing method that simultaneously allows evaluation of the liver and hepatic vasculature.

Patients with new-onset ascites should undergo diagnostic paracentesis, with removal of 20–30 mL for evaluation of fluid color, turbidity, and total protein and for calculation of the serum–ascites albumin gradient (SAAG).[6,7] A SAAG >1.1 g/dL is 97% accurate in identifying ascites resulting from portal hypertension (Table 24.1).[8] Infected ascites is a life-threatening complication, requiring timely assessment of the ascitic cell count and differential. A study of hospitalized patients with cirrhosis and SBP demonstrated a 3% increase in mortality for every hour that diagnostic paracentesis was delayed.[9] Fluid can be sent for triglyceride levels if chylous ascites is suspected, amylase for pancreatitis, cytology for malignancy, or *Mycobacterium* culture for tuberculosis.

PATHOPHYSIOLOGY

Portal hypertension from either increased hepatic resistance or increased portal blood flow is the key pathophysiologic event in the formation of ascites and is described in detail in Chapter 83. Normal portal venous pressure is <5 mm Hg. Once it is over 10 mm Hg, fluid from hepatic sinusoids and splanchnic capillaries overwhelms the peritoneal lymph drainage.[3,10,11] However, increased pressure is only one aspect of the pathophysiology, as fluid dysregulation and development of ascites results from a complex interplay of hemodynamic and hormonal responses.[7,12] In liver cirrhosis, hepatic sinusoidal congestion with progressive fibrotic transformation leads to endothelial cell dysfunction, causing nitric oxide–mediated vasodilation of splanchnic and peripheral arterial vascular beds. Initially, a hyperdynamic circulatory response compensates for the vasodilation to maintain adequate perfusion pressure. As vasodilation worsens and effective circulating volume decreases, however, compensatory activation of the sympathetic nervous and renin – angiotensin – aldosterone systems results in renal sodium and water retention, leading to fluid overload and hyponatremia (Fig. 24.1).[12–18] This process is hastened when infection from bacterial translocation causes endotoxin release, compounding vasodilation. Ultimately, tissue perfusion is compromised, leading to life-threatening organ dysfunction, the most salient being hepatorenal syndrome with decreasing glomerular filtration rate and severe renal vasoconstriction, as detailed in Chapter 84. In contrast to the mechanisms in cirrhosis, ascites in infection and malignancy is the result of inflammation and leakage of high-protein lymph.[3]

MANAGEMENT

After addressing underlying causes of cirrhosis, including alcohol cessation or hepatitis C treatment, ascites management is primarily focused on fluid removal. Initial treatment of cirrhotic ascites is salt restriction (no more than 2000 mg/day) and oral diuretics to promote natriuresis. The aldosterone antagonist spironolactone can be used alone, but the addition of the loop diuretic furosemide for patients with an inadequate response or moderate- to large-volume ascites is recommended.[19,20] Starting daily doses of 100 mg of spironolactone and 40 mg of furosemide achieve natriuresis without significant hypokalemia. Doses can be increased while maintaining the same ratio over 3–5 days to maximum daily doses of 400 mg of spironolactone and 160 mg of furosemide.[6,21] Initial goals of diuretic therapy are weight loss of 0.5 kg/day (or up to 1 kg/day in edematous patients) and a measured 24-hour sodium excretion of 78 mmol/day.[11,22] Side effects include intravascular volume depletion, renal insufficiency, and electrolyte abnormalities. If creatinine increases by more than 50% or more than 1.5 g/dL, or if sodium falls by more than 10 mEq/L, therapy should be adjusted.[22] Nonsteroidal antiinflammatory drugs (NSAIDs) should be avoided, not only because of the risk of renal injury but also because they impede diuretic-mediated sodium excretion.[23] Additionally, angiotensin-converting enzyme inhibitors and angiotensin receptor II antagonists should be used cautiously, given negative effects on arterial pressure and potential for worsening renal function.[6,21] Though more studies are needed, one small randomized controlled trial showed short term benefits of midodrine and adding midodrine 15-30 mg/day

TABLE 24.1 Causes of Ascites in the Normal or Diseased Peritoneum by Serum-to-Ascites Albumin Gradient (SAAG)

NORMAL PERITONEUM	
Portal Hypertension (SAAG >1.1 g/dL)	**Hypoalbuminemia (SAAG <1.1 g/dL)**
Hepatic congestion	Nephrotic syndrome
Congestive heart failure	Protein-losing enteropathy
Constrictive pericarditis	Severe malnutrition with anasarca
Tricuspid insufficiency	
Budd–Chiari syndrome	
Liver Disease	**Miscellaneous Conditions (SAAG <1.1 g/dL)**
Cirrhosis	Chylous ascites
Alcoholic hepatitis	Pancreatic ascites
Fulminant hepatic failure	Bile ascites
Massive hepatic metastases	Nephrogenic ascites
	Urine ascites
	Ovarian disease
DISEASED PERITONEUM (SAAG <1.1 g/dL)	
Infections	**Other Rare Conditions**
Bacterial peritonitis	Familial Mediterranean fever
Tuberculous peritonitis	Vasculitis
Fungal peritonitis	Granulomatous peritonitis
HIV-associated peritonitis	Eosinophilic peritonitis
Malignant Conditions	
Peritoneal carcinomatosis	
Primary mesothelioma	
Pseudomyxoma peritonei	
Hepatocellular carcinoma	

can be considered on a case-by-case basis, although no long term benefits have been shown to date.[6,24]

PARACENTESIS

Diuretics are started for initial control, but therapeutic paracentesis is indicated in settings of tense ascites to relieve abdominal pressure. The procedure is relatively safe when done under ultrasound guidance. Complications (<1%) include leakage of ascitic fluid, bleeding, infection, and bowel perforation.[25] Routine correction of thrombocytopenia or prolongation in the prothrombin time is not recommended, as paracentesis has been performed safely in patients with platelets <50,000/μL and international normalized ratio (INR) >2. In a retrospective study of 4729 procedures, the incidence of significant bleeding was relatively low (0.19%) despite coagulopathy in many patients.[26] The only real contraindication to paracentesis is disseminated intravascular coagulopathy, although other safety considerations include cooperation level of patient, pregnancy status, presence of bowel distention, and skin infection at insertion site.[21]

After removal of a large volume, paracentesis-induced circulatory dysfunction can result from effective hypovolemia with activation of the renin – angiotensin system, resulting in hyponatremia and renal impairment. When fluid removal exceeds 5 L, intravenous replacement of albumin is recommended (8 g/L of ascites removed), which is supported by data demonstrating improved survival.[27] Although large-volume paracentesis is time consuming and costly, benefits include improved patient comfort, shortened hospitalization, preserved hemodynamics, and a decreased risk of SBP and hepatic encephalopathy.[28]

PROGNOSIS AND COMPLICATIONS

Ascites signifies progression from compensated to decompensated liver failure and carries a 20% 1-year mortality.[29] Within the first decade of diagnosis, 50% of patients with cirrhosis will develop ascites.[30] Once complications such as refractory ascites or hepatorenal syndrome develop, yearly mortality increases to 75%.[31,32] Ascites features in a validated scoring system for liver failure, serving as one of five components of the Child-Turcotte-Pugh (CTP) score that also factors in encephalopathy, albumin, INR, and total bilirubin to predict mortality.[33] In a recent network meta-analysis of 49 randomized clinical trials with over 3500 patients investigating options for ascites management in decompensated liver cirrhosis, approximately one in three patients receiving a standard treatment of paracentesis followed by fluid replacement died within 11 months.[34] Though not a component of the current Model for End-Stage Liver Disease plus serum sodium score (MELD-Na) used in transplant allocation, the presence of moderate ascites correlates with a higher waitlist mortality for patients with MELD-Na scores <21 and is equivalent to an additional 3.5 MELD-Na unit points.[35] Given the poor prognosis, once ascites develops, patients should be evaluated for liver transplantation.

SPONTANEOUS BACTERIAL PERITONITIS

SBP occurs in 30% of patients with ascites, carries a 20% mortality rate, and is defined by[36]:

1. Positive bacterial culture (single organism)
2. Ascitic fluid polymorphonuclear cell count ≥250/mm^3
3. Absence of surgically treatable source of infection

SBP arises from translocation of intestinal bacteria, predominantly *Escherichia coli* and *Klebsiella*.[37] Common symptoms include fever, abdominal pain, nausea and vomiting, increasing encephalopathy, and decreased renal function. Prompt diagnostic paracentesis is indicated, with ascitic fluid sent for cell count, total protein, glucose, amylase, lactate dehydrogenase, Gram stain, and anaerobic and aerobic cultures. Cultures of ascitic fluid should be inoculated in blood culture bottles at the bedside to maximize chances of identifying a causative organism.[7,21] Patients with a low ascitic protein content (<1.5 g/L) are particularly at risk of developing SBP.[38] Treatment should start as soon as infection is suspected with a third-generation cephalosporin, such as ceftriaxone or cefotaxime, for a 5- to 7-day course.[6,21]

SBP should be differentiated from secondary bacterial peritonitis resulting from abscess or perforated viscus, as treatment is substantially different. Secondary bacterial peritonitis should be suspected if ascitic fluid analysis has a glucose <50 mg/dL, elevated lactate dehydrogenase, or polymicrobial culture results.[39] Further workup includes upright plain films, CT with water-soluble contrast, and surgery consultation.

After an initial SBP event, the chance of a repeat infection is 70%.[40] A meta-analysis of eight studies with 647 patients investigating antibiotic prophylaxis to prevent recurrent SBP demonstrated an overall mortality of 16% in the antibiotic group versus 25% for the control. Statistically significant improvements were seen in rates of reinfection and in a 3-month survival benefit.[41] Oral prophylaxis with norfloxacin

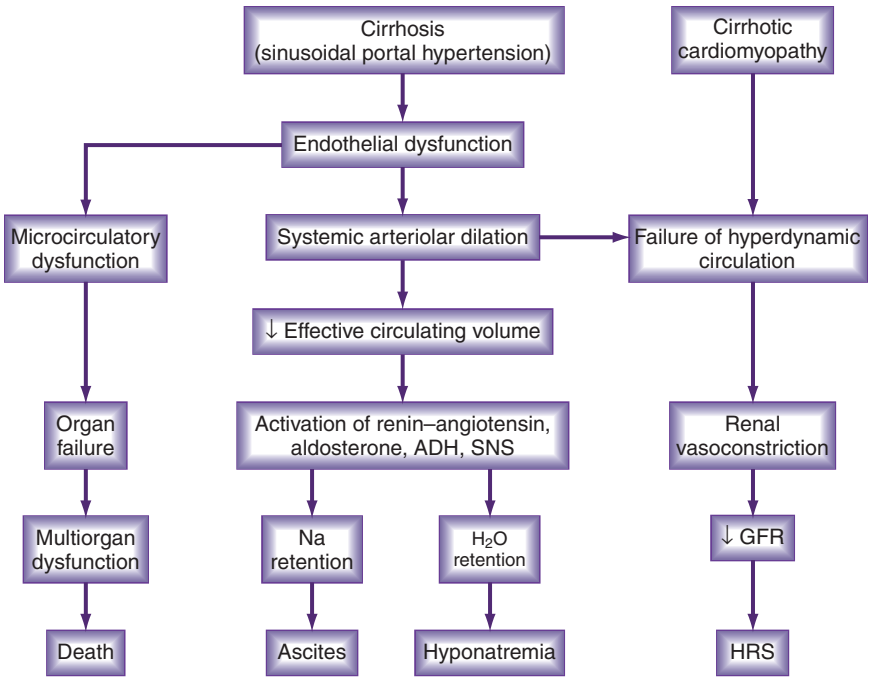

Fig. 24.1 Pathophysiology of Cirrhosis and Ascites. Cirrhosis is associated with splanchnic arterial vasodilation, leading to a decrease in effective circulating volume and a hyperdynamic circulation. The decrease in effective circulating volume causes the activation of renal sodium and water retentive pathways (e.g., RAAS, renal SNS, and ADH). Resulting sodium and water retention leads to ascites because of the spillage of excess sodium and water from hepatic lymph into the peritoneal cavity. As the disease progresses, a progressive decrease in effective circulating volume develops, causing severe renal vasoconstriction and a decrease in glomerular filtration rate (*GFR*). The onset of cirrhotic cardiomyopathy accentuates this problem and tips the patient over into hepatorenal syndrome (*HRS*). The accompanying circulatory disturbance leads to organ failure and death. Sepsis is frequently associated with this process. *ADH,* Antidiuretic hormone; *RAAS,* renin–angiotensin system; *SNS,* sympathetic nervous system. (From Salerno F, Camma C, Enea M, et al. Transjugular intrahepatic portosystemic shunt for refractory ascites: a meta-analysis of individual patient data. *Gastroenterology*. 2007;133:825–834.)

or trimethoprim/sulfamethoxazole is recommended for patients after one SBP episode and for those with active gastrointestinal bleeding, a low-protein ascitic fluid (<1.5 g/dL), impaired renal function (creatinine [Cr] ≥1.2 mg/dL), or liver failure (CTP score ≥9 and bilirubin ≥3).[6]

Refractory Ascites

Refractory ascites is diagnosed when maximal medical management for at least 1 week or repeated large-volume paracenteses within 4 weeks are insufficient to remove ascites.[15] Diuretic failure results from resistance to or complications from therapy, including renal impairment or electrolyte perturbations (hypokalemia or hyperkalemia, hyponatremia). Refractory ascites carries a mortality of 21% at 6 months and 70% at 2 years, so expedited evaluation for liver transplantation is indicated.[42] Treatment consists of serial therapeutic paracentesis, transjugular intrahepatic portosystemic shunt (TIPS), or liver transplantation (Table 24.2).

TIPS involves percutaneous placement of an expanding metal stent within an artificially created channel that diverts portal blood flow into the hepatic veins, thus decreasing portal hypertension and ascites. Consideration for TIPS occurs once patients require more than two large-volume paracenteses in a month. Complications include stent occlusion, worsened liver failure, heart failure, infection, renal failure, and increased hepatic encephalopathy. In a meta-analysis of TIPS versus repeated paracentesis aggregating six randomized controlled trials with a total of 390 patients, TIPS was shown to significantly improve liver transplant–free survival (hazard ratio [HR] = 0.61, 96% confidence interval [CI] 0.46–0.82, $P < .001$).[43] This is different from a previous Cochrane review of five randomized control trials dating from 1996 to 2004 comparing 162 patients who showed no difference in 30-day or 2-year mortality. However, patients who underwent TIPS showed a significant increase in hepatic encephalopathy (odds ratio [OR] 2.24, 95% CI 1.39, $P < .01$).[44] Selection of patients for TIPS is key. It is not recommended if bilirubin is >5 mg/dL, age >70 years old, MELD score >18, or CTP score >12.[45,46]

First tested in patients in 2010, the Automated Low-Flow Ascites Pump (ALFApump, Sequana Medical AG, Switzerland) is a surgically implanted device that drains ascites into the bladder. Ascites is directed from the abdominal cavity, out a peritoneal catheter, through a subcutaneous pump, and into a bladder catheter. Once in the bladder, the ascitic fluid can be eliminated out of the body through urination.[47] Between February 2010 and June 2011, 40 patients in multiple European centers underwent placement of an ALFApump for refractory ascites. Significant adverse events included infection, catheter dislodgement, and wound dehiscence leading to explantation of the device in 13 of the 40 patients.[48] In one single-center study of 21 patients, the ALFApump was successful in reducing the need for paracentesis, but was similarly limited because of the high rate of complications (15 of 21 patients), including catheter leakage, infection, and explantation.[49] The ALFApump is effective, and improvements in surgical technique could improve its safety profile. It could be a viable palliative treatment for patients with contraindications to TIPS or liver transplantation in select patient populations.

TABLE 24.2 Management of Refractory Ascites

Definitions	Ascites that is not eliminated even with maximum diuretic therapy Ascites that is not eliminated because maximum dosages of diuretics cannot be attained, given the development of diuretic-induced complications
Recommended therapy	Large-volume paracentesis + IV albumin (8 g/L of ascites), especially if more than 5 L ascites are removed Synthetic plasma volume expanders are not recommended Continue with salt restriction and diuretic therapy as tolerated to prevent ascites reaccumulation
Alternative therapy	TIPS for appropriately selected patients who require repeated paracenteses (>2 per month) or those in whom paracentesis is ineffective (i.e., loculated) ALFApump for patients who are not candidates for TIPS or liver transplant

Data from European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. *J Hepatol.* 2018;69(2):406–460. Erratum in: *J Hepatol.* 2018;69(5):1207.
IV, Intravenous; *TIPS,* transjugular intrahepatic portosystemic shunt.

KEY POINTS

- Ascites is most commonly the result of liver disease and has a 20% yearly mortality.
- Diagnostic paracentesis should be performed in all patients with new ascites to differentiate between ascites secondary to portal hypertension (SAAG >1.1 g/dL) from other conditions.
- Medical management includes sodium restriction and oral diuretics, usually starting with spironolactone 100 mg and furosemide 40 mg daily.
- SBP is a life-threatening complication, and treatment should begin promptly with a third-generation cephalosporin as soon as infection is suspected.
- Treatment options for refractory ascites include serial paracentesis, TIPS, or ALFApump, but expedited evaluation for liver transplantation should also begin for appropriate candidates.

References for this chapter can be found at expertconsult.com.

ANNOTATED REFERENCES

Bai M, Qi XS, Yang ZP, et al. TIPS improves liver transplantations-free survival in cirrhotic patients with refractory ascites: an updated meta-analysis. *World J Gastroenterol.* 2014;20(10):2704–2714.
This updated meta-analysis of six randomized controlled trials with 390 patients showed a significant improvement of transplant-free survival of cirrhotic patients with refractory ascites, decreased ascites recurrence, and improved hepatorenal syndrome despite a significantly higher number of hepatic encephalopathy episodes in the TIPS group.

European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. *J Hepatol.* 2018;69(2):406–460. Erratum in: *J Hepatol.* 2018;69(5):1207.
This comprehensive review provides evidence-based recommendations for management of the patient with decompensated cirrhosis, including management of ascites, refractory ascites, SBP, and other complications, including hepatorenal syndrome.

Saab S, Hernandez JC, Chi AC, et al. Oral antibiotic prophylaxis reduces spontaneous bacterial peritonitis occurrence and improves short-term survival in cirrhosis: a meta-analysis. *Am J Gastroenterol.* 2009;104:993–1001.
This meta-analysis of eight prospective clinical trials with a total of 647 patients randomized to oral antibiotic prophylaxis for SBP compared with placebo or no intervention documented an overall mortality benefit (RR = 0.65; 95% CI 0.48–0.88) for antibiotic treatment groups. The overall mortality rate was 16% for treated patients and 25% for the control cohort. Groups treated with prophylactic antibiotics also demonstrated a lower incidence of all infections (including SBP) of 6.2% compared with the control group rate of 22.2% (RR = 0.32; 95% CI 0.20–0.51).

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25

Acute Abdominal Pain

Marcus K. Hoffman and S. Rob Todd

INTRODUCTION

Diagnosing acute abdominal pain in critically ill patients can be difficult if the clinician tries to work through a comprehensive list of differential diagnoses (Fig. 25.1). The most common etiologies seen outside of the intensive care unit (ICU) also occur within it, but other diagnoses must be considered. Certain patient populations to include trauma patients, postoperative patients, and those who are immunosuppressed, to name a few, should illicit even broader differential diagnoses. This chapter focuses on the difficulties in diagnosing acute abdominal pain in the critically ill patient, highlighting those diagnoses most relevant in this population.

INITIAL APPROACH

The top diagnoses on the differential list are rather different for patients who present to the hospital with acute abdominal pain and are critically ill than for those patients in an ICU who develop acute abdominal pain. Paramount to narrowing down the differential diagnosis for acute abdominal pain for either scenario is gathering as much information as reasonably possible. For patients presenting with abdominal pain, the history of the present illness with associated symptoms can be revealing. Providers should query the past medical history, current medications, prior surgical procedures, prior hospitalizations, and any recent courses of antibiotics. For those hospitalized critically ill patients who develop abdominal pain, a thorough understanding of their hospital course to date will help reorder a blind differential diagnosis. For patients in an ICU, the bedside nurse can be a wealth of knowledge, especially when patients are intubated or have altered sensorium. Events in the preceding 24 hours may likely be the trigger for acute abdominal pain.[1] For example, diffuse abdominal pain after paracentesis or drain placement by interventional radiology might be concerning for an unsterile procedure seeding the abdomen or for iatrogenic bowel perforation. Mesenteric artery embolism is a rare complication of percutaneous coronary angioplasty.

PHYSICAL EXAMINATION

In certain disease pathologies, the physical examination is not especially enlightening, but in others, the diagnosis might be made without further workup. For example, septic shock may develop from strangulated inguinal or incisional hernias with ischemic or necrotic bowel driving the underlying pathobiology. All surgical scars should be noted, as they may add or remove some of the diffferential diagnoses (internal hernia after gastric bypass surgery or acute cholecystitis after cholecystectomy as respective examples). Furthermore, pointing out surgical scars is sometimes the cue necessary for patients or family members to recall past surgical procedures not initially reported. Right upper quadrant (RUQ) tenderness may be indicative of biliary pathology. Suprapubic pain may be indicative of genitourinary causes of illness. All tubes, drains, and catheters present should be inspected for location and quality and quantity of output. Finally, an assessment of the patient's vital signs and any hemodynamic-altering medications are important.

DIAGNOSTIC ADJUNCTS

The evaluation of critically ill patients with abdominal pain almost universally entails obtaining laboratory and imaging studies based on the history and physical examination. Laboratory studies include, yet are not limited to, complete blood counts with leukocyte differentials, comprehensive metabolic panels including a liver function panel with conjugated bilirubin, coagulation studies, arterial or venous blood gases, and lactic acid measurements. Additional diagnostic studies to consider include urine analysis and cultures, blood cultures, stool cultures, and *Clostridium difficile* toxin assays if there is a concern for that infection.

Radiographic adjuncts include plain radiographs, ultrasonography, computed tomography (CT), and nuclear imaging studies. Plain radiographs may prove useful in diagnosing a perforated viscus (perforated ulcer or diverticulitis), cecal or sigmoid or volvulus, or toxic megacolon. Ultrasonography is the modality of choice if a biliary pathology or ovarian torsion is suspected. The mainstay of imaging modalities is the CT scan of the abdomen and pelvis, with intravenous (IV) contrast when possible. For critically ill patients being evaluated for acute abdominal pain, enteral contrast adds little in diagnostic value, but frequently delays the acquisition of images while exposing the patient to the risk for aspiration. Enteral contrast may be useful if the patient had an intraabdominal operation with anastomosis of gastrointestinal tract within the last 2–3 weeks and there is a concern for anastomotic leak or if there is a concern for esophageal perforation or peptic ulcer perforation.

DIFFERENTIAL DIAGNOSIS BASED ON PHYSICAL EXAMINATION FINDINGS

Peritonitis

Peritonitis is defined as inflammation of the peritoneal cavity at the mechanistic level, but, in clinical vernacular, peritonitis refers to abdominal pain on palpation that spans all quadrants. The overwhelming majority of cases of peritonitis are secondary to gastrointestinal (GI) tract perforation. Peritonitis with chest or abdominal radiographs demonstrating free air under the diaphragm may be sufficient to warrant surgical exploration. Critically ill patients presenting to the emergency center most commonly have a perforated gastroduodenal

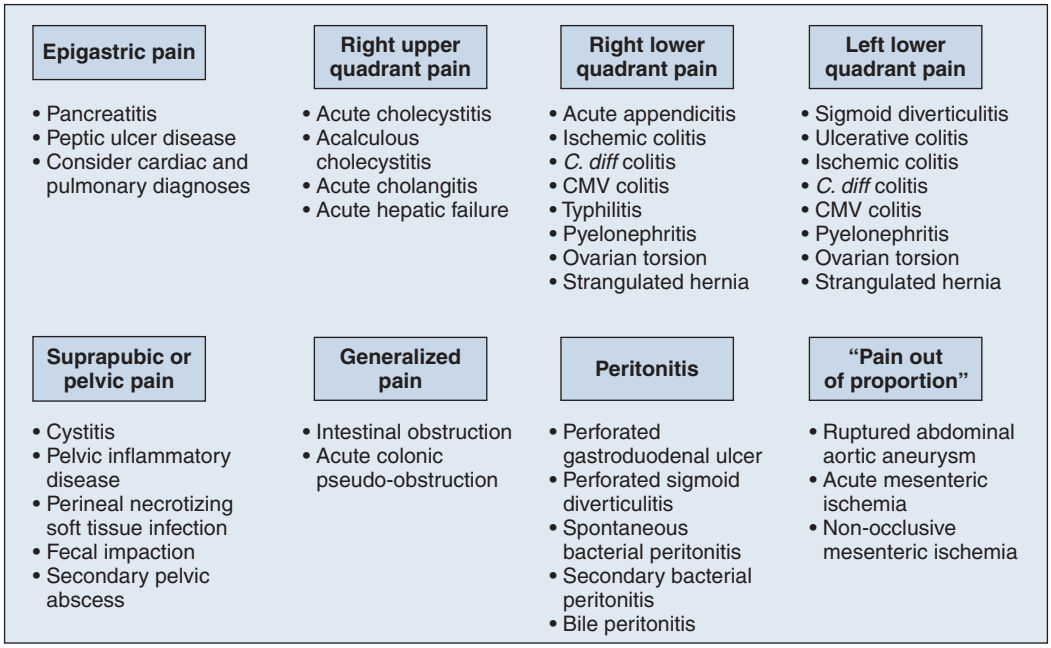

Fig. 25.1 Acute Abdominal Pain. Differential diagnosis based on physical examination findings. *C diff, Clostridium difficile; CMV,* cytomegalovirus.

ulcer or perforated sigmoid diverticulitis. Peritonitis and pneumoperitoneum in the ICU patient can be the result of perforation of any location in the GI tract.[2] It is frequently a late presentation of abdominal pain, especially if that pain cannot be communicated to medical staff for a variety of reasons, including intubation, sedation, and/or altered sensorium. If pneumoperitoneum is not present on the plain radiograph, the evaluation most typically proceeds to a CT of the abdomen and pelvis, where pneumoperitoneum or other stigmata of perforation are appreciated. Pneumoperitoneum can be seen for up to a week after laparotomy, laparoscopy, or percutaneous endoscopic gastrostomy (PEG) tube placement but frequently resolves within 3 days. Aside from expected pneumoperitoneum after PEG insertion or possibly attributed to barotrauma, any pneumoperitoneum with abdominal pain or clinical demise should prompt an urgent surgical consult.

In patients with cirrhosis and any degree of ascites, spontaneous bacterial peritonitis (SBP) must be considered and treated appropriately. A diagnostic paracentesis may aid in directing antimicrobial therapy. For patients with end-stage renal disease who undergo peritoneal dialysis, secondary bacterial peritonitis can occur because of unsterile dialysis technique or catheter damage. Intraperitoneal antibiotic treatment via catheter is a viable treatment option.[3] Finally, patients presenting after a cholecystectomy or liver biopsy can develop bile peritonitis from slow, progressive biliary leakage into the abdominal cavity, but are also at risk for iatrogenic intestinal injury during the aforementioned procedures.

"Pain Out of Proportion"

At the other end of the spectrum from peritonitis are patients who report severe pain, yet their physical examination does not elicit a significant response, classically referred to as "pain out of proportion." If this scenario arises and there is a palpable abdominal mass, the greatest diagnostic concern is a ruptured abdominal aortic aneurysm (AAA). Although an AAA can be diagnosed using ultrasonography, the imaging modality of choice remains CT.[4] This provides meaningful data that can be used to plan an endovascular repair. In the critically ill population, most cases of pain out of proportion are acute mesenteric ischemia, with the likely cause being embolic disease from atrial fibrillation. In such instances, laboratory studies may reveal a reactive leukocytosis and/or elevated lactic acid levels. A CT scan with IV contrast may reveal differences in bowel wall enhancement, a lack of IV contrast within the vasculature, or nonspecific findings such as intraperitoneal fluid. Early surgical consultation is warranted, as ischemia can be reversed if intervention occurs in a timely fashion.[5] Acute mesenteric ischemia from superior mesenteric artery occlusion can begin a sequence of ultimately fatal events if the entire small intestine is irreversibly ischemic at surgical exploration. Nonocclusive mesenteric ischemia is similar to acute mesenteric ischemia in that the bowel is not receiving adequate blood flow relative to what is being demanded. This supply-demand mismatch can be seen in cardiogenic shock or high-dose vasopressor use with enteral nutrition and seen in hemodialysis patients eating immediately after a dialysis session. A CT scan in this scenario may not show any of the findings noted earlier with acute mesenteric ischemia but may reveal pneumatosis intestinalis. First steps are to stop enteral feeds for heart failure and patients on high-dose vasopressors and to make sure dialysis patients are not hypotensive. Surgical exploration may not be warranted if abdominal pain has resolved and the patient is not clinically worsening, but pneumatosis intestinalis warrants surgical consultation.

Epigastric Pain

Epigastric pain in the critically ill patient can be the result of a wide variety of causes. Extraabdominal sources must be considered and evaluated, including pulmonary and cardiac pathologies. Epigastric pain and tenderness to palpation in the critically ill patient in the emergency setting without antecedent history should be evaluated for pancreatitis, to include a hepatic function panel, amylase and lipase, and a CT scan of the abdomen and pelvis.[6] The same presentation but with a recent history of pain that worsens is concerning for gastroduodenal ulceration, which may have perforated within the last few hours but has yet to result in peritonitis. A CT scan with oral contrast of the abdomen and pelvis may be useful in this latter scenario, as it can delineate the ulceration into the wall or demonstrate containment of a perforation.

Right Upper Quadrant Pain

As the primary occupant of the RUQ, the hepatobiliary system accounts for the most common causes of pain in this location. Any evaluation should begin with laboratory studies, including a hepatic function panel with total and direct bilirubin, in addition to gamma-glutamyl transpeptidase (GGTP). The imaging modality of choice is ultrasonography, looking for intrahepatic duct dilation, common bile duct diameter, gallbladder wall thickness or surrounding fluid, and biliary stones or sludge in the biliary system. Lack of findings on ultrasonography should prompt a CT scan of the abdomen and pelvis for further evaluation. Acute cholecystitis leads the differential list for critically ill patients in both the emergency center and ICU. Patients in the ICU setting receiving total parenteral nutrition (TPN) or vasopressors are especially at risk for acalculous cholecystitis.[7] Confirmation can be made by hepatobiliary iminodiacetic acid (HIDA) scan, but this imaging modality requires that the patient be stable enough to spend over 1–3 hours in the radiology department and has a high false-positive rate in the setting of prolonged bowel rest. Fevers, chills, and RUQ pain should raise concern for acute cholecystitis or cholangitis. Obligatory mention must be made of Charcot triad (jaundice, fevers, and RUQ pain) and Reynolds pentad (addition of hypotension and altered mental status), but note that although these are highly specific, they have extremely low sensitivities. Patients with significant physiologic reserve are candidates for endoscopic retrograde cholangiopancreatography (ERCP) and cholecystectomy for acute cholangitis and acute cholecystitis, respectively. For those patients who are too ill to undergo general endotracheal anesthesia, a cholecystostomy tube will temporize acute cholecystitis. The vast majority of patients with cholangitis respond to administration of antibiotics and resuscitation, but for those still too ill for ERCP, the intrahepatic biliary system can be decompressed via percutaneous transhepatic cholangiography (PTC) with tube placement for external drainage.[8]

Finally, patients with acute hepatic failure can develop RUQ pain as the liver swells from injury. This is commonly misdiagnosed as acute cholecystitis, as ultrasonography will demonstrate pericholecystic fluid and possibly wall thickening, but this is in the setting of the whole liver being edematous and swollen.[9] The distinguishing difference is that the patient is tender along the whole subcostal region of the liver, as opposed to only being tender at the location of the gallbladder. In acute hepatic failure or cirrhosis, HIDA scans are not especially helpful because of issues with initial hepatic uptake and thus should not be used for working up cholecystitis.

Right Lower Quadrant Pain

Discussions of right lower quadrant pain reflexively focus on appendicitis. Although appendicitis can cause severe illness if it festers for long enough untreated outside of the hospital, it is extremely rare in ICU patients. More commonly, the cecum and ascending colon develop various types of colitis. Ischemic colitis can result from embolic disease or low flow in the setting of high-dose vasopressors.[10] Not infrequently, these are diagnosed by either CT imaging with IV contrast or intraoperatively when patients continue to decompensate. Infectious colitis occurs secondary to a wide array of pathogens. *C. difficile* colitis results from prior antibiotic exposure, yet typically presents with more diarrheal complaints than abdominal pain. Cytomegalovirus (CMV) colitis is seen in immunosuppressed patients, specifically transplant patients. Neutropenic enterocolitis, also referred to as *typhlitis,* is almost exclusively described in the ascending colon of immunocompromised patients with profound neutropenia. The pathophysiology is thought to be bacterial invasion of the bowel wall. Treatment of the infectious colitis types listed begins with antibiotics specific to *C. difficile*, antiretrovirals active against CMV, and broad-spectrum antibiotics, respectively.[11]

Pyelonephritis, possibly with urosepsis, most commonly presents as right (or left) lower quadrant pain wrapping around to the back. In young females, lower quadrant pain is also concerning for ovarian torsion. Ultrasonography is the diagnostic modality of choice, as Doppler imaging can determine if arterial flow is present. Finally, strangulated hernias can present as lower quadrant pain causing critical illness, typically the result of physiologic effects of bowel necrosis. These may be clinically palpable and tender hernias, such as an inguinal hernia, or they may be more difficult or sometimes impossible to palpate, such as a femoral hernia, Spigelian hernia, or obturator hernia.

Left Lower Quadrant Pain

Left lower quadrant pain in the critically ill patient has an almost identical differential diagnosis as right lower quadrant pain, excluding appendicitis and neutropenic enterocolitis. Similar to appendicitis being the reflex thought in right lower quadrant pain, most providers reflexively think of diverticulitis with left lower quadrant pain. Patients may be critically ill upon presentation with diverticulitis, but this common presentation usually occurs with overall peritonitis on examination. Development of diverticulitis in ICU patients is a rare event, given that most patients are on enteral feeds and have bowel regimens. Although fulminant or toxic ulcerative colitis can present as right lower quadrant pain, it most commonly presents as left lower quadrant pain progressing to generalized abdominal pain as it advances from distal to proximal. For fulminant ulcerative colitis, emergent surgery is reserved for massive hemorrhage, perforation, or peritonitis; otherwise, high-dose IV steroids are the mainstay of initial therapy.[12]

Colonic ischemia resulting from endovascular or open AAA repairs most frequently presents as left lower quadrant pain. It is typically a crampy abdominal pain with loose bowel movements (with or without blood present). Abdominal tenderness in the left lower quadrant is especially concerning for transmural ischemia. Suspicion and prompt evaluation are of the utmost importance, as associated mortality is around 50% but increases up to 90% with delay in diagnosis.[4] Flexible sigmoidoscopy is employed to confirm the diagnosis. A worsening physical examination or overall status prompts surgical exploration to evaluate for transmural necrosis.

Suprapubic or Pelvic Pain

Suprapubic or pelvic pain most commonly occurs with cystitis or pelvic inflammatory disease; however, these do not frequently cause critical illness in otherwise healthy individuals. For patients presenting to an emergency center critically ill with suprapubic pain, patients must be examined for a possible necrotizing soft tissue infection of the perineum or genitals, which can extend up onto the abdominal wall.[13] In the ICU patient with suprapubic pain, cystitis and fecal impaction should be evaluated and treated appropriately. Finally, pelvic abscesses from other intraabdominal pathologies can occur.

Generalized, Nonspecific Abdominal Pain

Intestinal obstruction often presents with acute, diffuse, crampy abdominal pain coupled with nausea and vomiting, obstipation, distention, and tenderness to palpation. Obstruction can be partial or complete and can involve the small or large intestine. Obtaining an adequate history of previous surgeries and colonoscopies is important. Obstruction may be the result of adhesions or incisional hernias from prior surgical procedures. Fever, leukocytosis, and lactic acidosis are concerning for intestinal ischemia resulting from obstruction or herniation.[14] Plain radiographs will demonstrate air-fluid levels and dilated bowel (small or large). A CT scan of the abdomen and pelvis with oral contrast can often identify a transition point or other causes of obstruction like

volvulus or intussusception. Decreased intestinal wall enhancement on CT, peritoneal signs, and leukocytosis are predictive of intestinal ischemia in patients with small bowel obstructions and should prompt surgical exploration. Nonoperative management may be appropriate with nasogastric decompression and bowel rest. However, in bowel obstructions that do not resolve or have signs of ischemia present, surgical management is imperative.

Acute colonic pseudo-obstruction (Ogilvie syndrome) characteristically has significant dilation of the cecum and right colon without any anatomic obstruction. There is a strong association with opiate administration. Lower abdominal pain coupled with constipation, distention, nausea, vomiting, and paradoxical diarrhea are common. CT confirms the diagnosis by excluding evidence of mechanical obstruction or toxic megacolon resulting from colitis. Treatment consists of correcting any electrolyte abnormalities, decompressing the stomach, and avoiding narcotics. The anticholinesterase inhibitor neostigmine may be effective for colonic decompression but requires cardiac monitoring and should be used with caution in patients with asthma or cardiac abnormalities and the elderly.[15] Colonoscopic decompression should be attempted when supportive measures fail.[16] If decompression fails, worsening colonic distention can compromise bowel wall viability, seen as cecal ischemia and necrosis requiring colon resection.

Abdominal pain in the critically ill patient has a vast array of causes. A proper history and physical examination may give clues as to the specific cause. Aside from hepatobiliary pathology and ovarian torsion, CT is the mainstay of imaging. Oral contrast adds minimal additional information. Critically ill patients with abdominal pain warrant a prompt surgical consultation.

KEY POINTS

- The history of present illness, past medical history, physical examination, and antecedent hospital course can rapidly narrow down the differential diagnosis in acute abdominal pain in the critically ill patient.
- Laboratory values, plain radiographs, and CT scans are the mainstay of evaluating acute abdominal pain.
- Ultrasonography is most useful in evaluating pathologies of the hepatobiliary and genitourinary systems.
- Peritonitis is concerning for bowel perforation, and the radiographic evaluation should be initiated with an upright radiograph.
- "Pain out of proportion" is most concerning for acute mesenteric ischemia.
- Lower quadrant pain may be the result of genitourinary causes, but is most commonly the result of colonic pathologies.

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Ileus in Critical Illness

Stephen A. McClave and Endashaw Omer

INTRODUCTION

Evidence of ileus, gastroparesis, or small bowel dysmotility is common in the setting of critical illness. Data on the incidence of ileus estimate an occurrence ranging from 50% to 80% in critically ill patients,[1] with an average incidence of 38%.[2] In the postoperative surgical intensive care unit (ICU), evidence of postoperative ileus ranges from 24% to 75%.[3] Ileus can affect the entire gastrointestinal (GI) tract or just a segment, from the proximal gut, to the small bowel, to the colon. Definitions are poorly standardized and can be vague and elusive. Usually, ileus is characterized clinically by hypoactive or absent bowel sounds, abdominal distention, and delayed passage of stool and gas, but the process may involve nausea, vomiting, and abdominal tenderness. Objective measurements are limited mostly to research tools such as measuring gastric emptying by acetaminophen absorption tests or passage of radiolabeled carbon compounds, or small intestinal manometry. When present, ileus in critical illness has been shown to be associated with nutritional deficits, greater risk of aspiration, sepsis, prolonged mechanical ventilation, and increased allocation of healthcare resources.[4–6] Although similarities exist between the ileus of critical illness and postoperative ileus in the surgical ICU patient, the precipitating factors are different. These entities share similar pathophysiologic patterns, and both are usually self-limited, tending to resolve spontaneously within days.

Many aspects of ileus are counterintuitive.[7] Bowel sounds are not needed or required to initiate nutritional therapy, as recommended by the societal guidelines.[8] A nasogastric tube placed for gastric decompression in postoperative ileus would be expected to benefit the surgical patient, but instead actually worsens outcome by increasing the incidence of pneumonia and atelectasis and leading to slower return of GI function.[9] Surprisingly, gastric feeding is well tolerated in over 90% of critically ill patients.[10–13] When the level of infusion of formula within the GI tract is diverted from the stomach to the small bowel, there is little change in outcome.[8] Although multiple findings of GI dysfunction do reflect gastroparesis or intestinal dysmotility, other signs and symptoms are often included in the definition, which may or may not be related, such as diarrhea, GI bleeding, or increased abdominal pressure.[7]

What continues to stoke interest in this entity is the correlation between ileus and adverse outcomes.[7] The link to adverse outcome is shown in studies where evidence of GI dysfunction has prognostic value and is associated with increased ICU length of stay, duration of mechanical ventilation, and even mortality.[7] Ileus is also linked to decreased delivery of enteral nutrition (EN), feeding intolerance, or feeding failure. The presence of ileus does identify a patient at high nutritional risk, a patient who may be more difficult to feed, whose risk of complications is increased, and whose delivery of EN should be provided with more caution.[7] Critically ill patients need the therapeutic advantage of early EN; however, resolution of the ileus is important to facilitate further delivery of the nutritional regimen.

DEFINING GASTROINTESTINAL DYSFUNCTION

Definitions for ileus and GI dysfunction in critical illness vary over a wide spectrum of signs and symptoms. GI dysfunction usually relates to disordered motility and is most often defined by a constellation of symptoms, including nausea, vomiting, regurgitation, abdominal distention, and hypoactive-to-absent bowel sounds.[2,14] Feeding intolerance is defined separately as a reduced delivery of EN for whatever reason.[2,14] Often, the definitions of GI dysfunction have an overreliance on gastric residual volumes (GRVs) to make the definition.[14] Additional factors are added to the definition in a somewhat haphazard manner, such as intraabdominal hypertension, overt GI bleeding, and diarrhea.[14–18]

There is a difference in the definitions of ileus between a static score of signs and symptoms seen on admission to the ICU and a more graded series of findings suggesting a spectrum of increasing severity.[7] GI dysfunction is more of a static definition and is a greater issue on admission to the ICU. GI dysfunction in the acute and immediate postacute phases of critical illness is often influenced by prolonged bed rest, increasing disease severity, comorbidities, the metabolic state, and use of opioid narcotics.[7,10] Feeding intolerance, on the other hand, is a more dynamic process and is a greater issue with initiation and advancement of early EN.[7,10] Feeding intolerance is more likely to be influenced by nursing care, the existence of protocols, the culture or leadership of the ICU, and whether GRVs are used. A component of "grading" implies the continuum of a process over a spectrum from mild to severe degree, a contrived definition where such a spectrum may not exist.[7,14,17,19] The designation of increasing grades of GI dysfunction has been defined by a greater number of GI signs and symptoms, by a reduction in the delivery of EN, or by the finding of additional complications such as organ failure (as measured by Sequential Organ Failure Assessment or SOFA score), the presence of overt GI bleeding, or the development of intraabdominal hypertension.[14,17–19] Other systems designated an increased grade by whether there was a positive response, a poor response, or no response to therapy.[14]

What sustains interest in GI dysfunction is its correlation with adverse outcomes. Multiple studies have shown that evidence of ileus or GI dysfunction upon admission to the ICU is associated with prolonged duration of mechanical ventilation, increased ICU length of stay, and greater mortality.[2,14–20] In those studies describing a spectrum of severity of GI dysfunction, increasing grades were shown to be associated with a demonstrated stepwise reduction in survival.[14,17,18] In

one study, increasing grades of an abdominal GI score correlated with greater 28-day and 90-day mortality.[18]

For the critically ill patient receiving early EN in the ICU, use of these signs and symptoms of ileus or GI dysfunction to define "intolerance" is problematic.[7] No standardization of the practice exists. There are over 40 definitions of feeding intolerance in the literature,[2] and 88% of them rely heavily on the use of GRVs. There is large interobserver variability,[2] such that hypoactive bowel sounds had to be removed from the definition in one study because of discrepancies between clinical participants.[20] Clinical conditions can change the interpretation of these signs and symptoms. Abdominal distention, reduced bowel sounds, and cramping may be interpreted differently in a patient with hemodynamic instability on vasosuppressive therapy compared with a patient who is hemodynamically stable and not requiring these agents. A change in symptoms as EN is initiated may be more important than the findings of ileus on admission to the ICU. Homeostatic proteins such as albumin, prealbumin, and transferrin have prognostic value on admission but provide no nutritional information and are not markers of nutritional status or adequacy of nutritional support. Feeding intolerance is often defined by the reduced delivery of EN as a percentage of goal requirements, but this parameter can only be measured retrospectively. Protocols in the ICU may affect the perceived incidence of feeding intolerance, as protocols that direct slow ramp-up and encourage reaching only 80% of goal requirements may be misinterpreted as feeding intolerance.

MECHANISM OF ILEUS IN CRITICAL ILLNESS

Gastric emptying is affected by both zero-order and first-order kinetics.[21,22] Liquids empty by first-order kinetics, which relate to increased fundic pressure, cause a rapid parabolic emptying of liquids, and the rate of emptying speeds up with increasing meal volume.[21] This pattern of gastric emptying may remain normal even with advanced gastric dysmotility.[22] Solids empty by zero-order kinetics, which is related to the steady antral grinding of solids and a fixed rate of emptying through the pylorus unaffected by meal volume.[21,22] Formulas may have a hybrid pattern, combining both first-order and zero-order kinetics. For example, the infusion of enteral formulas should follow the first-order kinetics of liquid emptying unless casein in the formula begins to curdle, at which point the pattern would switch more to zero-order kinetics of solid emptying.

A number of clinical factors affect gastric emptying and subsequent dysmotility. Osmolarity of the formula is a key factor, as duodenal osmoreceptors will slow gastric emptying until the luminal contents are isosmotic. Increasing fat content slows gastric emptying. Source of protein is also a factor in gastric emptying, as whey protein has been shown to empty faster than casein protein.[23] With the metabolic stress of critical illness, corticotropin-releasing factor (CRF) causes increased production of corticosteroids, which has the effect of reducing gastric emptying.[24] Other factors may delay gastric emptying, such as elevated intracranial pressure, increasing intraabdominal pressure, hyperglycemia, and electrolyte abnormalities (especially potassium or sodium).[6] Altered antropyloroduodenal (APD) activity is reported in the ICU.[25,26] Gastric emptying may be adversely affected by central input from the vagus nerve or from neurohormonal feedback loops.[6]

Small bowel intestinal dysmotility occurs commonly in both medical and surgical ICU patients. Nearly 100% of surgical patients undergoing abdominal aortic aneurysm repair were shown in one study to have small bowel dysmotility,[27] whereas up to 42% of critically ill patients on mechanical ventilation in a medical ICU were shown to have evidence of intestinal dysfunction.[28] The pathophysiologic mechanism of small bowel dysmotility differs slightly from the process affecting gastric function. Intestinal dysmotility is characterized by an altered pattern in the migrating motor complexes. A number of factors contribute to intestinal dysmotility.[6] Proinflammatory cytokines such as interleukin-2 and interleukin-6 cause increased leukocyte migration and inflammation in the muscularis propria of the smooth muscle in the intestinal wall, leading to an inhibitory effect on contractility.[29] Ionic channels are altered in structure and function, causing abnormalities in the contractility of intestinal smooth muscle.[30] Tachykinins (substance P and neurokinin) elevated as part of the stress response cause increased activation of NK2 receptors, leading to inhibition of intestinal motility.[26] Nitric oxide (NO) and vasoactive intestinal peptide (VIP) are released in sepsis and cause suppression of migrating motor complexes.[31] Neurohormonal dysregulation leads to increased sympathetic activity, which causes a consequent reduction in intestinal motility.[32] Increased activation of nociceptor reflexes in a severity-dependent fashion (from incision of the skin only, to entry into the peritoneum, to manipulation of bowel) inhibits motility in postoperative surgery patients.[33]

Clinical factors may play a large role in perpetuating ileus in critical illness.[6] Electrolyte abnormalities, opioid analgesia, and excessive fluid resuscitation may all reduce intestinal motility. The use of crystalloid has a more inhibitory effect than use of colloid for volume resuscitation.[6] Use of a nasogastric tube for decompression, bowel wall edema, bowel manipulation at the time of surgery, sepsis, and intestinal hypoperfusion all may worsen the ileus seen in critically ill patients or postoperative patients in the surgical ICU.[6,9] Prolonged bed rest can lead to intestinal stasis.[2] Activation of Toll-like receptors in sepsis-induced ileus occurs as a direct result of release of lipopolysaccharide (LPS) endotoxin.[34] Alteration in the gut flora with emergence of a pathobiome has been correlated with dysmotility and feeding intolerance,[35] and a reduction in biliary and pancreatic secretions lose their trophic effect on intestinal function and subsequent motility[6] (Fig. 26.1A–C).

IMPLICATIONS FOR DELIVERY OF ENTERAL NUTRITION

The foundation of feeding in the ICU is by intragastric feeding. Placing a 10–12 French nasogastric tube requires a low level of expertise and usually promotes faster time to initiation of EN. Diverting the level of feeding from the stomach to the small bowel has surprisingly little effect on outcome parameters.[8] Meta-analyses of multiple randomized controlled trials of gastric versus small bowel feedings show that the only difference is a reduction in the diagnosis of pneumonia with small bowel feeding compared with gastric feeding.[8] No other outcome parameter changes by diverting the level of feeding, including duration of mechanical ventilation, ICU or hospital length of stay, and mortality. In fact, the largest multicenter trial by Davies and colleagues showed no difference in any outcome parameter between gastric and small bowel feeding.[36]

Early initiation of feeding in the ICU helps prevent ileus from setting up. In two trials involving patients with severe acute pancreatitis, expeditious placement of enteral access and initiation of enteral feeding minimized the duration of ileus and increased the success of enteral feeding.[37,38] In a study by Cravo and colleagues, delays in initiation of enteral feeding from 0 to 6 days prolonged the duration of ileus, leading to reduced success of enteral feeding and increased need for total parenteral nutrition (TPN).[37] A second trial by Eatock and colleagues, comparing gastric with small bowel feeding in pancreatitis, showed equal success with gastric feeding in every parameter evaluated.[38] The success of gastric feeding was attributed to the fact that feedings were started within 48 hours of onset of symptoms, such that less ileus and gastric stasis was incurred.

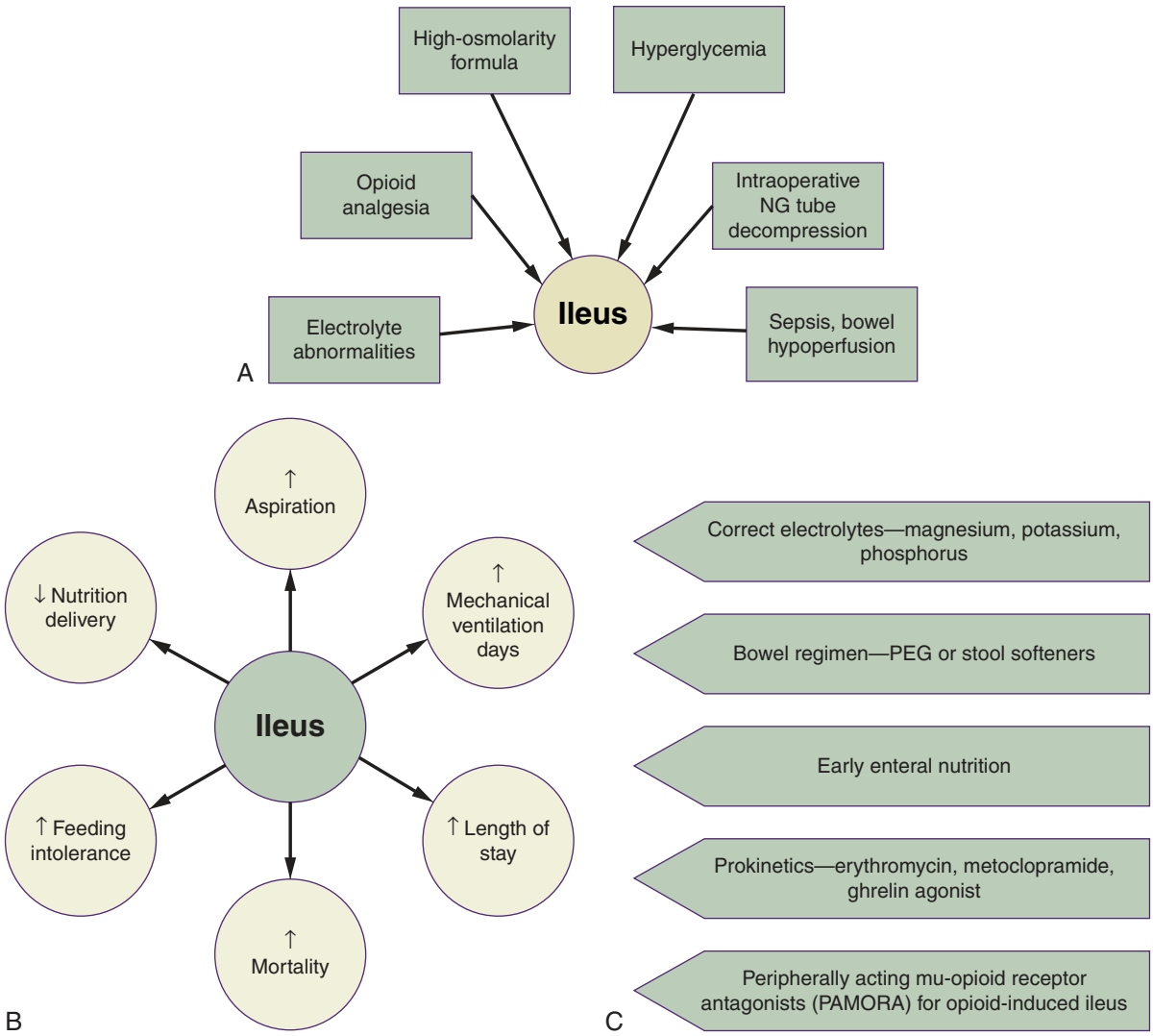

Fig. 26.1 Causes, Consequences, and Management Strategies of Ileus in Critical Illness. **A,** Causes. **B,** Consequences. **C,** Management strategy. *NG,* Nasogastric; *PEG,* percutaneous endoscopic gastrostomy.

Intermittent feeding may actually enhance tolerance and reduce GI dysmotility compared with continuous infusion.[39] Multiple studies in animal models show that intermittent feeding with 20- to 30-minute infusions repeated every 2 hours hastened the gastric emptying of liquids and increased mesenteric blood flow.[39] Protein synthesis was greater with intermittent feeding, and the components of the ileal brake (PYY and gastrointestinal inhibitory polypeptide) were increased, resulting in less diarrhea and more time for nutrients to be absorbed.[39]

When diarrhea or upper GI bleeding occurs, it should be evaluated independently and not lumped together with a number of other signs or symptoms attributed to GI dysmotility. In over 50% of cases, diarrhea is related to medications (especially sorbitol, which is a common mixing agent used by pharmacists to deliver medications by the enteral route).[40] Twenty percent of the time, diarrhea is related to *Clostridium difficile* or antibiotic-associated diarrhea. Most often, diarrhea is low-volume incontinence in the ICU and not related to GI dysfunction.[40] The workup of a GI bleed in the ICU again should not be attributed to GI dysfunction, but should be investigated independently. Minimal bleeding in a noncirrhotic ICU patient on mechanical ventilation may represent stress gastritis. Increased delivery of EN is effective in promoting mucosal blood flow and may be the best treatment in that setting. Clinicians should avoid the use of colorimetric cards to detect occult GI bleeding. Occult bleeding (as determined by such cards) should be differentiated from overt bleeding where there is obvious hematemesis, melena, or hematochezia. Cirrhotic patients should be differentiated from noncirrhotics, and a significant GI bleed where there is a drop in hemoglobin, volume contraction, and hemodynamic instability should be differentiated from insignificant bleeding.

A number of clinical strategies may be used in the ICU patient who shows evidence of ileus or significant GI dysmotility. Electrolytes should be corrected, minimizing subsequent alterations, particularly in potassium and magnesium. GRVs should not be used.[8] A bowel regimen that includes stool softeners or polyethylene glycol helps maintain the passage of stool and gas. Lubiprostone is an agent that actively increases water secretion by the intestine and helps promote bowel movements in the ICU.[6] Early enteral feeding should be promoted, and the use of protocols to direct delivery helps improve success. Prokinetic agents may play a role early on in the initiation of enteral feeding and include erythromycin, metoclopramide, and experimental ghrelin agonists. In patients on opioid narcotics, agents such as peripherally acting mu-opioid receptor antagonists may be

used, such as methylnaltrexone (Relistor), naldemedine (Symproic), or alvimopan (Entereg).[6]

Goal-directed fluid management is important to avoid bowel wall edema and increasing intraabdominal pressures. Small-peptide formulas with medium-chain triglycerides may stimulate peptide transporters and promote better gastric emptying.[6] Low-fat formulas likewise may enhance gastric emptying. Avoiding hyperglycemia with moderate to relatively stricter control of glucose levels is important, and variability in blood glucose may actually be more important than absolute levels.[6] Experimental agents that have been used in postoperative ileus include ceruletides (an analog to CCK), celecoxib (a cyclooxygenase inhibitor), and rosiglitazone (a PPAR-gamma activator), all of which have helped reduce ileus and promote early feeding.[6]

Certain findings on physical examination should cause the clinician to back off of enteral feeding if the ileus is sustained. Worsening of symptoms in the face of feeding, greater abdominal distention, vomiting, or sudden cessation in the passage of stool and gas should be interpreted with caution, as it may reflect intolerance, potential ischemic bowel, and a contraindication to further advancement. Increasing lactic acidosis or worsening radiographs showing pneumatosis intestinalis or a greater number of dilated loops of bowel can all reflect poor tolerance, intestinal dysmotility, and the increasing chance of intestinal ischemia.

CONCLUSIONS

Ileus should be expected in critical illness. The best use of signs, symptoms, or a scoring system for GI dysmotility may be that it differentiates patients at high nutritional risk from those at low risk.[7] Despite the common occurrence of gastroparesis and intestinal dysmotility, gastric feeding is tolerated well in the vast majority of critically ill patients.[12,13] Clinicians should avoid misinterpretation of findings. Evidence of intestinal dysmotility on admission should be interpreted in a similar fashion to that of other prognosticators such as reduced homeostatic proteins (albumin, prealbumin, transferrin) or elevated markers of inflammation (C-reactive protein and erythrocyte sedimentation rate).[7] Clinicians should stop using colorimetric cards to detect occult GI bleeding. Overt yet insignificant bleeding with no changes in hemoglobin in an ICU patient on mechanical ventilation should not deter delivery of EN.[7] Overt significant bleeding with a drop in hemoglobin and hemodynamic instability should lead to cessation of feeding until the source can be evaluated or determined.

Clinicians should monitor patients on enteral feeding by physical examination, intake and output records, and passage of stool and gas. GRVs are misleading and a poor sign of gastric emptying, aspiration risk, or intolerance. Use of GRVs invariably serves as an impedance to the delivery of EN.[8] With appropriate goal-directed fluid resuscitation, there may be little use for measuring intraabdominal pressure. Intraabdominal hypertension is disappearing with the strategy of conservative goal-directed fluid management. Mild increases in intraabdominal pressure may actually improve with the delivery of enteral feeding.[7] Physicians should be leery of a spectrum or gradation of findings where no spectrum exists.[7] Delivery of EN represents a challenge to the GI tract, and patients should be monitored closely, especially with initiation of enteral feeding.

Protocols help minimize the impact of ileus. Providing early EN helps stimulate motility and reverse the effects of ileus. Bowel regimens help reduce the signs or symptoms that might otherwise be interpreted as GI dysmotility. A change in response to initiation of enteral feeding may be more important than the static findings of GI dysmotility at the onset. The findings of ileus on admission provide prognostic information, but may be less useful or even counterproductive in directing subsequent nutritional therapy. Such findings should not dissuade the clinician from at least trying to feed the ICU patient and provide the clinical benefit of early enteral feeding.

KEY POINTS

- Gastroparesis and intestinal dysmotility are common, involving more than 75%–80% of critically ill patients in the ICU.
- Issues of ileus in critical illness are counterintuitive, as gastric feeding is tolerated in over 90% of ICU patients despite the frequent presentation of hypoactive bowel sounds, abdominal distention, and failure to pass stool and gas.
- Evidence of GI dysfunction on admission to the ICU correlates with adverse outcomes, prolonged duration of mechanical ventilation, increased hospital length of stay, and reduced survival.
- Ileus and gastroparesis may be worsened by delays in initiating feeding, poor control of hyperglycemia, overly aggressive fluid resuscitation, use of a high-fat hyperosmolar formula, continuous infusion of nutrients, and prolonged bed rest.
- Considerations to facilitate delivery of EN in critical illness include early initiation of therapy, selection of an isosmolar small-peptide formula with medium-chain triglycerides and whey protein, correction of electrolytes, employing goal-directed fluid volume resuscitation, use of crystalloid over colloid, avoidance of decompressive nasogastric tubes, routine placement on a bowel regimen, use of prokinetic agents in select patients, and intermittent infusion of enteral nutrients.
- Diarrhea and GI bleeding should be investigated independently, may be unrelated to dysmotility or ileus, and should not be considered an automatic contraindication to continued enteral feeding.
- The presence of ileus or GI dysfunction in critical illness identifies a patient at higher nutritional risk with an increased likelihood for complications and adverse outcomes, whose delivery of enteral feeding will be more difficult and require greater caution with close monitoring.

References for this chapter can be found at expertconsult.com.

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27

Diarrhea

Christian J. Brown, Tyler J. Loftus, and Martin D. Rosenthal

Diarrhea is one of the most common manifestations of gastrointestinal (GI) dysfunction in the intensive care unit (ICU); the reported incidence is between 2% and 63%.[1] *Diarrhea* is best defined as bowel movements that, because of increased frequency, abnormal consistency, or increased volume, cause discomfort to the patient or the caregiver. This definition demonstrates the subjectivity in diagnosing diarrhea, which complicates interpretation of the literature and limits applicability of guidelines. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) defines diarrhea more objectively as having loose, watery stools three or more times a day, further classified by chronicity:

- **Acute diarrhea** is a common problem that typically lasts 1 or 2 days and goes away on its own.
- **Persistent diarrhea** lasts longer than 2 weeks and less than 4 weeks.
- **Chronic diarrhea** lasts at least 4 weeks. Chronic diarrhea symptoms may be continual or may come and go.

The impact of diarrhea on patient care in the ICU, including its cost in morbidity and mortality, is unknown. However, it is undeniable that diarrhea remains a persistent problem in many ICUs not just for the patient but also for the care team (especially the bedside nurse).

CRITERIA

Several criteria diagnose diarrhea:

1. Abnormal frequency. Normal frequency is one or two bowel movements per day and is influenced by the amount of fiber in the diet. Three or more bowel movements per day is abnormal.[1]
2. Abnormal consistency. Abnormal consistency is described as either nonformed stool or stool having excessive fluid content that causes inconvenience to the patient, nursing staff, or caregiver. Normal stool water content is 60%–85% of the total weight.[1]
3. Abnormal amount. Stool amount and volume vary significantly with the amount and type of enteral intake. Insoluble fiber adds a significant amount of bulk volume. A normal amount is approximately 200 grams per day (g/d).[1] Abnormal amounts are greater than 300 g/d or volumes greater than 250 mL/d.[1,2]

To date, clinicians lack a consistent scale or index that allows a reliable and practical way of measuring stool volume, consistency, and frequency. In its absence, the bedside nurse remains the most reliable person to identify the presence of diarrhea.

PATHOPHYSIOLOGY

Bowel movements with normal physiologic volume, consistency, and frequency are the result of a GI tract that integrates motility, secretion, and absorption of fluids and adapts to the quality of the food bolus given. The result is a fecal bolus that is produced once or twice every 24 hours and has normal consistency and fluidity.

Diarrhea results when there is a disorder of GI physiology or when GI tract function is incapable of handling the food bolus (Fig. 27.1). There are several classifications of diarrhea, suggesting that no single classification is ideal for helping the clinician make patient care decisions. Perhaps the most useful approach is to classify diarrhea according to physiology:

1. Increased fluid secretion that overwhelms absorption. On average, up to 9 L of fluid is secreted into the GI lumen in addition to oral intake. Less than 1% of that fluid is contained in stool because of the amazingly large absorptive capacity of the small and large bowel. Within the intestinal mucosa, passive and active transport of sodium determines the amount of water that is absorbed. Stimulation of the active secretion of fluids into the GI lumen occurs when intracellular levels of the second messenger, cyclic adenosine monophosphate (cAMP), increases within enterocytes. Increased intracellular cAMP concentration promotes chloride secretion.[3] Thus diarrhea caused by excessive secretion of fluids is termed *secretory diarrhea*. Secretory diarrhea characteristically contains large amounts of fluid and is described as watery. Secretory diarrhea is observed in certain infectious diseases such as cholera and rotavirus infections. Secretory diarrhea also can be observed in endocrine disturbances associated with carcinoid syndrome or vasoactive intestinal peptide (VIP)–secreting tumors.
2. Gastroenteritis or infectious diarrhea occurs from GI tract inflammation with resultant increase in mucus secretion from the large bowel, leading to development of diarrhea. Excessive mucus secretion is observed in colonic infections such as bacterial (*Clostridium difficile* colitis), viral (norovirus), or parasitic (amebiasis).[4] The incidence of infectious diarrhea in the ICU is unknown, but increases with contaminated food products. Of particular concern is the contamination of the food being given in the ICU. Contamination of enteral formulas can occur at multiple levels, including preparation of the enteral product, use of open feeding systems, addition of modular dietary components, and contamination of the enteral access port (i.e., feeding tube, gastrostomy tube). The incidence of diarrhea resulting from contaminated feeding tubes is unknown.
3. Diarrhea resulting from increased osmotic load. Many substances taken orally are not fully absorbed and exert significant osmotic force, overwhelming the absorptive capacity of the GI tract. Many patients with diarrhea in the ICU fall into this category.
   A. Osmotic diarrhea caused by medications: Sorbitol is frequently and inadvertently given to patients in the ICU as a means of preparing many medications for delivery via feeding tubes and is an often-overlooked culprit causing diarrhea.[5] Other osmotic agents include GoLYTELY and magnesium-containing medications and electrolyte replacement formulations.

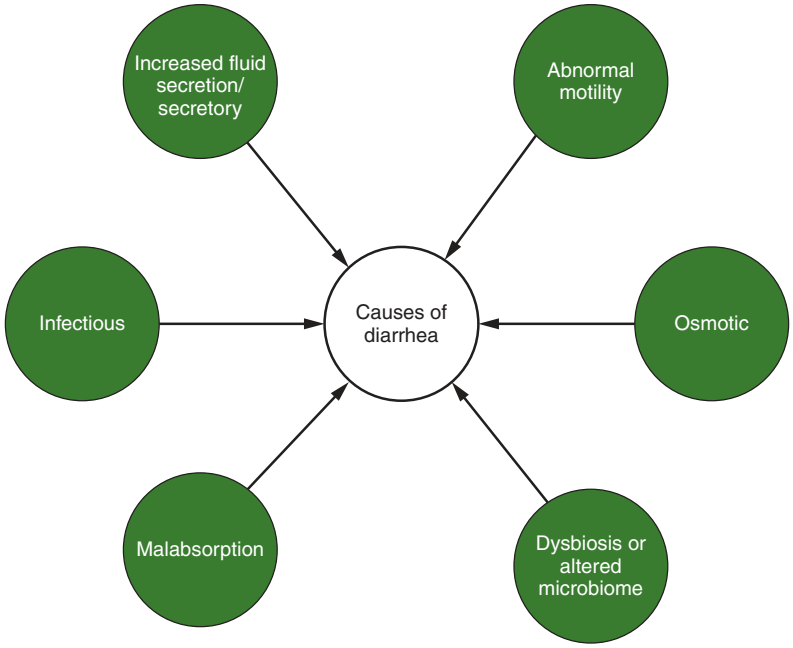

Fig. 27.1 Diarrhea: Abnormal Frequency, Consistency, and Amount. Acute diarrhea is a common problem that typically lasts 1 or 2 days and goes away on its own. Persistent diarrhea lasts longer than 2 weeks and less than 4 weeks. Chronic diarrhea lasts at least 4 weeks. Chronic diarrhea symptoms may be continual or may come and go. Consequences of diarrhea include wound breakdown, malnutrition, electrolyte imbalance, patient discomfort, and increased workload for nurses or caregivers.

B. Incomplete digestion and malabsorption: The incidence of malabsorption in the ICU is unknown. However, there are many instances where malabsorption should be considered the cause of diarrhea in the critically ill patient. These include:
   i. Incomplete protein digestion (azotorrhea): Protein digestion occurs mainly in the stomach by pepsin (only activated at low pH) and hydrochloric acid. In the ICU, many patients receive medications that raise gastric pH, such as histamine receptor type 2 (H_2) blockers and proton pump inhibitors.[6,7] In addition, feeding tubes frequently bypass the stomach, eliminating both gastric acid and gastric proteolytic digestion. Less frequent causes of azotorrhea are protein-losing enteropathies resulting from amyloidosis, sarcoidosis, inflammatory bowel disease, neoplasm, Ménétrier disease, and Zollinger-Ellison syndrome, to name a few.
   ii. Undigested carbohydrates: In addition to sorbitol (see earlier discussion), excessive glucose, lactose, or fructose in tube-feeding formulas can overwhelm the absorptive capacity of the small bowel, causing an osmotic influx into the gut lumen.[8]
   iii. Undigested fats: Steatorrhea (diarrhea caused by undigested fats) is characteristically observed in patients with pancreatic insufficiency. Inadvertent lack of mixing pancreatic enzymes with the food bolus can occur in patients with intestinal bypass or pancreatic fistulas or in patients who have large-volume gland necrosis from pancreatitis or a history of pancreatectomy. It is also observed in patients with incomplete bile production, such as patients with a biliary diversion.
   iv. Excessive dietary load: Diarrhea resulting from excessive load (overfeeding) of any of the main dietary components (protein, carbohydrate, or fat) can occur in the ICU. Iatrogenic overfeeding occurs in up to 33% of patients in the ICU and is a result of inappropriate estimations of caloric and protein needs or inadequate metabolic surveillance.[9] Excessive loads of protein, carbohydrate, or fat also occur with specialized formulas that contain altered amounts of one or more of these components. For example, certain diets are high in fat, overwhelming digestive and absorptive processes.
   v. Atrophy of the GI tract: Atrophy of the intestinal brush border is associated with decreased capacity of digestion and absorption. Atrophy occurs in malnourished patients; thus diarrhea commonly occurs in patients with hypoalbuminemia. Atrophy also occurs when enteral intake is interrupted for more than a few days. This is a particular problem in surgical patients when prolonged "bowel rest" results in disuse atrophy. A similar phenomenon occurs distal to an enterocutaneous fistula or ostomy, which, upon reversal, can result in diarrhea that slowly resolves as villous height returns to baseline.
4. Abnormal motility: Intestinal dysmotility is a frequent problem in the ICU. The use of promotility agents (e.g., erythromycin) can inadvertently cause diarrhea in these patients.
5. Abnormal gut flora: Normal colonic flora is essential for normal absorption and function of the large bowel. Antibiotics create massive disruptions in colonic flora and can sometimes lead to nosocomial infections with resultant diarrhea. Currently, *C. difficile* is the leading cause of nosocomial diarrhea, accounting for 30% of all antibiotic-associated diarrhea.[10] The gut microflora can be modulated through the use of probiotic agents, but this topic is under intense investigation, and no current guidelines exist regarding their use to treat or prevent diarrhea in ICU patients.[11]

CLINICAL CONSEQUENCES OF DIARRHEA

Untreated, diarrhea can lead to multiple problems. These include:
1. Wound breakdown and secondary soft tissue infection: Diarrhea can cause a moist, contaminated environment; if left untreated, this can

lead to skin breakdown and eventual soft tissue infection. Particularly concerning is the presence of decubitus ulcers; diarrhea can be either a causative factor or can worsen and complicate management.
2. Fluid and electrolyte disturbances are particularly frequent in patients with secretory diarrhea. In these patients, clinicians must pay attention to fluid replacement to avoid dehydration and correct metabolic acidosis and hypokalemia as needed.
3. Malnutrition: Inadequate nutrient absorption can lead to poor nutrient utilization. Malabsorptive diarrhea can be classified by stool enzyme and nutritional by-product measurements, such as fecal elastase and fecal fats.
4. Increased workload for nurses and caregivers: Diarrhea imposes a substantial burden on nurses and other caregivers. In addition, the presence of a soiled patient evokes a sense of poor quality of care. Maintaining a clean patient with diarrhea requires additional ICU personnel time and resources. The use of fecal management systems provides one strategy, but incurs the risk of ulceration. As with all clinical decisions, patient-specific risks and benefits must be weighed.

DIAGNOSIS

Careful and complete evaluation of diarrhea is necessary for good patient care. Unfortunately, diarrhea is often ignored or hastily treated while clinicians focus on other organ systems. Diagnostic laboratory tests are sparse, making it difficult to identify and treat the patient. The following diagnostic approach is suggested:

1. Does the patient really have diarrhea? It is important to question the accuracy of the diagnosis. The NIDDK definition of three or more loose stools a day should be applied. A concerted effort to diagnose diarrhea by all members of the ICU staff is essential. The creation of scales or indices could become particularly useful as a means of communication and could aid in assessing the effectiveness of treatment.
2. Can an iatrogenic cause explain the presence of diarrhea?
   A. Is the patient receiving prokinetic agents or stool softeners?
   B. Is the patient receiving medications with high concentrations of sorbitol?
   C. Is the patient being overfed?
   D. Is the patient intolerant to any of the components of the prescribed diet?
   E. Is a specialized diet providing an excessive amount of a substance (e.g., fat) that the patient is having difficulty digesting?
   F. Is bypassing the stomach or inhibiting acid secretion affecting the digestion of protein?
   G. Is the patient receiving any other medication that causes diarrhea?
3. Assessing the patient's absorptive or digestive capacity:
   A. Does the patient have gut atrophy, as seen with prolonged bowel rest, proximal fistula takedown, or ileostomy reversal? Would this patient benefit from an intestinal rehabilitation strategy?
   B. Is the patient malnourished?
   C. Does the patient have a condition (e.g., pancreatitis) that alters the secretion of digestive enzymes?
   D. Does the patient have a chronic disease process (e.g., short gut syndrome) that alters absorption?
4. Does the patient have an infection?
   A. Is there any evidence of contamination of feeding tubes? Is the feeding system a closed system? How often is it being changed?
   B. Is there cause for nosocomial bowel infection? Is the patient's *C. difficile* toxin negative?
   C. Has colonic flora been altered significantly with antibiotics?

TREATMENT

Treatment must address the underlying cause or causes. One or several reasons for the presence of diarrhea generally can be identified. Eliminating an infectious cause first has significant implications for treatment algorithms that use medications to slow fecal transit time. Slowing the progression of stool is not recommended for patients with *C. difficile* infection. Additionally, iatrogenic causes of diarrhea should be identified and corrected whenever feasible. For example, promotility and prokinetic agents should be discontinued. Treating teams must maintain good antibiotic stewardship and de-escalate and discontinue antibiotics as soon as possible.[12,13] Through appropriate use of antibiotics, the gut microbiome can be preserved, thus reducing chances of altered GI disturbances.

Once infectious sources and iatrogenic causes are excluded, clinicians should modify diets if the GI tract is being overwhelmed with high quantities of a particular nutrient. This is particularly important for patients receiving formulas that deliver excessive fat. In this circumstance, digestive enzymes such as pancreatic enzymes or bile substitutes should be supplemented when the disease process (or treatment) is associated with decreased production of these enzymes.

Bulk-forming agents can improve the consistency of the fecal bolus. These agents must be administered in appropriate amounts, because they can also cause diarrhea.[14] Agents that inhibit GI motility, such as loperamide or diphenoxylate and atropine, should be used with caution. These drugs are often ordered empirically and may worsen underlying pathology, especially when the causative agent is infectious, but can be very effective in appropriately selected critically ill patients.

Antibiotics for treating infectious diarrhea should be used with caution. If the diarrhea is causing minimal discomfort and is of no physiologic consequence, waiting for the results of tests for *C. difficile* is advised.[15]

Restoring normal colonic flora has become an increasingly frequent practice in the ICU. Provision of prebiotics and probiotics may have utility for treatment and prevention of common causes of diarrhea. Hempel et al. suggested in a 2012 meta-analysis that probiotics effectively treat antibiotic-associated diarrhea ($P < .001$ number needed to treat [NNT] 13), referencing 82 randomized controlled trials with over 11,000 patients.[17] Goldenberg et al. performed a Cochrane review and found that there was a significant correlation with the use of probiotics and prevention of *C. difficile* infection among 4200 patients.[18] The literature is evolving, but the most consistent signal is that microbiome diversity is important for treating and preventing these two forms of diarrhea. The strain of probiotic used in studies and reviewed in these meta-analyses is poorly documented. More research is needed to understand which probiotics confer the greatest benefits for distinct patient populations.

Stopping or decreasing the rate of enteral nutrition is only advisable if the patient is being overfed or exhibits intolerance to the diet. Only under exceptional circumstances should stopping oral intake and giving total parenteral nutrition be advocated as a treatment for diarrhea.

CONCLUSION

Diarrhea is a clinical manifestation of GI dysfunction in the ICU. The true incidence of diarrhea in ICU patients is unknown because of the lack of a universally accepted definition or concerted, systematic effort to study the problem. Despite these limitations, diarrhea can be effectively treated with careful clinical evaluation and simple therapeutic measures.

KEY POINTS

- Diarrhea is one of the most common GI dysfunctions that plague ICU patients and caregivers.
- Diarrhea has several causes in the ICU, of which infectious, malabsorptive, and secretory remain at large.
- Once the etiology is diagnosed, a treatment algorithm can be instituted.
- Infectious sources of diarrhea should be considered before using agents that decrease fecal transit time.
- Commonly used medications that reduce diarrhea are loperamide, diphenoxylate and atropine, fiber, and tincture of opium, which should be administered only after prokinetic/promotility and stool softener agents are discontinued.

References for this chapter can be found at expertconsult.com.

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28

Chest Pain

Daniel J. Rowan and David T. Huang

INITIAL APPROACH

Several life-threatening conditions can cause chest pain in the critically ill, and the initial approach should focus on prompt evaluation and resuscitation of the airway, breathing, and circulation. Assess the patient's level of consciousness, palpate the pulse, and listen to the breath sounds and heart. Obtain vital signs, including oxygen saturation by pulse oximetry, and ensure that the patient is attached to a cardiac monitor and has adequate intravenous (IV) access. Such measures will help ensure that critical abnormalities such as hypoxemia, hypotension, and unstable dysrhythmias are quickly identified and treated. These conditions, as well as the life-threatening causes of chest pain discussed here, are covered in greater detail in other chapters in this textbook.

HISTORY

After initial evaluation and stabilization, obtain a more detailed history. If the patient can communicate, start with an open-ended question like "What's going on, Mr. Jones?" Physicians often neglect to ask basic questions about the quality of chest pain, as was shown in a study of patients with aortic dissection (AD), and this omission is associated with a delay in diagnosis.[1] The use of a history-taking mnemonic can help avoid this mistake (see online supplemental table for further detail: eTable 28.1). Ask the bedside nurse about recent changes in the patient's condition. As an important subsequent step, a quick "chart dissection" should be performed, focusing on the findings at presentation, reason for intensive care unit (ICU) admission, past history, and progress notes. Attention should be given to recent procedures, previous diagnostic imaging such as chest computed tomography (CT), coronary angiography, or echocardiogram, in addition to electrocardiograms (ECGs). Much of the chest pain literature focuses on management in the emergency department (ED), and although the principles provided apply in both ED and ICU areas, there are also differences. Most notably, ICU patients are already admitted to the hospital and identified as critically ill, whereas ED patients are not. Key differences between assessment of chest pain in the ICU and ED are enumerated in Table 28.1.

PHYSICAL EXAMINATION

Inspect the chest for asymmetric excursions, rashes, or obvious sources of pain, such as chest tubes. Palpate the chest and neck for crepitus, which can result from a pneumothorax or pneumomediastinum. Check for pulsus paradoxus and jugular venous distention (JVD). Assess for asymmetry in the carotid, femoral, or radial pulses, which can be a sign of AD. If breath sounds are asymmetric, hyperresonance to percussion may confirm a pneumothorax. Cardiac auscultation may reveal a friction rub from pericarditis, "crunching" sounds from mediastinal emphysema (Hamman sign), a systolic murmur of aortic stenosis (AS), or an aortic insufficiency murmur from a proximal AD. A focused examination should include the abdomen to avoid missing an abdominal catastrophe masquerading as chest pain. Evaluate for evidence of shock, as demonstrated by coolness or mottling of the lower extremities, decreased urine output, or encephalopathy.

DIAGNOSTIC ADJUNCTS

In the absence of an obvious cause of chest pain (e.g., shingles), a portable chest x-ray (CXR) and ECG should be obtained. Serial cardiac enzymes (particularly high-sensitivity troponin) should be considered to exclude a myocardial infarction (MI). The ECG is often nonspecific but occasionally shows evidence suggestive of acute coronary syndrome (ACS), pericarditis, or pulmonary embolism (PE). The CXR is a useful screening tool for life-threatening causes of chest pain, such as pneumothorax or esophageal rupture. Both the ECG and CXR should be compared with those performed before the onset of pain.

IV contrast-enhanced CT can help diagnose a number of causes of chest pain, including PE, AD, esophageal rupture, pneumothorax, and pneumonia. The benefits of CT scanning, however, must be weighed against the risks of transporting a critically ill patient out of the ICU. Ultrasound (including echocardiography) can be rapidly performed at the bedside with minimal risk to the patient, and in the hands of a highly skilled clinician, can provide dynamic functional imaging and serve as a substitute for the CXR. Pericarditis with associated effusion, wall motion abnormality from MI, AS, AD, pneumothorax, or pleural effusions are all within the diagnostic scope of ultrasound. Ultrasound has the added benefit of providing information about cardiac function. Further discussion of the utility and implementation of bedside ultrasound can be found in greater detail in other chapters in this textbook. Diagnostic adjuncts should be used to augment pre-test probability for a particular diagnosis following a focused history and physical examination, as opposed to a "shotgun" approach to testing.

DIFFERENTIAL DIAGNOSES

1. Do not assume the admission diagnosis is correct or all-inclusive. Premature closure, that is, failing to consider alternative possibilities after a diagnosis has come to mind, is a common cause of medical error.[2] Premature closure likely contributes to the delay in diagnosis described in hospitalized patients with AD.[3]
2. Do not be biased by the type of ICU to which the patient is admitted. AD can present as a stroke, prompting admission to a neurologic ICU, or an acute abdomen can develop in a medical ICU patient.

ONLINE SUPPLEMENTAL eTABLE 28.1 OLDCAAR Mnemonic for Evaluating Pain

Domain	Suggested Questions
Onset	Sudden or gradual? Maximal pain at onset?
Location	Generalized or localized? Can you point with one finger to where it hurts?
Duration	When did it start? Just now, or did the pain occur earlier but you did not want to bother anyone? Is it constant or intermittent? If intermittent, is there a trigger, or is it random?
Character	Sharp? Dull? Ache? Indigestion? Pressure? Tearing? Ripping?
Associated symptoms	"Dizzy" (vertiginous or presyncopal)? Diaphoresis? Palpitations? Dyspnea? Nausea or vomiting?
Alleviating/aggravating	Position? Belching? Exertion? Deep breathing? Coughing?
Radiation	To the back? Jaw? Throat? Arm? Neck? Abdomen?

TABLE 28.1 Key Differences in the Assessment of Chest Pain in the Emergency Department vs. ICU

ED	ICU
History and Examination	
Evaluation aided by clinical decision rules, such as the HEART score, PERC, and Wells criteria	Most clinical decision rules are not validated in the ICU setting
Patients are generally participatory in history physical examination	History can be limited by comorbid conditions, and such as delirium or respiratory insufficiency
Assessment is often a first encounter, although prior visits increase the risk for representativeness	Evaluation often assisted by current course, creating the risk of premature closure of the loop bias
Workup and Management	
In the ED, management largely focuses on initial disposition, without the time for prolonged evaluation testing	In the ICU, workup is aided by continuous telemetry monitoring, serial reevaluation, and laboratory
Interpretation of cardiac biomarker elevation, ECG findings, and radiography more often clouded by intercurrent critical illness	

Evaluation in both the emergency department (*ED*) and the intensive care unit (*ICU*) relies upon a thorough history and physical examination and reasonable use of adjunctive testing, including laboratory assessment, electrocardiogram (*ECG*), chest x-ray (CXR), advanced imaging, and point-of-care ultrasound. Both initially focus on addressing and treating immediate life-threatening causes of chest pain. *PERC*, Pulmonary embolism rule-out criteria.

POTENTIALLY LIFE-THREATENING CAUSES OF CHEST PAIN

Acute Coronary Syndrome

ACS includes unstable angina, ST-segment elevation MI, and non-ST elevation myocardial infarction (NSTEMI). The classic symptoms include chest pressure radiating to the left arm, nausea, and diaphoresis, but this history has several diagnostic limitations. Although certain features (e.g., pain radiating down the left arm) are associated with a higher likelihood of ACS, and other characteristics (e.g., pleuritic, positional, or sharp pain) with a lesser likelihood, none can reliably confirm or exclude the diagnosis.[4,5] Reduction in pain after nitroglycerin is also not a reliable indicator of cardiac chest pain.[6] Conventional cardiovascular risk factors, including diabetes, smoking, dyslipidemia, hypertension, and a suggestive family history, predict the development of heart disease over years in asymptomatic patients but may be less useful in predicting ACS in patients with acute chest pain.[7] However, a recent cohort study of 1.3 million hospitalized patients identified a personal prior history of coronary disease, tachycardia, anemia, and leukocytosis to be associated with patients who developed in-hospital MI.[8]

There are no specific physical examination findings of ACS, but if the ACS is severe enough to induce left ventricular dysfunction, signs such as hypotension, JVD, and an S3 or S4 heart sound can be present. The ECG should be examined for ST-segment elevation or depression, Q waves, and T-wave inversions. An isolated ECG has limited sensitivity for diagnosing MI, but the yield increases with serial ECGs. Given the limitations of the ECG and of the history and examination findings, cardiac troponin should be measured in ICU patients with chest pain, and echocardiography provides complementary information by disclosing regional wall motion abnormalities.[9] Repeat measurement of troponin will help to further stratify patients.[10,11]

All patients suspected of having ACS should be treated with aspirin, if not contraindicated (e.g., AD also suspected), or alternatively prasugrel or ticagrelor if there is aspirin allergy. Dual antiplatelet therapy with a P2Y12 inhibitor (ticagrelor or prasugrel) should be considered in all, unless contraindicated.[12] Supplemental oxygen should only be applied to those patients with hypoxemia.[13] Sublingual nitroglycerin and IV morphine should be used to relieve pain if the systolic pressure exceeds 90 mm Hg and the patient has not recently taken a phosphodiesterase inhibitor (e.g., sildenafil). Further treatment of ACS is primarily dictated by ECG findings and the patient's clinical status, and in the setting of ST-segment elevation may include emergency percutaneous coronary intervention (preferred) or fibrinolysis when onsite interventional cardiac catheterization is unavailable. Depending on cardiac findings and the treatment administered, adjunctive therapies may include an anticoagulant, beta-blocker, statin, angiotensin-converting enzyme inhibitor or angiotensin receptor antagonist, and aldosterone receptor antagonist.[11]

Pulmonary Embolism

Approximately 1%–2% of ICU patients have been estimated to develop deep vein thrombosis (DVT) or PE, but the true incidence is probably higher, with autopsy studies identifying a significantly greater percentage.[14,15] ICU patients often have one or more risk factors for PE, including immobility, advanced age, obesity, recent surgery or trauma, mechanical ventilation, vasopressor use, advanced renal failure, sepsis, malignancy, and central venous catheterization.[16] Do not be deterred from evaluating for PE in patients receiving prophylactic anticoagulation, as risk of venous thromboembolism (VTE) persists despite its use, with various studies citing rates ranging from 5% to 10% in this cohort.[17] The burden of VTE in the ICU is high, with increased ICU length of stay and duration of mechanical ventilation associated with its diagnosis.[17,18]

Chest pain resulting from PE is often pleuritic and associated with dyspnea, hemoptysis, cough, or syncope.[19] Physical examination findings are generally nonspecific in PE. Unexplained tachypnea or tachycardia may be the only diagnostic clue. Hypoxia, though typical, is not a universal finding, and its absence cannot exclude PE. A large PE may present with hypotension or cardiovascular collapse. Signs of pulmonary hypertension and right heart failure, such as a loud second heart sound, JVD, or a right-sided S4 heart sound, may be present. Lung examination may reveal crackles, decreased breath sounds, wheezing, rhonchi, or a pleural friction rub. Physical evidence of concomitant DVT often includes unilateral lower extremity edema or erythema, but a significant percentage of diagnosed PEs are without associated DVT.[20]

The ECG is often normal, but may show sinus tachycardia (the most common finding), Brugada pattern, atrial fibrillation, or the classically reported S1Q3T3 pattern.[21] ST depressions and/or T-wave inversions in the precordial or inferior leads, ST elevation in aVr, qR pattern in V1, and right-axis deviation or right bundle branch block suggest increased right ventricular (RV) strain.[22] CXR can be normal

or reveal nonspecific findings such as pleural effusion, infiltrates, or atelectasis, and is only useful for ruling out alternative pathology.[23] Although D-dimer testing has been used to rule out VTE in outpatients with a low likelihood of this diagnosis, the D-dimer assay is less useful in the ICU setting.[17,24] Traditional risk stratification tools for PE, such as the Wells and Geneva scores, have also proven less sensitive in the ICU.[25]

CT pulmonary angiography can be rapidly performed and is the diagnostic test of choice for stable patients in whom there is moderate to high suspicion of PE, given its high sensitivity and specificity. A ventilation/perfusion scan can be time consuming and difficult to perform in mechanically ventilated patients, and interpretation is challenging in the presence of other lung pathology.[26] For patients with unstable hemodynamics, bedside transthoracic echocardiography (TTE), in addition to compressive ultrasound (CUS) of the lower extremities, may be used in tandem to assess for DVT and evidence of RV pressure overload.[27] Elevated troponin and B-type natriuretic peptide (BNP) are associated with a higher risk of mortality in PE.

Initial treatment of low-risk patients with PE involves anticoagulation with subcutaneous low-molecular-weight heparin or fondaparinux, IV unfractionated heparin, or direct oral anticoagulants. High-risk patients with hemodynamic instability and RV dysfunction resulting from PE may require systemic thrombolysis, with surgical embolectomy or catheter-directed thrombolysis recommended for those who have a contraindication to systemic thrombolytics.[26]

Thoracic Aortic Dissection

AD results from a tear in the aortic intima, allowing blood to dissect between the intimal and medial layers, generating a false lumen. This event has an incidence of 6–15/100,000.[28] The Stanford system classifies dissections as type A (involving the ascending aorta) or type B (involving the aorta distal to the left subclavian artery). Risk factors include hypertension, male sex, pregnancy, advanced age, atherosclerosis, diabetes mellitus, cocaine use, preexisting aortic and valvular disease, prior cardiac surgery, family history, Ehlers-Danlos syndrome, Turner syndrome, and giant cell arteritis. Patients younger than 40 years are more likely to have Marfan syndrome, Loeys-Dietz syndrome, bicuspid aortic valve, prior aortic surgery, or aortic aneurysm. The mortality rate is as high as 1%–2% per hour from symptom onset. A directed history remains critical to early diagnosis, with a particular focus on quality, radiation, and intensity of pain to ensure an accurate diagnosis.[1]

Many patients who complain of sudden onset of chest, back, or abdominal pain that radiates to the back often describe the pain as sharp, rather than tearing. AD can also present in a painless fashion, manifesting as syncope, stroke, or evolving heart failure.[29] Dissection can extend into any of the major aortic branches, causing a multitude of clinical presentations that arise in ischemia of the brain, heart, kidney, spinal cord, or gut.

Certain physical examination findings should raise the suspicion of AD. About one-quarter of patients have pulse deficits in the carotid, radial, or femoral arteries, and some have focal neurologic deficits related to cerebral or spinal cord ischemia and therefore can present as having a stroke or paraplegia.[30] Hypotension often occurs with type A dissection, whereas hypertension is more commonly seen in type B dissection. A significant difference in systolic blood pressure (>20 mm Hg) between the upper extremities may be detected, but this finding is not pathognomonic. A diastolic murmur of aortic insufficiency can result from retrograde dissection into the aortic valve, whereas a friction rub may be appreciated with concomitant large pericardial effusion or tamponade.

The ECG may be normal or show nonspecific ST-segment or T-wave changes or left ventricular hypertrophy secondary to hypertension. Rarely, the ECG reveals evidence of an MI from retrograde dissection into a coronary artery. Although patients may have an abnormality on CXR, such as widening of the mediastinum, an abnormal aortic contour, or displacement of intimal aortic calcification from the outer border of the aortic knob, this is not universal, and its absence can lead to delays in diagnosis.[31,32] The vast majority of patients undergo either CT angiography or transesophageal echocardiography for diagnosis, both of which have high sensitivity and specificity. Magnetic resonance imaging (MRI) may also have a limited role, although given its lack of generalized availability and lengthy examination duration, its use in this setting is less appealing.[33]

Initial management should focus on heart rate and blood pressure control, usually with beta-blockers, typically the rapidly titratable agent esmolol, and the use of a potent vasodilator such as nicardipine or clevidipine.[33,34] Emergent cardiothoracic surgical consultation is imperative. Further discussion of surgical operative strategy is beyond the scope of this chapter.

Pneumothorax

Pneumothorax is caused by air from the alveoli or the surrounding atmosphere entering the potential space between the parietal and visceral pleura. Pneumothorax in the ICU is often iatrogenic, resulting from mechanical ventilation (particularly with acute respiratory distress syndrome) and procedural attempts at central venous catheterization, thoracentesis, tracheostomy, transbronchial lung biopsy, or bronchoscopy.[35] Almost any lung pathology can contribute to the risk for pneumothorax, but a ruptured bleb from chronic obstructive pulmonary disease is most common. Patients with pneumothorax often complain of a sudden onset of ipsilateral pleuritic chest pain and dyspnea.

Chest examination may reveal palpable crepitus, decreased breath sounds, decreased chest wall excursion, or hyperresonance to percussion. Vital signs may be significant for tachycardia, hypoxia, or tachypnea. Patients with a tension pneumothorax classically have tracheal deviation, JVD, and hypotension. Patients receiving mechanical ventilation often, but not invariably, have increased peak inspiratory airway pressures. Signs of pneumothorax are nonspecific, and any worrisome deterioration of vital signs in a ventilated patient should prompt a diagnostic evaluation for pneumothorax.

CXRs are often performed in the semi-upright or supine position in the ICU, whereas the signature finding of pneumothorax, a visceral pleural line, is often seen only on an upright CXR. In supine patients, a deep sulcus sign may be seen where the costophrenic angle extends more inferiorly than normal, as air collects in this space. Alternatively, a sharp delineation of the cardiac silhouette from the lucency of an anteromedial pneumothorax may be seen. In an experienced operator's hands, ultrasound can rule out a pneumothorax with high sensitivity.[36] A CT scan is usually definitive.

Treatment of pneumothorax is contingent on its size, the patient's hemodynamic and respiratory status, and concurrent use of mechanical ventilation. Because of concern for conversion to tension pneumothorax in patients on mechanical ventilation, evacuation of air from the pleural space is often required with a tube thoracostomy. In patients with hemodynamic compromise from a suspected tension pneumothorax, treatment with immediate needle thoracostomy, followed by tube thoracostomy, should not be delayed while waiting for a CXR. For the vast majority of patients, a small-bore catheter placed via the Seldinger technique is as efficacious as standard chest tube placement in those with primary spontaneous pneumothorax.[37,38]

Esophageal Rupture

A full-thickness tear of the esophagus carries a high mortality risk, because of the intense inflammatory response to gastric contents in the mediastinum and pleural space, resulting in a chemical and bacterial mediastinitis, with development of sepsis and multisystem organ failure. Most cases of esophageal perforation are caused by upper gastrointestinal tract instrumentation. The risk of esophageal injury from a diagnostic endoscopy is low but increases dramatically when interventions such as dilation or stent placement are performed.[39] Esophageal rupture may be caused by other procedures commonly performed in the ICU, including nasogastric or tracheal intubation. Spontaneous rupture of the esophagus (Boerhaave syndrome) occurs from a sudden increase in intraluminal pressure, usually from vomiting or retching. Patients with esophageal disease such as cancer, Barrett esophagus, strictures, prior radiation, and varices are particularly vulnerable to rupture, most commonly at the left posterolateral aspect of the distal esophagus. With thoracic esophageal perforations, the pain localizes to the substernal or epigastric area, but it may occur in the neck with cervical perforations. Other associated symptoms include dysphagia, odynophagia, and dyspnea.

The patient is often febrile. Crepitus can be felt in the neck with perforation of the cervical esophagus. Mediastinal emphysema can be detected by a crunching sound on cardiac auscultation (Hamman sign). A CXR often reveals subcutaneous emphysema, pneumomediastinum, pneumothorax, or pleural effusion. The CXR is abnormal in almost 90% of cases, usually demonstrating left-sided infiltrate or effusion. A water-soluble contrast study of the esophagus or a CT scan of the chest and abdomen can be performed in cases where there is a high clinical suspicion and the CXR is nondiagnostic. Mortality increases with delays in treatment beyond 24 hours, and urgent diagnosis is imperative.[40]

Treatment may involve operative repair, endoscopic therapy, or conservative management, depending on the location of the leak, its containment, and the presence of sepsis. Conservative management consists of broad-spectrum antibiotics, ensuring coverage of both anaerobic and aerobic species (augmented by antifungal treatment in patients with relevant risk factors) and observation.[41,42]

Aortic Stenosis

AS causes left ventricular outflow obstruction, which leads to left ventricular hypertrophy. AS may result from a congenitally abnormal (bicuspid) valve, rheumatic heart disease, or valvular calcification. Clinical manifestations of AS, including angina, congestive heart failure, and syncope, occur when the hypertrophied left ventricle can no longer overcome the stenosis or when the hypertrophy itself causes diastolic dysfunction or excessive myocardial oxygen demand that predisposes to ischemia.

Physical examination features of AS include narrow pulse pressure, a delayed and slow rise of the carotid pulse (pulsus tardus et parvus), a systolic murmur at the right second intercostal space often radiating to the carotid arteries, and an S4 heart sound (if patients are in sinus rhythm). CXR and ECG may show signs of left ventricular hypertrophy, but the diagnostic study of choice is the echocardiogram.[43]

Definitive therapy involves valve replacement, either by conventional surgical approaches or, in well-selected cases, via transcatheter aortic valve replacement. Temporizing management focuses on cautiously decreasing afterload with vasodilators. Close hemodynamic monitoring is essential when using vasodilators because of the risk of hypotension and dysrhythmias, which are poorly tolerated. Angina and congestive heart failure are treated with oxygen and the careful administration of nitrates, morphine, and diuretics. Occasionally, balloon aortic valvuloplasty may be used to bridge patients until they can undergo surgical or transcatheter valve replacement.[44]

Miscellaneous

Other causes of potentially life-threatening chest pain in the ICU include pneumonia and acute abdominal processes. Pneumonia is often accompanied by pleuritic chest pain or shoulder pain referred from diaphragmatic irritation. Upper gastrointestinal pathology, such as cholecystitis, choledocholithiasis, cholangitis, or pancreatitis, may present with chest and abdominal pain radiating toward the back. A perforated ulcer can present with chest pain, and the diagnosis is often made when free air is incidentally discovered under the diaphragm on an upright CXR.

NON–LIFE-THREATENING CAUSES OF CHEST PAIN

The following causes of chest pain should be considered only after life-threatening causes have been excluded.

Pericarditis

Pericarditis is a relatively rare cause of chest pain in the inpatient setting.[45] The condition commonly results from viral or idiopathic causes, but other etiologies include bacterial infection, malignancy, tuberculosis, uremia, autoimmune diseases, transmural MI (Dressler syndrome), and cardiac surgery (postpericardiotomy syndrome). Chest pain from pericarditis is often retrosternal, pleuritic, and sharp, radiating to the back or arms and exacerbated when lying flat.

A pericardial friction rub is highly specific for pericarditis and is present in the majority of cases, heard best over the left sternal border with the patient sitting forward. Common ECG findings in pericarditis include diffuse ST-segment elevation without reciprocal ST depressions, absence of Q waves, and PR depressions.[45] Electrical alternans and low voltage on the ECG, coupled with cardiomegaly on CXR, strongly favor the concomitant presence of a large pericardial effusion. Although the ECG and CXR findings of pericardial effusion can be useful, echocardiography should be performed to confirm the diagnosis.

Treatment is aimed at the underlying etiology. Nonsteroidal antiinflammatory drugs (NSAIDs) relieve pain and inflammation in viral or idiopathic pericarditis. Colchicine may be used as an adjunct in reducing bouts of recurrent pericarditis.[46] Pericardiocentesis is performed for therapeutic purposes in the case of tamponade and for diagnostic purposes if tuberculosis, bacterial infection, or malignancy is suspected.

Esophageal Disorders

In patients with noncardiac chest pain, gastroesophageal reflux disorder and esophageal motility disorders (e.g., esophageal spasm) are commonly responsible. Esophageal disease is associated with pain precipitated by lying flat, postprandial pain, heartburn, or dysphagia. Because of the shared innervation of the heart and esophagus, visceral pain originating from these two organs can be similar in character. Empiric treatment with proton pump inhibitor or H_2 blocker may be considered. Additionally, a nasogastric tube with the distal tip in the esophagus can produce chest pain; this is easily remedied by advancing the tube distally into the stomach.

Musculoskeletal, Skin, and Psychiatric Disorders

Pain from costochondritis is often reproduced by direct palpation of the affected region or by arm movement and can be treated with NSAIDs. ICU patients may have other causes of chest wall pain, including rib fractures, chest tubes, postoperative pain after cardiothoracic surgery, or an intercostal muscle strain from vigorous coughing.

Herpes zoster should also be considered, which results from reactivation of the varicella-zoster virus within thoracic sensory ganglia, causing a painful, dermatomal rash on the chest. This pain of shingles may precede the rash by several days, often delaying its diagnosis. Treatment consists of antiviral medications, such as acyclovir or valaciclovir. Finally, it is imperative to rule out life-threatening causes of chest pain before attributing its etiology to anxiety. Psychiatric patients with cardiac or pulmonary disease can be challenging to diagnose, and a thorough approach is essential.

CONCLUSION

Attention to immediate life-threatening conditions and a thorough history and physical examination after initial stabilization are fundamental to managing chest pain in the ICU. A CXR, ECG, and serial cardiac enzymes should be ordered liberally, but intelligently. Focused ultrasound to assess the lungs, pleura, and heart can be helpful. A high index of suspicion for occult disease is necessary for complex ICU patients.

KEY POINTS

- Attention to detail with a brief but thorough history and physical examination are fundamental to managing chest pain in the ICU.
- A logical evaluation plan must simultaneously assess for and empirically treat immediately life-threatening etiologies of chest pain.
- Useful adjunctive testing includes ECG, CXR, cardiac enzymes, and focused ultrasound of the heart and lungs.
- Non–life-threatening causes of chest pain in the ICU are numerous, but should be diagnoses of exclusion.

References for this chapter can be found at expertconsult.com.

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An analysis of 100 cases identified premature closure—that is, failing to consider alternatives once an initial diagnosis was made—as the most common cause of diagnostic error by internists. This study underscores the importance of not assuming that the admission diagnosis is necessarily correct or the only problem.

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29

Biochemical or Electrocardiographic Evidence of Acute Myocardial Injury

Fabien Picard and Steven M. Hollenberg

The identification of myocardial injury is an important problem in the critical care setting. Biomarkers have been used to detect myocardial injury since 1954.[1] Since then, the sensitivity of serologic techniques has increased dramatically. Although increased sensitivity has allowed clinicians to detect smaller amounts of myocardial necrosis, this has also posed several interpretive challenges. What constitutes significant myocardial damage? How should evidence of myocardial necrosis be interpreted in the absence of classical clinical criteria for myocardial infarction? In response to some of these challenges, a task force has formulated a universal definition of myocardial infarction, updated in 2018 (Table 29.1).[2] These definitions rely on both electrocardiographic and biochemical information and stress that, in addition to biochemical findings, the diagnosis of myocardial infarction (MI) requires symptoms *or* characteristic electrocardiogram (ECG) changes *or* findings from imaging, angiography, or autopsy. The most important distinction for the clinician is between type 1 MIs (plaque rupture) and type 2 MIs (demand ischemia leading to infarction).

ELECTROCARDIOGRAPHIC EVIDENCE

Acute coronary syndromes (ACSs) are a group of conditions characterized by acute myocardial ischemia resulting from inadequacy of myocardial blood flow. The ACSs are classified by clinical, biochemical, and electrocardiographic data, initially dividing patients by ECG into those with ST elevation myocardial infarction (STEMI), who should be considered for immediate revascularization, and those without (non-ST elevation [NSTE-ACS]).[3] Patients with suspected ACS must have an ECG obtained and interpreted within 10 minutes of presentation.[4] Criteria for the diagnosis of STEMI include new ST elevation ≥0.1 mV at the J-point in at least two contiguous leads (except $V_{2–3}$) or new left bundle branch block (LBBB).[2,5] (In leads $V_{2–3}$ cut points are higher: ≥0.15 mV in women, ≥0.2 mV in men ≥40, and ≥0.25 mV in men <40.)

Many conditions that mimic STEMI lead to false positives.[2] An early repolarization pattern with up to 3-mm ST elevation in leads $V_{1–3}$ can be seen in some healthy individuals, typically in young men. Preexcitation, bundle branch block, pericarditis, pulmonary embolism, subarachnoid hemorrhage, metabolic disturbances (e.g., hyperkalemia and hypothermia), and left ventricular aneurysms can be associated with ST elevation in the absence of acute myocardial ischemia. On the other hand, some conditions can lead to false negatives, including prior MI, paced rhythm, and LBBB when acute ischemia is not recognized. These pitfalls are common, both in the real world and in large clinical trials.[6]

"Nondiagnostic" ECGs are common in the setting of true acute MI, characterizing up to 8% of such patients, with nonspecific changes occurring in another third.[7] These nondiagnostic ECG findings may be the result of occlusion of only small vessels or insensitivity of the 12-lead ECG to ischemia in the lateral or posterior myocardial territory. Supplemental leads, such as $V_{7–9}$, can improve sensitivity.[8] If ischemia is strongly suspected without ECG changes, serial ECGs or ECGs with additional leads should be performed[4] to increase the sensitivity of MI detection relative to single ECGs.[9]

ST-segment depression on an ECG identifies patients with ACS at high risk, as this is associated with the severity of coronary artery disease (CAD).[10] T-wave changes can also be prognostic. Patients presenting to the emergency department with ACS and isolated T-wave changes have a lower risk for adverse outcomes than those with ST depression but are at higher risk than those with a normal ECG.[11] In asymptomatic patients, most T-wave changes are nonspecific. However, in the intensive care unit (ICU), some patterns are strongly associated with myocardial ischemia. Marked symmetric precordial T-wave inversions ≥2 mm suggest acute ischemia, usually the result of a critical stenosis of the left anterior descending artery.[12]

CK-MB, TROPONIN, AND HIGH-SENSITIVITY TROPONIN

With cardiac cell death, proteins are released into the blood, and detection of these proteins has played a key role in establishing the diagnosis of ACS, predicting its outcome, and directing treatment. Creatine kinase (CK) and its isoenzyme MB (CK-MB) became the biomarkers of choice to establish myocardial injury and infarction in the 1970s, but have been superseded by troponin T and I, parts of the troponin-tropomyosin complex in cardiac myocytes, because of their increased sensitivity and specificity. Troponin elevations are much more sensitive and are highly specific for myocardial cellular injury; false positives because of fibrin interference or cross-reacting antibodies are infrequent.[13] Even minor increases in circulating troponin values correlate with adverse short-term and long-term outcomes in NSTE-ACS[13] and also identify the patients most likely to benefit from more aggressive antiplatelet strategies and from early coronary angiography and revascularization.[4]

The challenge for the clinician, and particularly for the intensivist, is that although the elevation of serum troponin is highly specific for myocardial cell damage, not all of the damage is a consequence of the rupture of an atherosclerotic plaque. Demand ischemia (type 2 MI) can also lead to troponin release. Other causes of elevated troponin, many of which are common in the ICU, are listed in Table 29.2.[2] This spectrum of troponin-associated conditions highlights the fact that MI should only be diagnosed in the appropriate clinical setting.[2] Troponin release in critically ill patients may not always represent myocardial cell death. Endotoxin, cytokines, and other inflammatory mediators, along with catecholamines and conditions such as hypotension, inotropes, or

TABLE 29.1 Clinical Classification and Definition of Different Types of Myocardial Infarctions

Type 1: MI Caused by Atherothrombotic CAD and Usually Precipitated by Atherosclerotic Plaque Disruption (Rupture or Erosion)

Detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL and with at least one of the following:

- Symptoms of acute myocardial ischemia
- New ischemic ECG changes
- Development of pathologic Q waves
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology
- Identification of a coronary thrombus by angiography, including intracoronary imaging or by autopsy

Type 2: Myocardial Injury in the Context of a Mismatch Between Oxygen Supply and Demand

Detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL and evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute coronary atherothrombosis, requiring at least one of the following:

- Symptoms of acute myocardial ischemia
- New ischemic ECG changes
- Development of pathologic Q waves
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology

TYPE 3: Cardiac Death in Patients with Symptoms Suggestive of Myocardial Ischemia and Presumed New Ischemic ECG Changes Before Ctn Values Become Available or Abnormal

Patients who suffer cardiac death, with symptoms suggestive of myocardial ischemia accompanied by presumed new ischemic ECG changes or ventricular fibrillation, but die before blood samples for biomarkers can be obtained, or before increases in cardiac biomarkers can be identified, or MI is detected by autopsy examination.

Type 4a: MI Associated with Percutaneous Coronary Intervention (≤48 Hours After the Index Procedure)

Coronary intervention–related MI is arbitrarily defined by an elevation of cTn values more than five times the 99th percentile URL in patients with normal baseline values. In patients with elevated preprocedure cTn in whom the cTn levels are stable (<20% variation) or falling, the postprocedure cTn must rise by >20%. However, the absolute postprocedural value must still be at least five times the 99th percentile URL. In addition, one of the following elements is required:

- New ischemic ECG changes
- Development of new pathologic Q waves
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology
- Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or a side branch occlusion/thrombus, disruption of collateral flow, or distal embolization

TYPE 4b: Stent/Scaffold Thrombosis Associated with Percutaneous Coronary Intervention

TYPE 4c: Restenosis Associated with Percutaneous Coronary Intervention

TYPE 5: MI Associated with CABG (≤48 Hours After the Index Procedure)

CABG-related MI is arbitrarily defined as elevation of cTn values >10 times the 99th percentile URL in patients with normal baseline cTn values. In patients with elevated preprocedure cTn in whom cTn levels are stable (<20% variation) or falling, the postprocedure cTn must rise by >20%. However, the absolute postprocedural value still must be >10 times the 99th percentile URL. In addition, one of the following elements is required:

- Development of new pathologic Q waves
- Angiographic-documented new graft occlusion or new native coronary artery occlusion
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology

CABG, Coronary artery bypass grafting; *cTn*, cardiac troponin; *ECG*, electrocardiogram; *MI*, myocardial infarction; *URL*, upper reference limit.
From Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction. *Circulation*. 2018;138(20):e618–e651.

hypoxia, may cause the breakdown of cytoplasmic troponin into smaller fragments that can pass through endothelial monolayers and subsequently be detected by sensitive troponin assays.[14] Although detectable troponin levels usually emanate from myocardial cells, they may not always represent either irreversible cell death or myocardial ischemia. Renal dysfunction is another factor associated with elevated troponin levels, and both the sensitivity and specificity of this biomarker are decreased in that population.

Regardless of the cause, it is clear that elevation of serum troponin levels is associated with a worsened outcome both in and out of the ICU, even after adjustment for severity of the disease.[15] What is less clear is whether myocardial dysfunction represents the proximate cause of the worsened prognosis. It is often difficult to exclude ischemia in critically ill patients, but in a study of patients with septic shock, troponin predicted mortality risk even in patients in whom flow-limiting lesions were excluded either by stress echocardiography or by direct examination at autopsy.[16]

These challenges are likely to be compounded by the wider use of high-sensitivity troponin (hs-cTn) assays.[17] Two large prospective multicenter studies have demonstrated that high-sensitivity cTn and hs-cTn assays have a higher diagnostic accuracy for the diagnosis of MI than less-sensitive cTn assays, especially in patients presenting early after chest pain onset.[18,19] The clinical introduction of hs-cTn assays is a trade-off: on one hand allowing earlier detection and exclusion of acute MI (AMI) in the first hours, but on the other, the detection of myocardial cell death associated with multiple

TABLE 29.2 Causes of Elevation of Cardiac Troponin Values

Myocardial Injury Related to Acute Myocardial Ischemia

Atherosclerotic plaque disruption with thrombosis.

Myocardial Injury Related to Acute Myocardial Ischemia Because of Oxygen Supply/Demand Imbalance

Reduced myocardial perfusion, for example:

- Coronary artery spasm, microvascular dysfunction
- Coronary embolism
  - Coronary artery dissection
  - Sustained bradyarrhythmia
- Hypotension or shock

Respiratory failure

- Severe anemia

Increased myocardial oxygen demand, for example:

- Sustained tachyarrhythmia
- Severe hypertension with or without left ventricular hypertrophy

Other Causes of Myocardial Injury

Cardiac conditions, for example:

- Heart failure
  - Myocarditis
  - Cardiomyopathy (any type)
  - Takotsubo syndrome
  - Coronary revascularization procedure
  - Cardiac procedure other than revascularization

Catheter ablation

- Defibrillator shocks
- Cardiac contusion

Systemic conditions, for example:

- Sepsis, infectious disease
  - Chronic kidney disease
  - Stroke, subarachnoid hemorrhage
  - Pulmonary embolism, pulmonary hypertension
  - Infiltrative diseases (e.g., amyloidosis, sarcoidosis)

Chemotherapeutic agents

- Critically ill patients
- Strenuous exercise

From Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction. *Circulation.* 2018;138(20):e618–e651.

noninfarction pathophysiologic conditions. That enhanced sensitivity challenges the clinician to differentiate them.[20] A further difficulty in the ICU is that patients may not experience classic symptoms of ischemia or may be unable to report them. Despite this potentially confounding factor, it is useful for the clinician to recall that an MI is diagnosed when biomarkers are elevated in a suggestive clinical setting.[2] A characteristic rise and subsequent fall should be seen, as an isolated high troponin value may not result from persisting ischemia.[21] Troponin levels should be repeated to define the clinical course. In addition, it is important to note that the diagnostic performance of hs-cTn assays is currently not established outside the setting of the patient presenting to the emergency department with chest pain.[20]

OTHER BIOMARKERS

Although some emerging biomarkers provide good sensitivity or specificity for the diagnosis of MI, others may provide useful information regarding prognosis.

Cardiac myosin-binding protein C (cMyC) is a cardiac-restricted protein that rapidly enters the systemic circulation after myocardial injury, is relatively more abundant than troponin, and has been recently identified as a new candidate biomarker of cardiac injury.[22] cMyC rises more rapidly in the systemic circulation than hs-cTnT, perhaps as a result of its higher myocardial concentration.[23] In a recent analysis of unselected patients presenting to the emergency department with symptoms suggestive of AMI, discriminatory power for MI was comparable for cMyC and other biomarkers, but the combination of cMyC with standard-sensitivity cTn led to an increase in area under the diagnostic curve and more accurately classified patients with a single blood test into rule-out or rule-in categories.[24] Validation in larger and more varied cohorts is needed.

The N-terminus portion of human albumin binds to transition metal ions. Under ischemic and oxidative conditions, this binding is inhibited, and detection of this ischemia-modified albumin (IMA) has been described as a marker of oxidative stress and hypoperfusion.[25] In MI, IMA levels rise within 6 hours and remain elevated for 12 hours, and a combination of IMA, ECG, and contemporary troponin assays was reported to have a negative predictive value of 97% for MI.[26] In patients with severe sepsis, IMA was a strong predictor of short-term mortality.[27] Its use, however, has not yet been confirmed to add value to contemporary hs-TnT assays,[25] and detection of high IMA levels in patients with cancer, infection, brain ischemia, liver disease, and end-stage renal disease limits the specificity of this test for the diagnosis of MI.

MicroRNAs (mi-RNAs), short, noncoding RNAs that regulate gene expression at the post-transcriptional level, are novel markers that may prove clinically useful. Three mi-RNAs (miR-133a, miR-208b, and miR-499) demonstrated high sensitivity and specificity for detecting AMI,[28] but a recent study demonstrated that sensitivity of current mi-RNA detection was inferior to troponin.[29] A multibiomarker combination of muscle-enriched mi-RNAs with cMyBP-C and cardiac troponins could open a new path of integrating complementary characteristics of different biomarker types.

The prohormone proBNP is released by the heart in response to stretching of the wall and after ischemia. Subsequently, it is cleaved into active B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP), both of which can be measured in blood. Higher BNP levels in ACS patients correlate with an increased risk of death, and BNP appears to confer information independent of other clinical markers, adding prognostic value to the Global Registry of Acute Coronary Events (GRACE) risk score.[30] Use of BNP in the ICU is complex, however; women and older individuals have higher BNP levels, and so age- and gender-specific cutoffs may be needed.[31] Whereas obese individuals have lower values, renal dysfunction increases BNP serum levels, sometimes dramatically.[32,33] BNP levels can also be increased in the setting of right ventricular strain. Consequently, in patients with pulmonary embolism, both elevated BNP and elevated troponin levels carry a worsened prognosis.[34] BNP remains a good indicator of ventricular dysfunction and myocardial wall stress, but which cutoff levels should be used in the ICU and what the clinician should do when the BNP exceeds those levels remain unclear.

KEY POINTS

- Of the five MI types, those most pertinent to the critical care setting are type 1 (plaque rupture) and type 2 (demand ischemia leading to infarction).
- "Nondiagnostic" ECGs are common in the setting of AMI.
- Troponin elevations are highly specific for myocardial cellular injury, but their release may not always indicate myocardial plaque rupture.
- High-sensitivity troponin assays have allowed clinicians to detect smaller amounts of myocardial necrosis, but this has also posed several interpretive challenges.
- Renal dysfunction is another factor associated with elevated troponin levels, decreasing both the sensitivity and specificity of this biomarker in this population.
- Emerging biomarkers have been shown to provide good sensitivity or specificity for the diagnosis of MI and may provide information regarding prognosis.

References for this chapter can be found at expertconsult.com.

ANNOTATED REFERENCES

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Guidelines for the diagnosis and management of non–ST-elevation acute coronary syndromes. The importance of prompt acquisition and interpretation of an electrocardiogram is emphasized, as is the value of early reperfusion therapy.

Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction. *Circulation.* 2018;138(20):e618–e651.
The latest update of a consensus definition of myocardial infarction that includes historical, clinical, electrocardiographic, and biochemical criteria. Key points involve the use of serial biochemical assays when warranted and a distinction between plaque rupture and demand ischemia as a cause of myocardial damage.

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30

Point-of-Care Ultrasound

Sumit P. Singh and Davinder Ramsingh

Recent advances in ultrasound technology have allowed ultrasound instruments to become smaller, more portable, and less expensive, so that this powerful imaging tool can be readily and repeatedly used in everyday intensive care unit (ICU) care.[1] The concept of point-of-care ultrasound (POCUS) refers to the use of portable ultrasonography at the patient's bedside for diagnostic and therapeutic purposes.[2] The provider acquires and interprets all images in real time and then uses that information to diagnose and direct therapy. Although comprehensive imaging can also be performed and interpreted at the point of care, the term POCUS typically refers to an ultrasound examination that is simple, rapid, and goal-oriented. It is a tool used most often to provide answers to acute "yes or no" clinical questions, but interpretations can be more nuanced, depending on the provider's qualifications, experience, and skill. Indeed, POCUS has been identified as a separate imaging modality with defined routes for training, reporting, and billing.[3,4]

In the acute care setting, this modality has demonstrated utility for nearly every component of bedside assessment, including cardiac, pulmonary, hemodynamic, vascular, neurologic, and gastrointestinal status. Recent evidence has demonstrated improved diagnostic accuracy for each of these systems after the operator receives training from a cost-free online curriculum (www.foresightultrasound.com).[5]

This chapter seeks to review the current use of POCUS in the critical care setting. Specifically this chapter will discuss the following areas: (1) ultrasound physics and probe selection, (2) assessment of pulmonary status, (3) advanced vascular access, and (4) additional areas of assessment. Chapter 31 provides a thorough discussion of echocardiography, including the echocardiographic assessment of intravascular volume status (preload responsiveness) and the use of echocardiography to diagnose shock and monitor response to treatment. Training on these topics using a model simulation–based educational curriculum has been shown be effective and to positively affect patient care.[6]

ULTRASOUND PHYSICS, PROBE SELECTION, AND MANIPULATION

Clinical ultrasound systems use transducers that emit and detect sound waves with a frequency between 2 and 27 MHz. Image production depends on the strength of the returning ultrasound signal and relates directly to the angle at which the ultrasonic beam strikes the acoustic interface. The ultrasound signal is described by its frequency and wavelength. A shorter wavelength (i.e., a higher frequency) provides better resolution but less penetration into tissues. Therefore higher-frequency probes (5–10 MHz) provide better resolution but are useful only for imaging superficial structures. Lower-frequency probes (2–5 MHz) provide better penetration but have lower resolution. Probe selection is based on matching the properties of the ultrasound probe with the particular structure that one is trying to image. Besides frequency, additional properties of the probe include the footprint (area emitting the ultrasound) and shape. Typical phased-array probes emit at 3–5 MHz, have a small footprint, and produce a wide ultrasound image by sending out packets of ultrasound that are stitched together. Curved linear probes emit at 4–7 MHz, have a large footprint, and are ideal for imaging of abdominal structures. These probes generate a wide image because of the way the ultrasound waves are emitted. Linear probes emit at 10–27 MHz and are used for imaging superficial structures (Fig. 30.1).

Acoustic gel is used to minimize the difference in acoustic impendence from the probe to the skin. Standard 2D image creation is called *B-mode (brightness mode)*. In this mode, there is a change in spot brightness for each ultrasound signal received by the transducer. M-mode (motion mode) is a graphic B-mode pattern that is a single screen line of ultrasound signal displayed over time and is used primarily to assess the motion of structures along the ultrasound beam. Doppler ultrasound is a modality that is used to determine direction and intensity of vascular flow by assessing the change in velocities secondary to the motion of the structure of interest (usually red blood cells). It is important to remember that Doppler signals are more accurate when the ultrasound signal is parallel to the direction of flow. With color Doppler, the Doppler echoes are displayed with colors corresponding to the direction of flow. With continuous wave Doppler, one assesses the summation of velocities of flow along a line of the ultrasound signal. With pulse wave Doppler, one is able to assess flow velocity in an exact location, but with the limitation of only being able to assess a restricted range of velocities. From each transducer position, the targeted structure is characterized by five major probe movements: (1) *slide* refers to motion in the long axis of the probe along the body, (2) *rock* refers to motion along the long axis of probe at a fixed point of the body, (3) *sweep* refers to motion in the short axis of the probe along the body, (4) *fan* refers to motion along the short axis of the probe at a fixed point of the body, and (5) *rotation* refers to moving the probe in a clockwise or counterclockwise direction.[7]

ASSESSMENT OF PULMONARY DISORDERS

When applicable to the condition or problem at hand, ultrasound assessment of pulmonary disorders holds potential value for the critical care physician. Ultrasound may provide noninvasive, immediate bedside

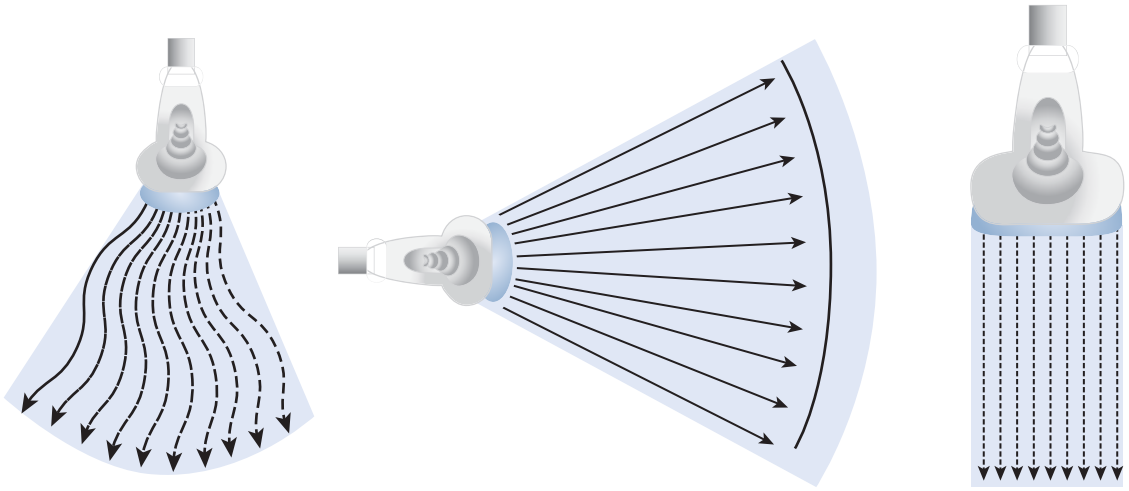

Fig. 30.1 Ultrasound Probe Types.

diagnosis, unlike a computed tomography (CT) scan, which requires transporting the patient. Ultrasound is especially useful in pregnant and pediatric patients, where minimizing radiation exposure is important. However, lung ultrasound does have some limitations. Central lung pathologies and areas under the ribs or scapula cannot be visualized. Examination of obese patients is difficult. Examination of trauma patients with subcutaneous emphysema is difficult or impossible.

Performing an ultrasound for detection of pneumothorax is a simple, easily learned technique. Studies showed that inexperienced, recently trained personnel produced high detection rates for pneumothorax.[8,9] Ultrasound of the lung relies on the physical principle that fluid collects in gravitationally dependent areas, whereas gas collects superiorly. Therefore positioning the patient appropriately for the examination is critical. In reporting the findings, the physician should specify both the patient's position (e.g., sitting, supine, right side down, or left side down) and the location of the probe. Probe placement should be posterior and inferior for detection of fluid but anterior and superior for detection of air. Although the probe can be placed transversely between two ribs, longitudinal placement with a view of the ribs is recommended because of the enhanced orientation provided by the rib shadows.

The curvilinear probe provides the best visualization of the pleural cavity. Although the lower frequency of 4–5 MHz does not allow the distinction of visceral from parietal pleura, it does permit visualization of normal lung "sliding" along the pleural surface and detection of air artifacts.

One of the initial steps in performing ultrasound of the lung is to visualize the diaphragm, which is a curvilinear hyperechoic structure that descends with every breath. The liver on the right side and the spleen on the left side serve as landmarks during this initial visualization.

A subcostal or transdiaphragmatic abdominal approach can also be used to visualize the pleural cavity, but a potential difficulty of this view is that "concave" organs, such as the spleen, may reverberate, producing artifacts that appear to be dense lesions in the pleural cavity.

A normal ultrasound image of the lung will have the following features:

1. Lung sliding: As the lung inflates or deflates, the visceral pleura moves against the parietal pleural. The ultrasound images show this to-and-fro pleural movement, called *lung sliding.* Lung sliding is more prominent at the lung bases than at the apex. It is absent in the presence of intervening pleural air (pneumothorax) or fluid (pleural effusion). Inflammation that causes adherence of the two pleural membranes will also lead to absence of lung sliding. In M-mode, lung sliding can be best seen with the muscle and parietal pleura represented as static horizontal lines above the to-and-fro movement of the visceral pleura and lung, which appears granular. This appearance on M-mode is called the *seashore sign* (Fig. 30.2).
2. A-lines: These are motionless horizontal reverberations of the pleural lining that give a regularly spaced, hyperechoic artifact on the ultrasound image.
3. B-lines: Also called *ultrasound lung comets,* B-lines may be considered the ultrasonic equivalent of radiologic Kerley B-lines that indicate lung edema. These artifacts have seven features: (1) have a "hydroaeric" comet tail, (2) are hyperechoic, (3) are well-defined, (4) arise from the pleural lining, (5) are associated with disappearance of A-lines, (6) move with lung sliding when present, and (7) feature a pattern of indefinite spreading in a cephalad direction.[10] B-lines are artifacts of water-thickened interlobular septa and indicate increasing amounts of extravascular pulmonary edema, such as occurs in congestive heart failure (Fig. 30.3).

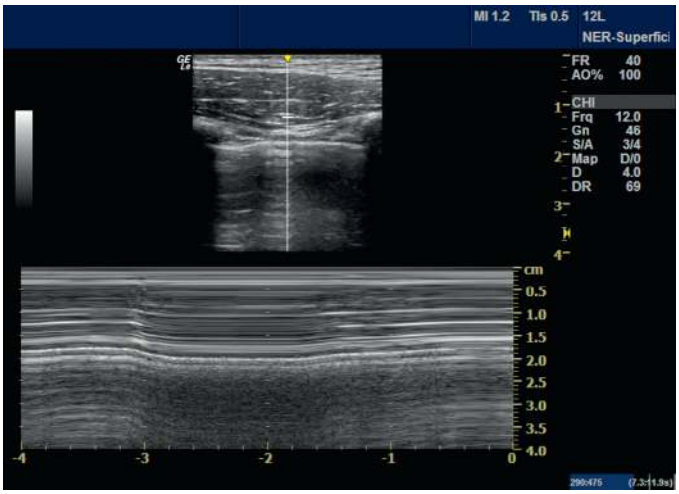

Fig. 30.2 Seashore Sign. M-mode ultrasound of normal lung.

Pleural Effusion

The pleural cavity is quite accessible to ultrasound visualization. Pleural effusions are best seen in dependent areas of the chest: that is,

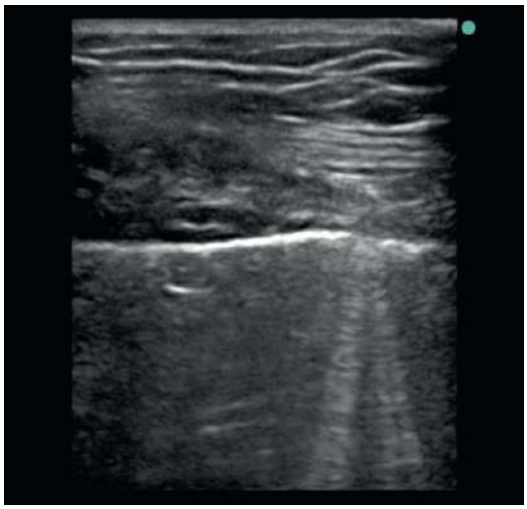

Fig. 30.3 B-line.

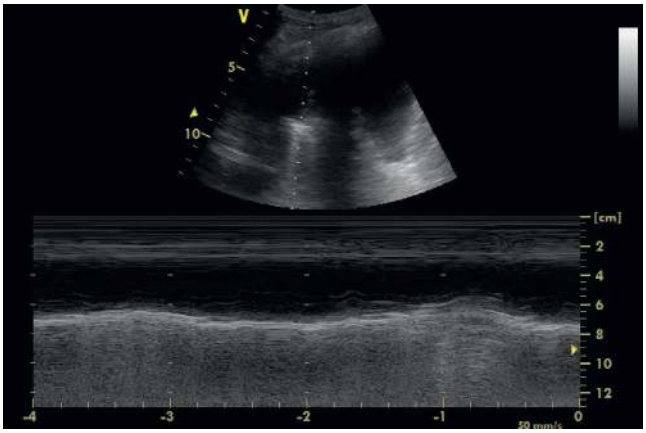

Fig. 30.4 Sinusoid Sign. The visceral pleura moves toward the parietal pleura with lung expansion, giving a sinusoidal sign on M-mode.

posterior or inferior areas. The fluid is bounded inferiorly by the diaphragm and peripherally by the visceral and parietal pleural margins. With respiration, the visceral pleura should move toward the parietal pleura, producing a sinusoid sign with M-mode, which is highly specific (97%) for the presence of a pleural effusion[11] (Fig. 30.4). At times, the lung may appear to be floating in the pleural liquid. A positive sinusoid sign can detect the presence of a low-viscosity pleural effusion, but it may be falsely negative if the pleural fluid is highly viscous.

Ultrasound is more sensitive and specific than either auscultation or chest x-ray and therefore is the method of choice to evaluate pleural effusions.[12,13] Effusions that produce a 1-cm thickness in dependent zones are easily detected, with accuracy exceeding 90%.[13] Anterior presentation of an effusion suggests that it is abundant. When large effusions are present, deeper structures can be visualized, such as a consolidated lung or the mediastinal contents. A large effusion may reveal air artifacts in the lung and allow the examiner to differentiate consolidated from aerated lung.

With experience, the examiner can estimate the volume of effusion as mild, moderate, or large. The echogenicity of an exudate allows the examiner to make an educated guess as to whether it is a transudate or an exudate; all transudates are anechoic, whereas exudative effusions are usually echogenic.

Hemothorax and purulent pleurisy present similar ultrasound patterns. Hemothorax produces an echogenic signal, indicating numerous particles floating within the effusion. In rare cases, the entire pleural cavity might be hypoechoic, mirroring the accompanying "whiteout" seen on chest x-ray. CT will be diagnostically helpful in these cases.

Ultrasound can facilitate thoracentesis. The patient should be positioned in a sitting or lateral decubitus position. It is important that the patient remain in the same position throughout the localization of the lesion and the subsequent procedure. Before performing thoracentesis, the operator should verify that the effusion is at least 1.5 cm thick and is visible over at least three intercostal spaces.[11] The operator should identify the most dependent part of the pleural cavity and carefully insert the needle under direct (real-time) ultrasound visualization, making every effort to avoid accidental puncture of other structures during the process. Ultrasound-guided thoracentesis is safe in mechanically ventilated patients.[11] After aspiration or biopsy, small pigtail catheters can be inserted and left in place for continuous drainage of the effusion.

Pulmonary Edema

Common practice in POCUS of the lung parenchyma is the evaluation of B-lines. The number of B-lines correlates with the amount of extracellular lung water and the pulmonary wedge pressure ($P < .001$).[10] Three or more B-lines in a single view are called *B+ lines* and represent interstitial edema.[14] The presence of B-lines in a patient with acute dyspnea, evaluated together with measurement of circulating N-terminal pro B-type natriuretic peptide and the Framingham criteria, helps distinguish between cardiogenic and noncardiogenic pulmonary edema ($P < .001$).[15] The presence of nine or more B-lines has been reported as 100% specific for cardiogenic dyspnea.[15] Ultrasound may be more than 90% sensitive and specific for acute cardiogenic pulmonary edema. Therefore when combined with bedside echocardiography to evaluate cardiac function, the diagnosis of congestive heart failure can be confirmed before administering a diuretic.

Lung Consolidation

Lung consolidation is associated radiographically with air bronchograms and is visualized on ultrasound as lenticular air pockets within hypodense areas of consolidated lung.

Lung ultrasound has been found to be comparable to chest x-ray in making a diagnosis of pneumonia.[16,17] The signal characteristics of pneumonic ultrasound depend on the stage of the infection. Subpleural consolidation with a treelike vascular pattern on Doppler might be present in the initial hepatization phase of lobar pneumonia. Lung sliding may be absent in the involved lobe secondary to inflammatory exudates. Later, during the resolution phase, ultrasound can detect the appearance of B-lines, which indicate increased aeration of the lung. Lung ultrasound can therefore be used to monitor the progression of pneumonia. Lung CT and ultrasound correlate closely as methods for evaluating reaeration.[18]

Pneumothorax

Ultrasound is highly accurate for detecting pneumothorax. The primary ultrasound feature is abolition of lung sliding, occasionally associated with A-lines and the absence of B-lines. In M-mode, this would give the appearance of multiple horizontal lines similar to a bar code. This nonspecific finding is seen in a number of other conditions, such as malignancy, chronic obstructive pulmonary disease (COPD), and pneumonia. More specific is the visualization of a lung point: that is, a point at which the lung and air can easily be visualized in the same M-mode image (Fig. 30.5). Moving the probe along the anterior, lateral, and posterior intercostal spaces and observation during an entire respiratory cycle at each locale can help locate a lung point. Additionally, evaluation for the absence of the lung pulse, which is an anteroposterior-directed pleural motion that is secondary to the transmission of cardiac movement across the thorax, can also help identify pneumothorax from

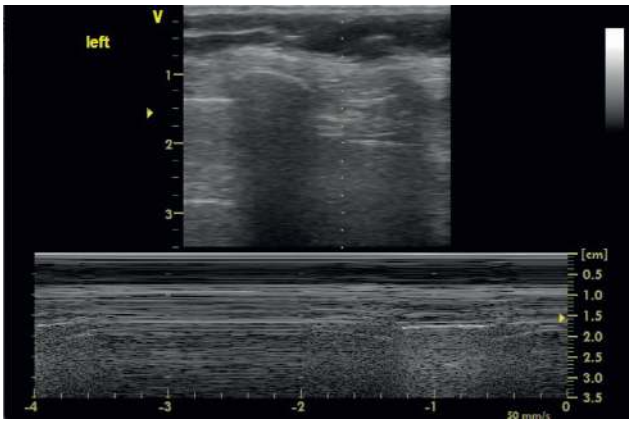

Fig. 30.5 Lung Point in M-mode. Both the bar code and seashore signs are seen as the lung point moves across the image.

other phenomena that can result in the absence of lung sliding (e.g., apnea, mainstem intubation, airway obstruction).

Chronic Obstructive Pulmonary Disease

Lung ultrasound in patients with COPD shows predominant A-lines with or without lung sliding but without a lung point. Ultrasound has an 89% sensitivity and 97% specificity for COPD.[10]

When using ultrasound to evaluate patients with dyspnea, it is advisable to first check for lung sliding and then for a lung point. The absence of lung sliding in association with the presence of a lung point indicates a diagnosis of pneumothorax. The presence of lung sliding with prominent B-lines (>3/field) indicates a diagnosis of pulmonary edema or pneumonia. The next steps are to check for the presence or absence of a dependent pleural effusion and evaluate for the presence or absence of lung consolidation. An exudative effusion, indicated by the absence of a sinusoidal sign in association with lung consolidation, favors the diagnosis of pneumonia. Absence of prominent B-lines and predominance of A-lines indicate either pulmonary embolism, worsening COPD, or pneumonia. Deep venous thrombosis (DVT) can be ruled out at this time by performing a venous examination of the lower and upper extremities. Absence of DVT and absence of any lung consolidation or pleural effusion favor the diagnosis of an exacerbation of COPD to explain the dyspnea. In patients with unclear or equivocal findings, further imaging modalities such as CT should be used.[10]

ADVANCED VASCULAR ACCESS

The use of ultrasound to aid in vascular access has advanced beyond its now-widespread use for central venous access. Specifically, ultrasound has proven to reliably aid the placement of difficult intravenous[19,20] and intraarterial catheters.[21,22] Use of ultrasound for peripheral venous access has been shown to significantly increase success rates as well.[23] A recent meta-analysis was conducted to compare an ultrasound guidance technique for central venous access with an anatomic landmark technique. That analysis indicated that ultrasound use decreased the risks of cannulation failure, arterial puncture, hematoma, and hemothorax.[24] However, it is important to emphasize that good anatomic knowledge and dynamic hand-eye-probe coordination to follow the needle tip are keys to success and avoidance of inadvertent arterial puncture.[25] Use of ultrasound has not eliminated complications related to injury of deeper structures (subclavian or vertebral artery) during insertion of internal jugular central lines.[25] This observation underlines the importance of formal training in ultrasound and simulated practice of central line placement, as supported by recently published guidelines.[25]

ADDITIONAL AREAS OF ASSESSMENT

POCUS is useful in assessing several other areas relevant to the issues faced by the critical care physician.

Deep Venous Thrombosis and Pulmonary Embolus

The current standard for evaluation of patients suspected to have DVT or pulmonary embolus involves CT pulmonary angiography and lower extremity compression ultrasonography. These tests are often performed despite a low pretest probability, and obtaining them potentially delays diagnosis.[26] A study in patients with a moderate to high probability of pulmonary embolus evaluated multiorgan ultrasound that was performed by intensivists, involved lung ultrasonography to search for subpleural infarcts, transthoracic echocardiography to detect right ventricular dilatation, and leg vein ultrasonography to detect DVT. The study reported that multiorgan ultrasound had a high sensitivity (90%) and specificity (86.2%) for the detection of pulmonary embolus.[27]

Airway Management

1. Endotracheal tube placement
   A report suggested the utility of ultrasound for verification of successful endotracheal intubation, reporting a sensitivity and specificity of 100% for the detection of successful endotracheal intubation versus esophageal intubation.[28] An evaluation of POCUS examination that included assessment for tracheal dilation with endotracheal tube cuff inflation and bilateral pleural lung sliding demonstrated a high degree of sensitivity (93%) and specificity (96%) to detect endobronchial versus tracheal intubation.[29]
2. Emergency cricothyroidotomy
   Surface landmarks for identification are often not reliable for the identification of the cricothyroid membrane, especially in obese and female patients.[30,31] Bedside ultrasound is a reliable modality for rapid identification of the anatomy for emergency cricothyrotomy (Fig. 30.6).[32]
3. Percutaneous tracheostomy placement
   Ultrasound improved success rates in accessing the trachea, with more than 90% correct placement with the first-pass attempt in a cadaveric study.[33] Real-time ultrasound has been used for percutaneous tracheostomies, with improved accuracy for midline placement of the needle.[34,35]

Gastric Volume Assessment

POCUS has also been used to assess gastric content and volume.[36,37] A grading system has been proposed based exclusively on qualitative sonographic assessment of the gastric antrum and has shown a strong correlation with predicted gastric volume (Fig. 30.7).[37] The presence of fluid in the antrum identified by ultrasound in both the supine and right lateral decubitus positions correlates with a large, clinically significant amount of gastric contents. This ability to detect gastric volume by POCUS may be useful in assessing aspiration risk.

Intracranial Pressure Estimation

POCUS has the potential to provide rapid assessment of elevated intracranial pressure (ICP), based on the measurement of the optic nerve sheath diameter. The optic nerve sheath is contiguous with the dura mater and has a trabeculated subarachnoid space through which cerebrospinal fluid circulates. The relationship between the optic nerve sheath diameter and ICP has been well established.[38,39] The sensitivity of ultrasonography in detecting elevated ICP was 100% (95% confidence interval [CI] 68%–100%), and specificity was 63% (95% CI 50%–76%).[38] An optic nerve sheath diameter of greater than 5 mm at a point approximately 2 mm from the retina suggests elevated ICP (Fig. 30.8).

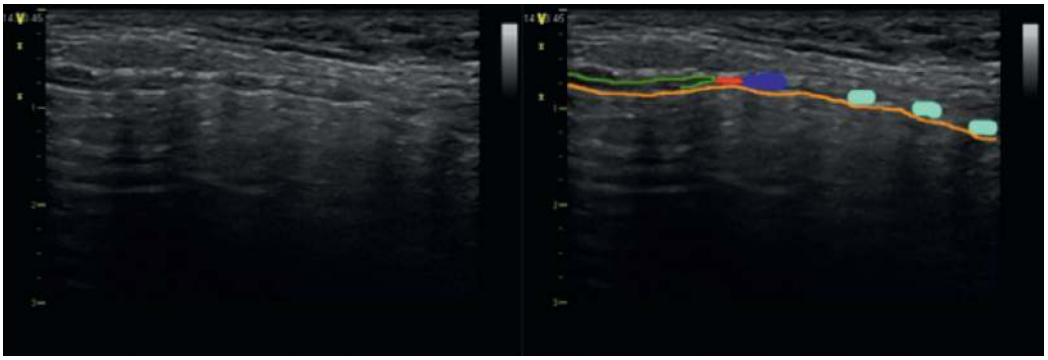

Fig. 30.6 Longitudinal Ultrasound View of the Trachea. Longitudinal midline-scan view of the neck shows the cricothyroid membrane in *red*. *Green* and *dark blue* represent the thyroid and the cricoid cartilages, respectively. The *orange lining* shows the air–tissue border between the trachea and air. *Light blue* indicates the tracheal cartilages.

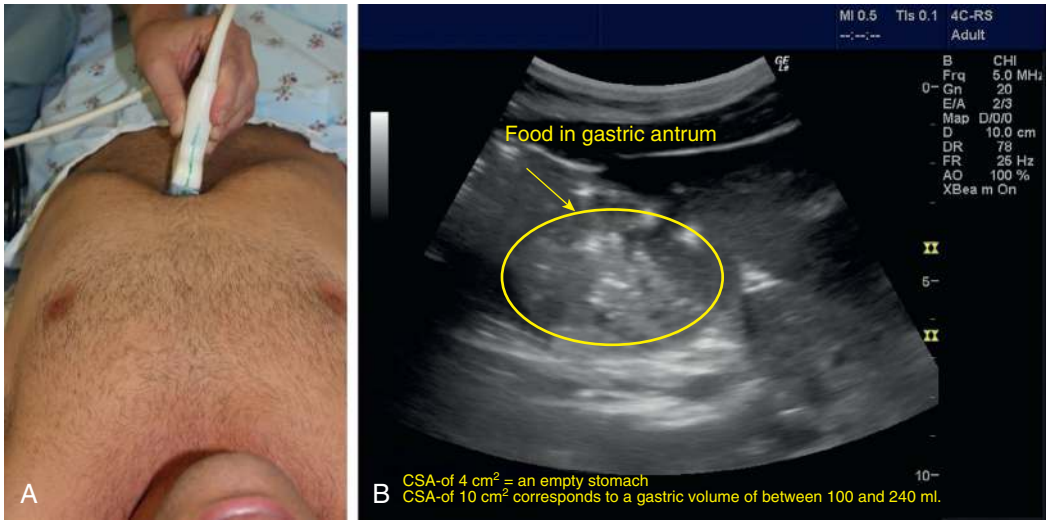

Fig. 30.7 Ultrasound of Gastric Antrum to Assess Gastric Volume. A, Probe (curved linear) position for gastric antrum acquisition. **B,** Ultrasound image.

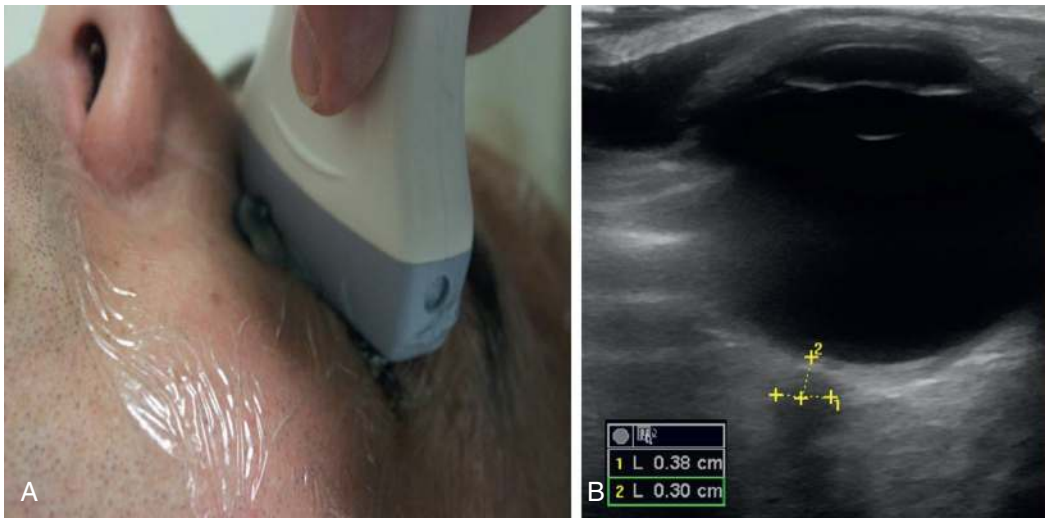

Fig. 30.8 Ultrasound of Optic Nerve Sheath Diameter. A, Probe (linear) position. **B,** Ultrasound image.

KEY POINTS

- Ultrasound instruments have steadily become less expensive and more portable, resulting in wider bedside application during physical examination to aid in clinical decision making. For this reason POCUS use and knowledge are becoming basic clinical skills for the critical care physician.
- Probe selection depends on the organ to be examined. Deeper structures need a lower-frequency probe, which allows better penetration.
- Doppler signals are more accurate when ultrasound signals are parallel to the direction of flow. Pulse wave Doppler can assess the flow velocity in an exact location, whereas continuous Doppler assesses for a summation of velocities along the line of ultrasound signal.
- Lung ultrasound allows comprehensive assessment of the pulmonary system, offering high degrees of sensitivity and specificity for the detection of pneumothorax, quantification of pleural effusion, and characterization of parenchymal air-space disease. Bedside ultrasound-guided thoracentesis is usually safe, even in mechanically ventilated patients.
- Successful and safe POCUS use for vascular access involves excellent anatomic knowledge and dynamic hand-eye-probe coordination to follow the needle tip at all times to prevent inadvertent arterial punctures and other complications.
- Evaluation for pulmonary embolus by POCUS involves a multiorgan examination including lung ultrasonography, echocardiography, and lower extremity assessment to detect DVT.
- POCUS has high sensitivity and specificity for the detection of successful endotracheal intubation in addition to identification of anatomic structures and landmarks for cricothyroidotomy and percutaneous bedside tracheostomy.
- POCUS is increasingly being used for the assessment of gastric volume and content, especially before intubation for assessing aspiration risk.

References for this chapter can be found at expertconsult.com.

ANNOTATED REFERENCES

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This article, formulated by a task force from the Society of Critical Care Medicine, reports recommendations for POCUS competency and credentialing.

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This article highlights the development of a whole-body POCUS training program, including metrics of performance and clinical utility.

Ramsingh D, Runyon A, Gatling J, et al. Improved diagnostic accuracy of pathology with the implementation of a perioperative point-of-care ultrasound service: quality improvement initiative. *Reg Anesth Pain Med.* 2020;45:95–101.
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Echocardiography

Wolf Benjamin Kratzert, Pierre N. Tawfik, and Aman Mahajan

Over the past 60 years, echocardiography has undergone substantial developments to become one of the most common modalities in the field of cardiovascular imaging. Starting in the 1980s, technologic advancements and the recognition of its potential moved echocardiographic imaging quickly into the operating room, emergency room, and intensive care unit (ICU). Today, it is fully integrated into medical subspecialties, such as anesthesiology, emergency medicine, critical care, and others.[1–3]

Several aspects differentiate critical care echocardiography from the comprehensive cardiology echocardiographic examination. Critical care echocardiography is focused on the immediate integration of diagnostic information into clinical management. In ICU patients, the interaction of heart and lung function and the presence of multiple medical interventions can make the interpretation of findings more complex. The ability to obtain adequate images can be limited. The hemodynamic profiles of patients tend to change continuously. Therefore 24-hour access to echocardiography is important.

INDICATIONS, CONTRAINDICATIONS, AND SAFETY

Indications for echocardiography, including the critical care and perioperative settings, are well established in the literature.[4–7] Although applications for echocardiography in the ICU continue to expand, the main indication remains the evaluation of hemodynamic instability and guidance of its clinical management (Table 31.1). Transthoracic echocardiography (TTE) represents the standard modality in the ICU, as it is noninvasive, readily available, and easy to use. Although TTE presents minimal risk to patients, acquiring satisfactory images is often problematic. In particular, surgical dressings, obesity, chronic obstructive pulmonary disease (COPD), and the requirement for mechanical ventilation can make imaging difficult. Problems associated with obtaining satisfactory images using TTE are the most common indication for transesophageal echocardiography (TEE) in the critical care setting, especially when patients are already intubated and sedated. Other less frequent indications are the need to diagnose cardiac valvular pathologies, endocarditis, or intracardiac thrombi or shunts. TEE requires advanced expertise and is an invasive procedure. As it carries increased risks of complications, absolute and relative contraindications are defined (Table 31.2), and risks and benefits must be considered before performing TEE.

IMPACT OF ECHOCARDIOGRAPHY IN THE ICU

Echocardiography is a valuable tool to identify the etiology of hemodynamic instability and to guide clinical management in a critical care setting.[8,9] Although some results support the view that echocardiography can affect the management of ICU patients,[10–12] definitive data regarding the impact of echocardiography on patient outcomes remain sparse.[13–15] One small study showed that using TEE to diagnose nonventricular pathologies as the etiology of hypotension was associated with improved ICU survival.[16] In a study of 220 ICU patients, Kanji and colleagues showed that therapy in subacute shock guided by limited TTE was associated with an improved 28-day survival and reduced the incidence of acute kidney injury (AKI) requiring renal replacement therapy (RRT).[17] Critical care echocardiography is increasingly accepted as a valuable tool for expedited diagnosis of emergent pathologies (i.e., cardiac tamponade, pneumothorax), serves as a noninvasive adjunct to workups of critical illness (i.e., shock etiology, fluid responsiveness), and may be informative when implementing mechanical ventilation (i.e., positive end-expiratory pressure [PEEP] titration).[1]

TRAINING, ACCREDITATION, AND INVESTIGATION

Although guidelines for training and accreditation for comprehensive echocardiography by cardiologists are well defined, similar guidelines are still evolving concerning the use of focused echocardiography by noncardiologists. Since about 2005, professional societies all over the world have been developing specific pathways and recommendations for training and accreditation requirements for focused critical care ultrasound. The first document on training and accreditation of echocardiography in intensive care developed by an international group of experts was published by the World Interactive Network Focused on Critical Ultrasound (WINFOCUS) in 2008.[18] In 2009 a working group formed by the American College of Chest Physicians and La Société de Réanimation de Langue Française published a consensus statement about competency for performing critical care ultrasonography.[19] Subsequently, an international expert group led by the European Society of Intensive Care Medicine proposed training guidelines and standardization of competency assessment for critical care ultrasonography, including echocardiography.[20] The same group published a consensus statement on the standards for advanced echocardiography in the ICU in 2014 and, recognizing heterogeneity in the existing literature, has recently emphasized the need for standardization in study design and reporting of research investigations.[21,22]

Billing

With the growing use of point-of-care (POC) echocardiography in the ICU, the question of reimbursement has been a topic of ongoing discussion. Several components of the focused critical care echocardiographic examination differ from the classic comprehensive echocardiographic examination. Physicians not fully accredited in echocardiography often perform the focused echocardiographic examination in critically ill patients, and the liability of interpretation only extends to the specific focus of the assessment. Images commonly are not stored for further clinical use. In the United States, Medicare uses the Current Procedural

TABLE 31.1 Indications for Echocardiography in the ICU

- Circulatory failure (hypotension, shock)
- Sepsis
- Low cardiac output state
- Cardiac arrest
- ACS
- Pulmonary embolism
- Suspected cardiac etiology of respiratory failure
- Aortic dissection
- Cardiac trauma
- Endocarditis
- Suspected cardiac etiology of systemic embolism
- Cardiac evaluation for potential organ donation
- Guidance and assessment of circulatory assist devices (TVPM, IABP, ECMO, VAD)

ACS, Acute coronary syndrome; *ECMO,* extracorporeal membrane oxygenator; *IABP,* intraaortic balloon pump; *TVPM,* transvenous pacemaker; *VAD,* ventricular assist device.

TABLE 31.2 Indications and Contraindications for TEE in the ICU

Indications	Contraindications
• Poor image quality in acute hemodynamic instability • Poor image quality second to severe obesity, emphysema, surgical drains/dressing • Comprehensive assessment of aortic dissection, endocarditis, valvular pathologies, prosthetic valves, intracardiac thrombus • Assessment of circulatory assist devices • Assessment of intracardiac shunt	Absolute: • Perforated viscus • Esophageal pathology (stricture, tumor, trauma, diverticulum, varices) • Recent esophageal or gastric surgery, status post esophagectomy or esophagogastrostomy • Active upper GIB • Cervical spine injury Relative: • Recent upper GIB • PUD • Coagulopathy, thrombocytopenia • Hiatal hernia

GIB, Gastrointestinal bleed; *PUD,* peptic ulcer disease.
TEE is mandatory for the comprehensive assessment of certain cardiac pathologies. In hemodynamic instability, when TTE imaging results in insufficient image quality, the intensivist has to weigh risk and benefits of performing an invasive TEE examination.

Terminology (CPT) code for the reimbursement of medical, surgical, and diagnostic services. Currently, the CPT coding does not incorporate an individual code for focused critical care ultrasound examinations, and its components do not fulfill the requirements of the standard diagnostic TTE examinations or the limited/follow-up examination, as described in their coding system. TEE requires specific competence and is performed by physicians with advanced training. When performed in the ICU, these examinations are commonly accepted using existing CPT codes for TEE examinations.[23]

POC echocardiography has the potential to reduce overall ICU costs considerably. By adding a noninvasive, less expensive diagnostic and monitoring technology, it can expedite and focus clinical management and decrease the risk to patients significantly. With standardization of critical care echocardiography training, its differentiation from the classic comprehensive training, and the increasing evidence of the benefits of POC echocardiography, a specific billing code for the focused examination is warranted.[24–26]

BASICS

Equipment

Typically, echocardiography equipment used in echocardiography laboratories and cardiac operating rooms features the newest and most advanced technologies. The most advanced equipment is not needed for use in a critical care setting. Several companies now offer machines with specific features geared toward use in emergency departments, trauma bays, or ICUs. These machines are used for the broad spectrum of critical care applications, including lung, vascular, and abdominal ultrasonography. The machines can be equipped with multiple software programs, including those useful for TTE and TEE. The ideal ICU ultrasound system is compact, portable, and durable. It requires minimal start-up time and has an easy-to-use operator interface. For routine daily use, it should have an extended battery life and internal storage capacity.

The transducers used for TTE and TEE examinations are typically phased-array transducers. They provide a frequency ranging from 1 to 10 MHz, which offers the optimal balance of penetration and resolution required to image the heart.

Knobology

Echocardiography machines have a collection of knobs and buttons to adjust image quality, use different modalities, and store images. As each manufacturer has a set arrangement of knobs, sliders, and buttons, it is essential for each operator to become familiar with the layout of the machine that he or she will use on a regular basis. The most important controls and their function are as follows:

GAIN: Adjusts overall image brightness
TIME-GAIN-COMPENSATION (TGC): Selectively adjusts sector image brightness
DEPTH: Adjusts depth of view
ZOOM: Selects specific image sector
FOCUS: Adjusts focal zone
DYNAMIC RANGE: Adjusts gray-scale to filter out background noise

Ultrasound Modalities

More so than during the examination of anatomic structures other than the heart, the use of multiple ultrasound modalities is essential for echocardiography. The most commonly used modalities in the ICU are two-dimensional (2D) imaging, motion mode (M-mode), color flow Doppler (CFD), pulsed wave Doppler (PWD), and continuous wave Doppler (CWD). 2D remains the initial and most commonly used mode of anatomic imaging and qualitative assessment of gross pathologies in the ICU. A modality less frequently used is M-mode. M-Mode represents a one-dimensional image against time and has the advantage of excellent temporal resolution, which is useful for the imaging of fast-moving structures like valvular leaflets.

When assessing hemodynamic profiles, the use of Doppler echocardiography, in addition to classic 2D imaging, provides the information needed for quantitative measurements. CFD displays blood flow velocity and direction of flow by color mapping. It combines qualitative 2D imaging with semiquantitative information about blood flow. CFD is useful for diagnosing intracardiac shunts or valvular pathologies and for seeking evidence of obstructions to blood flow. When a quantitative assessment is needed for the calculation of stroke volume (SV), cardiac output (CO), and pulmonary artery pressures (PAP), PWD and CWD are the modalities of choice. Both modes

provide information about blood flow direction and numeric estimates of blood flow velocity at the interrogated anatomic site. Whereas PWD measures blood flow velocity at the specific site of the sample volume and is limited by a certain velocity threshold called the Nyquist limit, CWD displays the maximum velocity along the whole interrogation beam without a velocity threshold. Both modalities require alignment of the interrogation beam with the direction of blood flow to minimize the underestimation of velocity caused by a suboptimal incidence angle. As with 2D imaging, several interventions can be applied to enhance Doppler quality and prevent artifacts as a result of the Nyquist limit. Most importantly, adjustment of the transducer location and frequency, sample volume depth, and movement of the baseline can maximize peak velocities with PWD.[27,28]

STANDARD VIEWS AND ANATOMY

When performing echocardiographic examinations, the position of the transducer in relationship to the body is called the *acoustic window,* and the image plane is defined as the *view*. Image planes are in reference to the point of focus, which most commonly is the left ventricle (LV).

Image Acquisition and Optimization

Following a consistent order of image acquisition minimizes the risk of missing images and pathologies and facilitates learning. Clockwise positioning and rotation of the transducer provides a simple and logical approach to the focused examination (Fig. 31.1).

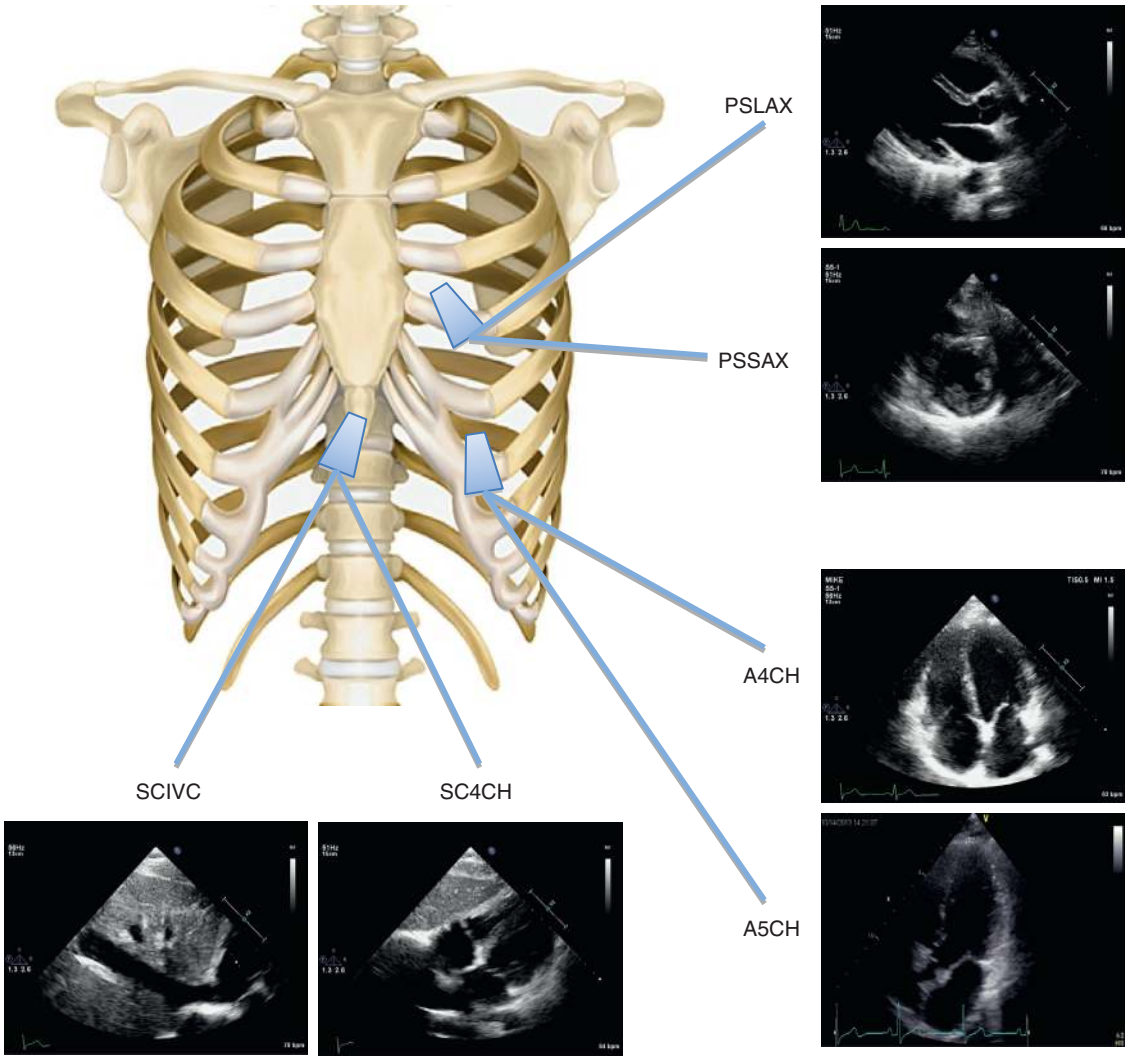

Fig. 31.1 TTE transducer position and imaging windows. Starting with the PS LAX and the probe marker toward 11 o'clock, the clockwise movement and rotation of the transducer will provide a systematic approach to obtaining acoustic windows and imaging views. Rotation of the transducer from the PS LAX view by 90 degrees clockwise will show the PS SAX view. In the PS SAX view, tilting the transducer cephalad or caudad will visualize the short axis of the AV, LV midpapillary, and LV apical. Further rotation of the transducer from 1 o'clock to 3 o'clock and movement to the apical position visualizes the A4CH view. Flattening of the transducer will show the LVOT and A5CH views. Counterclockwise rotation in the apical view will show the A2CH and A3CH views. Maintaining the probe marker in the 3 o'clock position visualizes the SC4CH view in the SC position. The slight rightward angle of the transducer provides the LAX of the IVC. *A2CH,* Apical two chamber; *A3CH,* apical three chamber; *A4CH,* apical four chamber; *A5CH,* apical five chamber; *AV,* aortic valve; *IVC,* inferior vena cava; *LAX,* long axis; *LV,* left ventricle; *LVOT,* left ventricular outflow tract; *PS LAX,* parasternal long axis; *PS SAX,* parasternal short axis.

Whether with TTE or TEE, standardized views are based on anatomic landmarks, which can be obtained at defined acoustic windows with specific transducer positions and angles. To avoid inadequate imaging and the risk of misinterpretation, knowledge of the specific anatomic landmarks defining each view is pertinent. In addition, the following techniques should always be used to optimize imaging. Body position: Extension of the left arm opens up the parasternal windows, and a slight left-side tilt can bring the cardiac apex closer to the chest wall. Flexing the legs at the hip facilitates the acquisition of subcostal windows. Image acquisition: Small changes in transducer position and angle, a change in the intercostal space above or below, and the use of TEE can provide improved imaging. Machine setting: Aside from adjusting gain, TGC, and dynamic range, precisely adjusting the focus and depth to the region of interest (ROI) is critical. In addition, using the zoom feature can be helpful. Especially in Doppler modes, these adjustments can improve measurements and avoid Doppler aliasing. Another option for improving image quality is contrasted echocardiography.[29] Even though not commonly used by intensivists when performing focused ICU examinations, injection of contrast media can significantly enhance opacification of the right and left ventricular chambers and enhance the definition of the endocardial border.[30]

Transthoracic Echocardiography

In TTE, three standard acoustic windows are used: the parasternal, apical, and subcostal positions (see Fig. 31.1). A fourth position called *suprasternal* is additionally used during comprehensive examinations and in the pediatric population.

Standard Transthoracic Views

The focused echocardiographic examination in the ICU commonly includes five major views: (1) the parasternal long-axis (PS LAX), (2) the parasternal short-axis (PS SAX), (3) the apical four-chamber (A4CH), (4) apical five-chamber (A5CH), and (5) the subcostal long-axis (SC LAX) (Table 31.3).[18,21]

PS LAX is obtained by positioning the transducer in the left third or fourth intercostal space (ICS), along the anterior midclavicular line, with the transducer marker directed toward the right shoulder (see Fig. 31.1). This view is primarily used to evaluate LV and right ventricle (RV) size and systolic function and to obtain quantitative measurements of ventricular size and wall thickness by the M-mode. The mitral valve (MV) and aortic valve (AV), including the left-ventricular outflow tract (LVOT) and aortic root, can be assessed with 2D and CFD for regurgitation, stenosis, or dynamic outflow obstruction. Additionally, this view can be used for the visualization of pericardial pathologies.

PARASTERNAL SHORT-AXIS VIEWS are obtained in the same transducer position as the parasternal long-axis view, with the transducer rotated 90 degrees clockwise and the marker directed toward the left shoulder (see Fig. 31.1). Within this view, multiple planes of the heart can be imaged depending on the tilt of the transducer. When tilting the probe from superiorly to inferiorly, visualization starting with the short axis of the AV over the basal and mid-SAX of the LV down to the apical segment of the LV is possible. This view is best used for the evaluation of LV size and systolic function. It is optimal for describing regional wall motion abnormalities, as all territories of coronary perfusion can be visualized simultaneously. In addition, the basal AV SAX view can provide information about the tricuspid valve (TV), including measurements of right ventricular systolic pressure (RVSP) by CWD.

APICAL VIEWS provide images of all four chambers (see Fig. 31.1). Most commonly used in the ICU are the A4CH and A5CH views. With the transducer positioned at the apex of the heart, commonly in the sixth or seventh ICS along the anterior axillary line, the probe marker is directed toward the left axilla. With tilting of the probe superiorly, the 4CH and 5CH views are obtained.

The 4CH view is used for the assessment of atrial and ventricular chamber sizes, biventricular systolic function, and regional wall motion abnormalities. Because of the optimal incidence angle and visualization of the TV, MV, and AV in the 4CH and 5CH views, quantitative

TABLE 31.3 Standard TTE Views, Anatomic Structures Seen, and Their Common Use

Standard TTE Views	Structures	Common Assessment
PS LAX	LA, LV, RV, MV, AV, LVOT, Desc Ao	LV and RV size, LV and RV systolic function, RWMA, AV and MV pathologies, LVOT obstructions (SAM), pericardial effusion/clot/tamponade, pleural effusion, LVOT diameter for SV calculation, aortic dissection and aneurysm
PS SAX AV	LA, RA, RV, PA, AV, TV, PV	AV pathologies, RV size and systolic function, TV pathologies, RVSP, intracardiac shunts, catheters/PM leads/cannulas
*PS SAX MID-PAP	LV, RV	LV size and systolic function, RWMA, pericardial effusion/clot/tamponade
*A4CH	LA, RA, LV, RV, MV, TV	LV and RV size, LV and RV systolic function, RWMA, LA and RA size, MV and TV pathologies, RVSP, TAPSE
A5CH	LA, RA, LV, RV, LVOT, AV, MV	LVOT obstructions (SAM), VTI LVOT and AV, AV pathologies
A2CH	LA, LV, MV	RWMA, MV pathologies
*SC SAX	RA, LA, RV, LV, diaphragm	Pericardial effusion/clot/tamponade, RV size and systolic function, RA size, catheters/PM leads/cannulas
*SC IVC LAX	IVC	Volume status, pericardial effusion/clot/tamponade
SC IVC SAX	IVC, Desc Ao	Volume status, pericardial effusion/clot/tamponade, aortic dissection and aneurysm, IABP

2CH, Two chamber; *4CH,* four chamber; *5CH,* five chamber; *A,* apical; *AV,* aortic valve; *Desc Ao,* descending aorta; *IABP,* intraaortic balloon pump; *IVC,* inferior vena cava; *LA,* left atrium; *LAX,* long axis; *LV,* left ventricle; *LVOT,* left ventricular outflow tract; *MV,* mitral valve; *PM,* pacemaker; *PS,* parasternal; *RA,* right atrium; *RV,* right ventricle; *RWMA,* regional wall motion abnormalities; *SAM,* systolic anterior mitral valve leaflet motion; *SAX,* short axis; *SC,* subcostal; *TV,* tricuspid valve; *VTI,* velocity-time interval.
As seen, the PS SAX, A4CH, and SC SAX in combination provide most information needed in the acute situation. Additional views for hemodynamic assessment are added to show the most common views used in the ICU.

measures by M-mode, CFD, CWD, and PWD are best obtained from the apical position. These views are mostly used by intensivists for quantitative evaluation of RV function and RVSP, LV cardiac output, and diastolic function, in addition to the evaluation of valvular pathologies by spectral-Doppler echocardiography.

From the 4CH position, a counterclockwise rotation of the transducer by 90 and 110 degrees will visualize the apical two-chamber (A2CH) and three-chamber views (A3CH), which completes the visualization of all LV wall segments when combined with the 4CH view.

SUBCOSTAL VIEWS are obtained by positioning the transducer in the subxiphoid or subcostal position while maintaining the marker directed toward the left lateral side of the patient. Aiming the probe toward the left shoulder and maintaining it flat on the abdomen, the heart is cut in a horizontal plane, showing all four chambers and particularly the RV free wall (see Fig. 31.1). A 90-degree rotation of the transducer counterclockwise while slightly aiming the probe toward the right shoulder will visualize the inferior vena cava (IVC) and its junction into the RA. These views can provide information about pericardial pathologies, such as pericardial effusion and tamponade. When angled slightly toward the right and caudad, global volume status can be assessed by measuring IVC diameter and dynamic collapse with respiratory variation (see Fig. 31.1).

Transesophageal Echocardiography

In the past, the use of TEE in a critical care setting was restricted by availability, technical issues, and the need for operator expertise. With improvements in equipment and growing expertise among intensivists, the use of this modality is increasing. Superior image quality and the ability to evaluate for certain pathologies remain the advantages of TEE over TTE.[31]

Safety of Transesophageal Echocardiography

TEE in ambulatory and nonoperative settings has an incidence of adverse events of between 0.2% and 0.5% and a mortality rate of <0.01%.[32] TEE in the ICU has slightly higher morbidity and mortality. Multiple studies show that the incidence of adverse events ranges from 1.6% to 5%.[16,33–35] In a review of 20 studies, Hüttemann and colleagues reported that the incidence of TEE-related complications in the ICU was 2.6%; there were no TEE-related deaths.[36] The main complications associated with TEE are arrhythmias, hypotension, airway compromise, and bleeding. These complications are more likely to occur in critically ill patients as compared with relatively healthier subjects because ICU patients often are hemodynamically unstable or already prone to hemorrhage. Nevertheless, if the operator is cognizant of the potential complications and takes pains to weigh the risks versus the benefits carefully, TEE can be performed safely in the ICU. Preparation of the patient before TEE is important. First, the indications for and specific questions to be answered by the examination have to be defined. Second, potential contraindications to TEE, such as recent esophageal or gastric surgery or active upper gastrointestinal bleeding, must be ruled out. Third, coagulation status must be assessed and abnormalities corrected, if possible. Fourth, nil per os (NPO) status must be assured. Fifth, the mode of sedation, the need for administration of paralytic agents, and airway protection have to be addressed. When performing the examination, insertion and manipulation of the probe should be tailored to the patient's condition and coexisting risk factors.

Standard Transesophageal Views

The TEE examination in the perioperative setting includes 20 standard views.[37] TEE in the ICU rarely requires a comprehensive examination. Several different protocols have been proposed for the focused TEE examination in critically ill patients, emergency room patients, or acute intraoperative emergencies.[38,39] The goal of the focused examination remains the same as with TTE, and unless prohibited by the severity of the situation, acquisition of standardized views should be obtained.

Although a comprehensive TEE examination uses views at four levels of the esophagogastric tract, the two main depths used during the focused examination are the midesophageal and transgastric planes. The midesophageal level provides optimal views for specific anatomic evaluation of cardiac structures, as the transducer is near the heart. Transgastric views are mainly used for quick evaluations of LV size, systolic function, and wall motion abnormalities. In addition, spectral-Doppler of the AV is performed in the deep transgastric view, as the incidence alignment angle is best in this location. The transgastric view can also show loculated or dependent pericardial effusions, which may be difficult to see in the midesophageal views.

HEMODYNAMIC ASSESSMENT

Echocardiography represents a method for the immediate diagnosis, management, and monitoring of hemodynamic profiles in critically ill patients. With an examination that rarely takes more than a few minutes to complete, echocardiography can provide the intensivist with anatomic information about the critically ill patient's intravascular volume status, the presence or absence of various forms of cardiac pathologies (e.g., pericardial effusion and tamponade; regional wall motion abnormalities), myocardial contractility, and ventricular dimensions. For the subsequent interpretation and use of this information, it is pertinent to incorporate the influence of concurrent pathologies and medical treatments on echocardiography findings. Especially common factors, such as arrhythmias, vasopressor or inotropic support, and mechanical ventilation, need to be considered during the qualitative and quantitative hemodynamic assessment.[40]

Cardiac Preload and Fluid Responsiveness

As the management of the critically ill patient has evolved, the question of volume (i.e., preload) responsiveness has taken priority over static parameters like central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP).[9] Many experts are skeptical about the clinical utility of static pressures for guiding the hemodynamic management of critically ill patients. Neither CVP nor PAOP is a good predictor of preload responsiveness (i.e., an increase in CO or SV after bolus administration of intravenous crystalloid or colloid solutions). With the validation of echocardiography, bedside examination is increasingly replacing invasive monitoring in the contemporary evaluation of cardiac preload and prediction of volume responsiveness.[9,41] While visualizing with echocardiography, a passive leg-raise maneuver (rapidly changing patient position for head of the bed from 30–45 degrees to 0 degrees while elevating the lower limbs to 30–45 degrees, thus moving 250–350 mL of blood from the leg to the heart) has proven to be a reliable technique to assess fluid responsiveness.[42,43] One meta-analysis of 23 studies and 1013 patients calculated a pooled sensitivity of 86%, specificity of 92%, and a summary Area under the curve receiver operating characteristics (AUROC) of 0.95 for the passive leg raise.[44] Cardiac output changes can be assessed after 1–2 minutes after the maneuver.[45] Assessment of IVC diameter and the collapsibility, cardiac chamber size, and ventricular outflow tract stroke volume (LVOT SV) measurements are among the most common methods used for qualitative and quantitative evaluation of these parameters.[46] Vignon and colleagues performed a multicenter prospective trial using passive leg raise and various echocardiographic indices to assess fluid responsiveness. Respiratory variation of the maximal Doppler velocity in the LVOT was the most sensitive indicator, and respiratory variation

of the superior vena cava diameter was the most specific in predicting fluid responsiveness.[47] However, both require the semi-invasive TEE.

Assessment of IVC size and its dynamic variation during changes in intrathoracic pressure with mechanical ventilation is the least laborious and the most common way for using echocardiography to evaluate cardiac preload and volume responsiveness in ICU patients. The average diameter of the IVC is 17 mm. The absolute IVC diameter by itself, unless <10 mm or >20 mm, does not correlate well with right atrial pressure (RAP) or preload responsiveness.[48] However, dynamic changes in the IVC diameter because of respiration can provide information about preload responsiveness.[46,48,49] Barbier and colleagues showed that dynamic changes in IVC diameter of >18% predict fluid responsiveness with a sensitivity and specificity of 90%–93%.[50] Feissel and colleagues confirmed these findings with a slightly different index of IVC collapsibility, showing a sensitivity and specificity of 90%–92%, respectively.[48] At the subcostal acoustic window, optimal measurements of the IVC diameter are made using the M-mode in the short-axis view. When interpreting information derived from IVC diameter measurements, it is important to incorporate the effects of atrial arrhythmias, significant tricuspid regurgitation, atrial shunting, or increased intraabdominal pressure on the appearance of the IVC.

Imaging of cardiac chamber size is routinely used in conjunction with other measurements to assess qualitatively intravascular volume status. The most common measurements are LV end-diastolic diameter (LVEDD) and the left ventricular end-diastolic area (LVEDA) using the SAX view of the LV (Fig. 31.2). Attention should be paid to poor image quality and foreshortening of the chamber, as these worsen endocardial border definition and lead to false calculations. Although the measurement of LVEDA provides a reliable estimation of left-ventricular volume in most patients,[51] low LVEDA does not necessarily indicate systemic hypovolemia; other causes of low LV preload must be considered. Other potential causes of impaired LV diastolic filling include loss

FS = [(EDD– ESD) / EDD] x 100

FAC = [(EDA – ESA) / EDA] x 100

Example:

FS_{LV} = *[(6.0 – 4.5) / 6.0] x 100*
= *25 %*

FAC_{LV} = *[(18.5 – 7.3) / 18.5] x 100*
= *60 %*

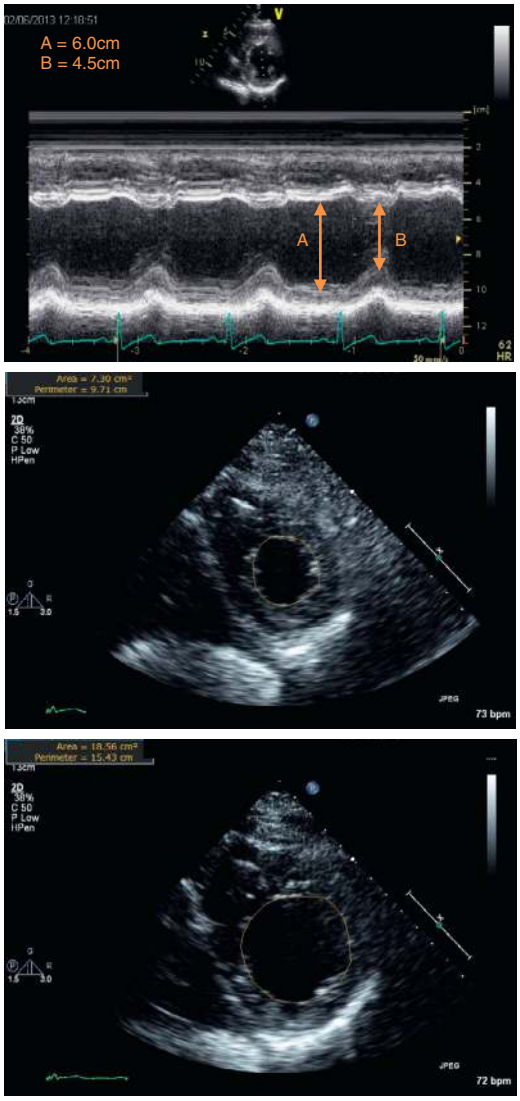

Fig. 31.2 Chamber size and semiquantitative calculation of left ventricular function. Fractional shortening methods used LV end-diastolic and end-systolic diameter from PS LAX or PS SAX midpapillary to calculate percentage value. Normal FS values are 25%–45%, correlating to normal ejection fraction. Fractional-area-change values correlate directly with ejection fraction. Measurements of area are taken from PS SAX midpapillary view. *EDA,* End-diastolic area; *EDD,* end-diastolic diameter; *ESA,* end-systolic area; *ESD,* end-systolic diameter; *FAC,* fractional area change; *FS,* fractional shortening; *PS LAX,* parasternal long axis; *PS SAX,* parasternal short axis.

of atrial contraction caused by arrhythmias, right ventricular dysfunction, and MV dysfunction. Apart from situations of severe hypovolemia,[52,53] quantitative measurements of left or right ventricular chamber size have not been shown to correlate reliably with cardiac preload and volume responsiveness.[54] Dynamic changes in LVEDA, however, correlate with volume responsiveness.[55]

Stroke Volume and Cardiac Output

Left-ventricular stroke volume (LV SV) and CO can be calculated using echocardiography.[56,57] Whereas CO measured by thermodilution is a reflection of right-sided CO, measurements with echocardiography use left-sided inflow and outflow at the level of the , LVOT, and AV. In addition, newer noninvasive modalities are based on PWD of aortic blood flow to assess cardiac output.[36] Although all of these anatomic locations have been validated in the literature, calculations using LVOT and AV are the most accurate when compared with the thermodilution method.[56,58] The continuity equation is used to calculate LV stroke volume by measuring LVOT diameter and LVOT velocity-time interval (VTI). Moreover, measurements by TTE are best obtained in the PSLAX and A5CH views. Once LV SV is calculated, multiplication by the heart rate (HR) provides CO (Fig. 31.3). As LV SV is dependent on the LV preload, limitations affecting LV filling, as mentioned earlier, have to be considered when calculating SV and CO.[59]

Right and Left Ventricular Afterload

With the ability to determine pressure gradients and flow in the heart by echocardiography, pulmonary vascular resistance (PVR) and systemic vascular resistance (SVR) can be indirectly calculated using the following equation:

$$\text{Resistance} = \Delta P/CO$$

Based on this concept, several small studies have shown an adequate correlation using transvalvular gradients at the TV and MV to calculate pulmonary and systemic vascular resistance. Clinically cumbersome and without broad validation in the literature, these methods are not used on a routine basis in the ICU. In clinical practice, qualitative aspects seen on echocardiography are used to assess SVR. Best seen in the LV SAX view, a hyperdynamic ventricle in the setting of normovolemia suggests a low SVR. From this view, measurement of LVEDD and visual estimation of LV contractility can be used for fast and easy qualitative SVR estimation.[60]

For the assessment of PVR at the bedside, indirect calculation of PAP by tricuspid regurgitation (TR) jet, when present, is commonly achieved using the modified Bernoulli equation (Fig. 31.4). Measurement of peak TR_{vel}, when added to RAP, provides an estimate of RVSP that correlates well with systolic pulmonary artery pressure (SPAP) in the absence of tricuspid or pulmonary valve pathology.

Left Ventricular Systolic Function

Assessment of LV systolic function is one of the key elements of the ICU echocardiographic examination. Not only can an assessment of LV systolic function provide information about the etiology of circulatory or respiratory failure, but it also can be used to guide and monitor ensuing medical management. Multiple methods are available for the echocardiographic evaluation of LV function (Table 31.4). In an acute setting, the fastest and easiest assessment of myocardial function and ejection fraction uses qualitative or semiquantitative methods. For the qualitative assessment, thickening of the myocardium and endocardial inward motion in the LV SAX view are used to estimate systolic function. Caution must be taken when the LV is small or there is significant LV hypertrophy (LVH), as LV function appears different depending on the intracavitary size. A simplified classification scheme for LV function

$$A_{LVOT} = D_{LVOT}^2 \times 0.785$$

$$SV_{LVOT} = A_{LVOT} \times VTI_{LVOT}$$

$$CO = SV \times HR$$

Example:

A_{LVOT} = $(1.9\ cm)^2 \times 0.785$
= $2.8\ cm^2$

SV_{LVOT} = $2.8\ cm^2 \times 25\ cm$
= $70\ cm^3$

CO = $70\ mL \times 80\ bpm$
= $5600\ mL/min$

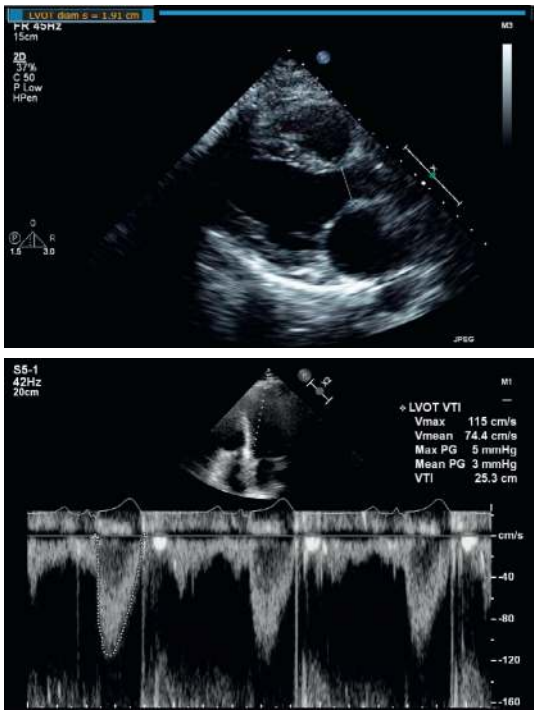

Fig. 31.3 LV SV and CO calculation. When LVOT diameter is measured in the PS LAX view, the LVOT area can be calculated. LVOT VTI is measured using PWD in the A5CH view. As seen in this example, the LV SV is 70 mL. When multiplying with an HR of 80 bpm, a CO of 5.6 L/min is estimated. A_{LVOT}, LVOT area; *CO,* cardiac output; D_{LVOT}, LVOT diameter; *HR,* heart rate; *LVOT,* left ventricular outflow tract; *SV,* stroke volume; *VTI,* velocity-time interval.

$$RVSP = (TR_{PEAK})^2 + RAP$$

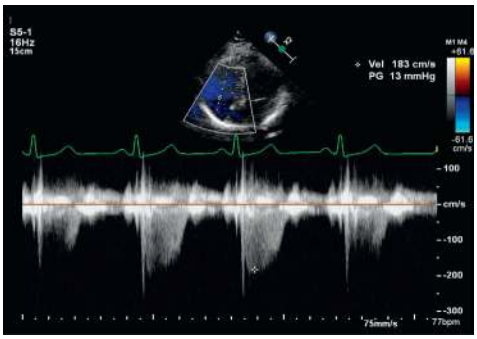

Fig. 31.4 RVSP measurement using the TR jet. After optimal alignment of the Doppler beam with the TR jet in the A4CH view, RVSP can be calculated by adding the square of the TR peak velocity in m/s to the RAP. When estimating an RAP of 10 mm Hg, RVSP in this example would be 23 mm Hg. *RAP,* Right atrial pressure; *RVSP,* right ventricular systolic pressure; *TR,* tricuspid regurgitation; TR_{PEAK}, peak velocity of TR jet.

TABLE 31.4 Methods for Assessment of the LV and RV

LV ASSESSMENT	NORMAL VALUES	
Assessment of LV Size	**Male**	**Female**
*LV size (midpapillary diameter)	EDD: 40–60 mm ESD: 25–40 mm	EDD: 35–55 mm ESD: 20–35 mm
Assessment of LV Systolic Function Qualitative		
Semi-quantitative		
*FS	25%–45%	
*FAC	35%–65%	
Quantitative		
2D volumetric EF	>55%	
3D volumetric EF	>55%	
*LV wall thickness	<10 mm	
dP/dt	>1200 mm Hg/sec	
Assessment of MR		
*Extent/quality of MR		
RV ASSESSMENT	**NORMAL VALUES**	
Assessment of RV size		
*RV size (RV basal EDD)	>4.2 cm	
*RV to LV ratio	>0.8	
Assessment of RV Systolic Function *Qualitative		
*FAC	35%–65%	
*TAPSE	>20 mm	
*RV wall thickness	<5 mm	
RV MPI	<0.40	
RV S′	>10 cm/s	
dP/dt		
3D RV EF		
Assessment of TR		
*Extent of TR		
*RVSP		

EDD, End-diastolic diameter; *EF,* ejection fraction; *ESD,* end-systolic diameter; *FAC,* fractional area change; *LV,* left ventricle; *MPI,* myocardial performance index; *MR,* mitral regurgitation; *S′*, velocity of RV free wall or TV annulus by PWD; *TAPSE,* tricuspid annular plane excursion. *Most commonly used methods in the ICU.

TABLE 31.5 Echocardiographic Signs Suggestive of Pericardial Tamponade

PERICARDIAL TAMPONADE

- Effusion/clot on echo
- Dynamic collapse of RA ÔÇ± RV
- IVC plethora
- Exaggerated transvalvular flow patterns of tricuspid and mitral valve >25% with respiration
- Increase in interventricular dependence with respiration

IVC, Inferior vena cava; *RA,* right atrium; *RV,* right ventricle. Respiratory-induced pulsus paradoxus with exaggerated changes in flow >25% is seen in mitral or tricuspid valve Doppler flow.

(i.e., hyperdynamic, normal, moderately depressed, or severely depressed) is usually sufficient in a critical care setting, and several authors have shown that little training is required to make this assessment reliably.[61,62] When performed by an experienced echocardiographer, estimates of LVEF correlate well with quantitative measurements.[63,64]

Semiquantitative measurements can be obtained using the LV SAX view by calculating fractional shortening (FS) or fractional area change (FAC) (see Fig. 31.2). Because this view only visualizes one plane of the myocardium, additional qualitative assessments of the complete LV should be performed to avoid errors resulting from coexisting regional wall motion abnormalities (RWMAs).

A more accurate (but more time-consuming) assessment of LV systolic function can be made by volumetric measurements. Both the area-length formula and Simpson's method reliably estimate LVEF.[65]

Right Ventricular Systolic Function

Compared with the assessment of LV function, assessment of RV function is more complex, as ventricular compliance, wall thickness, systolic function, and TV function are more closely linked.[66,67] Significant RV systolic dysfunction often presents with RV dilation and TV regurgitation. Simultaneously, normal RV function can be observed with RV dilation and significant TV regurgitation when the RV has time to adjust to chronically increased afterload by wall hypertrophy. Additionally, the RV has a complex geometric structure, making volumetric measurements and imaging difficult. For these reasons, an assessment of RV function is currently done using a combination of qualitative and semiquantitative measures (Table 31.5). Image acquisition is best using the PS LAX and A4CH views. Semiquantitative measures only assess certain regions of the ventricle, and caution must be taken not to extrapolate these findings. FAC is

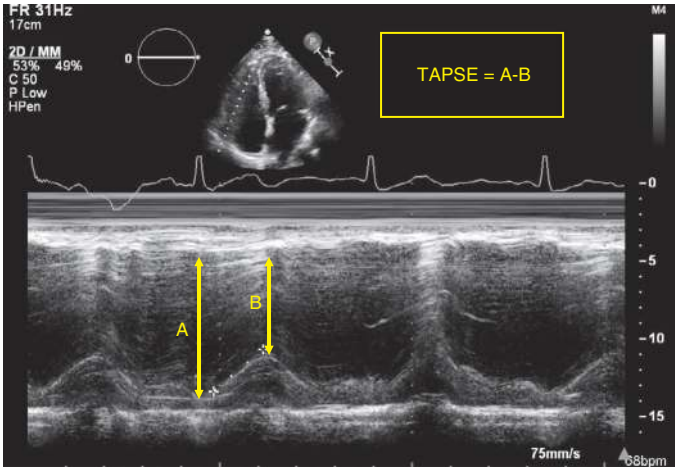

Fig. 31.5 Tricuspid annular plane systolic excursion (TAPSE). The distance of the tricuspid annulus from the apex is measured in the A4CH view. Subtraction of systolic from diastolic distance results in the TAPSE value. Normal values are greater than 20 mm.

currently recommended for semiquantitative calculation of RVEF, as traditional 2D methods assume symmetry of the ventricular structure,[68,69] and 3D methods are still being validated. Tricuspid annular plane systolic excursion (TAPSE) is easily obtained by TTE and is commonly used in combination with other methods (Fig. 31.5). RVSP, as described earlier, can reflect the ability of the RV to generate pressure and indirectly provides information about RV function. It is important to correlate measurements with factors that affect RV preload, PVR, and valvular function before making clinical judgments. Conditions that are commonly encountered in the ICU, such as acute respiratory distress syndrome (ARDS), acute pulmonary edema, volume overload, and arrhythmias, influence measured RVSP and often render it otherwise uninterpretable.[69,70]

CIRCULATORY FAILURE

Systematic Approach to Circulatory Failure

Circulatory failure is one of the most common indications for echocardiography in the ICU.[5,71] Several algorithms for hemodynamic assessment and management of circulatory failure by echocardiography have been described.[72–74] The algorithm should include the following steps: (1) seek to identify gross pathologies, such as cardiac tamponade, abnormal myocardial function, or marked hypovolemia or hypervolemia; (2) determine volume responsiveness and signs of low SVR; and (3) look for more subtle etiologies for hemodynamic instability like valvular pathologies (Fig. 31.6). Even though the clinical context will initially prompt evaluation for specific pathologies, it is important to perform a systematic assessment to avoid overlooking coexisting or complicating pathologies that need to be addressed or managed. When patients are being treated with inotropic agents or vasopressors, the echocardiographic findings must be interpreted in this context. The

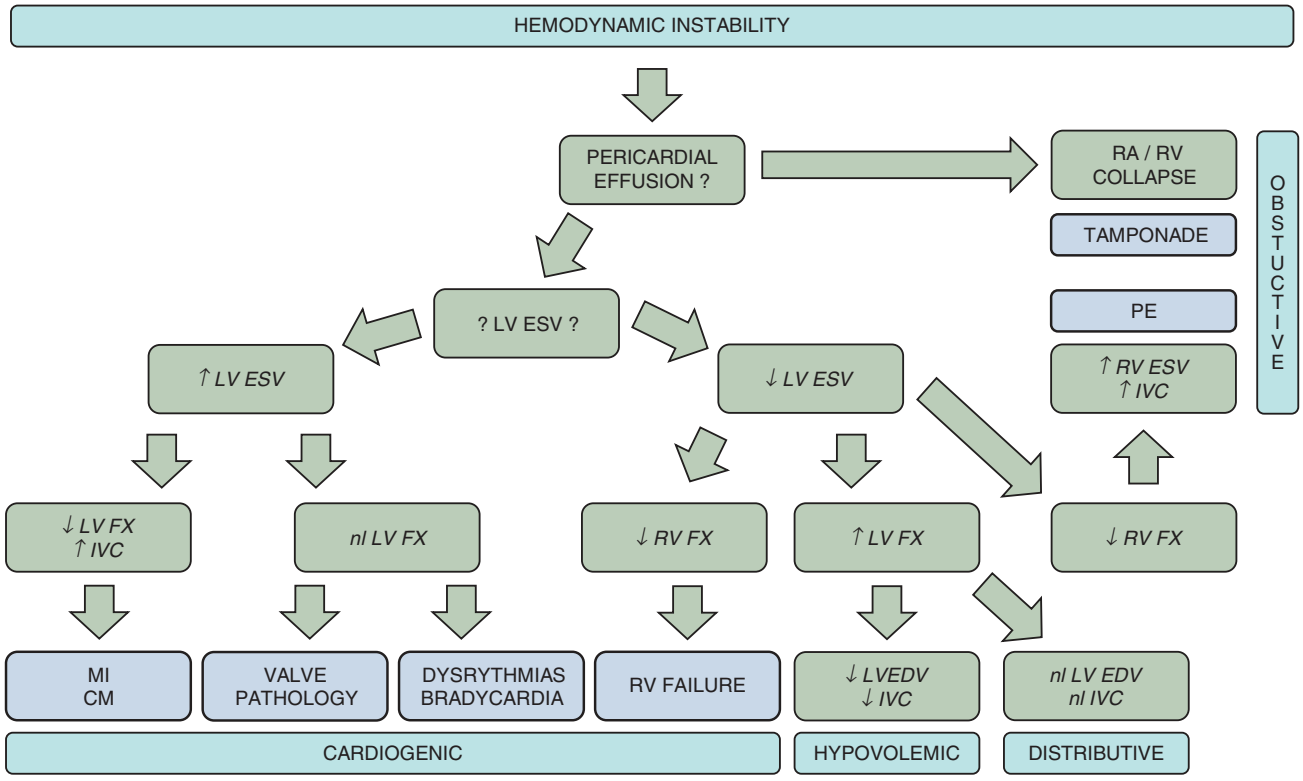

Fig. 31.6 Algorithm for the echocardiographic assessment of hemodynamic instability. After initial 2D assessment for hemodynamic-compromising pericardial effusion, evaluation of LV and RV size in systole and diastole and LV and RV systolic function is performed. Differentiation in cardiogenic, distributive, hypovolemic, or obstructive etiology of shock is often possible by following this algorithm. *CM,* Cardiomyopathy; *EDV,* end-diastolic volume; *ESV,* end-systolic volume; *FX,* systolic function; *IVC,* inferior vena cava; *LV,* left ventricle; *MI,* myocardial ischemia; *nl,* normal; *RA,* right atrium; *RV,* right ventricle; ↑, increased/hyperdynamic; ↓, decreased/depressed.

concurrent presence of different types of shock can complicate the hemodynamic assessment and the interpretation of echocardiographic findings. As myocardial function and SVR are pharmacologically altered, the underlying etiology for hemodynamic dysfunction may be obscured. Apparently normal ventricular function in the setting of sepsis can be observed with concomitant myocardial depression. Moreover, hyperdynamic ventricular function can be seen in both sepsis and hypovolemia. Therefore it is essential to correlate echocardiographic findings with the overall clinical picture. Table 31.6 shows the integration of echocardiographic findings and invasively measured values in different states of shock.

When monitoring clinical management, serial imaging must be performed and findings compared with previous ones. Additionally, management should be correlated to the overall picture, as not every patient with a certain hemodynamic disorder benefits from the same specific treatment.

Hypovolemic Shock

Hypovolemic shock is the result of an absolute or relative decrease in circulating volume secondary to volume loss or maldistribution. Echocardiography can identify intravascular hypovolemia and volume responsiveness using several approaches.[9] As described earlier, the IVC, LVEDD or LVEDA, and variation in LV SV are among the most used indicators (Fig. 31.7). An IVC diameter of <10 mm and significant changes in the IVC diameter with positive-pressure ventilation reflect systemic hypovolemia and suggest volume responsiveness.[48,50] If the EDD is <25 mm with hyperdynamic LV systolic function and "kissing" papillary muscles are seen during systole, then significant LV hypovolemia is present (Video 31.1).[52] Variations in LV SV reflected by changes in LVOT velocity predict the volume responsiveness. A change in LVOT V_{MAX} of >12% and a change in VTI_{LVOT} of >20% is seen in fluid responders.[75]

Cardiogenic Shock

Left heart failure resulting from systolic dysfunction is usually associated with low LVEF, low CO, systemic volume overload, and signs of pulmonary and hepatic congestion. Echocardiography can evaluate pathognomonic findings for heart failure and cardiogenic shock and possibly provide insights regarding etiology. Global myocardial dysfunction causing cardiogenic shock can be recognized when combining qualitative with supporting echocardiographic and clinical findings. Strong indicators for cardiogenic etiology of shock include enlarged LV size, qualitatively depressed LV function, FS <25%, low ejection fraction by FAC, and low CO by LVOT Doppler measurements.[76]

When assessing specific etiologies of cardiogenic shock, significant new RWMA and new or worsening mitral regurgitation can suggest acute myocardial ischemia (Video 31.2). Valvular pathologies, dynamic LVOT obstruction, and cardiac tamponade can cause hemodynamic instability, and these problems can be diagnosed using

TABLE 31.6 Echocardiographic and Hemodynamic Profiles in Different Shock States

	ECHO					INVASIVE MONITORING			
Type of Shock	Cardiac Function	LVESA	LVEDA	IVC	2D	Pulse Pressure	PAP	RAP CVP	SVO_2
Distributive	↑	↓	↓ / nl	↓ / nl		wide	nl	↓ / nl	↑
Hypovolemic	nl / ↑	↓	↓	↓		narrow	↓	↓	↓
Cardiogenic	↓	↑	↑	↑		narrow	↑	↑	↓
Obstructive Tamponade	nl / ↑	↓	↓	↑	Effusion/clot RA/RV collapse	narrow	nl	↑	↓
Obstructive PE	LV ↑ RV ↓	LV ↓	LV ↓	↑	RA/RV dilation RV failure	narrow	↑	↑	↓

CVP, Central venous pressure; *IVC,* inferior vena cava; *LVEDA,* left ventricular end-diastolic area; *LVESA,* left ventricular end-systolic area; *nl,* normal; *PAP,* pulmonary artery pressures; *PE,* pulmonary embolus; *RAP,* right atrial pressures; *SVO_2,* mixed venous oxygenation; ↑, increased; ↓, decreased. Different types of shock present with specific echocardiographic and hemodynamic findings.

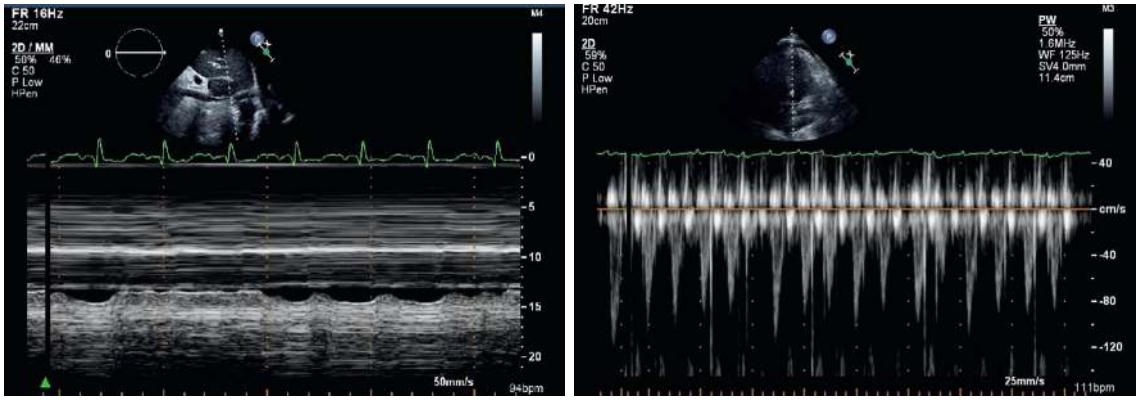

Fig. 31.7 IVC and LVOT velocities in hypovolemia. An IVC <1.5 cm with >50% respiratory collapse suggests intravascular hypovolemia. PWD of the LVOT shows respiratory variation in velocities. *IVC,* inferior vena cava; *LVOT,* left ventricular outflow tract; *PWD,* pulse wave Doppler.

echocardiography. Another important etiology of cardiogenic shock in the ICU is stress-induced cardiomyopathy (SCM). The incidence of this problem in ICU patients could be as high as 28%, and early diagnosis is facilitated using echocardiography.[77] Typical echocardiographic findings are apical ballooning with global LV dysfunction and compensatory hyperdynamic function of the basal segments (Video 31.3).

Right-sided heart failure, isolated or in the setting of biventricular failure, presents with slightly different echocardiographic findings. Mainly qualitative findings are depressed RV contractility, decreased ejection fraction by FAC, a TAPSE <16 mm in combination with RV dilation, RV/LV ratio of >0.8, and severe TV regurgitation (Video 31.4).[68] In this setting, low RVSP in conjunction with increased RAP, suggested by an IVC diameter >20 mm, can be the result of the inability of the myocardium to create adequate pressure. Evaluation of the LV often shows signs of hypovolemia with isolated RV failure caused by decreased LV preload.

The most common pathologies causing RV failure leading to acute cardiogenic shock are acute volume or pressure overload, new valvular pathologies, or acute ischemia. Chronic RV dysfunction predisposes patients to RV failure during critical illness from noncardiogenic causes. RV dilation, TV regurgitation, ventricular septal shifts, abnormal RVSP, and IVC dilation all help to inform the clinician about the etiology of acute RV failure. In particular, ventricular septal shifts have to be interpreted in this context, as they are commonly present in chronic valvular or pulmonary disease states and do not necessarily indicate the presence of acute RV failure (Fig. 31.8).

Distributive Shock

Septic shock can present with a highly variable clinical picture, and dynamic changes in the appearance of shock can occur within hours with or without intervention. The clinical picture of septic shock can range from aspects of a pure distributive shock to combinations of hypovolemic, cardiogenic, and distributive shock.[78,79] For this reason, echocardiography aids in the assessment and management of septic patients, and serial reevaluation is imperative to adapt to the dynamic evolution of the disease. Bedside echocardiography in the septic patient is focused on the systematic evaluation of volume status and fluid responsiveness, SVR, and ventricular function. Early echocardiographic signs supporting the diagnosis of septic shock are hyperdynamic LV systolic function and high CO levels in conjunction with small or normal LVEDA (Video 31.5). However, the findings will depend on intravascular volume status and RV function. It is important to differentiate between hypovolemia and low SVR in this situation, as the only distinction may be the difference in LVEDA (Video 31.1 vs. Video 31.5).

There are some caveats specific to the evaluation and monitoring of distributive shock. Fluid resuscitation often eliminates signs of hypovolemia, and vasopressors may depress the hyperdynamic appearance of the LV. If myocardial dysfunction is present, the ventricular function may appear normal or hyperdynamic on initial or follow-up imaging as opposed to the classic hyperdynamic shock picture. Inotropic support can alter echocardiographic findings even further.[80–82]

Obstructive Shock

Circulatory collapse caused by mechanical interference with ventricular filling or emptying is classified as an obstructive shock.[83] Potential

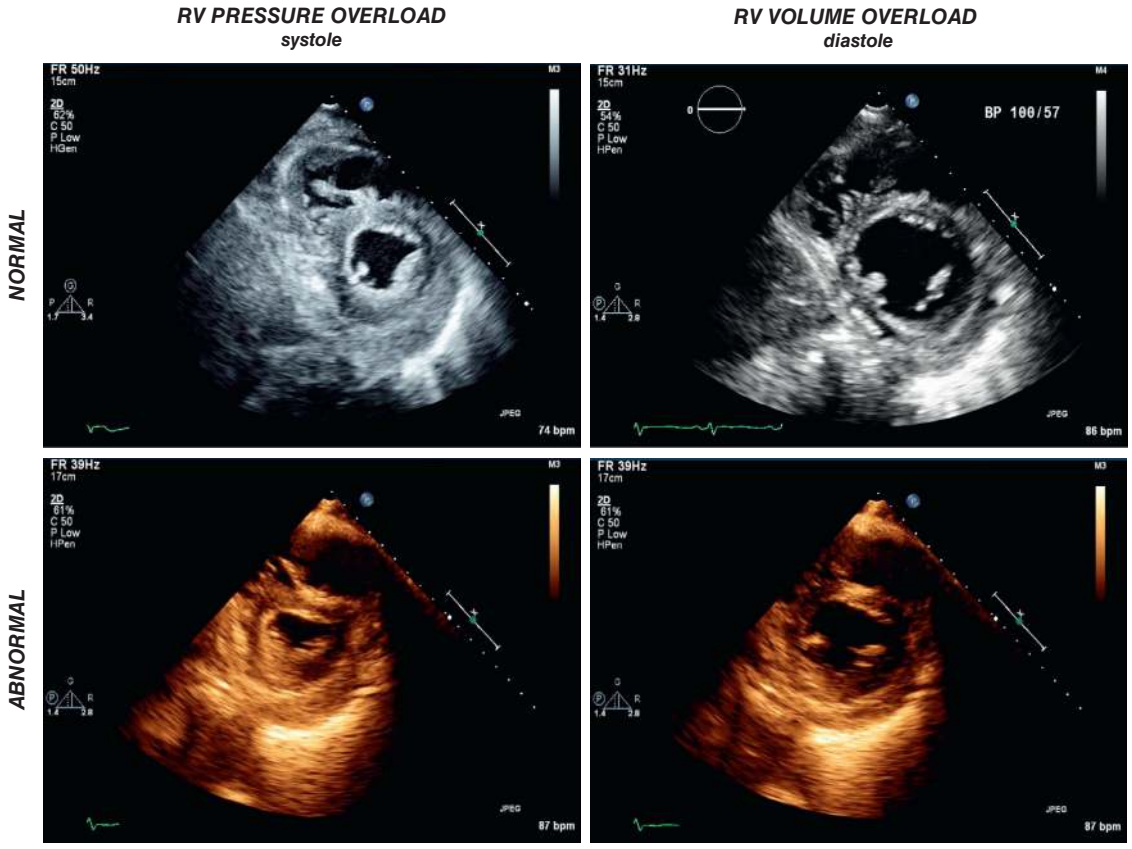

Fig. 31.8 Paradoxical interventricular septal shift. Pathologies causing RV pressure overload such as pulmonary hypertension will result in septal flattening during systole. With RV volume overload, a septal shift occurs in diastole. In acute RV failure, commonly both pathognomonic findings are seen. *RV,* Right ventricle.

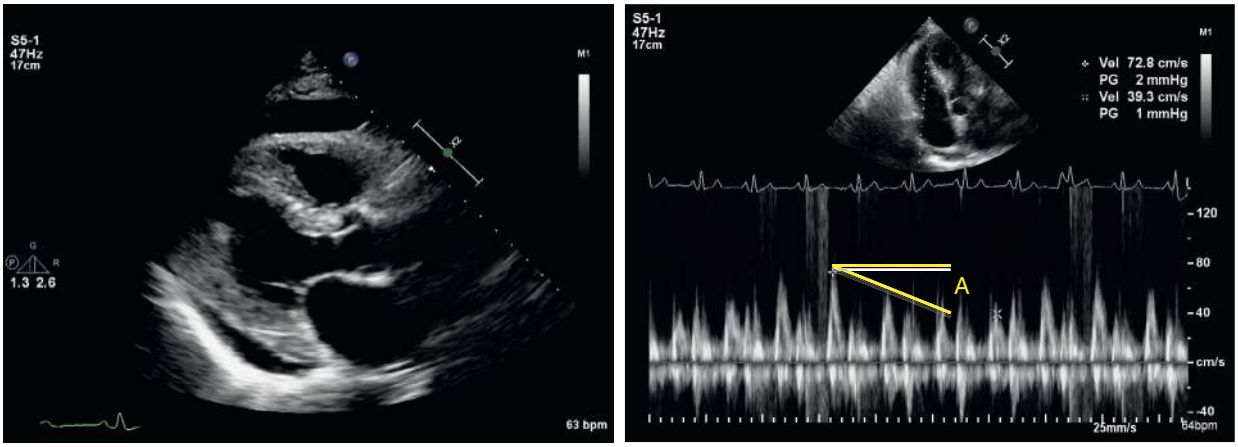

Fig. 31.9 Hemodynamic-compromising pericardial effusion/tamponade. Respiratory variation in TV inflow of >25% is suggestive of hemodynamic-compromising pericardial effusion and tamponade. It is important to differentiate a pericardial from a pleural effusion. The arrow marks the descending thoracic aorta. A pericardial effusion does not extend superiorly (leftward) past the descending thoracic aorta, whereas a pleural effusion projects more distal to the aorta with extension past the vessel toward the left of the image. Circumferential effusion, the diastolic collapse of RA or RV, and IVC plethora are additional signs suggestive of tamponade physiology, as seen in Video 31.6.

causes of obstructive shock include pericardial effusion and tamponade, tension pneumothorax, and pulmonary embolism, in addition to less common entities, such as intracardiac tumors or vena cava compression. As these processes are mechanical, echocardiography has the potential of visualizing the source of shock pathology directly aside from identifying the hemodynamic profile.

Pericardial effusion and cardiac tamponade are dynamic diseases closely linked to changes in intravascular volume status, intrathoracic pressures, and patient position. Although the etiology of an effusion cannot be defined by echocardiography, certain findings such as clot formation or stranding can hint toward hemorrhagic or purulent effusions of serous fluid (Fig. 31.9). When evaluating cardiac tamponade, echocardiography can exhibit signs suggestive of hemodynamically significant pericardial effusion or clot[84,85] (see Table 31.6 and Video 31.6). In postcardiac surgery patients, tamponade may not always be present with the classic circumferential effusion, and echocardiographic imaging should include an assessment for the localized clot or fluid collections in uncommon locations, such as the IVC-RA (right atrium) junction or posterior to the left atrium (LA).

A pulmonary embolism causes the obstruction of blood flow from the right side of the heart to the left. It commonly presents with signs of right-sided pressure overload and RV failure, in conjunction with a hypovolemic and hyperdynamic LV (Table 31.7 and Video 31.7).[86] The McConnell sign with akinesis of the RV free wall and normal function of the RV apex is pathognomonic but not always observed (see Video 31.7).[87] Occasionally, the obstructing embolism can be seen in the very proximal pulmonary vasculature. Additionally, it is pertinent to evaluate patients for intracardiac shunts, as these present a risk for paradoxical embolism and hypoxia and have a worse short-term prognosis.[88,89]

Tension pneumothorax can cause decreased cardiac preload, and echocardiographic findings show hypovolemia and possible mechanical cardiac compression or shift. Further imaging via chest ultrasound or radiography is necessary for the diagnosis. Other pathologies, such as extracardiac or intracardiac masses causing obstruction to ventricular filling, are uncommon. However, when these problems are present, echocardiography can be helpful for making the diagnosis and evaluating the hemodynamic significance.

TABLE 31.7 Echocardiographic Signs Seen With a Significant Pulmonary Embolism (PE)

PULMONARY EMBOLISM
• Clot in proximal pulmonary vasculature
• Depressed RV systolic function ± hypovolemic and hyperdynamic LV
• Interventricular septum shifts consistent with RV pressure overload
• McConnell sign
• Tricuspid regurgitation
• IVC plethora
• Intraatrial shunt

IVC, Inferior vena cava; *LV,* left ventricle; *RV,* right ventricle; *TR,* tricuspid valve.
Dependent on the extent of RV compromise, the LV will exhibit signs of hypovolemia. Classic sign of RV pressure overload shows a systolic shift of interventricular septum. Evaluation for intraarterial communication with right-to-left shunting is pertinent in patients with significantly increased right-sided pressures because of PE.

Echocardiography During Cardiopulmonary Resuscitation

Echocardiography is one important application of ultrasound in cardiac arrest. It focuses on identifying the immediate causes of cardiac arrest, such as cardiac tamponade, pulmonary embolism, hypovolemia, or myocardial failure, and can guide and follow resuscitation efforts.[90,91] Additionally, Salen and colleagues and Blyth and colleagues showed that the echocardiographic identification of cardiac activity can predict recovery of spontaneous circulation.[92,93] The best view for immediate evaluation in cardiac arrest is the LV SAX view. This is because it can provide information about extreme changes in volume status, myocardial function, and pericardial tamponade simultaneously. Additionally, it is easy to obtain and interpret. In the acute setting, TEE can often

provide better continuous imaging when chest compressions are ongoing, but it may interfere initially with intubation attempts.

SPECIFIC EVALUATION

Valvular Pathologies

A detailed assessment of valvular pathologies requires comprehensive echocardiographic skills and is performed by cardiologists or cardiothoracic anesthesiologists with advanced echocardiographic training. During limited ICU echocardiographic examinations, the operator should seek to identify gross valvular pathologies, as their presence can alter management. Aside from the immediate adjustment in hemodynamic management, any valvular pathology found on the basic bedside examination warrants further subsequent evaluation by a comprehensive examination.

Basic components of valve assessment include gross anatomic evaluation for obvious pathologies, such as calcifications or ruptured leaflets and papillary muscles (Table 31.8). CFD is used to recognize significant transvalvular flow acceleration suggestive of stenotic lesions or patterns of valvular regurgitation of hemodynamic significance. Basic quantitative measurements of transvalvular gradients by CWD can be obtained through AV and MV for grading of stenotic lesions and calculation of valve area, but this is part of the in-depth examination.[94,95] The five most common valvular pathologies are seen in Videos 31.8–31.12.

Cardiomyopathies and Dynamic Outflow Obstruction

Primary disease of the heart muscle plays a significant part in the overall morbidity and mortality of cardiovascular disease. Echocardiography provides information about the magnitude of systolic and diastolic heart failure, in addition to the etiology of cardiomyopathy. Echocardiography permits the assessment of immediate and long-term prognosis. As cardiomyopathies can alter the hemodynamic response to acute illnesses and their management in the ICU, it is important for the intensivist to know the echocardiographic patterns that are characteristic of these chronic disorders.[96]

Cardiomyopathies are commonly differentiated into three main types: (1) dilated cardiomyopathy, (2) hypertrophic cardiomyopathy, and (3) restrictive cardiomyopathy.[97] Dilated cardiomyopathy presents with echocardiographic findings of dilated ventricles and reduced ventricular systolic function (Video 31.13). Hypertrophic cardiomyopathy is characterized by symmetric or asymmetric concentric hypertrophy of the myocardium (Video 31.14). It is important to recognize a dynamic obstruction of the LVOT in hypertrophic obstructive cardiomyopathy (HOCM). This is because the presence of this problem alters the usual management of cardiogenic shock management because the administration of inotropic agents can be detrimental in patients with HOCM. Dynamic outflow obstruction in these cases is caused by the systolic anterior motion (SAM) of the mitral valve leaflet (Video 31.15).[98] As in HOCM, SAM can also be present after mitral valve surgery.[99]

Restrictive cardiomyopathy is more difficult to diagnose, as it presents with diastolic dysfunction of the ventricles, and echocardiographic findings require an evaluation of diastolic function. For the intensivist, if evaluation for diastolic dysfunction is difficult, findings of atrial enlargement with small ventricles and subjective restricted ventricular function are often the best supportive indicators for restrictive cardiomyopathies.[96]

Infectious Pathologies and Embolic Sources

TEE is used in the evaluation of infectious and embolic sources in patients with unexplained sepsis or embolic strokes. In an acute setting, transthoracic findings of new regurgitant valvular lesions in the setting of bacteremia can be suggestive of infectious endocarditis. However, TEE is warranted for the optimal assessment when vegetations are anticipated (Video 31.16). As differentiation can be difficult and an evaluation for coexisting involvement of the valvular structures is pertinent for possible surgical management, comprehensive TEE is commonly performed by cardiologists.[100] When the etiology of a stroke in the absence of an infection is unclear, or in the event of planned cardioversion for prolonged supraventricular tachyarrhythmias in patients with a high risk of thrombus formation, TEE is performed to evaluate for the presence of a left atrial appendage clot.[101] Additionally, when evaluating for cardiac sources of thromboembolic events, the presence of intracardiac shunts as the source for paradoxical events should be ruled out. As these are not always detected by

TABLE 31.8 Common Valvular Pathologies and Their Echocardiographic Findings

Valve Pathologies		Findings
Aortic stenosis (AS)	2D	Calcification of leaflet and annulus, restrictive leaflet motion, LVH
	CFD	Transvalvular flow acceleration, AI
	CWD	Transvalvular flow acceleration, increased peak mean, and peak gradient rounded Doppler profile
Aortic insufficiency (AI)	2D	Leaflet disruption, LV enlargement
	CFD	Regurgitant diastolic flow, turbulent flow, regurgitant jet direction
	CWD	Regurgitant diastolic flow, Doppler profile density, diastolic flow reversal in proximal thoracic aorta
Mitral stenosis (MS)	2D	Calcification of leaflet and annulus, restrictive leaflet motion, dilated LA
	CFD	Transvalvular flow acceleration, PISA, MR
	CWD	Transvalvular flow acceleration increased peak mean and peak gradient
Mitral insufficiency (MR)	2D	Leaflet pathology, chordal tethering, dilated annulus, LA enlargement, LV enlargement
	CFD	Regurgitant systolic flow, turbulent flow, regurgitant jet severity and direction
	CWD	Regurgitant diastolic flow, Doppler profile density, diastolic flow reversal in proximal thoracic aorta
	PWD	Pulmonary vein flows blunting/reversal
Tricuspid regurgitation (TR)	2D	Dilated annulus, leaflet pathology, RA enlargement, RV enlargement
	CFD	Regurgitant systolic flow, turbulent flow, regurgitant jet severity and direction
	CWD	Regurgitant diastolic flow, Doppler profile density
	PWD	Hepatic vein flows blunting/reversal

LA, Left atrium; *LVH,* left ventricular hypertrophy; *PISA,* proximal isovolumetric flow acceleration.

simple CFD interrogation, a bubble study during a Valsalva maneuver is performed to aid in the detection of right-to-left shunting.[102]

Aortic Pathologies

Echocardiographic assessment of aortic disease in acute hemodynamic instability in critically ill patients mainly focuses on the evaluation of aortic dissection. As TTE is of limited utility for evaluation of the thoracic and abdominal aorta, TEE is the modality of choice.[103] TEE has been shown to be equally accurate when compared with computed tomography (CT) or magnetic resonance imaging (MRI) in the diagnosis and confirmation of thoracic aortic dissection.[104] The evaluation includes the visualization of the dissection flap, identification of the true and false lumens, estimation of blood flow, and determination of active extravasation. When the aortic root is involved, assessment includes evaluation for subsequent complications, including aortic insufficiency (AI), pericardial effusion, and acute ischemia secondary to coronary involvement.

Trauma

Echocardiography in critically ill patients after trauma can evaluate the hemodynamic status and anatomic pathologies after forceful injuries.[105] After blunt chest trauma, echocardiography is a useful tool in the initial evaluation.[106] Catastrophic structural injuries, such as cardiac tamponade, cardiac rupture, coronary artery thrombus, disruption of valvular structures, and traumatic aortic injury, can be identified quickly.[73] More commonly, patients only present with signs of cardiac contusion, and echocardiography can assist with identification of myocardial dysfunction in the acute setting. Specific TTE views are part of the standard algorithms for an emergency ultrasound, such as the focused assessment with sonography in trauma (FAST) or focused cardiac ultrasound (FOCUS) examinations.[107–109] When available and no contraindications are present, TEE can also diagnose aortic injury, although CT is preferred for rapid evaluation.[110,111]

Interventional Use of Echocardiography

Interventional procedures involving cardiac structures are common in the ICU, and basic ultrasound and echocardiography play important roles in the conduct of these interventions. TTE or TEE performed at the bedside alleviate the need for transporting patients to the cardiac catheterization laboratory or procedure room for fluoroscopic guidance. This eliminates the risks that are associated with moving critically ill patients. Use of echocardiography can also decrease exposure to radiation.[112] Although the basic ultrasound can assist significantly in multiple types of procedures, including venous and arterial vascular access and drainage of pleural effusions or other fluid collections, echocardiography can assist in more advanced procedures. TTE can assist with pericardiocentesis and with gross localization of a transvenous pacemaker lead.[113–115] TEE provides optimal image quality for specific cardiovascular interventions, such as an intraaortic balloon pump (IABP) placement and positioning of extracorporeal membrane oxygenation (ECMO or ventricular assist device (VAD) cannulas.[73,116–118] TEE best evaluates mechanical assist devices. Thromboembolic events, overt hemolysis, or fluctuation in device power or flow warrant the evaluation for thrombus formation, cannula position, and device function.[119,120]

Hypoxemia

Echocardiography can assist in the diagnosis and management of acute respiratory failure. In pulmonary edema, differentiation between cardiogenic and noncardiogenic etiology aids in medical management. Either by invasive measurements or echocardiographic evaluation, estimation of LA and LV filling pressures is pertinent for the diagnosis of hydrostatic pulmonary edema. When a regular rhythm is present, LV filling pressures can be estimated by transmitral and pulmonary venous Doppler studies and is the most commonly used parameter for an easy, reproducible assessment in the ICU.[121] Common cardiac causes for pulmonary congestion are volume overload, acute mitral or aortic valve regurgitation, mitral stenosis, and severe LV systolic and diastolic dysfunction. All these problems can be assessed using 2D, CFD, and spectral Doppler echocardiographic modalities. In noncardiogenic ARDS, echocardiography can allow the clinician to assess changes in RV function with adjustments of mechanical ventilation.[122] Severe ARDS with increased pulmonary resistance and the use of high levels of PEEP may lead to acute or pulmonary issues with sudden RV failure and subsequent hemodynamic and respiratory decompensation.[123] Similarly, acute increases in pulmonary vascular resistance caused by pulmonary embolus (PE) can cause RV failure.[124] In these cases, echocardiography is often used as a supportive tool for the diagnosis and assessment of hemodynamic significance.

Another common cause of hypoxemia in mechanically ventilated patients is the presence of intracardiac shunts. With a prevalence of >25% in the general population, intraatrial communications, such as patent foramen ovale (PFO) and atrial septum defects (ASDs), are frequently clinically silent.[125,126] In healthy patients with PFO or ASD, shunting typically is either absent or directed from left to right. During critical illness, however, increased right-sided pressure caused by pulmonary hypertension, RV failure, volume overload, or TV regurgitation is common and can lead to right-to-left shunting, resulting in hypoxemia from the admixture of nonoxygenated with oxygenated blood.[73] Echocardiographic evaluation focuses on detection of intracardiac shunting and directional flow of the shunt by 2D echocardiography and CFD.

FUTURE DIRECTIONS

Many miniaturized and TTE and TEE devices have been introduced recently into the critical care environment for the use by noncardiologists for goal-directed therapy of the hemodynamically unstable patient. Handheld TTE devices demonstrate usefulness in the clinical setting when used by intensivists after undergoing brief training.[127–130] Miniaturized, disposable TEE probes that provide monoplane images have been introduced for continuous use up to 72 hours. The initial experience has demonstrated good utility in the management of hemodynamically unstable patients.[131,132] These novel monitoring devices for continuous echocardiographic imaging have great potential for providing many features of a regular TEE while minimizing the risks and allowing for use over time.[133,134] Advanced echocardiographic modalities, such as contrast echocardiography and endocardial border tracking, can be valuable when available.[135–137]

On the operator side, more intensivists are becoming skilled in echocardiography, and ICU fellowship programs increasingly teach focused echocardiography. With the growing importance of critical care echocardiography, critical care societies across the world propose the further integration of formal echocardiographic training into ICU fellowship training. Specific criteria are being defined for the future trainees, and courses in focused ICU echocardiography are offered for the practicing intensivist.[18–20]

Despite significant advancements in the field over the past decade, a broader validation of echocardiographic use in the ICU is needed. Outcome-based studies looking at the use of focused echocardiography as a monitoring tool and integration into goal-directed therapy will be helpful in strengthening the broad use of this valuable modality.

KEY POINTS

- TTE and TEE are valuable diagnostic and monitoring tools in the critical care setting and can have a significant impact on the management and outcome of critically ill patients.
- Training, accreditation, and maintenance of expertise in focused echocardiography are essential, and further development of these areas by national societies is needed.
- An understanding of ultrasound physiology, the echocardiography machine, anatomy, and normal echocardiographic findings is essential for the appropriate use of echocardiography in the ICU.
- The most common use of bedside echocardiography is the evaluation of acute circulatory and respiratory failure.
- An algorithmic approach to the hemodynamically unstable patient is warranted, and repeated echocardiographic assessment to confirm and adjust medical management needs to ensue until the patient stabilizes.
- Interpretation of echocardiographic findings should take into account the patient's history, pathophysiology, and current medical interventions.
- Management based on echocardiographic information needs to follow the complete clinical picture of the critically ill patient.
- With rapid advancement in ultrasound technology, pocket-sized handheld TTE devices and miniaturized TEE probes for continuous monitoring are being developed and will further promote the integration of focused echocardiography in the daily critical care practice.

References for this chapter can be found at expertconsult.com.

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Updated ACC/AHA/ASE guidelines regarding the clinical application of echocardiography. Regarding critical care, the new guidelines highlight the utility of transthoracic echocardiography in the detection of central pulmonary emboli and emphasize the potentially superior utility of transesophageal echocardiography. The use of echocardiography in blunt thoracic trauma is also reviewed.

Grider D, Society of Critical Care Medicine. *Ultrasonography in Critical Care.* Society of Critical Care Medicine. Available at https://www.sccm.org/Communications/Critical-Connections/Archives/2018/Ultrasonography-in-Critical-Care.
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Roshdy A. Echodynamics: Interpretation, limitations, and clinical integration. *J Intensive Care Med.* 2018;33(8):439–446.
Review of considerations, indications, and limitations of echocardiographic assessment in complex critical illness physiology. For example, the inferior vena cava is often used to assess volume status and fluid responsiveness. However, it is less reliable when low tidal volumes are delivered, when low lung compliance occurs, when a patient is spontaneously breathing, and when excessive probe pressure is applied to the abdomen.

Vieillard-Baron A, Millington SJ, Sanfilippo F. A decade of progress in critical care echocardiography: A narrative review. *Intensive Care Med.* 2019;45:770–788.
An updated report of the areas in critical care, emergency medicine, and perioperative care where echocardiography may have a potential benefit or impact. Key messages, including the need to perform echocardiography for any hemodynamically unstable patient and that each critical care unit should have some individuals trained in advanced echocardiography, highlight the now-ubiquitous use of echocardiography in intensive care medicine.

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Cardiovascular Monitoring

Arthur Pavot, Xavier Monnet, and Jean-Louis Teboul

INTRODUCTION

Over the last decades, cardiovascular monitoring techniques used in the intensive care unit (ICU) and operating room (OR) have progressively evolved from invasive toward less invasive approaches. In the 1990s, the pulmonary artery catheter (PAC) was at its apogee,[1] as it was the only method to assess and monitor hemodynamics at the bedside. The PAC has provided clinicians with measurements of cardiac output (CO), pulmonary artery pressure (PAP), cardiac filling pressures, and mixed venous blood gases. Modified versions of PAC provided continuous monitoring of CO and of mixed venous oxygen saturation (SvO_2). However, a progressive decline of use of the PAC has been observed since 1995.[1] In addition to invasiveness, there were multiple reasons for such a decline: (1) evidence of insufficient physician knowledge in measuring and interpretating the PAC data[2,3]; (2) a report from a nonrandomized outcome study showing increased mortality associated with PAC vs. no PAC[4]; (3) findings from randomized controlled trials showing no outcome benefits of using PAC in ICU patients[5,6]; (4) development of bedside echocardiography in the ICU that allows better assessment of cardiac function; (5) emergence of transpulmonary thermodilution (TPTD),[7] esophageal Doppler (ED),[8] and minimally invasive or noninvasive pulse wave analysis (PWA) CO monitors.[9–11] The latter monitoring systems, which provide real-time and continuous CO and fluid responsiveness variables, belong to the class of functional hemodynamic monitoring devices. Use of such devices in goal-directed therapy strategies in the perioperative period of high-risk surgical patients has been reported to improve outcome in comparison to standard management using central venous pressure (CVP) and mean arterial pressure (MAP).[12] During recent years, the importance of predicting fluid responsiveness has also been emphasized in the ICU setting. This can be explained by (1) the demonstration that approximately half of ICU patients are fluid nonresponders[13] and (2) the fact that fluid overload is associated with increased mortality of ICU patients.[14] Numerous studies have documented the superiority of dynamic over static variables to predict fluid responsiveness.[15] Accordingly, many intensivists and anesthesiologists prioritize the use of devices that provide dynamic variables such as pulse pressure variation (PPV) and stroke volume variation (SVV)[15] or that facilitate tests such as passive leg raising (PLR)[16,17] or end-expiratory occlusion (EEO).[17–20] Thus it is easy to understand why in this context, the place of the PAC, which cannot provide adequate assessment of fluid responsiveness, has decreased over time.

In this chapter, we review the most used hemodynamic monitoring devices in the ICU and the OR settings, ranging from the invasive to less invasive ones. We emphasize the clinical relevance of the hemodynamic information they provide and the advantages and limitations of their use, knowing that they generally gain in safety what they lose in precision. We also discuss the place of hemodynamic monitoring in patients with shock and in patients in the OR setting.

THE AVAILABLE HEMODYNAMIC MONITORING DEVICES

The Pulmonary Artery Catheter

Description

The most commonly used PAC model is a fluid-filled catheter of 7 or 7.5F external diameter and 80-cm length that connects to an electronic pressure transducer. The distal lumen, ending at the tip of the catheter, enables blood sampling and pressure measurement at the level of the pulmonary artery. A few millimeters before its termination, a latex balloon surrounds the catheter. Temporary balloon inflation totally occludes the pulmonary artery branch (10–15 mm diameter) into which the catheter has been placed and allows the measurement of the pulmonary occlusion artery pressure (PAOP). A proximal lumen at the level of the right atrium allows measuring the right atrial (central venous) pressure. A thermistor located close to the tip of the catheter continuously senses the changes in blood temperature induced by thermal injection via the proximal lumen. This allows calculating thermodilution CO according to the Stewart-Hamilton principle.

Based on this minimal configuration, alternative PAC models can be equipped with:

- An ultra-fast thermistor providing calculation of right ventricular (RV) ejection fraction and RV end-diastolic volume
- A thermal filament for continuous CO measurement
- A fiberoptic probe for reflectance photometry and continuous assessment of SvO_2

Pulmonary Artery Catheter–Derived Variables

The PAC provides the physician with hemodynamic variables (right atrial pressure, PAP, PAOP, and CO) and with tissue perfusion variables such as SvO_2 and the mixed venous carbon dioxide pressure ($PvCO_2$). Simultaneous acquisition of arterial blood gases allows calculation of oxygen consumption (VO_2) and oxygen delivery (DO_2), using the time-honored Fick principle.

Pulmonary artery occlusion pressure. The PAOP is obtained after inflation of the distal balloon with 1.5 mL of air. This temporarily occludes a branch of the pulmonary artery of around 13 mm diameter and thus interrupts flow through the column of blood linking the balloon with a pulmonary vein of similar diameter. The PAOP reflects the pressure in a large pulmonary vein and thus approximates both the left atrial pressure (LAP) and left ventricular (LV) end-diastolic pressures (LVEDP).

It is recommended to measure PAOP at the end of expiration, a time when intrathoracic pressure is closest to its value at atmospheric pressure. Positive end-expiratory pressure (PEEP) or auto-PEEP may lead to overestimation of PAOP at end expiration as a measure of LV filling pressure (LVFP). Obtaining transmural PAOP, a better marker

of LVFP, requires subtraction from the end-expiratory PAOP a value that estimates the transmitted PEEP or auto-PEEP into the thorax. This value can be obtained by the product of PEEP (or auto-PEEP) by the ratio of the difference between the PAOP values at end expiration, and at end inspiration over the driving pressure (difference between plateau pressure and PEEP).[21]

Even if it reflects LAP, PAOP overestimates LVEDP in cases of mitral stenosis or insufficiency and underestimates LVEDP in the case of severe aortic insufficiency or reduced LV compliance.

Although the main interest of the transmural PAOP is to estimate the LVFP, the intramural PAOP is also used to reflect the pulmonary capillary pressure (Pcp). However, because PAOP reflects the pressure in a large pulmonary vein, it underestimates Pcp, particularly when CO is high and when pulmonary venous resistance is elevated, as during acute respiratory distress syndrome (ARDS).[22,23] The Pcp could be estimated from the PAP trace decay during the seconds after the distal balloon inflation, after extrapolation back toward time zero of the slow component of the pressure decay. For adequate precision, this calculation requires a computerized mathematical method.[23] Because Pcp is not measured in routine practice, PAOP provides only a rough estimate of the Pcp needed to differentiate between hydrostatic and increased permeability pulmonary edema. However, authentic increased permeability pulmonary edema also can be associated with elevated PAOP.[24]

Cardiac output. The CO can be measured using the thermodilution principle. Two methods of measurement are currently used:

- The intermittent thermodilution method requires the injection of a cold saline bolus through the proximal lumen of the catheter. The decrease in blood temperature is recorded by the distal thermistor, and CO is calculated from the Stewart-Hamilton equation. At least three measurements must be averaged for a reliable estimation of CO. Severe tricuspid regurgitation leads to underestimation of CO.[25]
- The "continuous" thermodilution method is based on automatic heating of blood by means of a proximal thermal filament (located about 15 cm from the tip of the PAC). The external monitor activates the heating filament for 1–4 seconds in a pseudorandom sequence. The resulting series of heat signals from the distal thermistor are analyzed stochastically to determine a single thermodilution curve. This technique has the advantage of continuously displaying CO and avoiding repeated manipulations of the lines and bolus injections. However, it does not enable real-time CO monitoring, because the average of successive CO measurements is delayed as compared with the intermittent technique.[26] This limits the ability to detect rapid hemodynamic changes induced by therapy or to track hemodynamic instability during high-risk surgery.

Mixed venous blood oxygen saturation. Because pulmonary arterial blood blends the mix from all venous territories of the body, measuring SvO_2 with the PAC enables assessment of global tissue oxygenation.

Two techniques are currently available. The first one requires sampling of the pulmonary artery blood through the distal tip of the PAC. The second technique uses PAC models, which enable a continuous "in vivo" monitoring of SvO_2 through fiberoptic spectrophotometry. The latter method has the advantage of avoiding repeated blood samplings and provides real-time monitoring of SvO_2.

Physiologically, SvO_2 depends on arterial oxygen saturation (SaO_2), VO_2, CO, and hemoglobin concentration (Hb), according to the formula derived from the Fick equation applied to oxygen: $SvO_2 = SaO_2 - [VO_2 / (CO \times Hb \times 13.4)]$. Because CO, Hb, and SaO_2 are the key determinants of DO_2, SvO_2 is an integrative variable, which is considered a marker of the global balance between actual VO_2 and DO_2.[23] SvO_2 values range from 65% to 77% in healthy subjects.

Useful interpretation of SvO_2 presents several difficulties.[27] First, a low value of SaO_2 results in a decreased SvO_2, which is no longer considered a marker of the VO_2/DO_2 balance. Second, a normal or high SvO_2 value can be observed during certain shock states (e.g., sepsis) because of impaired oxygen extraction capability. This difficulty emphasizes that when SaO_2 is normal, SvO_2 is a marker of the balance between DO_2 and VO_2 but does not faithfully reflect oxygen demand. Third, for constant VO_2, Hb, and SaO_2, the relation between SvO_2 and CO is hyperbolic. Thus although changes in SvO_2 parallel changes in CO in low CO states, marked changes in CO do not significantly alter SvO_2 in hyperdynamic ones. Fourth, in shock states characterized by DO_2/VO_2 dependency, changes in CO result in parallel changes in VO_2 such that SvO_2 will not change if DO_2 is below its critical value. Fifth, SvO_2 is the flow-weighted average of the venous saturation values from all organs of the body. Organs having high blood flow and low oxygen extraction, such as the kidneys, have a greater influence on SvO_2 than organs with low blood flow and high oxygen extraction, such as the myocardium. In sepsis, interpretation of SvO_2 is further complicated by the local maldistribution of blood flow. Nevertheless, in any shock state, monitoring SvO_2 is helpful because a low value (<65%) should prompt clinicians to increase DO_2 in order to improve tissue oxygenation.[27] On the other hand, a high value of SvO_2 suggests that attempts to increase DO_2 have little chance to improve tissue oxygenation significantly or ultimately benefit outcome.[28]

Veno-arterial carbon dioxide tension difference. The veno-arterial carbon dioxide tension (PCO_2) difference (ΔPCO_2) is the difference between $PvCO_2$ and PCO_2 in arterial blood ($PaCO_2$). Its normal value ranges from 2 to 5 mm Hg.

The Fick equation applied to carbon dioxide (CO_2) indicates that the CO_2 excretion (equivalent to CO_2 production [VCO_2] in a steady state) equals the product of CO by the difference between the CO_2 content in the mixed venous blood and in the arterial blood. The normal relationship between CO_2 content and PCO_2 is almost linear over the usual physiologic range of the CO_2 contents. Thus by substituting PCO_2 for CO_2 content, $\Delta PCO_2 = k \times VCO_2 / CO$, where k is a constant. Accordingly, ΔPCO_2 would be linearly related to VCO_2 and inversely related to CO.

The ΔPCO_2 is considered a marker of the adequacy of venous blood flow to remove the total CO_2 produced by the peripheral tissues.[29] An increased ΔPCO_2 suggests that the CO is not high enough with respect to the global metabolic conditions. A high ΔPCO_2 should prompt clinicians to consider measures aimed at increasing CO so as to reduce tissue hypoxia. Conversely, a normal ΔPCO_2 suggests that increasing CO is not a priority.

Complications Associated With Pulmonary Artery Catheters

The complications associated with the use of a PAC are relatively rare and can be related to (1) PAC insertion (e.g., arterial puncture, bleeding, pneumothorax, ventricular extrasystoles), (2) PAC maintenance (e.g., bacterial colonization, infectious endocarditis, venous thromboembolism), (3) balloon inflation (e.g., rupture of a pulmonary artery branch, false aneurysm of the pulmonary artery), and (4) PAC withdrawal (e.g., transient ventricular arrhythmias, knotting of the catheter). Some of these complications relate to the poor experience of the user and to the PAC length of stay. The PAC should be carefully removed as soon as no longer needed, and its use should not be prolonged longer than 3 or 4 days.

Systems Integrating Transpulmonary Thermodilution and Pulse Wave Analysis

Description

Two commercialized devices integrate the TPTD and the PWA methods: the PiCCO (Pulsion, Germany) and the VolumeView (Edwards LifeSciences, USA). They require the insertion of a standard central

catheter in the superior vena cava and a specific thermistor-tipped arterial catheter, which is usually inserted in the femoral artery. The arterial catheter can also be inserted in the radial, brachial, and axillary arteries if site-specific catheters are used. In practice, a bolus of cold saline (15 mL) is injected through the venous catheter. The thermistor at the tip of the arterial catheter detects the change in blood temperature induced by the cold bolus injection. In addition to providing TPTD-derived variables,[30] cold bolus injections allow calibrating the PWA-based CO, which is derived from the analysis of the ABP waveform.

Transpulmonary Thermodilution–Derived Variables

Transpulmonary thermodilution cardiac output. Similar to the intermittent PAC thermodilution, the area under the TPTD is inversely related to CO according to the Stewart-Hamilton principle. Because the thermistor is located in a femoral artery and not in a pulmonary artery, the TPTD curve has a longer appearance time, a less negative peak value, and a longer return time to baseline temperature compared with the PAC thermodilution curve. Nevertheless, there is a good agreement between CO values measured by the two methods in humans.[31] Although the PAC thermodilution should theoretically provide more accurate CO measurements (less indicator loss between the injection and the sampling sites) than TPTD, the latter has the advantage of being less influenced by respiration and severe tricuspid regurgitation. Cold saline (<8°C) injection should be preferred to room-temperature saline injection to avoid multiplying the risks of errors of measurements and to avoid overestimating CO.[32] The result of three cold bolus injections performed at random should be averaged to obtain an acceptable precision.[33] The least significant change is around 12%, which is comparable with that of the PAC.[33]

Global end-diastolic volume. Through a combined analysis of the thermodilution curve and of its natural logarithmic transformation, TPTD can estimate several volumes of fluid inside the thorax[34] (Fig. 32.1). In the PiCCO device, the global end-diastolic volume (GEDV) equals the product of CO by the difference between mean transit time and downslope time. In the VolumeView device, the calculation of GEDV takes into account the ratio of the maximal ascending and descending slopes of the TPTD curve. The GEDV represents the sum of the maximal volume of the four cardiac chambers and thus represents a volumetric measure of global preload.[35] As such, it can be helpful for identifying the mechanism of shock and following the effects of therapies, but like every static preload marker, it cannot be used to assess preload responsiveness.[36]

Extravascular lung water and pulmonary vascular permeability index. The extravascular lung water (EVLW) reflects the amount of fluid contained in the lung interstitial space and in the alveoli (i.e., pulmonary edema). The EVLW is inferred from the analysis of the TPTD curve (see Fig. 32.1) and has been validated against a reference method in humans.[37] The normal range of EVLW values is between 3 and 10 mL/kg. The TPTD detects short-term and small changes in EVLW.[38] The value of EVLW is that it tracks an independent risk factor for mortality in patients with ARDS.[39]

The pulmonary vascular permeability index (PVPI) is automatically calculated as the ratio between EVLW and the total pulmonary blood volume and therefore could reflect the integrity of the alveolocapillary barrier. It enables one to distinguish increased permeability pulmonary edema from hydrostatic pulmonary edema.[40,41] An increased PVPI is the physiologic hallmark of ARDS and could be integrated in its definition.[42]

In clinical practice, the combination of EVLW and PVPI can help clinicians guide fluid management during ARDS in cases of therapeutic conflicts. High values of EVLW and PVPI may indicate a high risk of fluid administration and prompt clinicians to refrain from increasing the rate of fluid infusion. In addition, repetitive measurements of PVPI may help monitor improvement or worsening of patients with ARDS, as PVPI is correlated with the oxygenation-based severity of ARDS, according to the criteria of the Berlin definition.[43]

Cardiac function index and global ejection fraction. The TPTD also provides the cardiac function index (CFI), which is the ratio of TPTD CO and GEDV, and the global ejection fraction (GEF), which is the CFI divided by heart rate multiplied by 4. The CFI and GEF behave as markers of cardiac systolic function[44–46]: they increase with dobutamine and do not change with volume expansion,[45] and their changes with cardiovascular therapies are correlated with changes in echocardiographic LV systolic function indices.[44–46] Thus through CFI and GEF, TPTD enables a rapid and easy detection of a decreased systolic function, which needs to be further confirmed by echocardiography.

Pulse Wave Analysis–Derived Variables

Pulse wave analysis–based cardiac output. The PWA represents a method of continuous CO monitoring based on the ABP waveform recorded through an arterial catheter. The PiCCO and the VolumeView technologies use the femoral artery catheter also used for TPTD measurements. The original algorithm used by the PiCCO was based on the three-element Windkessel model. It calculated the stroke volume by determining the area of the systolic portion of the arterial blood pressure (ABP) curve and dividing it by the aortic impedance. The latter was automatically determined during a calibration process consisting of measuring stroke volume with an independent technique: namely, TPTD. The current algorithm takes into account not only the area under the systolic part of the ABP curve but also the shape of the curve, the dicrotic notch position, and certain mechanical properties of the arterial system, such as the compliance/resistance couple. At the time of calibration, arterial compliance is calculated as τ/vascular resistance, where τ is a constant quantifying the diastolic pressure decay. Vascular resistance is determined at the time of calibration from the MAP and the TPTD CO. Compliance and resistance are updated on a beat-to-beat basis according to a proprietary algorithm. In spite of this automatic updating, there is a potential drift with time, making recalibration mandatory. In septic patients receiving vasopressors, the agreement between PWA CO (before recalibration) and TPTD CO (after recalibration) has been reported to be acceptable when the time elapsed between two calibration processes was less than 2 hours.[47] The VolumeView device uses a slightly different algorithm that also requires frequent recalibration.

Pulse pressure variation and stroke volume variation. Among all the heart-lung interaction indices, PPV has attained the highest level of evidence.[48,49] The PiCCO calculates it automatically and displays its value in real time. The SVV can also be monitored by the PiCCO and the VolumeView devices. The PPV and SVV cannot be reliably interpreted in cases of spontaneous breathing activity, low V_T ventilation, cardiac arrhythmias, or intraabdominal hypertension.[50] In case of low V_T, the changes in PPV during a transient increase in V_T reliably predict fluid responsiveness.[51] Alternatively, measuring the changes in PWA-based CO during PLR[17] or EEO[18] is helpful in situations where PPV and SVV fail to predict fluid responsiveness.

Advantages and Limitations of Transpulmonary Thermodilution Devices

As it provides a number of hemodynamic variables, TPTD belongs to the advanced hemodynamic monitoring technologies that are recommended in patients with circulatory failure, along with the PAC.[52,53] It requires the insertion of a large-diameter arterial catheter, which may precipitate adverse events that occur most frequently during insertion and removal. Even though these events are uncommon,[54] TPTD is still an invasive technique, which should be used only in selected patients.[52,53]

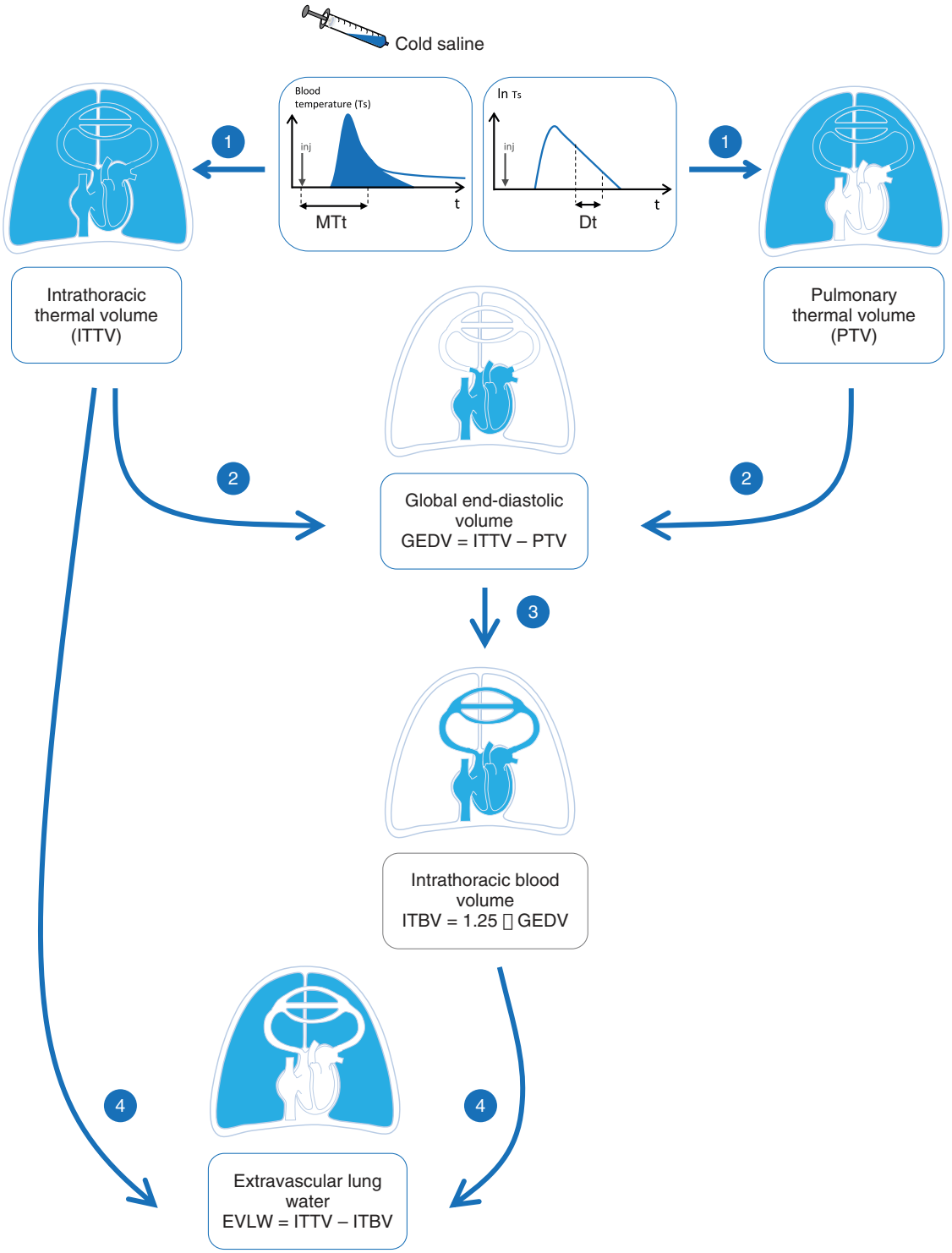

Fig. 32.1 Measurement of extravascular lung water by single thermal indicator dilution. *Dt,* Downslope time; *MTt,* mean transit time. (From Monnet X, Teboul JL. Transpulmonary thermodilution: Advantages and limits. *Crit Care.* 2017;21[1]:147.)

The TPTD remains valid during continuous venovenous hemofiltration at high flow rates.[55] By contrast, TPTD is unreliable during extracorporeal membrane oxygenation, because of the shunting of the cold indicator. Regarding preload and cardiac function TPTD-related indices, the main limitation is the impossibility to distinguish right ventricular (RV) from LV dysfunction. For instance, in case of isolated RV dysfunction, GEDV will increase and CFI (and GEF) will decrease, and the LV function can be normal.[44,45,56] It is recommended not to inject the cold bolus into a femoral vein because of the risk of overestimation of GEDV.[57] The EVLW measurements are less reliable in cases of large pulmonary vascular occlusions as a result of impeded distribution of the cold indicator through lung areas.[58] However, occlusions of small vessels that occur in ARDS or during hypoxic vasoconstriction have no consequences for EVLW monitoring.[59,60] PEEP decreases

EVLW to a small but systematic extent, which might be related to impeded drainage by lung lymphatics.[61] Pneumonectomy and lung resection decrease EVLW. The PVPI shares the same limitations as EVLW.

Lithium Dilution

The lithium dilution technique (LiDCOplus monitor, LiDCO Ltd., UK) provides intermittent CO measurements. A small amount of lithium chloride (0.002–0.004 mmoL/kg) is injected as a bolus through a central vein catheter. The changes in lithium concentrations are detected by blood being drawn out of a radial artery catheter over a specific lithium-selective sensor. Using the Stewart-Hamilton principle, CO can be thus calculated. Such CO measurements have been demonstrated to be reliable when compared with values obtained by PAC thermodilution.[62] To achieve an acceptable precision, three lithium dilution measurements should be averaged. This allows changes in CO ≥14% to be reliably detected.[63] The major inconvenience of LiDCOplus is the need for lithium injection, which cannot be repeated infinitely.

The LiDCOplus monitor also allows a beat-to-beat CO measurement with the pulse power analysis through a radial artery catheter. As the PiCCO monitor, the LiDCOplus monitor contains a proprietary algorithm (PulseCO) for converting a pressure-based signal into a flow measurement. The PulseCO algorithm is based on the physics of conservation of mass and energy. Manual calibration of the PulseCO is performed using the lithium dilution technique. The agreement between lithium dilution CO and the pulse power algorithm in the PulseCO monitor was reported to remain acceptable for up to 4 hours in ICU patients.[64] Using the PulseCO software, the LiDCOplus also allows PPV and SVV monitoring.[65]

Invasive Pulse Wave Analysis–Based Cardiac Output Monitoring Devices

Characteristics of the Devices

As they do not require external calibration by an indicator dilution method, these devices do not require any specific sensor-tipped catheter. They can be connected to any arterial line.[9–11]

The FloTrac device (Edwards LifeSciences, USA) estimates stroke volume as the product of pulsatility and a so-called "K" factor. Pulsatility is estimated from the standard deviation of arterial pulse pressure measurements. K quantifies arterial compliance and resistance and is estimated from the patient's morphometric data, which are compared with a large database of pressure waveform recordings. K is automatically adapted every 60 seconds by taking into account some geometric properties of the ABP curve, such as skewness and kurtosis.

With the ProAQT (Pulsion, Germany), the starting value of CO is not estimated from the Windkessel model, but through "auto-calibration" that uses the patient's own biometric data, MAP, and heart rate. After the initial auto-calibration, the ProAQT performs PWA with a method that is similar to that of the PiCCO. An automatic auto-calibration of CO can also be performed at any time. The ProAQT device can be "externally" calibrated using another technique (e.g., echocardiography), which is manually entered in the system.

With the LiDCOrapid (LiDCO Ltd., UK), the proprietary algorithm uses the patient's biometric characteristics to determine the starting CO value, which is then continuously updated according to the pulse power algorithm. Thus the LiDCOrapid cannot measure accurate values of CO but can only display trends. Nevertheless, external calibration can be performed on demand with an independent CO measurement.

The MostCare (Vygon, Italy) is the only currently available PWA monitor for which neither calibration nor adjustments based on user-entered data are required. This system is based on the pressure recording analytical method (PRAM) that performs a beat-to-beat analysis of the ABP waveform using the complex theory of perturbations.[66]

Advantages and Limitations

The uncalibrated PWA devices provide real-time CO monitoring, which allows early detection of hemodynamic instability and short-term effects of cardiovascular therapies. These monitors are helpful to assess fluid responsiveness by providing PPV and/or SVV and allowing performance of dynamic maneuvers such as PLR and EEO (changes in PWA-based CO) or V_T challenge (changes in PPV or SVV).[67] The absence of an external calibration requirement makes these devices easy to use. However, the absence of external calibration is also a disadvantage, as any drift of the ABP signal cannot be corrected and can lead to erroneous CO values. This can occur over time.[47] With the exception of the PRAM method,[10,11] acute changes in vascular tone may also result in inaccurate CO measurements, making such uncalibrated devices poorly reliable in cases of septic shock and/or use in vasopressors.[68–71] This is why uncalibrated PWA-based CO monitors are not recommended in ICU patients with shock.[52,53] However, they can have a place in the OR setting when CO monitoring is deemed to be necessary.[72] These conditions are suitable for such devices, as surgical procedures are generally short, seldom require vasopressors, and prioritize the detection of hypovolemia.

Esophageal Doppler

Principle

The use of ED is aimed at monitoring CO by continuously measuring the blood flow in the descending thoracic aorta. The device consists of a flexible probe introduced in the esophagus, which, in its thoracic portion, runs parallel to the descending aorta. At the tip of the probe, a Doppler transmitter/receiver records the velocity of red blood cells circulating in the thoracic aorta. Today, one single device (CardioQ, Deltex Medical, UK) is available on the market.

Measured Variables

Cardiac output. Blood flow in the descending aorta is assessed by measuring the velocity of blood passing the ED; the heart rate; and the estimation of the descending aorta diameter from the patient's weight, height, and age. From the value of aortic blood flow, the ED device infers the value of CO, based on the hypothesis that there is a constant distribution of the systemic blood flow between the upper territories and the descending aorta.

Clinical studies showed that ED CO agrees with PAC CO in ICU patients and in patients undergoing surgery.[73] ED CO monitoring has been reported to reliably track the CO changes caused by hemodynamic interventions.[74] The least significant change of ED CO is about 7%[75]

Respiratory variation of aortic blood flow and velocity. The CardioQ device automatically measures the respiratory variation of aortic velocity. The respiratory variation of blood flow in the descending aorta has been reported to reliably predict fluid responsiveness in mechanically ventilated patients,[76] but shares the same limitations as PPV and SVV.

Indicators of left ventricular systolic function and cardiac preload. Acceleration of the aortic blood flow and its maximal velocity have been demonstrated to reflect cardiac contractility.[77] The duration of the aortic blood flow corrected for heart rate (flow time corrected) is considered a marker of cardiac preload, but it also increases when LV afterload decreases. Despite its inclusion in several protocols of intraoperative fluid management, it cannot reliably predict fluid responsiveness.[76]

Advantages and Limitations

The ED monitoring is almost noninvasive, rapid to learn, and easy to use. It is indicated for the perioperative monitoring of high-risk surgical patients and is quite suitable for assessing the short-term effects of

PLR, for example.[78] However, its use in the ICU setting is limited, in part because the probe moves in the patient's esophagus if the patient is not deeply sedated. Another weakness of the currently commercialized device is the absence of measurement of the diameter of the descending aorta, which is an elastic structure that varies with ABP.[79] Considering it to be constant leads to underestimation of CO changes when ABP varies simultaneously.[79] Finally, the ED cannot estimate as many variables and thus provide as much useful information as PAC and TPTD do, which limits its interest in complex patients with shock.

Bioimpedance and Bioreactance

Bioimpedance

Principle. The bioimpedance technique uses the variation of thoracic impedance related to the fluid shift resulting from the ejection of the stroke volume throughout cardiac cycles.[80] An alternating electric current is applied to the thorax through voltage-generating electrodes, and using mathematical models, the stroke volume is calculated from the differences between inward and outward currents.[81]

Advantages and limitations. Despite being easy to use, this technique suffers from several major limitations. Reaching a correct signal/noise ratio can be challenging. The major limitations are the presence of intrathoracic extravascular fluids (pulmonary edema, pleural effusion), which attenuate the detected signal of arrhythmias, of motion, or of electrical interference. Accordingly, the reliability of this technique has been questioned in spite of several adjustments of its underlying mathematical algorithms.[82]

Bioreactance

Principle and information provided. To improve the signal/noise ratio, computing of the bioimpedance signal has been modified. The revisited technique, called *bioreactance,* focuses not only on the shift in amplitude but also on the phase between the inward and the outward current over the cardiac cycle. It relies only on the pulsatile flow (i.e., the aortic blood volume) and thus is free from potential extravascular thoracic fluids.[83] The Starling SV device (Baxter International, Inc., USA) uses four electrodes placed on the right and left upper and lower parts of the thorax, and the device displays a CO value calculated from the averaged values of the left and right sides.

Advantages and limitations. The major advantage of bioreactance is that it is totally noninvasive. When compared with PAC thermodilution, bioreactance apparently exhibits acceptable accuracy for assessing CO in patients after cardiac surgery.[83] However, its reliability has been seriously questioned in ICU patients,[84–86] including patients with sepsis[84] and cardiogenic shock.[86] The current version of the device (Starling SV) allows monitoring of CO closer to real time than did the previous one (NiCOM; Cheetah Medical, USA) and is able to assess the effects of the PLR test,[87] which the previous version did not.[85] Nevertheless, an important limitation of the bioreactance is that CO is the only value that it can provide.

Noninvasive Arterial Pressure Waveform–Based Cardiac Output Monitoring Devices

Principle and Information Provided

The Clearsight (Edwards Lifesciences, USA) and the NICCI (Pulsion, Germany) devices use the volume clamp method to obtain noninvasive ABP, PPV, and CO monitoring. The Clearsight includes an inflatable cuff, which is wrapped around a finger and a photoplethysmographic device that measures the diameter of the finger arteries at each systole. A fast servo-controlled system immediately inflates the cuff in order to keep the arteries' diameter constant. Therefore the counterpressure is equivalent to the finger ABP, and its continuous measurement allows estimating the finger ABP curve. A brachial ABP waveform is then reconstructed using a transfer correction and a level correction based on a clinical database. The Clearsight includes a proprietary PWA software that computes CO from the systolic pressure area and a physiologic three-element Windkessel model.[88] The NICCI device also uses the volume clamp principle, but the sensor contains two finger cuffs and performs an automatically alternating continuous measurement at the patient's finger.

Advantages and Limitations

Such PWA-based CO monitors could be used in situations requiring hemodynamic intervention when more invasive monitoring modalities are not readily available.[72] As they can provide only CO, PPV, and/or SVV, they are more suitable for use in the OR setting than in the ICU. Relatively good agreement with CO PAC was reported in the perioperative period of cardiac surgery.[89–91] By contrast, a poor agreement between Clearsight CO and TPTD CO and between their changes after a fluid challenge was found in ICU patients.[92] A recent meta-analysis included 19 studies that compared CO obtained by either the Clearsight or the NICCI with thermodilution CO.[93] The percentage error was acceptable (<30%) in only 2/5 of the OR studies and in only 2/14 of the ICU studies.[94] Another study pooled the data of 342 patients and showed that volume clamp CO and bolus thermodilution CO were poorly interchangeable, not only for absolute values but also for the trends.[93] This was particularly true in cases of norepinephrine use and of low ABP.[93]

HEMODYNAMIC MONITORING STRATEGY IN PATIENTS WITH SHOCK (FIG. 32.2)

Careful clinical examination should first be performed in the early phase of shock, as it can provide useful information about the causative mechanism. Furthermore, particular attention should be paid to markers of skin perfusion. The presence of mottling or of prolonged capillary refill time (CRT) is suggestive of a low CO with an excellent specificity but a low sensitivity.[95] A strategy guided by CRT was demonstrated to be noninferior[96] and even better[97] than a strategy based on decrease in blood lactate concentration during early resuscitation of septic shock.

Insertion of an arterial catheter has been recommended in patients with shock.[52,53] In addition to providing real-time accurate measurement of ABP, it allows monitoring PPV. The arterial catheter also allows performing repeated blood sampling that enables arterial blood gas measurement.

Insertion of a central venous catheter has also been recommended in patients with shock.[52,53] It provides measurements of CVP. The transmural value of CVP is a reflection of RV filing pressure and can help to detect RV dysfunction, which then needs confirmation by echocardiography. The intramural value of CVP reflects the backpressure to the perfusion of most vital organs. In this sense, the perfusion pressure is better reflected by the MAP-CVP difference (also called the *mean perfusion pressure;* MPP) than by the MAP alone, especially when CVP is high. The MPP, and not the MAP, was demonstrated to be well associated with the progression of acute kidney injury in ICU patients with a cutoff value of 60 mm Hg.[98] However, neither CVP[13,15] nor its changes during PLR[99] should be used to predict fluid responsiveness. The central venous catheter also provides oxygen saturation ($ScvO_2$), which is considered a reasonable surrogate of SvO_2.[52,53] Specific fiberoptic catheters measure $ScvO_2$ in real time, avoiding any manipulation. However, they are costly, and it is generally considered that intermittent blood sampling is sufficient in practice to obtain $ScvO_2$. In cases of shock, a low $ScvO_2$ (e.g.,

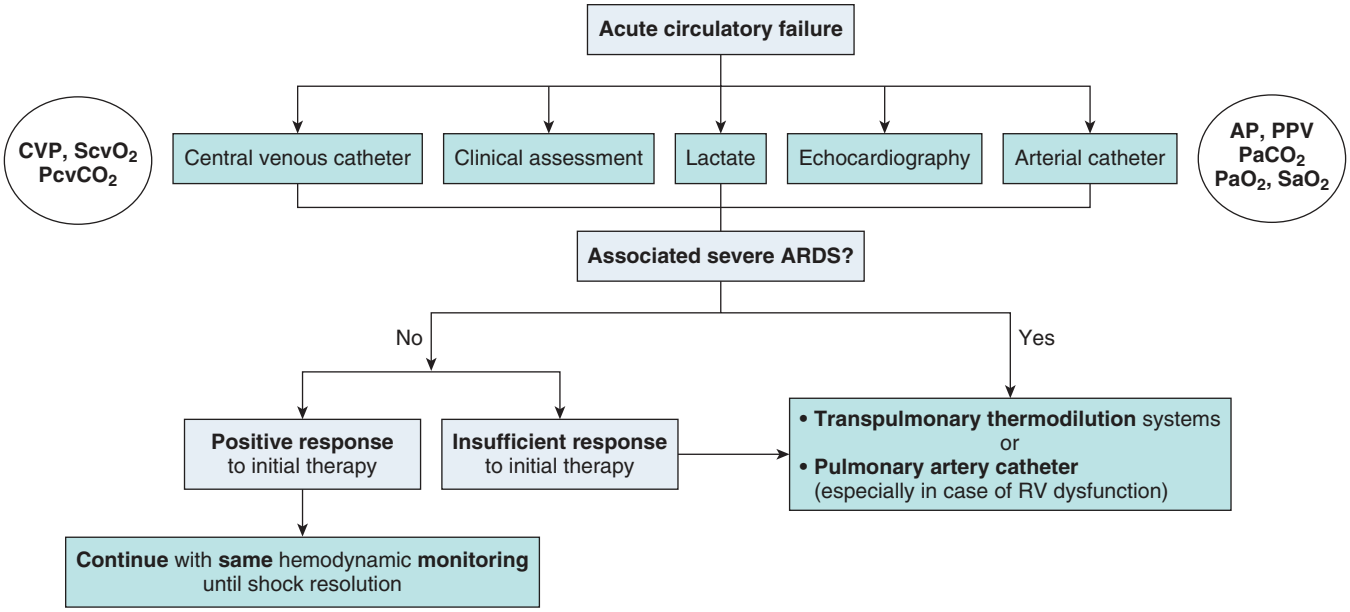

Fig. 32.2 Simplified algorithm for the choice of hemodynamic monitoring in patients with acute circulatory failure. *AP,* Arterial pressure; *ARDS,* acute respiratory distress syndrome; *CVP,* central venous pressure; *$PaCO_2$,* carbon dioxide pressure in the arterial blood; *PaO_2,* oxygen pressure in the arterial blood; *$PcvCO_2$,* carbon dioxide pressure in the central venous blood; *PPV,* pulse pressure variation; *RV,* right ventricular; *SaO_2,* arterial blood oxygen saturation; *$ScvO_2$,* central venous blood oxygen saturation. (From Teboul JL, Saugel B, Cecconi M, et al. Less invasive hemodynamic monitoring in critically ill patients. *Intensive Care Med.* 2016;42[9]:1350–1359.)

<70%) is suggestive of insufficient DO_2 and should prompt clinicians to increase DO_2.[52,53] Conversely, a high value of $ScvO_2$ (e.g., >80%) is suggestive of altered oxygen extraction capabilities. Finally, the central venous catheter provides the central venous carbon dioxide pressure ($PvCO_2$). The difference between $PcvCO_2$ and $PaCO_2$ is generally accepted as a reasonable surrogate of ΔPCO_2[53] and thus may be a good indicator of the adequacy of CO to the global metabolic conditions. In conditions where oxygen extraction is altered and $ScvO_2$ lies within the normal range, an abnormally high $PcvCO_2$-$PaCO_2$ difference (>6 mm Hg) suggests that CO may need to be raised to improve tissue oxygenation.[53] A normal $PcvCO_2$-$PaCO_2$ difference suggests that increase in CO is not a prioritized therapeutic option.

Echocardiography, which is not a monitoring device per se, is the best tool to assess cardiac function at the bedside. It is recommended to be performed as soon as possible in patients with shock.[52,53]

Therefore in the early phase of shock states, several pieces of useful information can be obtained from basic hemodynamic monitoring. In the majority of cases, a logical therapeutic decision based on this information can be made. If the hemodynamic condition improves with the initial therapy, such basic hemodynamic monitoring should be continued until shock resolution. If the hemodynamic response is absent or insufficient, it is recommended to use an advanced monitoring technology such as the PAC or the TPTD system (see Fig. 32.2). The PAC can be useful in the case of severe RV dysfunction diagnosed by echocardiography. The TPTD system is potentially helpful in cases of associated ARDS, as it offers the advantage of reliably assessing the benefit/risk ratio of fluid management: the expected benefit can be assessed by fluid responsiveness indices (obtained from PWA), and the risk can be assessed by EVLW and PVPI. In cases of severe ARDS associated with shock, it has been recommended to use advanced monitoring devices at an earlier phase.[52,53]

In patients with shock, there is a consensus to not use devices such as minimally invasive or noninvasive PWA-based CO monitors.[52,53] First, their validity has been seriously questioned under conditions of alteration of the vascular tone and/or use of vasopressors, and second, they provide intensivists with hemodynamic variables other than CO and fluid responsiveness indices.

It should be emphasized that no monitoring device can change the outcome by itself. The outcome can be improved only if the information provided by the device is appropriately collected and interpreted.

HEMODYNAMIC MONITORING STRATEGY IN THE OPERATING ROOM SETTING

Uncalibrated PWA monitors and ED monitoring have a place in the OR setting when CO monitoring is judged to be helpful for the patient's management. Use of such monitors in goal-directed therapy strategies in the perioperative period of high-risk surgical patients was demonstrated to potentially improve outcome.[12] The choice of ED vs. minimally invasive vs. noninvasive device is not fully codified. It depends on the local policies, the type of surgery (high vs. intermediate vs. low risk), and the patient's clinical condition (high vs. low risk). Some teams use pulse oximeters that can display the variation of the plethysmographic signal—used as a surrogate of PPV—for guiding fluid administration. Doing so is an important issue during surgery,[100] although its relevance has been recently questioned by a meta-analysis.[101] In some specific high-risk procedures (e.g., liver transplantation, esophagectomy, cardiac surgery), some teams monitor hemodynamics using advanced technologies (PAC, TPTD), which can be continued during the postoperative period. Transesophageal echocardiography can also be used in cardiac surgery patients either alone or along with invasive technologies.

THE FUTURE OF HEMODYNAMIC MONITORING

In an ideal world, the future of hemodynamic monitoring should be the addition of what we already have plus what we do not have so far but what we need. Today, we have essentially hemodynamic monitoring devices able to monitor traditional macrocirculatory variables. The two main characteristics of the most valuable current hemodynamic monitoring systems are (1) their invasiveness, even if the terms "minimally invasive" or "less invasive" are often used, and (2) their inability to precisely assess the microcirculation: adequacy of tissue perfusion and oxygenation. Is noninvasiveness the future that we expect? The answer should be positive only if noninvasiveness is associated with accuracy and precision. The current noninvasive CO monitors are used in the OR setting not for their numerical accuracy, but for their theoretical ability to track *changes* in CO. This can be enough in this setting because patients—even high-risk ones—are usually not sick before starting surgery, so that their starting CO is generally normal. What is important in this situation is to reliably track any abrupt decreases in CO. By contrast, in ICU patients, one needs both to measure accurate and precise CO values and to reliably track CO changes. To date, no noninvasive continuous hemodynamic system is able to do this. Hopefully, future technologic advances will provide ICU doctors and nurses with reliable noninvasive hemodynamic monitoring systems.

Another important aspect is to be able to monitor microcirculation and tissue perfusion. We know that correcting macrocirculatory variables cannot guarantee that tissue hypoperfusion has been fully reversed, too. Over the last decade, some technologies have been developed to monitor microcirculation (e.g., sublingual microcirculation) or tissue oxygenation. However, these techniques are still used for research purposes and not for routine practice.[52] We can expect in the near future a technologic jump in this field, allowing ICU caregivers to monitor microcirculation in real time. This would be a first step to integrate new microcirculatory variables in therapeutic strategies.

In addition, progress in technology and data processing that will inevitably occur should make this field very different in the near future from what we currently know. One can expect advances in terms of graphical displays, computerization, miniaturization, connectivity, data transfer from bedside monitors to personal interfaces, and implementation of novel sensors using micro- and nano-electromechanical systems. Finally, advances in artificial intelligence (predictive analytics, machine learning) should certainly help with integrated analysis of many hemodynamic variables collected by the monitoring systems. This should allow clinicians to better analyze the patient's true hemodynamic status and needs and/or to anticipate hemodynamic instability. There are currently devices that use machine learning to predict hypotension in the OR setting.[102] Numerous applications of artificial intelligence will undoubtedly occur in the next few years for hemodynamic monitoring and for therapeutic decision-making processes.[103] The challenge for the intensivist will be to intelligently use artificial intelligence for the benefit of their patients.[103]

KEY POINTS

- Pulmonary arterial catheter use has decreased since the mid-1990s, not only because of its invasiveness but mostly because of the development of bedside echocardiography and the emergence of other hemodynamic monitoring devices.
- Transpulmonary thermodilution coupled with pulse wave analysis provides a reliable measure of cardiac output, extravascular lung water, and preload responsiveness indices.
- Uncalibrated invasive pulse wave analysis monitoring devices provide hemodynamic information from a simple arterial catheter. They belong to the class of functional hemodynamic monitoring devices and could prove helpful to assess fluid responsiveness. However, their ability to accurately estimate cardiac output has been questioned in cases of altered vascular tone, limiting their interest for patients with shock and/or who receive vasopressors.
- Esophageal Doppler monitoring is a minimally invasive method to estimate cardiac output and indices of fluid responsiveness. It is better indicated in high-risk surgery patients than for patients with shock.
- The bioreactance method estimates cardiac output noninvasively. It uses skin surface electrodes delivering a low-amplitude and high-frequency current traversing the thorax. It has a limited place in severe, critically ill patients. More validation studies are necessary to clarify its place in other settings, such as the emergency room.
- Volume clamp methods uses the finger blood pressure to estimate cardiac output noninvasively using pulse wave analysis. However, their reliability has been questioned in critically ill patients. They are not recommended for patients in shock.
- The hemodynamic monitoring strategy to be employed in patients with shock is not strictly codified. Nevertheless, it is logical to take into account clinical information, data obtained from arterial central venous catheters, and, if possible, echocardiographic findings before making therapeutic decisions. In cases of insufficient response to the initial therapy, the use of a pulmonary artery catheter or transpulmonary thermodilution should be considered.

References for this chapter can be found at expertconsult.com.

ANNOTATED REFERENCES

Jozwiak M, Silva S, Persichini R, et al. Extravascular lung water is an independent prognostic factor in patients with acute respiratory distress syndrome. *Crit Care Med.* 2013;41:472–480.
This study showed that extravascular lung water and pulmonary vascular permeability are independent factors associated with mortality in patients with acute respiratory distress syndrome.

Monnet X, Marik P, Teboul JL. Passive leg raising for predicting fluid responsiveness: A systematic review and meta-analysis. *Intensive Care Med.* 2016;42:1935–1947.
This meta-analysis confirms the ability of the passive leg raising test to predict preload responsiveness. It emphasizes the fact that real-time cardiac output measurements are mandatory for assessing the hemodynamic effects of passive leg raising.

Myatra SN, Prabu NR, Divatia JV, et al. The changes in pulse pressure variation or stroke volume variation after a "tidal volume challenge" reliably predict fluid responsiveness during low tidal volume ventilation. *Crit Care Med.* 2017;45:415–421.
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Richard C, Warszawski J, Anguel N, et al. Early use of the pulmonary artery catheter and outcomes in patients with shock and acute respiratory distress syndrome: A randomized controlled trial. *JAMA.* 2003;290:2713–2720.
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In this meta-analysis, noninvasive cardiac output monitoring using volume clamp method devices failed to reliably estimate CO, especially in critically ill patients.

Teboul JL, Saugel B, Cecconi M, et al. Less invasive hemodynamic monitoring in critically ill patients. *Intensive Care Med.* 2016;42:1350–1359.
In this paper authored by an expert panel from the European Society of Intensive Care Medicine, a strategy in terms of hemodynamic monitoring in patients with acute circulatory failure has been proposed.

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33

Bedside Monitoring of Pulmonary Function

John D. Davies and Amanda M. Dexter

PULSE OXIMETRY

Pulse oximetry is a microprocessor-based measurement that incorporates both oximetry and plethysmography to provide continuous noninvasive monitoring of the oxygen saturation of arterial blood (SpO_2). Often considered the "fifth vital sign," pulse oximetry is one of the most important technologic advances for monitoring patients during anesthesia, in the intensive care unit (ICU), on the general ward, in the emergency department, and during a wide variety of procedures. It can quickly detect even small changes in the effectiveness of oxygen uptake from the lung and how efficiently oxygen is carried to the tissues. Common applications for pulse oximetry may include mechanical ventilation, surgical monitoring, sleep evaluations, and effectiveness of certain clinical interventions.

The most common pulse oximeter probe is embedded into either a reusable clip probe or a single-patient adhesive probe and consists of two light-emitting diodes on one side and a light-detecting photodiode on the opposite side. Advantages of the reusable clip probe include utilization rapidity, ease of sampling different sites, and cost-effectiveness.[1] Advantages of the single-patient adhesive probe include less potential for infection transmission, more secure placement, and the ability to monitor at more body sites.[1] The most appropriate type of probe depends on the clinical situation. Either a finger, toe, or earlobe serves as the sample "cuvette" because the skin in these areas has a high vascular density. Pulse oximetry targets the signal arising from the arterial bed as light absorbance fluctuates with changing blood volume. Arterial blood flow causes signal changes in light absorption (the pulsatile component called *photoplethysmography*) that can be distinguished from venous and capillary blood in the surrounding tissues (the baseline, or direct current, component; Fig. 33.1).

According to the Beer-Lambert law, the concentration of a substance can be determined by its ability to transmit light.[2] Oxygenated hemoglobin (HbO_2) and deoxygenated or "reduced" hemoglobin (HbR) species absorb light differently, so the ratio of their absorbencies can be used to calculate HbO_2 saturation. The standard pulse oximeter emits two wavelengths of red light (660 nm and 940 nm) from the light-emitting diode on one side of the probe, through the capillary bed, to a light-detecting photodiode on the other side. Red light emitted at 940 nm is mainly absorbed by HbO_2, whereas red emitted at 660 nm is mainly absorbed by HbR. The difference between the transmitted light and unabsorbed light represents the amount of hemoglobin-bound oxygen and is expressed as a percentage.

In addition, there are two minor hemoglobin (Hb) species: **carboxyhemoglobin** (COHb) and **methemoglobin** (MetHb). Fractional SaO_2 is the proportion of HbO_2 relative to all four hemoglobin species:

$$HbO_2 = HbR + COHb + MetHb$$

Measuring fractional hemoglobin requires a co-oximeter that incorporates four wavelengths to distinguish each species (Fig. 33.2). In contrast, oxygen saturation as determined by pulse oximeter (SpO_2) uses two wavelengths, so that it measures functional SaO_2:

$$HbO_2 + HbR$$

Accuracy and Precision

The accuracy of pulse oximeters has improved over the years. In critically ill patients with an arterial oxygen saturation (SaO_2) >90%, it is now estimated that the mean difference between SpO_2 and SaO_2 is less than 2%.[3,4] Also, the standard deviation of the differences between the measurements represents the precision and has been estimated to be less than 3%.[3,4] However, when the SaO_2 drops below 90%, the accuracy of SpO_2 measurements decreases.[2]

The oxyhemoglobin dissociation curve must be taken into account when interpreting the SpO_2 (Fig. 33.3). If the curve is in a normal position, then high SpO_2 values (96%–98%) represent a PaO_2 in the range of 80–100 mm Hg, whereas SpO_2 values in the low to mid 90s represent a PaO_2 in the range of 60–80 mm Hg. An SpO_2 <90% indicates PaO_2 values that enter into the hypoxemic range. If the curve shifts to the left, a lower PaO_2 will produce a higher SpO_2, whereas the reverse is true if the curve is shifted to the right. Although a left shift in the oxyhemoglobin dissociation curve increases the affinity of Hgb for oxygen, it also makes it more difficult for the Hgb to release oxygen molecules. A right shift in the curve makes it more difficult for the Hgb to load oxygen molecules (see Fig. 33.3).

Dynamic Response

Because pulse oximeters detect very small optical signals (and reject a variety of artifacts), data must be averaged over several seconds, thus affecting the response time.[5,6] A prolonged lag time is more common with finger probes than with ear probes and is attributed to hypoxia-related peripheral vasoconstriction.[5–7] Bradycardia is also associated with a prolonged response time.

Sources of Error

Despite recent technologic advances, there still are a number of factors that may affect the accuracy of the pulse oximeter. Table 33.1 lists the most common ones.

Motion Artifact and Poor Perfusion

Motion artifact and poor perfusion are the most common sources of SpO_2 inaccuracies, which occur because the photoplethysmographic pulse signal is very low in these settings compared with the total

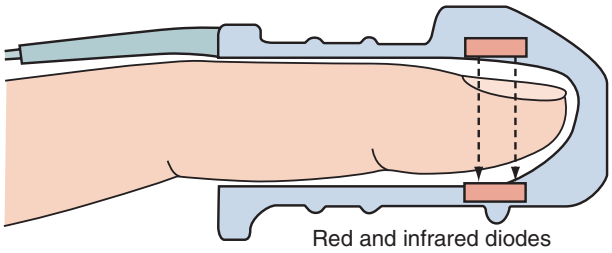

Fig. 33.1 Schematic depiction of the pulse oximeter light absorption signal. (Adapted with permission from Phillips Medical Systems, Carlsbad, California.)

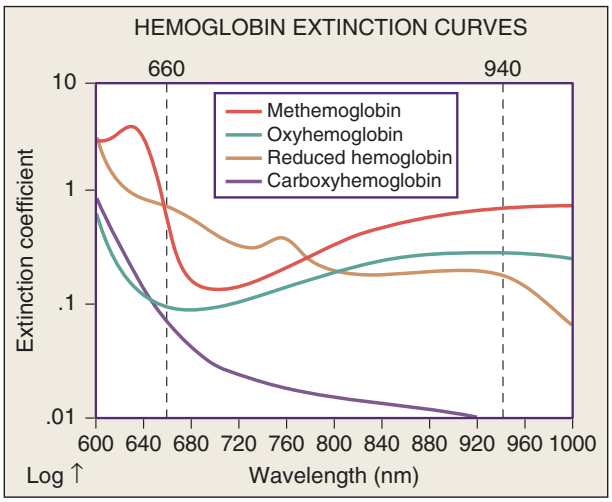

Fig. 33.2 Extinction coefficients of the four types of hemoglobin at the red and infrared wavelengths. Methemoglobin absorbs light at both wavelengths to an equal extent; absorption of red light by carboxyhemoglobin is similar to that of oxyhemoglobin. (From Tremper KK, Barker SJ. Pulse oximetry. *Anesthesiology.* 1989;70:98–108.)

TABLE 33.1 Common Factors Affecting Pulse Oximetry Measurements

Factor	Effect
Carboxyhemoglobin (COHb)	Slight reduction in accuracy of the assessment of oxygen saturation (SaO_2) by pulse oximetry (SpO_2) (i.e., overestimates the fraction of hemoglobin available for O_2 transport)
Methemoglobin (MetHb)	At high levels of MetHb, SpO_2 approaches 85%, independent of actual SaO_2
Methylene blue	Transient, marked decrease in SpO_2 lasting up to several minutes; possible secondary effects as a result of effects on hemodynamics
Anemia	If SaO_2 is normal, no effect; during hypoxemia with Hb values less than 14.5 g/dL, progressive underestimation of actual SaO_2
Ambient light interference	Bright light, particularly if flicker frequency is close to a harmonic of the light-emitting diode switching frequency, can falsely elevate the SpO_2 reading
Blood flow	Reduced amplitude of pulsations can hinder obtaining a reading or cause a falsely low reading
Motion	Movement, especially shivering, may depress the SpO_2 reading
Nail polish	Slight decrease in SpO_2 reading, with greatest effect using blue nail polish, or no change
Sensor contact	"Optical shunting" of light from source to detector directly or by reflection from skin results in falsely low SpO_2 reading
Skin pigmentation	Small errors or no significant effect reported; deep pigmentation can result in reduced signal
Tape	Transparent tape between sensor and skin has little effect; falsely low SpO_2 has been reported when smeared adhesive is in the optical path
Vasodilation	Slight decrease in SpO_2
Venous pulsation	Artifactual decrease in SpO_2

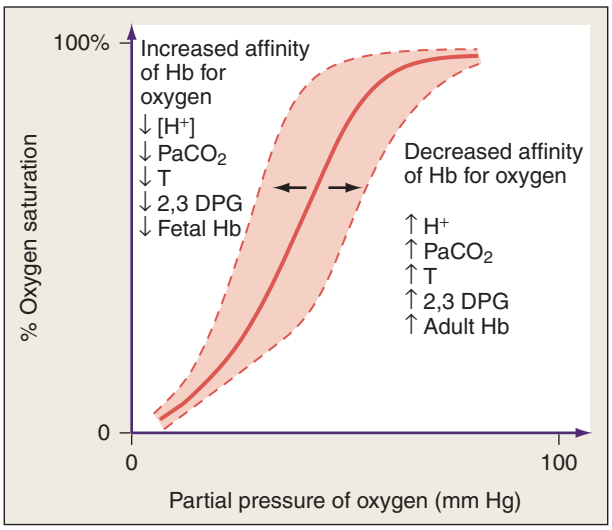

Fig. 33.3 Oxyhemoglobin dissociation curve relates oxygen saturation and partial pressure of oxygen in the blood. The curve is affected by many variables. *2,3 DPG,* 2,3-Diphosphoglycerate; *Hb,* haemoglobin; *$PaCO_2$,* partial pressure of carbon dioxide.

absorption signal.[8,9] The combination of motion artifact and poor perfusion substantially lowers SpO_2 accuracy compared with either artifact alone.[10] Causes of motion artifact include shivering, twitching, agitation, intraaortic balloon pump assistance, and patient transport.[11,12] Signs of motion artifact include a false or erratic pulse rate reading or an abnormal plethysmographic waveform. Peripheral hypoperfusion from hypothermia, low cardiac output, or vasoconstrictive drugs may increase bias, reduce precision, and prolong the time to detect a hypoxic event.[12]

Newer technologies have helped reduce the incidence of these problems, but have not eliminated them as sources of error. Relocation of the probe may be required to obtain a more accurate signal.

Dyshemoglobins and Vascular Dyes

Significant amounts of COHb or MetHb can cause errors in SpO_2 measurements. COHb and HbO_2 absorb equivalent amounts of red light. Because the amount of COHb is elevated in the setting of carbon monoxide poisoning, this results in a falsely elevated SpO_2 value because the pulse oximeter reports on total Hb saturation and not just HbO_2 saturation. The patient, however, could be experiencing profound hypoxemia. In contrast, MetHb causes substantial absorption of both red and infrared light, so the ratio approaches 1 (estimated SpO_2

of 85%).[2] Significant levels of MetHb falsely lower SpO_2 values even when the actual SaO_2 exceeds 85% and falsely elevates values when the true SaO_2 is less than 85%.[2] Additionally, the administration of methylene blue or indocyanine green dyes for diagnostic tests causes a false, transient (1- to 2-minute) drop in SpO_2 to as low as 65%.[13,14]

There are some newer pulse oximeters that claim to measure actual hemoglobin concentration, but validation study results have yielded mixed results.[15,16]

Nail Polish and Skin Pigmentation

Both dark skin pigmentation and dark nail polish interfere with absorption of the wavelengths used by pulse oximetry. Pulse oximeters thus have greater bias and less precision in dark-skinned patients.[8] Whereas an SpO_2 of 92% is sufficient to predict adequate oxygenation in light-skinned patients, a saturation of at least 95% is required in dark-skinned patients.[17] Also, dark nail polish colors can falsely lower SpO_2 values, whereas red polish tends not to affect pulse oximetry accuracy.[18] However, with newer technology, the negative effects of nail polish have been lessened. A study conducted with modern equipment showed an effect of dark nail polish on pulse oximetry readings, but the error was not clinically relevant.[19] When nail polish cannot be removed, mounting the oximeter probe sideways on the finger may yield a more accurate reading.[20]

Ambient Light, Anemia, and Hyperbilirubinemia

Although pulse oximeters compensate for the presence of ambient light, the sensor should be shielded from intense light sources with an opaque material. Falsely low SpO_2 readings occur when even minor gaps exist between the probe and skin, allowing light reflected off the skin's surface to "shunt" directly to the photodiode.[21] Xenon surgical lamps and fluorescent lighting can also cause falsely low SpO_2 values.[22] Under conditions of moderate to severe anemia (e.g., Hb 8 g/dL) and severe hypoxemia (SaO_2 54%), SpO_2 bias is markedly increased (by approximately −14%).[23] Hyperbilirubinemia does not affect SpO_2 directly.[24] However, carbon monoxide is a by-product of heme metabolism, and deeply icteric patients tend to have higher levels of COHb,[24] so SpO_2 may be falsely elevated under those conditions.

Pulsus Paradoxus

Pulsus paradoxus refers to an exaggerated fall in a patient's blood pressure during inspiration. A recent meta-analysis evaluated the relationship between pulsus paradoxus and pulse oximetry. The findings suggested that pulse oximetry plethysmograms can also be used as a noninvasive method for estimating pulsus paradoxus.[25] The authors further suggested that earlier recognition and improved management of elevated pulsus paradoxus may be achievable through the use of a pulse oximeter.[25]

Reflectance Pulse Oximetry

Reflectance pulse oximetry was designed to counter signal-detection problems associated with finger probes during hypoperfusion. The reflectance sensor is designed for placement on the forehead just above the orbital area, where superficial blood flow is abundant and less susceptible to vasconstriction.[26] Whereas traditional probes work by transilluminating a tissue bed and measuring the forward-scattered light on the opposite side of the finger, toe, or earlobe, reflectance probes are constructed with the light-emitting diodes and the photodetector located along the same surface. The photodetector measures the back-scattered light from the skin.[26] In addition, tolerance to site of placement for reflectance pulse oximetry has allowed fetal monitoring during labor.[27] Intraesophageal SpO_2 monitoring is currently under investigation.[28] Anasarca, excessive head movement, and difficulty in securing the probe site are some of the common problems encountered with reflectance pulse oximetry.[29] Light "shunting" from poor skin contact and direct sensor placement over a superficial artery are associated with artifacts.[30] However, recent studies have shown reflectance pulse oximetry to be as effective as phalanx finger sensors in many situations.[31–34]

Clinical Applications

Continuous pulse oximetry provides an early warning sign of evolving hypoxemia. A large single-center randomized controlled trial of perioperative patients found reported incidence rates of hypoxemia (SpO_2 less than 90%) to be 7.9% in patients monitored with pulse oximetry and only 0.4% in patients monitored without an oximeter.[35] From a surgical perspective, a study reported that continuous monitoring of SpO_2 revealed episodic and severe hypoxemic events, with some desaturations lasting as long as 21 ± 15 minutes.[36] Pulse oximetry has also been shown to aid in titrating FiO_2 in patients receiving mechanical ventilation. Two large clinical trials investigated whether or not the SpO_2/FiO_2 (S/F) ratio could be a reliable proxy for the PaO_2/FiO_2 (P/F) ratio in patients with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). The S/F ratio was reported to be a dependable surrogate in patients undergoing surgery, patients requiring increased levels of positive end-expiratory pressure (PEEP), and in calculating the sequential organ failure assessment scores.[37]

CAPNOMETRY

Capnometry affords the measurement and numeric display of expired carbon dioxide (CO_2) at the patient's airway opening. When a waveform plotting CO_2 against time or volume is also displayed, the process is referred to as **capnography**, and the waveform is referred to as a **capnogram**. Capnometry is most commonly used on patients receiving mechanical ventilation and uses infrared light projected through a gas sampling chamber to a detector on the opposite side. CO_2 absorbs infrared light at a peak wavelength of approximately 4.27 μm.[38,39] More infrared light passing through the sample chamber (i.e., less CO_2) causes a larger signal in the detector relative to the infrared light passing through a reference cell. The sample chamber is either connected directly to the Y-adapter of the ventilator circuit (mainstream) or by a sampling line at the Y-adapter that continuously aspirates gas into a sampling chamber located inside the monitor (sidestream). A colorimetric CO_2 detector is an example of a mainstream capnograph. This device has a pH-sensitive indicator that changes color in response to varying CO_2 concentrations during inspiration and expiration. A normal capnograph has a square-wave pattern with four different phases, which begins during the inspiratory phase and will continue through the entire expiratory phase (Fig. 33.4).[39] Phase I is the inspiratory baseline, which is caused by inspired gas with low levels of CO_2. Phase II is the exhalation of mixed fresh and alveolar gas, resulting in a very rapid increase in CO_2 levels. Phase III is the alveolar plateau, where the last of the alveolar gas is sampled; this is commonly the **end-tidal exhaled gas concentration** (P_{ETCO_2}). Phase IV reflects the reversal of gas flow direction (the expiratory downstroke) and the beginning of inspiration.

Abnormal Capnographs

The expired CO_2 waveform can distinguish a variety of pulmonary and airway pathologies. An esophageal intubation is discernible when the end-tidal waveform becomes lower and lower with subsequent breaths and the patient becomes more hypoxic. Other reasons for a flat tracing include capnograph disconnection, near-complete airway obstruction, endotracheal tube perforation, or cardiac arrest.[39,40] An asthmatic

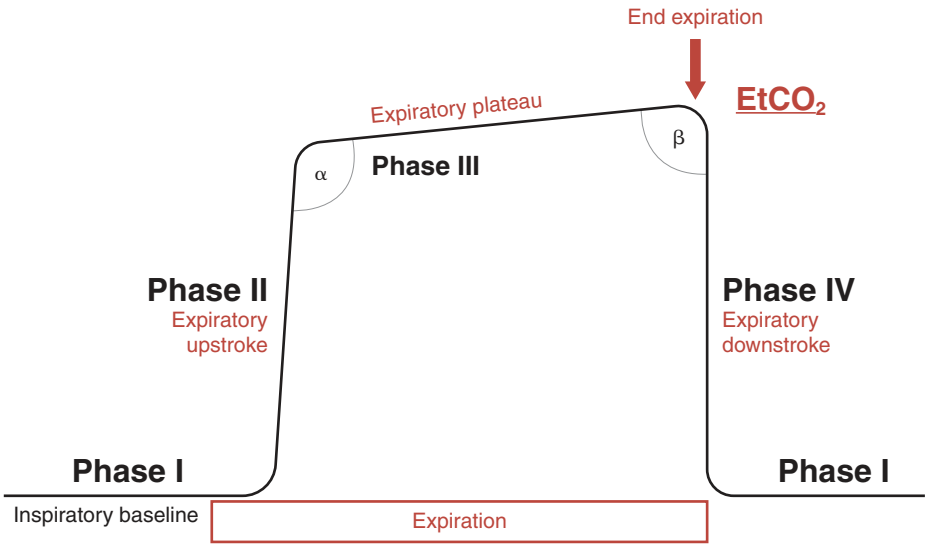

Fig. 33.4 Normal capnography trace. (From Kerslake I, Kelly F. Uses of capnography in the critical care unit. *BJA Education*. 2017;17:178–183.)

patient experiencing a bronchospasm would exhibit the classical sawtooth slope waveform. As the airway obstruction worsens, the slope of the transitional phase becomes more gradual. In patients with emphysema, the alveolar slope would be reversed. Because of a reduced gas exchanging surface and an abnormally increased lung compliance, alveolar gas exchange occurs quite rapidly; thus the waveform peak represents arterial CO_2. A "pigtail" capnograph pattern is typically seen in patients with poor lung compliance. A sudden peak of expired CO_2 occurs because of sudden airway closure.

Clinical Applications

Unlike PO_2 concentrations, venous and arterial blood have PCO_2 values that differ by a relatively small amount. Capnometric determination of the partial pressure of CO_2 in end-tidal exhaled gas (P_{ETCO_2}) is often used during mechanical ventilation as a surrogate with which to monitor changes in the partial pressure of CO_2 in the alveolar gas and (with less precision) in the arterial blood ($PaCO_2$). Although widely available today, how best to use P_{ETCO_2} as a representation of $PaCO_2$ remains unclear in ICU practice. Although perhaps not an exact match for $PaCO_2$, P_{ETCO_2} does provide a valuable trending tool. Also, with newer technologies, the accuracy of P_{ETCO_2} measurements is improving. A recent study reported strong correlations between P_{ETCO_2} and $PaCO_2$ across a wide range of dead-space conditions.[41] Capnometry is used for a variety of purposes, such as in the diagnosis of a pulmonary embolism, determination of lung recruitment response to PEEP, detection of auto (or intrinsic) PEEP (PEEPi), evaluation of weaning progress, and as an indirect marker of elevated dead-space ventilation. Other uses include the assessment of cardiopulmonary resuscitation, indirect determination of cardiac output through partial CO_2 rebreathing, verification of endotracheal cannulation, detection of airway accidents, and even determination of feeding tube placement. Guidelines for the use of capnometry/capnography are outlined by the American Association for Respiratory Care (AARC) (Box 33.1).[42]

$PaCO_2$-P_{ETCO_2} Gradient

Normal subjects have a $PaCO_2$-P_{ETCO_2} gradient of 4–5 mm Hg.[43,44] In critically ill patients, the $PaCO_2$-P_{ETCO_2} gradient can be markedly elevated, with a tendency toward wider gradients in obstructive lung diseases (7–16 mm Hg) than in ALI or cardiogenic pulmonary edema (4–12 mm Hg).[38,41,44–46] The strong correlation between ΔP_{ETCO_2} and $\Delta PaCO_2$ ($r = 0.82$), along with minor bias and reasonable precision between P_{ETCO_2} and $PaCO_2$, suggests that arterial blood gas monitoring may not be needed to assess ventilation unless the ΔP_{ETCO_2} exceeds 5 mm Hg.[47] Nevertheless, several studies have found that the ΔP_{ETCO_2} often falsely predicts the degree and direction of $\Delta PaCO_2$.[45–49] Therefore despite P_{ETCO_2} monitoring, routine arterial blood gas analysis is still required in critically ill patients.

Several factors determine the $PaCO_2$-P_{ETCO_2} gradient. Whereas $PaCO_2$ reflects the mean partial pressure of CO_2 in alveolar gas ($PaCO_2$), P_{ETCO_2} approximates the peak $PaCO_2$. During expiration, lung regions with high ventilation-to-perfusion ratios dilute the mixed CO_2 concentration so that P_{ETCO_2} is usually lower than $PaCO_2$. However, when CO_2 production is elevated (or expiration is prolonged), P_{ETCO_2} more closely resembles mixed venous PCO_2, as a higher amount of CO_2 diffuses into a progressively smaller lung volume. Thus the $PaCO_2$-P_{ETCO_2} gradient can be affected by changes in respiratory rate and tidal volume (VT) because of alterations in expiratory time and by CO_2 production and mixed venous CO_2 content. In fact, it is not uncommon for P_{ETCO_2} to marginally exceed $PaCO_2$. Inotropic or vasoactive drugs may affect the $PaCO_2$-P_{ETCO_2} gradient in an unpredictable manner, either by increasing cardiac output and pulmonary perfusion (thereby reducing alveolar dead space) or by reducing pulmonary vascular resistance and magnifying intrapulmonary shunt by countering hypoxic pulmonary vasoconstriction.

Certain mechanical factors can cause either inconsistencies or inaccuracies in P_{ETCO_2}. The sample tubing length and aspirating flow rates used in sidestream capnometers affect the time required to measure changes in tidal CO_2 concentration. At respiratory frequencies above 30 breaths/min, capnometers tend to underreport the true P_{ETCO_2}. This may occur because of gas mixing between adjacent breaths during transport down the sampling line and in the analysis chamber.[50] This problem can be avoided with mainstream analyzers, which provide near-instantaneous CO_2 measurement (less than 250 msec).[51]

$PaCO_2$-P_{ETCO_2} Gradient, PEEP, and Lung Recruitment

PEEP may recruit collapsed alveoli, improve ventilation-perfusion matching, and reduce alveolar dead space, but excessive levels cause overdistention and increased alveolar dead space. Because the

Box 33.1 American Association for Respiratory Care (AARC) Clinical Practice Guideline: Capnography/Capnometry During Mechanical Ventilation

Indications

- There are three broad categories of indications for capnography/capnometry: verification of artificial airway placement, assessment of pulmonary circulation and respiratory status, and optimization of mechanical ventilation.
  - Verification of artificial airway placement. Even when the endotracheal tube is seen to pass through the vocal cords and tube position is verified by chest expansion and auscultation during mechanical ventilation, providers should obtain additional confirmation of airway placement with waveform capnography or an exhaled CO_2 or esophageal detector device.
  - Assessment of pulmonary circulation and respiratory status. Capnography assists in:
    - Determining changes in pulmonary circulation and respiratory status sooner than pulse oximetry. In patients without lung disease, substantial hypercarbia may present before pulse oximetry notifies the clinician of a change in ventilation.
    - Monitoring the adequacy of pulmonary, systemic, and coronary blood flow, in addition to estimation of the effective (nonshunted) pulmonary capillary blood flow by a partial rebreathing method.
    - Evaluating the partial pressure of exhaled CO_2, especially P_{ETCO_2}.
    - Screening for pulmonary embolism.
  - Optimization of mechanical ventilation. Capnography during mechanical ventilation allows:
    - Continuous monitoring of the integrity of the ventilator circuit, including the artificial airway or bag mask ventilation, in addition to potentially detecting mechanical ventilation malfunctions.
    - Decreasing the duration of ventilatory support.
    - Adjustment of the trigger sensitivity.
    - Evaluation of the efficiency of mechanical ventilation by the difference between $PaCO_2$ and P_{ETCO_2}.
    - Monitoring of the severity of pulmonary disease and evaluating the response to therapy, especially therapies intended to improve the ratio of dead space to tidal volume (VD/VT) and ventilation-perfusion matching ($\dot{V}/\dot{Q}$).
    - Monitoring of $\dot{V}/\dot{Q}$ during independent lung ventilation.
    - Monitoring of inspired CO_2 when it is being therapeutically administered.
- Graphic evaluation of the ventilator-patient interface. Evaluation of the capnogram may be useful in detecting rebreathing of CO_2, obstructive pulmonary disease, the presence of inspiratory effort during neuromuscular blockade, cardiogenic oscillations, esophageal intubation, and cardiac arrest.
- Measurement of the volume of CO_2 elimination to assess metabolic rate and/or alveolar ventilation.
- Monitoring of VD/VT to determine eligibility for extubation in children.
- There is a relationship between VD/VT and survival in patients with acute respiratory distress syndrome.

Contraindications

- There are no absolute contraindications to capnography in mechanically ventilated patients, provided the data obtained are evaluated with consideration given to the patient's clinical condition.

Hazards/Complications

- Hazards/complications are different for the two types of capnographic devices.
  - Mainstream:
    - Dead space. Adapters inserted into the airway between the airway and the ventilator circuit should have a minimal amount of dead space. This effect is inversely proportional to the size of the patient being monitored.
    - The addition of the weight of a mainstream adapter can increase the risk of accidental extubation in neonates and small children.
  - Sidestream:
    - The gas sampling rate from some sidestream analyzers may be high enough to cause auto-triggering when flow triggering of mechanical breaths is used. This effect is also inversely proportional to the size of the patient.
    - The gas sampling rate can diminish delivered VT in neonates and small patients while using volume-targeted or volume-controlled ventilation modes.

Assessment of Need

- Capnography is considered a standard of care during general anesthesia.
- The American Society of Anesthesiologists has suggested that capnography be available for patients with acute ventilatory failure on mechanical ventilatory support.
- The American College of Emergency Physicians recommends capnography as an adjunctive method to ensure proper endotracheal tube position.
- The 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care recommend capnography to verify endotracheal tube placement in all age groups.
- Assessment of the need to use capnography with a specific patient should be guided by the clinical situation. The patient's primary cause of respiratory failure and the severity of his or her condition should be considered.

Assessment of Outcome

- Results should reflect the patient's condition and should validate the basis for ordering the monitoring. Documentation of results (along with all ventilatory and hemodynamic variables available), therapeutic interventions, and/or clinical decisions made based on the capnogram should be included in the patient's chart.

Monitoring

- During capnography, the following should be considered and monitored:
  - Ventilatory variables: tidal volume, respiratory rate, positive end-expiratory pressure, inspiratory-to-expiratory time ratio (I:E), peak airway pressure, and concentrations of respiratory gas mixture.
  - Hemodynamic variables: systemic and pulmonary blood pressures, cardiac output, shunt, and ventilation-perfusion imbalances.

From AARC clinical practice guideline: Capnography/capnometry during mechanical ventilation. *Respir Care*. 2011;56:503–509.

$PaCO_2$-P_{ETCO_2} gradient correlates strongly with the physiologic dead space–to–tidal volume ratio (VD/VT), this gradient may be useful in titrating PEEP in patients with ALI or ARDS. An animal model of ARDS found that stepwise application of PEEP progressively reduced the $PaCO_2$-P_{ETCO_2} gradient and coincided with maximal or near-maximal improvements in oxygenation.[52] However, PEEP applied beyond the lowest $PaCO_2$-P_{ETCO_2} gradient caused a secondary rise in the gradient, along with decreased cardiac output. Another study found that the $PaCO_2$-P_{ETCO_2} gradient narrowed (from 14 to 8 mm Hg) and oxygenation improved when PEEP was set at the lower inflection point of the pressure-volume inflation curve of the respiratory system.[53] When PEEP was set 5 cm H_2O above the lower inflection point, the $PaCO_2$-P_{ETCO_2} gradient rose to 11 mm Hg and cardiac output trended downward. In patients without a clear lower inflection point, the

$PaCO_2$-P_{ETCO_2} gradient did not change in response to PEEP. Thus in a subset of ARDS patients, the $PaCO_2$-P_{ETCO_2} gradient may be an effective way to titrate PEEP.

Newer-generation ventilators have integrated mainstream "volumetric" CO_2 (Vcap) sensors that allow for simultaneous bedside measurements of physiologic and alveolar dead space.[54] Measurement of dead space could potentially provide a monitoring parameter to follow in assessing pulmonary function, as discussed later.[54] Although Vcap is a promising physiologic tool, further research is needed to define its diagnostic value.

P_{ETCO_2} Monitoring During Cardiopulmonary Resuscitation

Monitoring end-tidal CO_2 concentration is a reliable method for evaluating the effectiveness of cardiopulmonary resuscitation.[55] In animal models, P_{ETCO_2} is strongly correlated with coronary perfusion pressure and successful resuscitation,[56] whereas in humans, changes in P_{ETCO_2} are directly proportional to changes in cardiac output.[57] P_{ETCO_2} during precordial compressions can distinguish successful from unsuccessful resuscitation technique, with values greater than 10 mm Hg[58] or greater than 16 mm Hg[59] associated with successful resuscitation.

Measurement of Dead-Space Ventilation

Ventilation-perfusion abnormalities are the primary physiologic disturbance in nearly all pulmonary diseases and the principal mechanism for elevated $PaCO_2$.[60] Dead-space ventilation (VD), the portion of VT that does not encounter perfused alveoli, directly affects CO_2 excretion and is used as an indirect measure of ventilation-perfusion abnormalities. Physiologic VD represents the summation of dead-space components attributable to anatomic-conducting airways and underperfused alveoli.

Physiologic VD/VT historically has been measured during a 3- to 5-minute exhaled gas collection into a 30- to 60-L Douglas bag. An arterial blood gas reading is obtained during the midpoint of the collection. VD/VT is calculated using the Enghoff modification of the Bohr equation, whereby the difference between $PaCO_2$ (a surrogate for the mean $PaCO_2$) and mean expired CO_2 tension (P_{ECO_2}) is divided by $PaCO_2$:

$$\frac{VD}{VT} = \frac{(PaCO_2 - P_{ECO_2})}{(PaCO_2)}$$

The dead-space volume per breath or per minute can be determined by multiplying VD/VT by the simultaneously measured average VT or minute ventilation ($\dot{V}_E$)[61]:

$$VD = \frac{(PaCO_2 - P_{ECO_2})}{(PaCO_2)} \times VT \text{ or } VD = \frac{(PaCO_2 - P_{ECO_2})}{(PaCO_2)} \times \dot{V}_E$$

Alveolar minute ventilation is obtained by subtracting the physiologic VD per minute from the $\dot{V}_E$. It can also be calculated as the volume of CO_2 produced per minute ($\dot{V}CO_2$) divided by the $PaCO_2$[61]:

$$\dot{V}_A = \frac{(\dot{V}CO_2)}{(PaCO_2)} \times 0.863$$

Although expired gas collection with a Douglas bag is the classic method for measuring VD/VT, the gas collection system requires additional valving and connectors, making the procedure time-consuming and awkward. Metabolic monitors produce equally accurate, reliable results and are less cumbersome.[62,63] The Douglas bag method and metabolic monitors, however, do share a limitation when used on a mechanically ventilated patient. During mechanical ventilation, gas is compressed in the circuit, which dilutes the fractional expired CO_2 concentration. A correction factor can be used to offset the mathematical effects of gas compression. Volumetric capnography is a convenient alternative method of measuring P_{ECO_2} and VD/VT and has the advantage of being measured at the patient, thus eliminating the effects of compression volume contamination and the need to apply a correction factor.[64] In patients with ARDS, it has been shown that measurements of VD/VT using volumetric capnography are as accurate as those obtained through the use of a metabolic monitor.[65]

A significant source of measurement error for VD/VT is the contamination of expired gas with circuit compression volume. During positive-pressure ventilation, part of the VT is compressed in the circuit, and during expiration, this gas mixes with CO_2-laden gas from the lungs. The dilution of the expired CO_2 results in a falsely elevated VD/VT that is directly proportional to the peak inspiratory pressure and circuit compliance. Clinically, correcting VD/VT for compression volume is done by multiplying the measured P_{ECO_2} by the ratio of the ventilator-set VT to the VT delivered to the patient.[65]

Clinically, VD/VT may assist in the management of pulmonary disease in terms of both ventilator adjustments and diagnostic testing. VD/VT tends to decrease as lung units are recruited but increase with lung overdistention during PEEP titration in ARDS. A recent study involving the use of dead-space calculations in ARDS reported that increased dead space is associated with higher mortality in the early and intermediate phases of ARDS.[66] Fletcher and Jonson used VD/VT to optimize VT and inspiratory time settings during general anesthesia.[67] Measuring VD/VT may assist in identifying patients who can be removed from mechanical ventilation. Hubble and coworkers found that values less than 0.50 predicted successful extubation, and values greater than 0.65 identified patients at risk for postextubation respiratory failure.[68]

One of the main clinical uses of VD/VT is to aid in the diagnosis of acute pulmonary embolism. VD/VT is comparable to radioisotopic lung scanning in detecting acute pulmonary embolism, with a value less than 0.40 suggesting that a significant embolus is improbable.[69] Single-breath estimates of alveolar VD are also capable of identifying patients with a pulmonary embolus.[70] Increased physiologic VD/VT (greater than 0.60) was found to be significantly associated with mortality in patients with ARDS and in neonates with congenital diaphragmatic hernia.[71,72] The finding that VD/VT is elevated early in the course of ARDS and is associated with increased mortality risk may be particularly useful. The efficacy of new therapies for ARDS may be judged, in part, by their ability to reduce VD/VT.

Transcutaneous Monitoring

Transcutaneous blood gas monitoring involves the use of a skin surface sensor to provide continuous noninvasive estimates of arterial PO_2 and PCO_2 (TcO_2 and $TcCO_2$, respectively). The sensor warms the skin to promote "arterialization" and to increase the permeability of the skin to O_2 and CO_2. Elements of the sensor include a heating element, an O_2 electrode, and a CO_2 electrode. The electrodes measure the gas tensions in an electrolyte gel located between the sensor and the skin. Similar to end-tidal CO_2 ($ETCO_2$) monitoring and pulse oximetry, transcutaneous monitoring has the potential advantages over direct arterial blood gas sampling of reducing the amount of blood drawn, time spent for analysis, patient discomfort, and associated costs. $TcCO_2$ tends to be more reliable than $ETCO_2$, most likely because of the greater diffusion capacity of CO_2 through the skin and the skin's own O_2 consumption.[73] $TcCO_2$ has historically been used more frequently in neonatal and pediatric populations, but recent technologic advances have extended its utilization to adults, despite the blunting

effects of a thicker epidermis. Transcutaneous blood gas monitoring has been commonly used to provide a picture of PCO_2 trends in patients with acute and chronic respiratory failure.[74] It has been shown to be particularly accurate in neonates because of their thin, poorly keratinized skin, which has fewer barriers to diffusion of capillary gases.[75]

The gradient between $TcCO_2$ and $PaCO_2$ is influenced by skin perfusion and skin temperature. Thus factors affecting cutaneous vasoconstriction (e.g., vasopressors, cardiac output, cutaneous vascular resistance) could potentially influence $TcCO_2$ measurements. Technical factors that can affect the accuracy of $TcCO_2$ measurements are similar to those of $ETCO_2$ monitoring and center around the inevitable gradient with $PaCO_2$.

The accuracy of transcutaneous arterial blood gas measurement in adults remains a point of debate. A number of studies have reported that $TcCO_2$ monitoring is accurate in adult patients with respiratory disorders.[76–79] Some studies have even suggested that $TcCO_2$ monitoring may be more accurate than $ETCO_2$ monitoring owing, in part, to the elimination of dead space.[80–82] Transcutaneous monitoring has been used in several clinical settings to determine the presence of hypoventilation or respiratory depression, including sleep studies, ventilatory management, bronchoscopies, and pulmonary function studies. However, some reports suggest that $TcPO_2$ is not accurate enough to be used clinically for ICU applications in adult populations or even in preterm infants.[83,84]

ASSESSMENT OF PULMONARY MECHANICS

Assessment of basic pulmonary mechanics is crucial to monitoring pulmonary function during mechanical ventilation. Monitoring pulmonary mechanics assists the clinician in adjusting ventilator settings, diagnosing lung conditions, and assessing the severity of lung impairment. At the bedside, changes to these mechanics can occur rapidly, meriting a speedy response, or they may reveal as slow trends in pulmonary conditions, prompting care plan adjustments. Assessment of pulmonary mechanics during constant-flow controlled ventilation requires the measurement of VT, peak inspiratory flow rate, and four pressures: peak airway pressure (Paw); end-inspiratory plateau pressure; end-expiratory pressure in the circuit; and, if auto-PEEP is suspected, end-expiratory pressure measured during an end-expiratory pause maneuver. Static measurements of pulmonary mechanics rely on circuit occlusions to create a no-flow situation, whereas dynamic measurements assess mechanical properties of the respiratory system continuously during mechanical ventilation (including flow-related components). From these measured variables, the compliance and resistance of the respiratory system are determined.

Compliance

Under conditions of passive mechanical ventilation, peak airway pressure denotes the total force per unit area necessary to overcome the resistive and elastic recoil properties of the respiratory system (i.e., both lungs and chest wall) and is expressed as the ratio of volume added (tidal volume) to pressure increment applied. Compliance determined from airway pressure is a measure of the elastic properties of the respiratory system, including the series-coupled lung and the chest wall. In clinical practice, pulmonary compliance is separated into two different measurements, dynamic compliance and static compliance. Dynamic compliance is the ratio of volume added to the inflation Paw above PEEP and therefore includes the resistive forces in the tracheobronchial tree. A more useful measurement is that of static compliance. Static compliance requires the use of an end-inspiratory hold. During an end-inspiratory pause, peak airway pressure dissipates down to a stable plateau pressure. At the end of the inspiratory hold maneuver, "static" conditions usually exist (resistive forces have been dissipated), and the corresponding "plateau pressure" represents the elastic recoil pressure of the respiratory system (Fig. 33.5).

Dividing the VT by the plateau pressure (Pplat) minus the PEEP yields the static compliance of the respiratory system (Crs-stat). Mechanically ventilated patients with "normal" lung physiology have a static respiratory compliance of 50–100 mL/cm H_2O.[85] Even at moderate levels of VE (greater than 10 L/min), dynamic gas trapping can occur (creating auto-PEEP) and, if suspected, Crs-stat must be calculated using total PEEP (PEEPtot) measured during an end-expiratory pause, rather than the PEEP applied at the airways:

$$\text{Crs}-\text{stat}=\frac{\text{VT}}{(\text{Pplat}-\text{PEEPtot})}$$

During patient-triggered ventilation, the assessment of pulmonary mechanics becomes more difficult because of the patient's spontaneous efforts, which may falsely raise or lower the Pplat. Obtaining an accurate measurement requires that the clinician perform the inspiratory hold when spontaneous efforts are absent, and the applied pause will most likely be of shorter duration.

Resistance

Respiratory system resistance (Rrs) is the ratio of the airway to alveolar pressure difference (Paw – Pplat) to flow. It describes the opposition to air flow through the respiratory tract during inspiration, including frictional forces. It is calculated as the difference between Paw and Pplat divided by the preocclusion peak inspiratory flow rate ($\dot{V}_I$) and expressed as cm H_2O/L per second:

$$\text{Rrs}=\frac{(\text{Paw}-\text{Pplat})}{\dot{V}_I}$$

Graphically, that pressure overcoming Rrs can be depicted as the difference between Paw and Pplat (see Fig. 33.5). Resistance, however, is flow dependent, because the driving pressure necessary to overcome resistance increases disproportionately to flow (because of increased turbulence). Therefore Rrs can be accurately determined only for a specified inspiratory flow (square wave) pattern. The level of Rrs strongly depends on the diameter of the airways and whether airflow is laminar or turbulent. Turbulent flow is commonly present in large

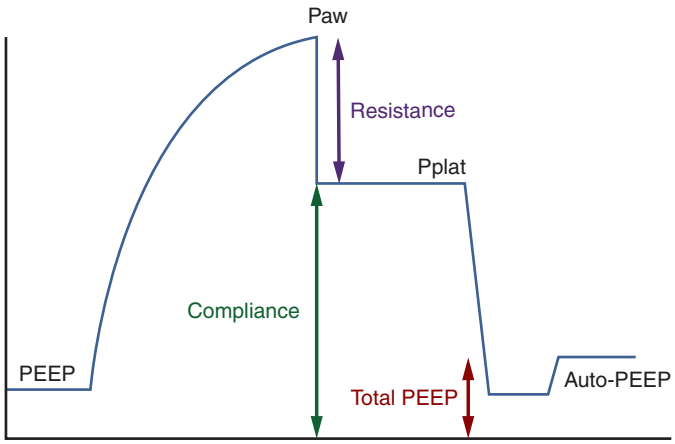

Fig. 33.5 Elements of an inspiratory pressure waveform. *Auto-PEEP,* Auto positive end-expiratory pressure; *Paw,* peak airway pressure; *PEEP,* positive end-expiratory pressure; *Pplat,* plateau pressure.

airways and at major bifurcations, whereas laminar flow is present at the slower velocities in the peripheral conducting airways. Poiseuille's law explains how relatively small changes in the radius of the airways cause large changes in airway resistance: $R = 8\ nl/\pi r^4$.[86]

Compliance and Resistance in Normal and Pathologic Conditions

In mechanically ventilated normal patients, compliance ranges from 50 to 100 mL/cm H_2O, and Rrs is 1–8 cm H_2O/L per second.[85,87] The effects of compliance and Rrs can also be displayed graphically from the monitor tracings of the mechanical ventilator. Fig. 33.5 illustrates where, during inspiration with an inspiratory pause, the effects of respiratory system compliance and resistance are visualized. In the face of decreasing compliance, an elevation in Pplat can be seen with little change to the Paw–Pplat differential. An increase in the Paw–Pplat differential with an unchanged Pplat represents an increased Rrs. Abnormalities in compliance and resistance in patients are dependent on both the cause and severity of the disease. Decreased compliance may occur in the case of ARDS, atelectasis, pneumothorax, lung fibrosis, or chest wall stiffness.[85–87] Assuming normal chest wall properties, monitoring compliance in ARDS patients can provide useful information about the volumetric capacity of aerated lung, as compliance reflects primarily the number rather than the stiffness of alveolar units. For this reason, compliance is also influenced by predicted lung size. An increase in compliance of individual lung units occurs in patients with emphysema. Increased Rrs may occur in the case of chronic obstructive pulmonary disease (COPD) or asthma, a narrow endotracheal tube, excessive secretions, use of a heat and moisture exchanger (HME), and incorrect positioning or kinking of the endotracheal tube.

Dynamic Gas Trapping and Intrinsic Positive End-Expiratory Pressure

At end expiration, if there is insufficient time for a patient to exhale completely to resting volume, gas gets trapped in the lungs, creating alveolar pressure that is above the set circuit baseline pressure. This phenomenon is referred to as *intrinsic PEEP (PEEPi)* or *auto-PEEP* (the terms are often used interchangeably). PEEPi can be measured by an end-expiratory circuit occlusion maneuver, whereby after a normal expiratory time elapses, both the inspiratory and expiratory ventilator valves close for 3–5 seconds, allowing alveolar pressure to equilibrate with the circuit pressure (see Fig. 33.5). This pressure represents the global average PEEPi through the airway channels that remain open at end expiration. The presence of PEEPi may also be detected by observing the expiratory flow graphic during tidal breathing. Fig. 33.6 shows the flow pattern from a patient who has normal exhalation mechanics (green tracing) contrasted with an expiratory flow waveform from a patient who had insufficient time for exhalation (red tracing). This graphical method of PEEPi identification does not quantify the amount of PEEPi. It is very important, however, to keep in mind that different degrees of PEEPi may coexist in the lungs because of regional variations in lung mechanics and differing time constants caused by the underlying pathology. PEEPi is more common in mechanically ventilated patients with COPD (in which dynamic hyperinflation slows elastic recoil) and patients who require high respiratory rates (which allow inadequate time for complete exhalation). There is evidence associating ventilator-triggering asynchrony (including missed, untriggered efforts) to PEEPi.[88,89] Trigger asynchrony may manifest itself as delayed triggering (in which there is a significant time lag between the initial patient effort to get a breath and the ventilator recognizing the effort) or as a missed trigger (the ventilator doesn't recognize patient effort and doesn't respond at all to the effort). PEEPi can predispose the patient to increased work of breathing, barotrauma, hemodynamic instability, and difficulty in triggering the ventilator.

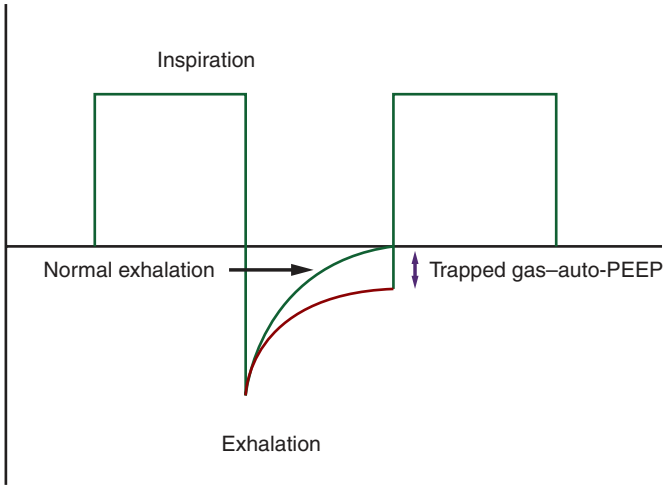

Fig. 33.6 Expiratory flow. *Green,* normal expiration; *red,* expiratory flow leading to auto-PEEP.

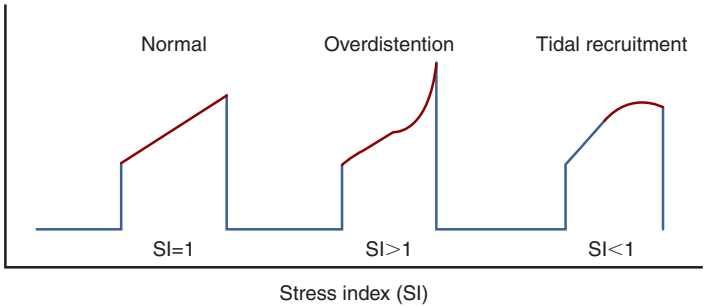

Fig. 33.7 Graphic representation of the stress index concept. The stress index is the coefficient b of a power equation (airway pressure = a · inspiratory time^b + c).

Stress Index

An alternative ventilatory measurement has been described in the literature to assist in lung protective management strategies. The visualization and assessment of a constant slope or "straight line" in the pressure-time ventilator waveform during inflation with constant ("square wave") flow, also known as the *stress index (SI),* has been used as a tool to help lessen the incidence of ventilator-induced lung injury (VILI) in mechanically ventilated patients.[90–93] Under such conditions, time is a linear analog of volume, so that the inflation Paw vs. time slope represents the inverse of compliance or elastance. To perform the SI, the patient must be placed on volume assist control ventilation with a square wave of flow and then the pressure-time waveform is observed (Fig. 33.7). The patient must also be passive during this maneuver. Any patient effort will distort the pressure-time waveform, thus preventing proper interpretation. The SI can be characterized by three profiles: (1) linear (normal), (2) upward convexity (overdistention), and (3) downward concavity (tidal recruitment). If an upward convexity is present, clinicians should consider lowering either the Vt or PEEP level to relieve overdistention. A downward concavity indicates improving respiratory system compliance. In this situation, PEEP could be added to take up some of the recruitment that occurs during the tidal breath. A linear SI is thought to be more optimal.[90–92,94]

Pressure-Volume Curves

A pressure-volume (P-V) curve traces changes in pressures and corresponding changes in volume. The static or quasi-static pressure-volume relationship can be used to analyze the elastic properties of the respiratory system and help guide mechanical ventilation.[95,96] P-V curves usually have a sigmoidal shape (Fig. 33.8). When inflation begins below functional residual capacity (FRC), there is relatively little volume change as transpulmonary pressure increases. This is referred to as the *starting compliance* and corresponds to the first 250 mL of volume change.[97] It reflects either the relatively high pressure required to overcome small airway closure in the dependent lung zones or the relatively small volume of aerated lung tissue as inflation commences. Typically, this low-compliance segment in the P-V curve is followed by an abrupt slope change with an appearance convex to the horizontal pressure axis that is termed the **lower inflection zone**, or Pflex. A common interpretation of the lower inflection "point" (actually a range) is that it signifies the pressure at which there is rather abrupt reopening of collapsed peripheral airways and alveoli.[98–100] Above the lower inflection point, the P-V curve becomes more linear, even though recruitment continues to occur to a limited extent.[101] As the total lung capacity is approached, compliance decreases and the P-V curve becomes concave to the pressure axis (bow-shaped). This appearance is thought to signify the loss of distensibility at maximal inflation. This change "point" (actually a zone) is termed the **upper inflection point.**[101]

As the lung is deflated, the linear portion of the curve is referred to as the *deflation compliance,* or true physiologic compliance, as it represents the elastic properties of the lung after full recruitment.[102] As lung deflation proceeds below FRC, an inflection point often occurs on the deflation limb that represents small-airway closure.[102] This airway closure tends to occur at a lower pressure than the lower inflection point on the inflation limb because the minimal force necessary to maintain patent airways is less than the pressure needed to recruit collapsed ones. Ideally a P-V curve should be constructed under static conditions (no flow) to eliminate the flow-resistive effects, which would distort the curve (super syringe method). However, because of the long duration required to construct the curve and the fact that the patient needs to be removed from the ventilator (risking derecruitment), this is unrealistic in the clinical arena. Most newer-generation ventilations employ a constant flow technique using extremely low inspiratory and expiratory flows (minimal flow-resistive effects) to accurately construct a P-V curve.[103] With either of these methods, the patient cannot make any spontaneous efforts, as that will render appropriate interpretation of the curve impossible.

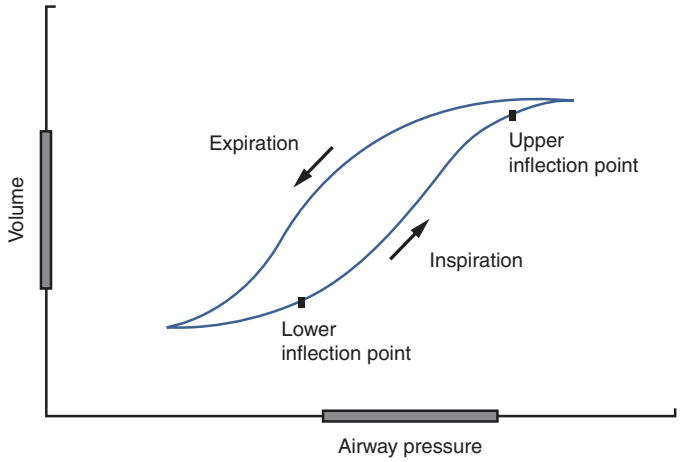

Fig. 33.8 Pressure-volume curve.

Hysteresis

Hysteresis refers to the difference in pressures necessary to achieve the same volume during inflation versus deflation. Compliance tends to be higher during deflation than inflation because higher pressures may be required during inspiration to overcome surface forces and recruit collapsed alveoli. This "extra" pressure is not required during deflation to prevent derecruitment. Ultimately then, the deflation limb may be more important for setting PEEP, as prevention of alveolar collapse—not reopening—is PEEP's primary purpose.[104]

ASSESSMENT OF BREATHING PATTERN AND CENTRAL DRIVE

Rate and Tidal Volume

Basic assessment of the respiratory pattern includes the measurement of respiratory rate and tidal volume (VT). A normal respiratory rate is 12–24 breaths/min, and mechanical ventilation is generally indicated when the rate exceeds 30 breaths/min.[105] A VT of 5 mL/kg is considered sufficient to maintain unassisted breathing.[106] Tachypnea is often the earliest sign of impending respiratory failure, even when arterial blood gases remain within normal limits. This may reflect the fact that muscle fatigue (which results from a mechanical workload that exceeds the power capacity of the ventilatory muscles) occurs before overt ventilatory pump failure. If untreated, a rapid, shallow breathing pattern can develop that will be progressively ineffective in maintaining acceptable arterial blood gas values.

Of particular interest is the utility of breathing pattern in assessing the feasibility of weaning from mechanical ventilation. Typically, patients who fail to wean are more tachypneic (respiratory rate greater than 30 breaths/min) and have an abnormally low VT (less than 200 mL). The respiratory rate–VT ratio, also known as the rapid shallow breathing index (RSBI), is a method that helps in evaluating readiness to wean. The RSBI is thought to be an accurate predictor of breathing effort.[107,108] An RSBI threshold of less than 105 has both a high positive predictive value (0.78) and high negative predictive value (0.95) for the ability to maintain unassisted breathing.[109] Although not an absolute predictor in and of itself, RSBI can be a valuable tool in helping to predict readiness to wean.

Central Ventilatory Drive

In some situations, clinicians may want to assess the central ventilatory drive. A heightened drive will increase the patient's work of breathing during mechanical ventilation.[110] Measuring the respiratory rate corresponding to the minute ventilation gives the clinician an indication of the central ventilatory drive, but it is influenced by respiratory system compliance and does not reflect the depth of the drive. Depth of the drive can be measured by a brief (100 msec) inspiratory occlusion shortly after the onset of an effort, called $P_{0.1}$. Briefly occluding the airway at the onset of inspiratory effort results in isometric contraction of the inspiratory muscles, so $P_{0.1}$ is relatively independent of respiratory system mechanics.[111] Measuring airway pressure at 100 msec indirectly reflects efferent motor neuron output. An increasing stimulus to the inspiratory muscles causes a more forceful contraction, with a proportional increase in pressure development. The selection of 100 msec is based on the fact that conscious or nonconscious perception of (and response to) sudden load changes requires approximately 250 msec.[112] During mechanical ventilation, the lag associated with the trigger phase provides sufficient time to measure $P_{0.1}$. Many of the newer ventilators now incorporate an automated $P_{0.1}$ maneuver.

In a healthy adult at rest, $P_{0.1}$ tends to range between 0.5 and 1.5 cm H_2O. In adult patients receiving mechanical ventilation, values exceeding 3.5 cm H_2O are considered elevated respiratory effort.[112]

A limitation of the $P_{0.1}$ is that it dissociates from ventilatory drive when muscle weakness is present or hyperinflation alters the force-length relationship of the inspiratory muscles.

KEY POINTS

- Pulse oximetry is a noninvasive and painless assessment tool that rapidly measures even small changes in oxygen saturation levels.
- Oxyhemoglobin and carboxyhemoglobin absorb equivalent amounts of red light, so carbon monoxide poisoning can result in falsely elevated oxygen saturation as measured by the pulse oximeter (SpO_2).
- Motion artifact and low perfusion are the most common sources of SpO_2 inaccuracies.
- Capnometry is an intensive care monitoring tool that displays the partial pressure concentration of carbon dioxide exhaled from the lungs both numerically and as a graphical waveform.
- In normal subjects the gradient between the partial pressure of carbon dioxide in arterial blood and the partial pressure of carbon dioxide in end-tidal exhaled gas ($PaCO_2$-P_{ETCO_2} gradient) is approximately 4–5 mm Hg, whereas in critically ill patients, the $PaCO_2$-P_{ETCO_2} gradient can be markedly elevated and inconsistent, particularly in those with obstructive lung disease (7–16 mm Hg).
- The $PaCO_2$-P_{ETCO_2} gradient is affected by changes in respiratory rate, tidal volume, CO_2 production, and mixed venous CO_2 content.
- Respiratory system compliance can be determined by applying an end-inspiratory hold (plateau pressure) during static conditions (no flow or patient spontaneous efforts).
- Intrinsic PEEP is measured by performing an expiratory hold, allowing the pressure in the patient's lungs to equilibrate with the circuit.
- When using the pressure-volume curve of the respiratory system (during quasi-static conditions) for lung protection in patients with ARDS, PEEP is set 2 cm H_2O above the lower inflection point to maintain lung recruitment, and tidal volume is set below the upper inflection point to prevent lung injury from excessive stretch.
- The stress index is used to assess the shape of the pressure waveform during constant-flow volume control.
- A threshold value of less than 105 for the respiratory rate/tidal volume ratio (RSBI) has both a high positive predictive value (0.78) and a high negative predictive value (0.95) for the ability to maintain unassisted breathing.
- Occlusion pressure at 100 msec ($P_{0.1}$), defined as the negative pressure measured 100 msec after the initiation of an inspiratory effort performed against a closed valve, is correlated with central respiratory drive and respiratory effort.

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This landmark paper introduced one of the most important clinical applications of capnography: the monitoring of spontaneous circulation and the effectiveness of precordial compressions in the setting of cardiac arrest. A sudden rise in end-tidal CO_2 concentration from approximately 1%–3% (7–20 mm Hg) coincides with the return of spontaneous circulation.

Nuckton TJ, Alonso JA, Kallet RH, et al. Pulmonary dead-space fraction as a risk factor for death in acute respiratory distress syndrome. *N Engl J Med*. 2002;346:1281–1286.
This study provides the first evidence that a pulmonary-specific variable can independently predict the risk of death in patients with ARDS. Dead-space fraction may prove to be a useful measurement by which to judge the efficacy of future therapies for ARDS.

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This case series report introduced one of the most crucial concepts and monitoring imperatives of invasive mechanical ventilation. This description of the mechanics and clinical implications of dynamic hyperinflation remains one of the most lucid in the critical care and pulmonary literature.

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34

Arterial Blood Gas Interpretation

A. Murat Kaynar

Although arterial blood gas (ABG) data provide critical information to the practitioners of critical care medicine, ABG analysis is among the most frequently ordered test in the intensive care unit (ICU), is overused, and is associated with burdens to our patients (discomfort, blood loss) and healthcare systems.[1–5] Therefore appropriate understanding and use of this clinical test is important for optimal care. There are no randomized trials performed on data; however, studies looking at the utility of ABG in relation to clinical outcomes have given mixed results and collectively underscore the need to use ABG information obtained in the ICU within a specific and appropriate clinical context.[6–8] Since the 1950s, the development of polarographic electrodes by Clark for oxygen (O_2) and Severinghaus and Bradley and Stow and coworkers for carbon dioxide (CO_2) has permitted measurement of the partial pressures of oxygen (PaO_2) and carbon dioxide ($PaCO_2$) in arterial blood.[9–11] Cremer, Haber, and Klemensiewicz developed the pH electrode in the early 20th century. ABG remains the definitive method to diagnose, categorize, and quantitate respiratory and metabolic failure.[12]

WHY AM I OBTAINING THE ARTERIAL BLOOD GAS?

Acute metabolic acidosis is common among critically ill and results from complex causes. Unfortunately, the clinical focus often shifts from treating the underlying causes to correcting the pH itself. Thus the primary question to ask ourselves before reflexively ordering the next ABG should be "Why am I ordering this test?"

A pH value less than 7.38 defines acidemia, whereas severe acidosis is a pH of 7.20 or lower.[13] In acute severe metabolic acidemia, where the pH is <7.20, the incidence is 6% among the critically ill and carries an associated ICU mortality rate of almost 60%.[14] Interestingly, studies suggest that the presence of an arterial line is the most powerful predictor for obtaining an arterial blood sample for ABG, regardless of the PaO_2, $PaCO_2$, Acute Physiology and Chronic Health Evaluation (APACHE) II score, or presence of a ventilator.[1,15] In addition, there are no published guidelines and only limited trials that provide guidance to clinicians regarding the indications for sampling ABGs.[16] Protocolized care may be able to reduce the number of unnecessary ABGs without negative effects on patient outcomes.[1,4]

The indications for ABG analysis have to be guided by the clinical context. Already deployed technologies, such as pulse oximetry and transcutaneous CO_2 detection, decrease the frequency of using ABGs.[17,18] Yet we still need to give clinicians a "rule of thumb" for sampling ABGs. One attempt at constructing such an "ABG indications" list might be:

- After initiation of mechanical (invasive/noninvasive) ventilation
- Tracking the acute respiratory distress syndrome (ARDS) clinical course
- Presence of hypoxemic and/or hypercapnic respiratory failure
- Presence of acute circulatory failure
- Management of complex acid-base disorders

ARTERIAL BLOOD GAS SAMPLING

The ABG samples are either obtained from an arterial catheter or direct arterial puncture into a heparinized syringe. It used to be customary to flush a syringe with heparin and then use that syringe to sample ABGs; however, work in both adult and pediatric patients showed that excess heparin decreased the $PaCO_2$, PaO_2, HCO_3^-, and base excess, while the pH remained unchanged. Thus excess liquid heparin tends to promote the interpretation of metabolic acidosis with respiratory compensation.[19,20]

While the most common site for arterial puncture is the radial artery, femoral and brachial arteries are also commonly used to sample arterial blood. Risks associated with arterial punctures are hematoma formation, ischemia to the hand or lower extremity, arterial injury, pseudoaneurysms, and arteriovenous fistulae.[16,21–24] Once obtained, the arterial blood sample must be processed immediately and in accordance with the best laboratory practices. In addition to differences between laboratories, calibration discrepancies and contamination of electrodes with protein or other fluids may alter results.[25,26]

Using the polarographic electrodes, PaO_2, $PaCO_2$, and pH are directly measured; oxygen saturation is calculated from standard O_2 dissociation curves and may be directly measured with a co-oximeter.[9–12,27] A co-oximeter is a blood gas analyzer that measures not just the partial pressure of gases but also the concentration of oxygen associated with different types of hemoglobin based on their absorption spectra (Beer-Lambert law). The use of co-oximetry is usually indicated when:

- A toxin such as cyanide is suspected
- Hypoxia fails to improve with the administration of oxygen
- There is a discrepancy between the PaO_2 on a blood gas determination and the oxygen saturation on pulse oximetry (SpO_2)
- The clinician suspects dyshemoglobinemias such as methemoglobinemia (Met-Hb) or carboxyhemoglobinemia (CO-Hb)[28]

Pulse oximetry, unfortunately, does not differentiate among the different types of hemoglobin. For example, in the case of Met-Hb, the SpO_2 may read 86%, but desaturation can be demonstrated with co-oximetry, recording 68% oxyhemoglobin and 32% Met-Hb.[28,29]

The bicarbonate (HCO_3^-) concentration is then calculated using the Henderson-Hasselbalch equation:

$$pH = pK_A + \log([HCO_3^-]/[CO_2])$$

where pK_A is the negative log of the dissociation constant of carbonic acid (HCO_3^-).

The *base excess* is the quantity of strong acid required to titrate blood to pH 7.40 with a $PaCO_2$ of 40 mm Hg at 37°C. In reality, acid is not titrated but calculated using a variety of normograms.[30–34] Such

calculations focus only on the metabolic sources for pH and $[H^+]$ changes. Similarly, bicarbonate is a calculated value that assumes $PaCO_2$ to be 40 mm Hg.

The following are some of the details that contribute to erroneous readings and interpretations.

Steady State

The ABG has to be collected when a patient reaches a steady state during the clinical course, allowing for the arterial and alveolar gases to equilibrate. Equilibration may take up to 20 or 30 minutes in the case of patients with chronic obstructive pulmonary diseases (COPDs).[35]

Anticoagulants

As mentioned in the Arterial Blood Gas Sampling section, excess heparin may affect the $PaCO_2$, PaO_2, HCO_3^-, and base excess, while not interfering with the pH. Only 0.05 mL is required to anticoagulate 1 mL of blood. Knowing that the "dead space" volume of a standard 5-mL syringe is approximately 0.02 mL, it is safe to assume that just having heparin in that dead space would suffice to provide anticoagulation up to 2 mL of blood sample. New prefilled syringes (sodium or lithium heparin) overcome these problems.[19]

Processing Delay

Although the blood sample resides in the syringe until analyzed, it does consume O_2 and produce CO_2. Red blood cell glycolysis could generate more lactic acid through the aerobic glycolysis and lower the pH.[36,37] If the sample remains unanalyzed at room temperature for more than 15 minutes, there would be significant increases in $PaCO_2$ and decreases in pH. When the sample is stored on ice, however, it can be processed up to 2 hours after collection without affecting the blood gas values, even on Mt. Everest.[38–41]

Venous Sampling

If no arterial blood sample is obtained, venous blood gas analyses would be of limited help; however, venous samples do yield estimates for $PaCO_2$ and lactatemia.[42,43] This is discussed later in the chapter.

At times the intended arterial puncture results in inadvertent venous sampling. One can recognize venous sampling when:

- The practitioner fails to observe a flash of blood during syringe filling
- The blood gas analyses clearly are not compatible with the clinical condition
- There is unexpectedly low PaO_2 and high $PaCO_2$
- SpO_2 by simultaneous pulse oximetry exceeds the SaO_2 in the measured ABG

Collection Equipment and Technique

If the dead space were high in the syringe, it would lower the $PaCO_2$. Additionally, a needle smaller than a 25-gauge may cause hemolysis.

If an arterial line is in place, one must minimize the dead space of the system (priming the volume from sampling port to catheter tip) to prevent dilution; the safe upper limit would be two times the dead space.[3]

Hyperventilation

Hyperventilation resulting from anxiety and/or pain may acutely alter results from baseline values.

Leukocytosis

Leukocytosis decreases the PaO_2 and pH and elevates $PaCO_2$ in stored samples. Such PaO_2 decreases are most noticeable at higher PaO_2 levels, are attributable to cellular oxygen consumption, and may be attenuated when samples are stored at colder temperatures.

Hypothermia

Blood gas values are temperature dependent, and as the temperature decreases, solubility of CO_2 increases and partial pressures decline. Thus if blood samples are warmed to 37°C before analysis (as is common in most laboratories), PaO_2 and $PaCO_2$ will be overestimated and pH underestimated in hypothermic patients. The following correction formulas can be used:

- Subtract 5 mm Hg PO_2 per 1°C that the patient's temperature is less than 37°C.
- Subtract 2 mm Hg $PaCO_2$ per 1°C that the patient's temperature is less than 37°C.
- Add 0.012 pH units per 1°C that the patient's temperature is less than 37°C.

Although there is an extensive literature on the so-called "pH-stat" and "alpha-stat" assessment of ABGs, in summary the *pH-stat* acid-base approach aims at maintaining the patient's pH in a constant range via managing pH at the patient's temperature. As in the formulas provided earlier, *pH-stat* is temperature corrected. On the other hand, *alpha-stat* aims at the ionization state of histidine, and it is maintained by managing a standardized pH (measured at 37°C). Alpha (normally about 0.55) is the ratio of protonated imidazole to total imidazole on the histidine moieties of proteins. *Alpha-stat* is not temperature corrected; as the patient's temperature falls, the partial pressure of CO_2 decreases and solubility increases. Thus a hypothermic patient with a pH of 7.40 and a PCO_2 of 40 mm Hg (measured at 37°C) will actually have a lower $PaCO_2$ because of its lower partial pressure, and this will manifest as a *relative respiratory alkalosis. pH-stat,* with its goal of maintaining $PaCO_2$ of 40 mm Hg and pH of 7.40 at the patient's actual temperature, results in higher $PaCO_2$ *(respiratory acidosis)*.[44–46]

HYPOXEMIA, HYPOXIA, AND ARTERIAL BLOOD GAS ANALYSIS

The PaO_2 is primarily used to assess oxygenation, and it is reliable within a dynamic range between 30 and 200 mm Hg; however, the reliability of the reported oxygen saturation of blood (SaO_2) ranges within a much narrower range: between 30 and 60 mm Hg.[47] The noninvasive method of measuring oxygen saturation by pulse oximetry (SpO_2) or by ABG analysis (SaO_2) is a better indicator of arterial oxygen content than PaO_2, because only ~2% of the oxygen is carried in dissolved form, and the greatest amount (98%) is carried by Hb. When using SpO_2, one has to be cognizant about its shortcomings, including interference by indicator dyes used during procedures.[48,49]

Hypoxemia is defined as a PaO_2 of less than 80 mm Hg in adults breathing room air; *hypoxia* denotes tissue- or cell-level decreases in oxygen availability. Thus tissue or end-organ hypoxia in patients with hypoxemia depends on the severity of the hypoxemia and the ability of the cardiovascular system to compensate. Hypoxia is unlikely to occur in response to mild hypoxemia itself (PaO_2 = 60–79 mm Hg) when cardiovascular reflexes and integrity remain intact. Moderate hypoxemia (PaO_2 = 45–59 mm Hg) may be associated with hypoxia in patients with anemia or cardiovascular dysfunction. Hypoxia is almost always present with severe hypoxemia at levels of PaO_2 <45 mm Hg. Although the PaO_2 might be low at 45 mm Hg, the mitochondrial oxygen partial pressure necessary to complete oxidative phosphorylation is around 0.5–3 mm Hg (i.e., several orders of magnitude lower), suggesting that this buffer may be a reason why some accommodated patients with cyanotic diseases and elite Everest climbers without supplemental oxygen might have an average PaO_2 of 26 mm Hg and yet survive without significant end-organ injury.[50–57]

Acute respiratory insufficiency occurs when the lungs no longer meet the metabolic demands of the body, which by tradition is divided into two types:

- Type I, hypoxemic respiratory insufficiency: PaO_2 ≤60 mm Hg when breathing room air at 1 atm.
- Type II, hypercapnic respiratory insufficiency: $PaCO_2$ ≥50 mm Hg.

The tripartite information that can be gathered from ABG analyses are (1) oxygen saturation and content, (2) CO_2 as a marker of ventilation, and (3) acid-base status. Here we discuss all three components.

Alveolar Ventilation

The arterial CO_2 partial pressure ($PaCO_2$) reflects the CO_2 content of the sample. The CO_2 content basically is the balance between the quantity of CO_2 produced and its excretion through alveolar ventilation (VA). This relationship can be expressed by the expression:

$$PaCO_2 \sim CO_2/VA$$

The alveolar ventilation is that portion of total ventilation that participates in gas exchange with pulmonary blood. If the metabolic rate remains unchanged and CO_2 production is assumed to be in steady state, then:

$$1/VA \sim PaCO_2$$

Therefore when steady state is reached, $PaCO_2$ becomes a useful tool assessing alveolar ventilation. If $PaCO_2$ is >45 mm Hg, it is *alveolar hypoventilation*, and if $PaCO_2$ is <35 mm Hg, it is called *alveolar hyperventilation* (primary or compensatory for metabolic disturbance).

Oxygenation

Tissue oxygenation depends on the delivery of oxygenated blood (both dissolved and bound to hemoglobin). The PaO_2 is the partial pressure of oxygen in the blood, and this dissolved fraction makes a very small direct contribution to oxygen delivery (<2%); yet even this quantity may be useful in the setting of severe anemia.[58,59] The PaO_2 is dependent on the fraction of inspired oxygen (FiO_2), ventilation and perfusion matching (V ~ Q), and the mixed venous oxygen saturation ($SmvO_2$). The PaO_2 must be assessed within a clinical context along with the inspired oxygen and age of the patient.

Relationship Between PaO_2 and FiO_2

The PaO_2 alone provides limited information about the efficiency of alveolar-capillary oxygen exchange unless FiO_2 is also considered in the interpretation. In addition to the FiO_2, the other major determinant of PaO_2 is the degree of intrapulmonary venous admixture and shunting (Fig. 34.1). Although PaO_2 and FiO_2 alone do not quantitate the intrapulmonary shunt in the diagnosis and management of lung diseases nor in themselves guide the approach to respiratory support, they provide an overall indication regarding the category and severity of diagnosis, after which various formulas could be used for calculating the intrapulmonary shunt.

The classic "shunt equation" requires mixed venous sampling through a pulmonary artery catheter and the alveolar-arterial oxygen gradient equation (Table 34.1):

$$Q_s/Q_t = (C_cO_2 - C_aO_2)/(C_cO_2 - C_vO_2),$$

where:

Q_s is blood flow through the shunt
Q_t is total cardiac output
C_cO_2 is pulmonary end-capillary O_2 content
C_aO_2 is arterial O_2 content
C_vO_2 is mixed venous O_2 content

Clinically the so-called "P/F ratio" (PaO_2/FiO_2) is most commonly used to approximately quantitate the degree of venous admixture,

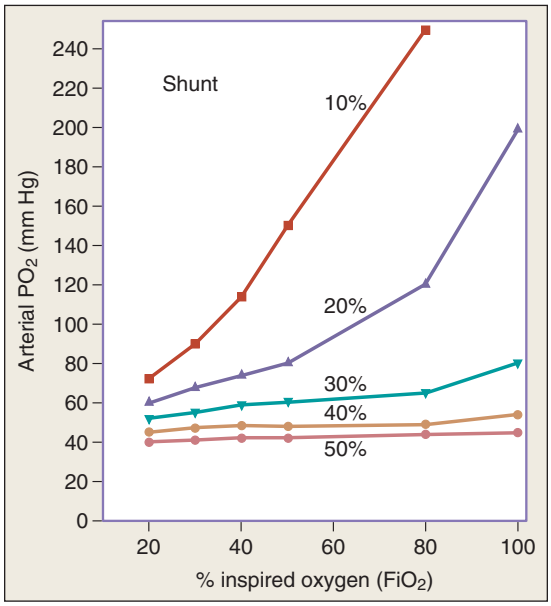

Fig. 34.1 The Effect on PaO_2 on Increasing FiO_2 According to Shunt Fraction.

TABLE 34.1 Formulas for Evaluating Gas Exchange in Patients

Age-adjusted PaO_2: Expected PaO_2 − 0.3 (age − 25)
Expected PaO_2 at 1 Torr is ~ 100 mg/Hb; an approximation could be done as: Expected PaO_2 ~ FiO_2 (%) * 5
The alveolar-arterial gradient: $AaDO_2 = (FiO_2 * (\text{barometric pressure} - 47)) - (PaO_2 + PaCO_2)$
Oxygenation index = ((mean airway pressure * FiO_2)/PaO_2) * 100
Dead space to tidal volume ratio: $Vd/Vt = (PaCO_2 - P_ECO_2)/PaCO_2$
The normal range is 20%–40%

composed of ventilation/perfusion mismatching (V/Q) and true shunt. Because the normal PaO_2 in an adult breathing room air with an FiO_2 21% is 80–100 mm Hg, the normal value for PaO_2/FiO_2 ranges between 400 and 500 mm Hg. A PaO_2/FiO_2 ratio of less than 200 most often indicates a shunt of greater than 20% of total cardiac output. This ratio has also been incorporated since 1994 into the ARDS definition.[60–62] When used in an unqualified fashion, a notable limitation of the PaO_2/FiO_2 ratio is that it does not take into account changes in $PaCO_2$ at low FiO_2, nor the influences of positive end-expiratory pressure (PEEP) and body position.

Age

Arterial oxygen tension decreases with age (see Table 34.1). For example, at age 60 years, FiO_2 21%, and 1 atmospheric pressure, the PaO_2 is 85–90 mm Hg; this value decreases to 80–85 mm Hg at the age of 80 years.

Acid-Base Balance

The normal diet generates volatile acid (from CO_2 production), primarily because of carbohydrate metabolism, and nonvolatile acids (e.g., phosphates and sulfates) from protein metabolism. The function of the homeostatic system is to maintain pH within a narrow range, and pH homeostasis is accomplished through the interaction of the lungs, kidneys, and blood buffers. Alveolar ventilation allows for excretion of CO_2, while the kidneys reclaim filtered bicarbonate (HCO_3^-)

excrete the daily acid load generated from dietary protein intake. Less than half of this acid load is excreted as *titratable acids* (i.e., phosphoric and sulfuric acids); the remaining acid load is excreted as ammonium. The blood pH is determined by the balance of these processes.[63]

The current mainstream understanding of the acid-base system dates back to the 1950s, when the concepts of the Henderson-Hasselbalch equation were combined with the Brønsted-Lowry theory, toward the *bicarbonate ion*–centered approach.[64,65] Stewart repackaged the pre-1950 ideas of acid-base in the late 1970s, including the Van Slyke definition of an acid. Using physical chemistry, Stewart promoted a new understanding of acid-base balance.[64,66] The resultant strong ion difference (SID) and the concentration of weak acids (particularly albumin) pushes bicarbonate into a minor role as an acid-base indicator rather than as an important mechanism:

$$SID = ([Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}]) - [Cl^-] + [lactate])$$

Although the SID is not the anion gap (AG), it does share a number of parameters, and the trends will often be close. The normal SID has not been well established, but the quoted range is 40–42 mEq/L. As the SID approaches zero, anions accumulate and the balance tilts towards acidity. This model makes it easier for clinicians to understand the commonly observed "hyperchloremic acidosis" after 0.9% saline administration and the systemic alkalosis of hypoalbuminemia (regarded as a weak acid).[67,68]

For practical reasons, the HCO_3^--centered approach is still more commonly used than the Stewart approach to understand and manage acid-base balance.[69] The Henderson-Hasselbalch equation describes the $pH = pK + \log (HCO_3^-/H_2CO_3)$. If all the constants are removed, the equation can be simplified to $pH = HCO_3^-/PaCO_2$. The HCO_3^- is controlled mainly by the kidney and blood buffers, whereas $PaCO_2$ is regulated by the lung adjustment of the blood level of volatile acid and carbonic acid. Buffer systems can act within a fraction of a second to prevent excessive changes in pH. The respiratory system takes about 1–15 minutes and the kidneys many minutes to days to readjust H^+ ion concentration. However, according to the Stewart approach, the use of bicarbonate increases the pH by increasing the sodium concentration of the plasma compared with chloride and not by simple addition of bicarbonate ions, as many of the latter rapidly convert to CO_2.[70] Although the use of bicarbonate is attractive and commonly practiced, we must use restraint in using bicarbonate in the critically ill without good justification. For example, a prospective study of 1700 patients with sepsis and acidosis who received bicarbonate in the first 2 days of hospital admission did not detect improved outcome.[71] Similarly, in a prospective randomized trial including 400 ICU patients with severe acidemia (pH <7.2, $PaCO_2$ 45 mm Hg, lactate >2 mM), early bicarbonate infusion with a pH goal >7.30 did not improve 28-day mortality or reduce the incidence of organ insufficiency.[72]

The Anion Gap

According to the principle of electrochemical neutrality, total **cations** must equal total **anions**, and so in considering the commonly measured cations and anions, a fixed number should be derived from their numeric difference. The measured cations are in excess; mathematically, this "gap" is automatically filled with unmeasured anions to preserve electrochemical neutrality. There is never a "real" AG; rather, it is an expression of nonroutinely measured anions. The AG is calculated using the following formula[73]:

$$AG = ([Na^+] + [K^+]) - ([Cl^-] + [HCO_3^-]) \text{ (Normal: } 10 \pm 2 \text{ mEq/L)*}$$

*Due to low concentration of K^+, it is not usually included in the calculation of AG.

During critical illness, albumin typically decreases rapidly, which is an important contributor to the "normal" AG. Therefore as the albumin concentration falls, it tends to reduce the size of the AG, or have an alkalinizing effect. Various corrections are available; however, Figge's AG correction (AG_{corr}) is most commonly used[73]:

$$\text{Albumin gap} = 40 - \text{measured albumin (normal albumin} \sim 40 \text{ g/L)}$$

$$AG_{corr} = AG + (\text{albumin gap}/4)$$

A STEPWISE APPROACH TO ACID-BASE DISORDERS

Step 1: Do a Comprehensive History and Physical Examination

The history and physical examination can often give clues as to the underlying acid-base disorder (Table 34.2). For example, severe diarrhea could lead to loss of HCO_3^- with subsequent *non–anion gap metabolic acidosis*. Patients with COPD would have chronic respiratory acidosis because of CO_2 accumulation counterbalanced by metabolic alkalosis, resulting in a normal pH.

Step 2: Order Simultaneous Arterial Blood Gas Measurement and Chemistry Profile

As mentioned in the previous section, the HCO_3^- is calculated in the ABG; therefore it is important to obtain a chemistry panel to have data that are actually measured. In addition, Na^+ and Cl^- provide additional information about the volume status and strong ion difference.[74–77]

Step 3: Check the Consistency and Validity of the Results

Normal ABG results are provided in Table 34.3.

Step 4: Identify the Primary Disturbance

With the ABG results in hand, the practitioner then has to determine whether the patient is significantly acidemic (pH <7.35) or alkalemic

TABLE 34.2 Common Clinical Presentations and Associated Acid-Base Disorders

Phenotype	Acid-Base Status
Pulmonary embolism	Respiratory alkalosis
Shock	Lactic acidosis (metabolic)
Sepsis	Metabolic acidosis and respiratory alkalosis
Vomiting	Metabolic alkalosis
Diarrhea	Metabolic acidosis
Acute kidney injury	Metabolic acidosis
Cirrhosis	Respiratory alkalosis
Pregnancy	Respiratory alkalosis
Diuretics	Metabolic alkalosis unless thiazides are used
COPD	Respiratory acidosis
Diabetic ketosis	Metabolic acidosis (ketoacidosis)
Ethylene glycol poisoning (antifreeze)	Metabolic acidosis
Excessive 0.9% saline use	Metabolic non-anion gap acidosis

COPD, Chronic obstructive pulmonary disease.

TABLE 34.3 Normal Acid-Base Values

	Mean	1 ± SD	2 ± SD
$PaCO_2$ (mm Hg)	40	38–42	35–45
pH	7.4	7.38–7.42	7.35–7.45
HCO_3^-	24	23–25	22–26

TABLE 34.4 Acid-Base Disorders

Phenotype	Diagnostic Criteria
Respiratory acidosis	$PaCO_2$ >45 mm Hg
Respiratory alkalosis	$PaCO_2$ <35 mm Hg
Acute respiratory acidosis	$PaCO_2$ >45 mm Hg and pH <7.35
Chronic respiratory acidosis	$PaCO_2$ >45 mm Hg and pH = 7.36–7.44
Acute respiratory alkalosis	$PaCO_2$ <35 mm Hg and pH >7.45
Chronic respiratory alkalosis	$PaCO_2$ <35 mm Hg and pH = 7.36–7.44
Acidemia	pH <7.35
Alkalemia	pH >7.45
Acidosis	HCO_3^- < 22 mEq/L
Alkalosis	HCO_3^- >26 mEq/L

TABLE 34.5 Compensation Formulas for Simple Acid-Base Disorders

Acid-Base Disorder	Compensation
Metabolic acidosis	Change in $PaCO_2$ = 1.2 × change in HCO_3^-
Metabolic alkalosis	Change in $PaCO_2$ = 0.6 × change in HCO_3^-
Acute respiratory acidosis	Change in HCO_3^- = 0.1 × change in $PaCO_2$
Chronic respiratory acidosis	Change in HCO_3^- = 0.35 × change in $PaCO_2$
Acute respiratory alkalosis	Change in HCO_3^- = 0.2 × change in $PaCO_2$
Chronic respiratory alkalosis	Change in HCO_3^- = 0.5 × change in $PaCO_2$

(pH >7.45) and what the primary cause is (metabolic, driven by HCO_3^-, or respiratory, driven by CO_2) (Table 34.4).

Step 5: Calculate the Expected Compensation

Any alteration in acid-base equilibrium sets into motion a compensatory response by either the lungs or the kidneys. The compensatory response attempts to return the ratio between $PaCO_2$ and HCO_3^- to normal with subsequent normalization of pH. Compensation is usually predictable; the adaptive responses for the simple acid-base disorders have been quantified experimentally[78] (Table 34.5). One then has to evaluate the compensatory responses and any secondary (uncompensated) acid-base disturbances.

Step 6. Calculate the "Gaps"

Calculate the Anion Gap

In high-AG metabolic acidosis, acid dissociates into H^+ and an unmeasured anion. H^+ is buffered by HCO_3^-, and the unmeasured anion accumulates in the serum, resulting in an increase in AG. In non–AG metabolic acidosis, H^+ is accompanied by Cl^- (a measured anion); therefore there is no change in AG. Acid-base disorders may present as two or three coexisting disorders. It is possible for a patient to have an acid-base disorder with normal pH, $PaCO_2$, and HCO_3^-, the only clue to an acid-base disorder being an increased AG. If the AG is increased by more than 5 mEq/L (i.e., an AG >15 mEq/L), the patient most likely has a metabolic acidosis. Compare the fall in plasma HCO_3^- ($25 - HCO_3^-$) with the increase in the plasma AG (ΔAG); these should be of similar magnitude. If there is a gross discrepancy (>5 mEq/L), then a mixed disturbance is present.

The **anion gap** is calculated by subtracting the serum concentrations of chloride and bicarbonate (**anions**) from the concentrations of sodium (**cations**):

$$([Na^+] + [K^+]) - ([Cl^-] + [HCO_3^-])^*$$

- If increase in the AG exceeds the fall in HCO_3^-, it suggests that a component of the metabolic acidosis is a result of HCO_3^- loss.
- If the increase in AG is less than the fall in HCO_3^-, this suggests coexisting metabolic alkalosis.

TABLE 34.6 Causes of an Increased Osmolal Gap

Ethylene glycol	Alcohol
Methanol	Isopropyl alcohol (nongap)
Mannitol	Sorbitol
Paraldehyde	Acetone

Osmolar Gap

Calculate the osmolar gap in patients with an unexplained AG metabolic acidosis to exclude ethylene glycol or methanol toxicity (Table 34.6). The serum osmolality is calculated as:

$$2 \times [Na^+] + [\text{Glucose}]/18 + [\text{BUN}]/2.8$$

with normal levels ranging around 280–290 mOsm/kgH_2O

The osmolal gap is defined as the difference between measured and calculated osmolality:

$$\text{Osmolar gap} = \text{Osmolality}_{\text{measured}} - \text{Osmolality}_{\text{calculated}}$$

(normal value less than or equal to 10 mOsm/kg H_2O)

COMMON ACID-BASE DISTURBANCES IN THE ICU

Metabolic Acidosis

The rate and degree of metabolic acidosis mainly depend on the underlying cause and the rapidity with which the causative condition develops. An acute, severe metabolic acidosis results in myocardial depression with a reduction in cardiac output, decreased blood pressure, and decreased hepatic and renal blood flows; the cardiovascular system also becomes less responsive to vasopressor agents.[79] Reentrant arrhythmias and a reduction in the ventricular fibrillation threshold can occur.[80]

The acute correction of metabolic acidosis has been a standard of care for intractable metabolic acidosis during acute coronary events; however, clinical trials did not show improved outcomes and led to paradoxical central nervous system acidosis, leading subsequently to its removal from current advanced cardiovascular life support (ACLS) algorithms.[81–83]

A metabolic acidosis in the critically ill patient requires an aggressive approach to the diagnosis and management of the underlying causes (Fig. 34.2 and Table 34.7). In most patients the causes are

*Because of the low concentration of K^+, it is not usually included in the calculation of AG.

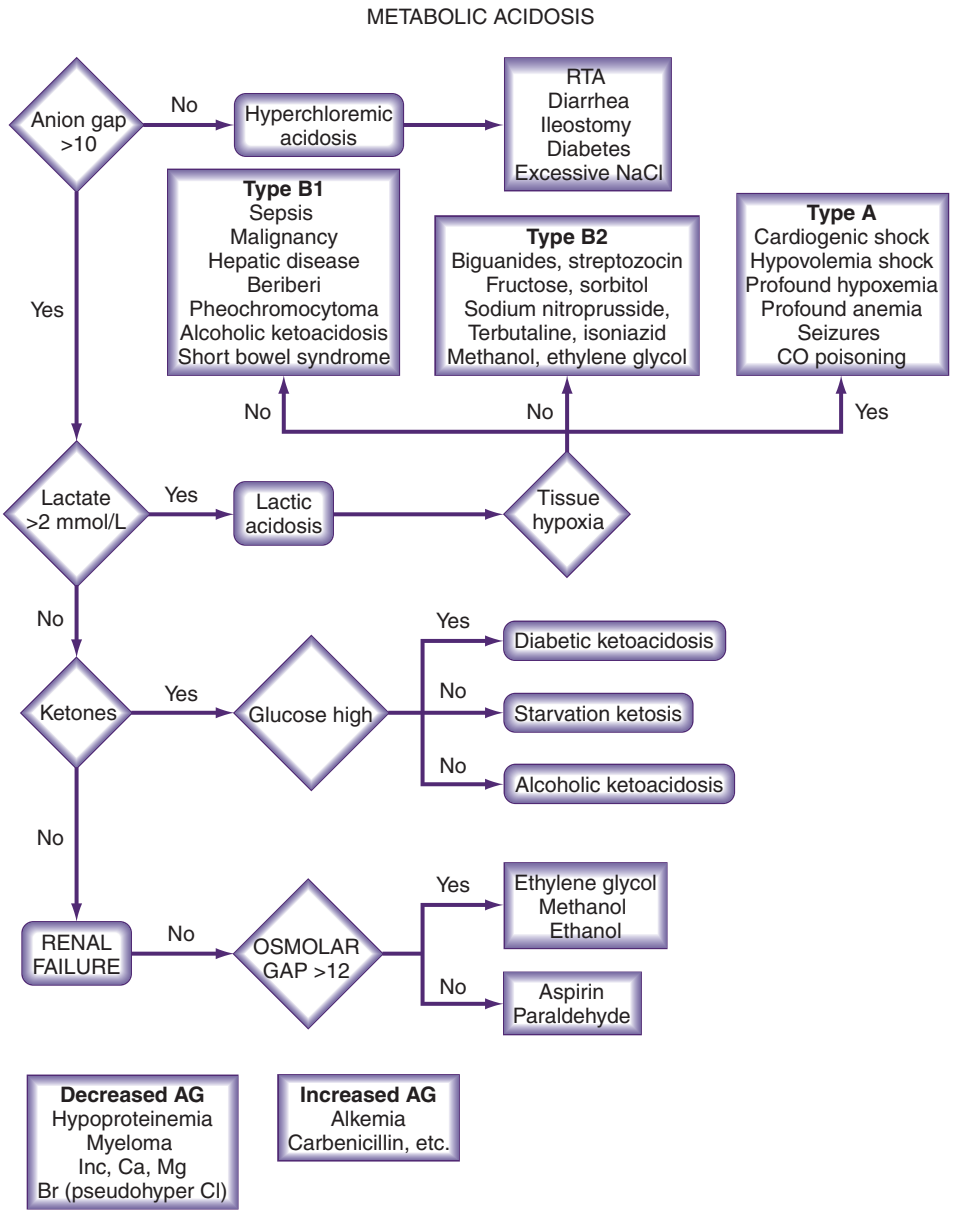

Fig. 34.2 Algorithm for Diagnosing Metabolic Acidosis.

TABLE 34.7 Causes of Metabolic Acidosis

Increased Anion Gap	Normal Anion Gap
Acute kidney injury	Hypokalemic acidosis
Rhabdomyolysis	Hyperkalemic acidosis
Ketoacidosis	
Lactic acidosis	
Toxins: 5-oxoproline	
Beriberi	

clinically obvious, with lactic acidosis (tissue hypoxia or sepsis), ketoacidosis, and acute kidney injury (AKI) being the most common.[84–86] In patients with an unexplained AG metabolic acidosis, drugs such as salicylates, methanol, or ethyleneglycol toxicity should always be considered.[87,88] Accumulation of 5-oxoproline related to the use of acetaminophen is a rare cause of an AG metabolic acidosis.[89] Long-term use of lorazepam can result in the accumulation of its vehicle, propylene glycol, resulting in worsening AKI, metabolic acidosis, and altered mental status.[90,91] Propylene glycol toxicity is typically observed after prolonged (>7 days), high-dose (average 14 mg/h), continuous lorazepam infusion and can be recognized by an increased osmolar gap.[92] Similarly, first reported in children and then recognized also in adults, prolonged high-dose propofol (>100 μg/kg/min) is occasionally associated with the "propofol infusion syndrome" characterized by rhabdomyolysis, metabolic acidosis, and renal and cardiac failure, requiring vigilance and early cessation of sedation and use of alternatives.[93,94] It has also been suggested that frequent assessment of creatinine kinase or lipid panels would alert the clinicians of an impending "propofol infusion syndrome."[95]

The prognosis is related to the underlying disorder causing the acidosis. In almost all circumstances, the treatment of a metabolic acidosis involves treatment of the underlying disorder. Except in specific

circumstances, there is no scientific evidence to support treating a metabolic or respiratory acidosis with sodium bicarbonate.[96] However, independent of the underlying cause, use of bicarbonate among critically ill patients may help restore cardiovascular responsiveness to vasoactive agents.[97] Bicarbonate increases hemoglobin-oxygen affinity, known as the *Bohr effect,* leading to potential tissue hypoxemia,[98] hypertonic state, and low plasma calcium concentrations because of albumin chelation.[99] Furthermore, the intracellular pH is a determinant of cellular function. The intracellular buffering system, including proteins, is much more effective in restoring pH to normal than are extracellular buffers.[100,101] Consequently, patients may tolerate a pH as low as 7.00 during sustained hypercapnia without obvious adverse effects. Paradoxically, sodium bicarbonate can decrease intracellular pH in circumstances where CO_2 elimination is fixed. In addition, infusion of bicarbonate can lead to a variety of problems in patients with acidosis, including fluid overload, hypernatremia, and postrecovery metabolic alkalosis. Furthermore, studies in both animals and humans suggest that alkali therapy may only transiently raise the plasma bicarbonate concentration. This finding appears to relate in part to CO_2 generated as the administered bicarbonate buffers excess hydrogen ions. Unless the minute ventilation (M_V) is increased in ventilated patients, CO_2 elimination will not increase and paradoxically may worsen the intracellular acidosis. Currently, there are no data to support the use of bicarbonate in patients with lactic acidosis.[96,102]

Bicarbonate is frequently administered to "correct the acidosis" in patients with diabetic ketoacidosis (DKA). However, paradoxically, bicarbonate has been demonstrated to increase ketone and lactate production.[103] Studies have demonstrated an increase in acetoacetate levels during alkali administration, followed by an increase in 3-hydroxybutyrate levels after its completion.[103,104] In pediatric patients, treatment with bicarbonate may prolong hospitalization.[105] In addition, bicarbonate may decrease cerebrospinal fluid (CSF) pH as increased CO_2 produced by buffering acid crosses the blood-brain barrier, combines with H_2O_2, and regenerates H^+. Therefore the general consensus is that adjunctive bicarbonate is unnecessary and potentially disadvantageous in severe DKA.[81]

Bicarbonate is considered "lifesaving," however, in patients with severe ethylene glycol and methanol toxicity. In hyperchloremic acidosis, endogenous regeneration of bicarbonate cannot occur (bicarbonate has been lost rather than buffered). Therefore even if the cause of the acidosis can be reversed, exogenous alkali is often required for prompt attenuation of *severe acidemia*. Bicarbonate therapy therefore is indicated in patients with severe *hyperchloremic acidosis* when the pH is less than 7.2; this includes patients with severe diarrhea, high-output fistulas, and renal tubular acidosis. To prevent hypernatremia, 3 × 50 mL ampules of $NaHCO_3^-$ (each containing 50 mmol of $NaHCO_3^-$) may be added to 1 L of 5% dextrose water and infused at a rate of 100–200 mL/h.

Lactic Acidosis

Lactate is the by-product of pyruvate use, and it is converted by lactate dehydrogenase. Either in hypoxia or during sepsis, lactic acid is preferentially produced. Lactic acid, like most substances with a pKa of less than 4 (pKa 3.78), circulates almost entirely as the freely dissociated anion, lactate (i.e., it releases its proton) at physiologic pH—strongly favoring the rightward diving of this equation:

$$CH_3CHOCOOH \leftrightarrow CH_3CHOCOO^- + H^+$$

Hyperlactatemia refers to an elevated plasma concentration of lactate anions. In clinical practice, *lactic acidemia* is defined as a pH less than 7.35 with a lactate concentration greater than 4 mmol/L. Lactic acidemia typically develops as a result of endogenously produced lactic acid, with lactate being measured as the dissociated base. During critical illness, the source of lactate is often believed to be ischemic anaerobically metabolizing tissues, such as the gut and muscle. In addition to ischemia, the Warburg effect with dysregulated glycolysis is a major nonischemic cause for lactatemia.[106,107] Furthermore, it should be noted that both the pH and AG are insensitive markers of an elevated lactate; patients with an elevated lactate level may have a normal pH and AG.[108] According to the Stewart interpretation, lactic acidosis occurs because of an increase in strong anions. As for other causes of metabolic acidosis, the Surviving Sepsis Campaign guidelines do not suggest the use of bicarbonate for plasma pH >7.15 among patients with lactic acidosis.[109]

D-Lactic Acidosis

Certain bacteria and viruses in the gastrointestinal (GI) tract may convert carbohydrates into organic acids or promote lactate dehydrogenase (LDH) activity.[110,111] The two factors that make this possible are slow GI transit (blind loops, obstruction) and change of the normal flora (usually with antibiotic therapy).[112] The most prevalent organic acid is D-lactic acid. Because humans metabolize this isomer more slowly than L-lactate and production rates can be very rapid, life-threatening acidosis can be produced.[113] The usual laboratory test for lactate is specific for the L-lactate isomer. Therefore to confirm the diagnosis, the plasma or more easily tested urinary D-lactate must be specifically requested.[114]

Metabolic Alkalosis

Metabolic alkalosis is a common acid-base disturbance in ICU patients characterized by an elevated serum pH (>7.45) secondary to plasma bicarbonate (HCO_3^-) retention. Metabolic alkalosis is usually the result of several therapeutic interventions in the critically ill patient (Table 34.8). Nasogastric drainage, diuretic-induced intravascular volume depletion, hypokalemia, and the use of corticosteroids are common causes of metabolic alkalosis in these patients. In addition, citrate in transfused blood is metabolized to bicarbonate, which may compound the metabolic alkalosis. Type II respiratory failure promotes compensatory retention of bicarbonate that may result in a posthypercapnic metabolic alkalosis when ventilation is normalized. In many

TABLE 34.8 Causes of Metabolic Alkalosis

Low Urine Chloride (Volume or Saline Responsive)	High Urine Chloride With Hypertension
Gastric volume loss	Primary and secondary hyperaldosteronism
Diuretics	Apparent mineralocorticoid excess
Posthypercapnia	Liddle's syndrome (autosomal dominant, pseudoaldosteronism)
Villous adenoma (rare)	Conn syndrome
Cystic fibrosis (if there has been excessive sweating)	Cushing disease
High Urine Chloride Without Hypertension	
Bartter syndrome	
Gitelman syndrome (autosomal recessive hypokalemic metabolic alkalosis)	
Excess bicarbonate administration	

patients, therefore, events that generated the metabolic alkalosis may not be present at the time of diagnosis.

Metabolic alkalosis may adversely affect cardiovascular, pulmonary, and metabolic function. It can decrease cardiac output, depress central ventilatory drive, shift the oxyhemoglobin saturation curve to the left (decreasing the offloading of hemoglobin-bound oxygen), worsen hypokalemia and hypophosphatemia, and negatively affect the ability to wean patients from mechanical ventilation. Rising serum pH has been shown to correlate with ICU mortality. Correction of metabolic alkalosis has been shown to increase minute ventilation, increase arterial oxygen tension and mixed venous oxygen tension, and decrease oxygen consumption. It is therefore important to correct significant metabolic alkalosis in the majority of critically ill patients. In the case of cardiac arrest, it is also challenging to correct metabolic alkalosis in a rapid fashion.[115–117]

The first therapeutic maneuver in patients with a metabolic alkalosis is to replace any volume deficit with normal saline (0.9% NaCl) and correct electrolyte deficiencies. Aggressive potassium supplementation is warranted to achieve a K^+ above 4.5 mEq/L. If these interventions fail, ammonium chloride, hydrochloric acid, or arginine hydrochloride may be given.[117,118] The disadvantage of these solutions is that they are difficult to use and require the administration of large volumes of hypotonic fluid. Extravasation of hydrochloric acid (even at 20–25 mmol/h) may result in severe tissue necrosis, mandating administration through a well-functioning central line. Acetazolamide is a carbonic anhydrase inhibitor promoting the renal excretion of bicarbonate and has been demonstrated to be effective in treating metabolic alkalosis in ICU patients. A single dose of 500 mg is recommended. The onset of action is within 1.5 hours, with duration of approximately 24 hours, and doses may be repeated.[117,119–121]

Respiratory Acidosis

Respiratory acidosis is also a common occurrence among the acutely ill, especially in those who are not mechanically ventilated, in addition to patients receiving lung-protective mechanical ventilation.[122] Failing respiratory muscles, pain preventing effective breathing, increased abdominal pressures, and centrally acting agents that suppress respiratory drive all depress ventilation, leading to increased CO_2 retention with subsequent respiratory acidosis. Among these patients, treating the underlying cause would lead to definite resolution, yet temporizing measures such as mechanical ventilation would be required.

In patients on lung-protective modes of mechanical ventilation, the so-called "permissive hypercapnia" itself has been suggested to have directly beneficial effects, yet later evidence did not support this contention.[123]

Respiratory Alkalosis

Respiratory alkalosis is induced by hyperventilation with causes originating from *central, hypoxemic, pulmonary,* and *iatrogenic* causes. Central causes include head injury, stroke, hyperthyroidism, anxiety-hyperventilation, pain, fear, stress, drugs, medications such as salicylates, and various toxins. In the case of medication-induced respiratory alkalosis, the ABG and further studies with toxicology panel would help to identify the causes. Hypoxia could lead to hyperventilation to correct hypoxia at the expense of CO_2 loss. Pulmonary causes include pulmonary embolisms, pneumothorax, pneumonia, and acute asthma or COPD exacerbations. Iatrogenic causes are almost universally induced by hyperventilation among intubated patients receiving mechanical ventilation support.[124]

Respiratory alkalosis may be an acute process or a chronic process. These are determined based on the level of metabolic compensation for the respiratory disease. Excess HCO_3^- levels are buffered to reduce levels and maintain a physiologic pH through the renal decrease of H^+ excretion and increasing HCO_3^- excretion; however, this metabolic process occurs over the course of days, whereas respiratory disease can adjust CO_2 levels in minutes to hours. Therefore acute respiratory alkalosis is associated with high bicarbonate levels because there has not been sufficient time to lower the HCO_3^- levels, and chronic respiratory alkalosis is associated with low to normal HCO_3^- levels.[1,8,9]

VENOUS BLOOD GAS ANALYSIS

There is a strong correlation between arterial and venous blood pH and HCO_3^- levels in patients with DKA and uremia.[120,121] In published studies, the difference between arterial and venous pH varied from 0.04 to 0.05, and the difference in bicarbonate levels varied from −1.72 to 1.88. However, the correlation between arterial and venous $PaCO_2$ was relatively poor.[125–127] Actually, this difference may be used to evaluate the adequacy of oxygen availability to the tissues (see later). Similarly, an excellent correlation has been demonstrated between mixed venous pH and HCO_3^- with arterial pH and HCO_3^- in critically ill patients.[128,129] Yet in shock states this tight association does not hold true; the correlation between arterial and venous pH, HCO_3^- and $PaCO_2$ is poor.[130,131] During cardiopulmonary resuscitation, the arterial blood vs. mixed venous blood pH were 7.41 vs. 7.15; likely $PaCO_2$ was 32 mm Hg vs. 74 mm Hg, respectively.[132,133]

Once shock is resolved, in patients without hypercarbia, ABG would not be necessary; pulse oximetry and venous blood gas analysis would be enough to make a clinical judgment. Furthermore, a venous blood gas can be useful to screen for arterial hypercarbia, with a venous $PvCO_2$ of >45 mm Hg being highly predictive of arterial hypercarbia.[134]

Mixed Venous/Central Venous Oxygen Saturation

Monitoring of SvO_2 has been used as a surrogate for the balance between systemic oxygen delivery and consumption during the treatment of critically ill patients.[135] An SvO_2 of less than 65% indicates inadequate oxygen delivery; however, this sample needs to be collected from the distal post of a pulmonary artery catheter (PAC), an invasive device whose use has not been shown to routinely improve patient outcome. Therefore most clinicians use the central venous oxygen saturation ($ScvO_2$) as a surrogate.[136,137]

There are multiple reasons why $ScvO_2$ and SvO_2 can differ. First of all, the vena caval blood streams into the right atrium and ventricle, and complete mixing occurs only during ventricular contraction. In addition, blood from the coronary sinus and Thebesian veins results in further discrepancies.[138,139] Thus SvO_2 is a better indicator of whole-body balance of oxygen supply and demand, whereas $ScvO_2$ more closely reflects the status of upper body tissues. In hemodynamically stable, healthy patients, $ScvO_2$ is usually 2%–5% less than SvO_2 because of the high oxygen content of effluent venous blood from the kidneys.[140] This changes during shock as blood is redistributed to the upper body at the expense of the splanchnic and renal circulations. In shock states, $ScvO_2$ may exceed that of SvO_2 by up to 20%.[141] This tendency also applies in patients with cardiogenic, septic, and hemorrhagic shock.[142] Therefore one has to assess these saturation values within the context of the clinical scenario.[137,141,143–147] In patients with sepsis and liver failure, a low $ScvO_2/SvO_2$ is usually indicative of decreased cardiac output, and normal values do not necessarily indicate resuscitation or adequate tissue oxygenation.[148–150] In liver failure, all pathologic collaterals may result in "arterialization" of the venous blood. In addition, cytopathic hypoxia (e.g., because of cyanide) may further decrease oxygen uptake and result in a

"spuriously high" $ScvO_2$.[151] Interestingly, patients dying of both sepsis and liver failure usually have a high $ScvO_2/SvO_2$.[152] In a recent goal-directed sepsis study, the mean $ScvO_2$ was 74% at enrollment, and less than 10% of patients required specific interventions to achieve values above 70%.[153]

In addition, a high mixed venous-to-arterial PCO_2 gradient is a predictor of decreased cardiac output and global tissue ischemia.[154–156] This observation has been confirmed by Adrogue et al, Mecher et al, Bakker et al, Levy et al, and Nassar et al, who demonstrated that a high mixed venous-to-arterial PCO_2 gradient is a sensitive marker of global tissue ischemia and fluid responsiveness during cardiogenic and septic shock.[133,157–160] Recent work suggests that central venous-to-arterial PCO_2 gradient (>6 mm Hg) reliably indicates success of resuscitation in septic shock.[161]

In summary, for hemodynamically unstable patients and those with complex acid-base disorders, as a rule of thumb, venous blood gas cannot be substituted for an ABG analysis. In these situations, both arterial and mixed venous/central venous blood gas analyses provide useful information.

KEY POINTS

- ABG analysis is the gold standard for the assessment of oxygenation, ventilation, and acid-base status for critically ill patients as long as it is obtained and interpreted within the clinical context.
- Pulse oximetry can provide a surrogate measure of arterial oxygen tension (PaO_2). Venous pH and bicarbonate (HCO_3^-) allow for the estimation of arterial pH and HCO_3^- in hemodynamically stable patients, yet one needs to be cautious during shock states. Venous carbon dioxide tension is a poor proxy of arterial $PaCO_2$. Venous blood gas analysis can be useful to screen for arterial hypercarbia, with a venous PCO_2 level above 45 mm Hg being highly predictive of arterial hypercarbia.
- The indications for ABG sampling have not been well defined; however, an ABG should generally be performed on admission to the ICU, after endotracheal intubation, and as the clinical context changes.
- ABG sampling does not have to be performed after each ventilator change or after each step during liberation from the ventilator.
- Because metabolic acidosis may have serious hemodynamic consequences, its etiology has to be determined and treatment initiated immediately.
- In most clinical situations, sodium bicarbonate ($NaHCO_3$) is of no therapeutic utility during metabolic acidosis.
- In patients with a metabolic alkalosis, correct any volume and potassium deficits first, then consider initiating acetazolamide and/or HCl infusions.
- The central venous oxygen saturation ($ScvO_2$) and the central venous-to-arterial $PaCO_2$ gap have utility in assessing the adequacy of resuscitation and oxygen delivery.

References for this chapter can be found at expertconsult.com.

ANNOTATED REFERENCES

The traditional vs. the new perspective on acid-base balance:

Although the bedside clinician needs a handy tool to understand the acid-base balance to diagnose and manage their patients appropriately, the academic disagreements are still viable on the topic of acid-base balance. In summary, the traditional approach suggests that activity of H^+ in a biologic space is determined by the mass balance of H^+; proton transfer reactions via proton donors (weak acids) and proton acceptors (weak bases); and mass balance of proton donors and proton acceptors (Arrhenius, Sørenson, Henderson, Hasselbalch, Brønsted and Lowry, Van Slyke, Lewis, Severinghaus, Astrup, Siggard-Anderson, Schwartz, and Relman).

In 1978 Stewart questioned the traditional dogma by proposing that a complex mixture of ions regulates the activity of H^+ over the physiologic pH range (Na^+, K^+, Ca^{2+}); nonvolatile proton donators/acceptors transfer H^+ within the physiologic pH range (albumin, phosphate, hemoglobin, metabolizable organic compounds); and the volatile bicarbonate-CO_2 buffer system is composed of CO_2, HCO_3^-, H_2CO_2, and CO_3^{2-}. The following are useful literature articles on the topic.

Elbers PW, Van Regenmortel N, Gatz R. Over ten thousand cases and counting: acidbase.org is serving the critical care community. *Anaesthesiol Intensive Ther*. 2015;47(5):441–448.

A new reference of a handy online web tool to understand acid-base balance and the freely available textbook of Dr. Stewart. The web tool helps calculate the strong ion difference.

Kurtz I, Kraut J, Ornekian V, et al. Acid-base analysis: A critique of the Stewart and bicarbonate-centered approaches. *Am J Physiol Renal Physiol*. 2008;294(5):F1009–F1031.

The authors support the idea that the H^+/HCO_3^- approach based on the Henderson-Hasselbalch equation is mechanistically more robust than the Stewart or strong ion approach. Accordingly, CO_2/HCO_3^- is useful in the hands of the clinicians to approach all the acid-base derangements seen clinically; however, it is qualitative in nature and cannot quantify acid or base loads that result in metabolic acid-base disorders despite the concomitant use of base excess information—all leading to the argument for a more quantitative measurement: the Stewart approach. However, both are "equilibrium equations" and have similar predictive value for clinical acid-base disorders, suggesting the favorite approach by the authors is the Henderson-Hasselbalch equation.

Oxygen tension: From a global perspective to a regional assessment

The concept of partial pressure of oxygen measured in arterial blood gas analyses could be easily applied to oxygen tension measurements in regional perfusion. A recent work on brain tissue oxygen tension is relevant to the intensivist.

Rosenthal G, Hemphill III JC, Sorani M, et al. Brain tissue oxygen tension is more indicative of oxygen diffusion than oxygen delivery and metabolism in patients with traumatic brain injury. *Crit Care Med*. 2008;36(6):1917–1924.

The specific determinants of low brain tissue oxygen tension ($P_{bt}O_2$) after severe traumatic brain injury (TBI) remain poorly defined as to whether it reflects cerebral oxygen diffusion or cerebral oxygen delivery and metabolism. The group measured $P_{bt}O_2$ directly and the cerebral venous blood gases from a jugular bulb venous catheter. After multiple models of logistic regression, there is a strong association between brain tissue oxygen tension and diffusion of dissolved plasma oxygen across the blood-brain barrier, suggesting that $P_{bt}O_2$ represents the cerebral blood flow and cerebral arteriovenous O_2.

Other uses of CO_2 measurements: Evidence is suggesting that CO_2 could be used as endpoints for resuscitation in sepsis

Al Duhailib Z, Hegazy AF, Lalli R, et al. The use of central venous to arterial carbon dioxide tension gap for outcome prediction in critically ill patients: A systematic review and meta-analysis. *Crit Care Med*. 2020;48(12):1855–1861.

This review included 21 studies (n = 2155 patients) from medical (n = 925), cardiovascular (n = 685), surgical (n = 483), and mixed (n = 62) ICUs

comparing central CO_2 gap. A high CO_2 gap was associated with higher lactate levels (mean difference 0.44 mmol/L; 95% confidence interval [CI], 0.20–0.68 mmol/L; P = .0004), lower cardiac index (mean difference, −0.76 L/min/m; 95% CI, −1.04 to −0.49 L/min/m; P = .0001), central venous oxygen saturation (mean difference, −5.07; 95% CI, −7.78 to −2.37; P = .0002), and increased mortality (odds ratio, 2.22; 95% CI, 1.30–3.82; P = .004) in patients with shock. Yet it was not associated with longer ICU or hospital length of stay, requirement for renal replacement therapy, longer duration of mechanical ventilation, or higher vasopressors and inotropes use. The working hypothesis for the increased CO_2 gap is decreased cardiac output, yet this has to be tested further.

Guzman JA, Dikin MS, Kruse JA. Lingual, splanchnic, and systemic hemodynamic and carbon dioxide tension changes during endotoxic shock and resuscitation. *J Appl Physiol.* 2005;98(1):108–113.

The authors studied LPS-induced circulatory shock and resuscitation sublingual and intestinal mucosal blood flow and PCO_2 in a canine model. The shock did induce increased sublingual and splanchnic PCO_2, and the levels were nearly reversed after fluid resuscitation while the systemic hypotension persisted. Changes in sublingual and splanchnic PCO_2 paralleled gastric and intestinal PCO_2 changes during shock but not during resuscitation. This and other work suggest the utility of PCO_2 in estimating tissue perfusion.

Mesquida J, Saludes P, Gruartmoner G, et al. Central venous-to-arterial carbon dioxide difference combined with arterial-to-venous oxygen content difference is associated with lactate evolution in the hemodynamic resuscitation process in early septic shock. *Crit Care.* 2015;19:126.

Because normal or high central venous oxygen saturation $ScvO_2$ values cannot discriminate if tissue perfusion is adequate, other markers of tissue hypoxia are required. The authors studied the ratio of central venous-to-arterial carbon dioxide difference ($PcvaCO_2$ gap) to arterial-venous oxygen content difference ($CavO_2$) ratio to predict lactate evolution in septic shock. The high $PcvaCO_2/CavO_2$ ratio had a high predictive power towards no improvement in lactate clearance. The regional oxygen concentration (ROC) had an area under the curve (AUC) of 0.82, and when the $PcvaCO_2/CavO_2$ ratio was set at 1.4 mm Hg ⋮ dL/mL O_2, it carried a sensitivity of 0.80 and specificity of 0.75 for lactate improvement. This ratio and the use of PCO_2 could be used towards predicting the outcome from sepsis.

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35

Tracheal Intubation

June M. Chae, John D. Davies, and Alexander S. Niven

INTRODUCTION

Tracheal intubation is a commonly performed, high-risk procedure in critically ill patients. There are important differences between elective intubation in the operating room compared with emergency intubation in the intensive care unit (ICU). Risks associated with emergent intubation in the critically ill include hypoxemia, hemodynamic instability, cardiac arrest, and death, underlining the importance of a systematic approach to optimize physiologic conditions and maximize first-attempt success. Although a wide variety of advanced airway devices are now available to help overcome anatomic difficulties and deliver rescue oxygenation, the best evidence-based approach for utilizing these tools in the ICU patient remains poorly defined. The goal of this chapter is to provide a systematic approach using best evidence to maximize the success and safety of tracheal intubation in the ICU.

PATIENT FACTORS AND AIRWAY ASSESSMENT

Reported complication rates from tracheal intubation in the critically ill range from 4.2% to 22% and remain unacceptably high in comparison with operating room procedures.[1–5] The Fourth National Audit Project of the Royal College of Anaesthetists and the Difficult Airway Society (NAP4) reported that 25% of adverse airway events occurred in the ICU and emergency department (ED). Inadequate identification of high-risk patients combined with poor planning, inadequate preparation, and ineffective teamwork were the primary causal and contributing factors to these adverse events.[6]

Physiologic Assessment

Decompensated cardiopulmonary disease and shunt physiology make preoxygenation more difficult in the critically ill, shortening the safe apnea time during intubation before hypoxemia develops.[7] Hemodynamic instability is an independent predictor of death after intubation, underscoring the importance of an individualized approach to high-risk patients, including those with severe valvular disease, pulmonary hypertension, right ventricular failure, and high shock index.[8–10] The combination of desaturation and hypotension increases the likelihood of cardiac arrest.[8]

Anatomic Assessment

Emergent airway management leaves little time to perform a thorough airway assessment and less time to plan the approach when high-risk features are present. In conscious and cooperative patients, an inability to bite the upper lip with the lower incisors may be the single best predictor of difficult laryngoscopy.[11] Other features predict difficult laryngoscopy. These include those that limit the ability to open the airway (interincisor distance, large tongue), displace the tongue into the submental space (large tongue, short mandible, short thyromental and hyomental distances), and/or impair alignment of the visual axes (cervical mobility).[12] Features that predict difficult bag-valve-mask ventilation (BMV) include obesity, facial hair, advanced age, history of sleep apnea, and being edentulous. Features that predict difficult supraglottic device use include restricted mouth opening, a distorted airway, reduced lung compliance, and upper airway obstruction.

Common methods of airway assessment are limited in their ability to correctly identify patients with a difficult airway (positive predictive value, 4%–27%).[13,14] The MACOCHA score, a seven-item prediction scale for the critically ill, is the only validated tool for identifying high-risk patients.[15,16]

OPTIMIZING AIRWAY MANAGEMENT IN THE CRITICALLY ILL

Positioning

Optimal patient positioning is important to maximize the success of both preoxygenation and laryngoscopy attempts. Upright positioning can optimize functional residual capacity (FRC), especially in obese and pregnant patients, which combined with careful preoxygenation, can prolong the safe apnea time during intubation.[12] A recent randomized trial showed increased difficulty with direct laryngoscopy using the "ramped" position (head of bed elevated 25 degrees, face parallel to the floor) compared with the "sniffing" position (supine, neck flexed, head extended).[17] Combining ramped with sniffing positions may improve first-pass intubation success, especially in obese patients.

Preoxygenation and Apneic Oxygenation

Critically ill patients run higher risks of life-threatening hypoxemia. Preoxygenation is generally limited by the size of the FRC and the ability to denitrogenate this space. In the critically ill, the degree of physiologic shunting is a major limiting factor to preoxygenation. Rapid-sequence intubation has an inherent delay of 45–90 seconds between medication administration and laryngoscopy.[18] A recent multicenter trial demonstrated that mask ventilation during the apneic period after induction reduced the incidence of severe hypoxemia without increased aspiration risk.[19] Noninvasive positive pressure ventilation (NIV) and high-flow nasal cannula (HFNC) have been shown to improve preoxygenation. A randomized trial failed to demonstrate clear benefit with routine apneic oxygenation in the critically ill, and this practice remains controversial.[20] In patients with refractory hypoxemia there is no safe apnea time, and awake intubation should be strongly considered when oxygenation can be assured during the procedure.

Rescue Oxygenation

Avoiding hypoxemia is essential to preserve safe patient conditions during intubation. If oxygen saturations drop significantly during this

procedure, the first rescue maneuver is the two-person BMV technique using an oropharyngeal airway and meticulous attention to patient positioning. If this maneuver proves inadequate, a second-generation supraglottic airway should be used expediently.[12,21,22] Airway managers must also be prepared to perform an emergent cricothyrotomy when a definitive airway cannot be secured and life-threatening hypoxemia persists after such maneuvers.

Hemodynamics

Critically ill patients are at risk for periprocedural hypotension, which can lead to cardiac arrest.[8] Hypotension during intubation occurs commonly, often the result of decreased circulating catecholamines, the physiologic effects of many induction medications such as increased venous capacitance after their administration, and decreased venous return from positive pressure ventilation.[23] Push-dose vasopressors with phenylephrine, ephedrine, and epinephrine can be considered; norepinephrine and epinephrine are more commonly used for continuous infusion.[24] Although a routine intravenous fluid bolus before induction as part of an "intubation bundle" has been shown to reduce the incidence of associated cardiovascular collapse in a single-center quality improvement intervention, this practice remains controversial because of a recent multicenter trial that demonstrated no attributable benefit.[3,23]

Soiled Airway

A soiled airway increases the risk for aspiration complications and decreases first-pass success. Emesis, hematemesis, and hemoptysis are more often encountered during emergency airway management. Training in the management of soiled airways is also limited. Although poorly studied, the suction-assisted laryngoscopy and airway decontamination (SALAD) technique has proved popular with many emergency airway managers. This technique involves passing the tip of a rigid (Yankauer) suction catheter from the left side of the mouth into the proximal esophagus after the upper airway is cleared to control further airway soilage during the intubation attempt.[25]

RAPID-SEQUENCE INTUBATION AND AIRWAY PHARMACOLOGY

Rapid-sequence intubation (RSI) is the standard of care in most emergency airway management settings because of its high rate of success.[26] The goal of RSI is to rapidly optimize conditions for intubation before desaturation and to prevent aspiration.[12] Medication administration in critically ill patients is challenging because of preexisting cardiopulmonary derangements and the concern for failed airway attempts. Except when a pulseless or unresponsive patient demands immediate intervention or does not require them, selecting and preparing appropriate medications should be a routine part of intubation preparation and planning. Common agents, indications, and doses are summarized in Table 35.1.[27] Drugs administered before induction are particularly useful in the setting of severe exacerbations of obstructive lung disease and significant intraocular or intracranial hypertension.

Initial induction agent doses should be reduced by 25%–50% in the elderly and in patients with hypotension, hypovolemia, or significantly impaired cardiac function. Propofol tends to provide for glottic visualization at full induction doses but causes significant hypotension. Etomidate has less associated hypotension and myocardial depression. It reduces adrenal steroidogenesis, but single doses do not appear to increase mortality even in septic patients.[28] Ketamine increases heart rate, blood pressure, and cardiac output and has been shown to provide similar intubating conditions and outcomes as etomidate in a large, prospective randomized trial.[29] Its use in the setting of increased intracranial pressure (ICP) is controversial.[30,31] Caution should be taken in the catecholamine-depleted patient, as ketamine can act as a negative inotrope.[32–34] Although ketamine can relieve bronchospasm, it may also increase orotracheal secretions and promote laryngospasm.[32,33]

TABLE 35.1 Common Medications Used During Tracheal Intubation

PREINDUCTION MEDICATIONS

Drug	Dose, Common Indications	Cautions
Fentanyl	2–3 micrograms/kg IV, 1–2 min CAD, aneurysm, increased ICP	Hypotension Masseter, chest wall rigidity
Esmolol	2–3 mg/kg IV Neurosurgery, head injury	Bradycardia Hypotension, bronchospasm
Lidocaine	1.5 mg/kg IV, 2–3 min Asthma, COPD, increased ICP	Hypotension

INDUCTION MEDICATIONS

Agent	Onset (seconds)	Duration (minutes)	Dose
Propofol	9–50	3–10	0.5–2 mg/kg
Etomidate	30–60	3–5	0.2–0.3 mg/kg
Ketamine	60–120	5–15	2 mg/kg

NEUROMUSCULAR BLOCKERS

Agent	Onset (seconds)	Duration (minutes)	Dose	Off-Label Dosing
Succinylcholine	30–60	5–15	1.0–1.5 mg/kg	Manufacturer's recommendation 0.6 mg/kg
Rocuronium	45–60	45–70	0.6–1.2 mg/kg	
Atracurium	60–90	35–70	0.4–0.5 mg/kg	

CAD, Coronary artery disease; *COPD*, chronic obstructive pulmonary disease; *ICP*, intracranial pressure; *IV*, intravenous. From Reynolds SF, Heffner J. Airway management of the critically ill patient. *Chest*. 2005;127:1397–1412.

The combination of an induction agent such as propofol with a paralytic reliably produces optimal intubating conditions.[35,36] Historically, succinylcholine has been one of the most commonly used depolarizing muscle relaxants because of its rapid onset of action and very short duration. In situations where succinylcholine may be considered unsafe (Box 35.1), rocuronium or atracurium will provide a similar onset of action but a much longer duration of paralysis.

In recent years, the availability of sugammadex, a drug that rapidly reverses the effects of the steroidal neuromuscular blocking agents (NMBAs), has prompted increased rocuronium use, especially if paralytic choice is limited by contraindications to succinylcholine.[24,37] Caution is recommended in patients with renal impairment. When required, the rocuronium–sugammadex complex can be removed by hemodialysis.[38]

LARYNGOSCOPY

Recent years have seen the development of a wide array of commercially available airway equipment, with mixed availability and familiarity in many ICUs.[39] Most experts recommend the selection of a limited list of airway tools most appropriate for a given ICU population to facilitate familiarity and training.

Direct Laryngoscopy

Macintosh and Miller blades are designed for rapid endotracheal tube (ETT) placement. The Macintosh blade is broad, curved, and includes a flange to displace the tongue to the left when the blade is introduced into the mouth from the right side (paraglossal approach). The blade is advanced toward midline, and the tip is directed into the vallecula once the epiglottis comes into view. Gentle blade traction will lift the epiglottis and expose the glottic aperture. The Miller blade is longer and straighter, with a slightly curved tip. It is generally inserted using a midline approach, and the distal end is used to directly lift the tip of the epiglottis. Care must be taken with both blades to apply caudal and anterior force, holding the laryngoscope handle near its base and keeping its angle less than 45 degrees to the patient to avoid dental damage. Blade sizes 3 or 4 are appropriate for most adult procedures. The broader surface of the Macintosh blade may provide better upward displacement of excess upper airway soft tissue, and the longer and narrower profile of the Miller blade may assist in the setting of narrow mouth opening or a long epiglottis. When using any blade, a stylet is generally used to help guide the ETT through the vocal cords and can be shaped with a distal bend to aid in tracheal placement.

Indirect Laryngoscopy

Indirect laryngoscopy devices provide video or optical imaging using mirrors and prisms to improve glottic visualization in individuals in whom alignment of the airway axes is difficult. Some devices incorporate an acutely angulated blade (i.e., GlideScope, McGrath, C-MAC), whereas others incorporate a channel (i.e., Airtraq, Pentax) to facilitate ETT placement through a more anterior glottis with the head in a neutral position.[40]

Confidently interpreting research that compares direct and indirect laryngoscopy is difficult. Some literature suggests that indirect laryngoscopy offers little advantage in the average patient, but affords high rates of intubation success in patients with difficult airway risk factors, obesity, or failed direct laryngoscopy attempts.[41–45] Videolaryngoscopy (VL) can accelerate training performance with novices and provides a high rate of first-time success in the hands of less experienced intubators.[46–48]

Several trials have demonstrated improved glottic visualization but no clear benefit in the rate of first-pass success using indirect laryngoscopy for emergency airway management.[49–54] Lascarrou and colleagues compared VL with direct laryngoscopy (DL) without excluding predicted or historically difficult intubations and not only found no difference in success but also found an increase in severe complications with McGrath Mac VL. DL failure is frequently associated with the inability to visualize the glottis, whereas failure in VL is often related to the inability to pass the ETT.[53] Each device has unique technical considerations with which operators must become familiar to maximize their potential benefit.

BOX 35.1 Contraindications to Succinylcholine

History of malignant hyperthermia
Hyperkalemia
Upper, lower motor neuron lesions
Myopathy
Crush injury
Severe burns (>24 hours)
Prolonged immobility

DIFFICULT AIRWAY MANAGEMENT

A difficult airway is defined as the presence of clinical factors that complicate ventilation or intubation.[55] The incidence of difficult airways encountered during emergent intubations is reported to be 10%.[4,56] Although the best management approach to a difficult airway in the ICU is not well studied, a recent systematic review of published guidelines found substantial similarities. The algorithms analyzed recommended a stepwise approach to airway management, using tracheal intubation, face mask ventilation, and supraglottic airway devices, followed by an early emergency surgical airway if these attempts are unsuccessful and a life-threatening situation exists.[57]

In the setting of a predicted difficult airway, indirect optical devices and VLs provide better glottic visualization and maximize the likelihood of intubation success. In one large single-institution study, a gum elastic bougie was the preferred method to successfully manage patients with incomplete glottic visualization and those for whom glottic intubation is not possible.[4] Although controversial, one large single-institution study reported that use of a bougie combined with either DL or VL as a primary intubation strategy was associated with a significantly higher rate of first-pass success compared with using an ETT and stylet.[58] This strategy requires further study in the critical care setting before widespread adoption.

An intubating supraglottic device (SGD) is also an appropriate primary or rescue strategy. SGDs, such as the laryngeal mask airway and King tube, can be placed into the upper airway to reestablish adequate oxygenation and ventilation without significant technical expertise in many cases. Intubation through SGDs has proven successful after failed direct laryngoscopy and usually provides a rapid primary approach in patients with a predicted difficult airway.[59,60] A number of current SGDs also provide the option of one-step intubation through the device (Ambu Aura-i, CookGas LLC, Air-Q/ILA, LMA Fastrach, and Classic Excel, i-Gel).

Surgical cricothyroidotomy is reserved for the emergency airway situation when an extraglottic airway cannot be effectively employed because of upper airway abnormalities, blood, or secretions that obviate proper placement and function. Cricothyroidotomy can be performed most rapidly using a rapid four-step technique.[61] Passing a bougie through the neck incision to serve as an ETT guide has been reported successful even in the hands of the novice nonsurgeon.[62] A cricothyroidotomy kit that uses a Seldinger approach is also available

but has been associated with longer time to placement.[63] Major complications include esophageal perforation, subcutaneous emphysema, and bleeding.

Cooperative patients with slowly progressive respiratory failure and predicted difficult airways can be considered for awake intubation. Awake intubation provides the opportunity to preserve spontaneous respiration and prolong the available time for intubation attempts. Upright fiber-optic–assisted intubation through a Williams or Ovassapian intubating airway is a common and effective approach. Preinsertion, patient candidates typically require a combination of nebulized or atomized lidocaine directed at the base of tongue and tonsillar pillars. Low-dose narcotics such as remifentanil appear to be superior to dexmedetomidine when combined with low-dose midazolam for sedation.[64] Unfortunately, the time required for appropriate airway preparation can be challenging in critical care practice, limiting broad-based application of this technique.

HUMAN FACTORS

Training

Current airway management training is highly variable, even among anesthesia providers.[65–68] A recent meta-analysis suggested that the level of training, as opposed to specialty type, was the key factor for optimizing proper airway management.[69,70] The appropriate volume and scope of airway training required, however, remains a topic in need of further research. Novices can attain reasonable competence with direct laryngoscopy after 30–50 cases and may accelerate their skills using video-assisted instruction, but performance continues to improve even after 100 intubations.[71–73] Box 35.2 provides a suggested list of airway management topics for training, but these recommendations are based only on expert opinion.[74] The development of a vast array of advanced airway management devices has only complicated efforts to standardize training and approaches to ICU airway management. In a national survey of 180 American ICU and anesthesiology directors, only 70% had a difficult airway cart in their ICU, and 60% of the respondents reported that they had not been trained in the use of such equipment.[39]

Preparation

NAP4 found that preparation, equipment, and communication errors were the most common causes of complications during airway management in ICUs and EDs in the United Kingdom.[6] These data underline the importance of deliberate planning and preparation to maximize patient safety and procedure success.

BOX 35.2 Fundamental Airway Knowledge and Skills

Face mask ventilation, airway positioning
Laryngeal mask airway (LMA, including intubating devices)
Oral endotracheal intubation (direct laryngoscopy [DL])
Simple maneuvers (positioning, BURP*) to improve DL
Use of stylet, gum elastic bougie
Rapid-sequence induction
Fiber-optic intubation via conduit (oropharyngeal airway, LMA)
Percutaneous cricothyrotomy

* *BURP*, Backwards, upwards, and rightwards positioning.
From Goldmann K, Ferson DZ. Education and training in airway management. *Best Pract Res Clin Anaesthesiol.* 2005;19(4):717–732.

Resource management principles important for an efficient airway management team include explicit role assignments, closed loop communication, and standardized guidelines for equipment, medication preparation, and positioning. Clear articulation of the primary and backup airway management plans and discrete oxygen cutoffs (which should prompt termination of intubation efforts and resumption of BMV ventilation) provide shared situational awareness and guidance to maintain quality control and safety throughout the procedure.

Checklists and Maximizing Patient Safety

The American Society of Anesthesiologists recommends that an airway assessment be performed before all intubations and emphasizes a systematic approach that maximizes oxygen delivery and considers an awake procedure, a variety of noninvasive techniques, and preservation of spontaneous ventilation.[55] Other recent studies have also underlined the importance of having a systematic approach to airway assessment, patient and equipment preparation, and procedure planning in order to maximize intubation success. Jaber and colleagues demonstrated that implementation of a protocolized ICU intubation bundle (Box 35.3) reduced complications by 25%.[3]

Improved patient safety and reduced need for emergent surgical airways have been achieved through implementation of a standardized, team-based approach that includes proactive identification of patients with known difficult airways, ready availability of advanced airway equipment, simulation-based airway skills and teamwork training, a mandatory bedside procedure checklist, and postevent debriefs.[75,76] The APPROACH mnemonic (Box 35.4) is one structured checklist tool aimed at ensuring that these standardized interventions are consistently performed.[77]

CONCLUSION

Tracheal intubation in the ICU remains a high-risk procedure, and a systematic approach that emphasizes planning, preparation, and teamwork is necessary to maximize its outcome and safety.

Although intensivists should maintain facility with DL, there are growing data supporting the use of indirect laryngoscopy as both a primary and rescue technique in the ICU. In the setting of an emergency airway, an extraglottic airway or surgical airway should be rapidly employed. If oxygenation and ventilation can be reestablished, a wider variety of techniques can be considered.

Airway management in the critically ill patient goes beyond performing laryngoscopy; it is about preventing hypoxemia and cardiovascular collapse through preparation; consideration of difficult anatomic, physiologic and situational factors; and optimizing the chances of first-pass success.

KEY POINTS

- A systematic approach that emphasizes planning, preparation, and teamwork is the best proven method to reduce risks associated with airway management in the ICU.
- An extraglottic airway should be employed early in the patient with inadequate oxygenation and ventilation.
- Optimizing difficult anatomic, physiologic, and situational factors will enhance the chances of first-pass success.

References for this chapter can be found at expertconsult.com.

BOX 35.3 ICU Intubation Bundle Used in a Large Multicenter Study to Improve Patient Outcomes

Preintubation

1. Presence of two operators
2. Fluid loading (isotonic saline [500 mL]) in the absence of cardiogenic pulmonary edema
3. Preparation of long-term sedation
4. Preoxygenation for 3 minutes with NIPPV in case of acute respiratory failure (Fio_2 100%, pressure support ventilation level between 5 and 15 cm H_2O to obtain an expiratory tidal volume between 6 and 8 mL/kg and PEEP of 5 cm H_2O)

During Intubation

5. Rapid-sequence induction: etomidate (0.2–0.3 mg/kg) or ketamine (1–3 mg/kg) combined with succinylcholine (1–1.5 mg/kg) in the absence of allergy, hyperkalemia, severe acidosis, acute or chronic neuromuscular disease, burn patients for more than 48 hours, and major crush injury
6. Sellick maneuver

Postintubation

7. Immediate confirmation of tube placement by capnography
8. Norepinephrine if diastolic blood pressure remains <35 mm Hg
9. Initiate long-term sedation
10. Initial "protective ventilation": tidal volume 6–8 mL/kg of ideal body weight for a plateau pressure <30 cm H_2O

Fio_2, Inspired oxygen fraction; *NIPPV*, noninvasive positive pressure ventilation; *PEEP*, positive end expiratory pressure.
From Jaber S, Jung B, Corne P, et al. An intervention to decrease complications related to endotracheal intubation in the intensive care unit: a prospective, multiple-center study. *Intensive Care Med.* 2010;36:248–255.

BOX 35.4 The CHEST APPROACH to Airway Management

Assess the airway—it's all in your **HAND**
History of difficult intubation
Anatomic considerations
- 3-3-2 rule
- Modified Mallampati Classification
- Other risk factors for airway distortion, obstruction

Neck mobility
Difficult airway should be considered if concerns with any of the factors noted earlier
Preoxygenate using 100% oxygen, bag-valve-mask with PEEP valve
Prepare
Patient: Sniffing position, headboard off and patient head just below the intubator's xiphoid process
Medications: Free-flowing IV, premedication, induction, paralytic, and vasopressor agents
Right side: Suction, endotracheal tube with stylet and syringe attached
Left side: Laryngoscope handle, blades, oral and nasal airways, end-tidal CO_2 detector
Review team member roles, primary and backup intubation plans
Oxygen cutoffs: Identify signals to abort, reinitiate bag-valve-mask ventilation
Administer medication, if indicated
Confirm endotracheal tube placement using two indicators (including end-tidal CO_2)
Hold endotracheal tube until secured

IV, Intravenous; *PEEP*, positive end expiratory pressure. From American College of Chest Physicians Airway Management Program Curriculum, 2013.

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Tracheostomy

Pierpaolo Terragni, Daniela Pasero, Chiara Faggiano, and V. Marco Ranieri

INDICATIONS

Airway access for the treatment of upper airway obstruction or mechanical ventilation (MV) can be obtained by either orotracheal intubation (OTI) or placement of a tracheostomy tube. During general anesthesia or after episodes of acute respiratory failure, patients are usually mechanically ventilated through an orotracheal tube, which can be easily and rapidly inserted as an initial airway device. When prolonged MV is provided or protection from tracheal aspiration is needed, a conversion to tracheostomy is mandatory and offers several potential advantages.

The introduction of the percutaneous tracheostomy (PT) by Ciaglia in 1985 as an alternative to surgical tracheostomy (ST) attracted interest regarding its indications.[1] Initially, PT was reserved for patients with few risk factors and favorable neck anatomy; however, with wider use, the indications expanded and PT has largely replaced surgical procedures. During the past decade, use of PT has increased, both for prolonged ventilation and in case of upper airway obstruction secondary to trauma or surgery of the face and neck region.[2] Although an improvement of survival rates in intensive care units (ICUs) among patients receiving tracheostomy has been reported, the hospital mortality rate was similar between patients with or without tracheostomy. However, patients who required tracheostomy and were discharged at home had double the mortality of nontracheostomized patients.[3]

More recent studies report further data on long-term outcomes in patients with tracheostomy and a better outcome among patients <65 years of age, although the overall 1-year mortality is still high (46.5%), whereas, not surprisingly, in patients >65 years of age a 50% higher mortality is observed. These data show trends toward earlier tracheostomies, shorter hospital length of stay, and increased discharges to long-term facilities versus home, with a stable and high long-term mortality rate. Therefore what has really changed is the location of death that has been shifted to post–acute care facilities.[4]

According to these outcome data, and considering its invasiveness and procedural risks, tracheostomy should be considered only when prolonged MV is expected or the upper airway cannot be secured safely by other means.

Advantages of Tracheostomy

European surveys investigating the use of tracheostomy in critically ill patients reveal heterogeneity regarding techniques, timing, operator experience, and settings.[5] Tracheostomy offers many clinical benefits for patients with respiratory failure or individuals requiring prolonged MV or airway protection because of neurologic dysfunction. Compared with OTI, it provides safer airway protection and increases patient mobility by decreasing the risk of accidental extubation because of more effective securing of the tracheal cannula: patients with tracheostomy have a 1% incidence of accidental decannulation, compared with a rate of 8%–21% of accidental orotracheal tube dislocation.[6] Moreover, because the internal cannula is not affected by head and neck movement, the occurrence of lesions resulting from tracheal mucosal abrasion and laryngeal damage is low.[5]

Additionally, easier airway suctioning and secretions management improve pulmonary secretion management and oral hygiene; therefore tracheostomy allows better patient comfort that might facilitate communication with family members and nurses. Patients can be mobilized earlier and more easily, with faster return to oral feeding, shorter nasogastric tube dwell time,[7,8] and reduced risk of tracheoesophageal fistula occurrence.

Use of a tracheostomy tube can aid in weaning from MV, because the direct approach to the trachea (with an internal diameter greater than in the translaryngeal approach) and reduced length all reduce airflow resistance; it also allows faster resumption of autonomous respiration, with less use of sedative agents, fewer days on the ventilator, shorter length of stay in the ICU, and reduced use of resources.[3,9,10] Although PT continues to gain acceptance as the method of choice, no single technique has been shown to be superior to another in any clinical situation. Furthermore, PT has a steep learning curve and requires mastery of procedural skills and extensive expertise.

TRACHEOSTOMY TECHNIQUES

Percutaneous Dilational Tracheostomy vs. Surgical Tracheostomy

Tracheostomy techniques are evolving and improving. Two basic methods are available: PT and ST. The choice of whether to use one or the other depends on available resources, operator experience, and degree of patient complexity.

ST presents a similar risk of operative complications (minor or major hemorrhage, tracheo-innominate fistula, subglottic stenosis, oxygen desaturation, subcutaneous emphysema, pneumothorax, accidental decannulation, and airway loss) compared with PT.

Several meta-analyses (Delaney and colleagues on 1212 patients, Higgins and Punthakee on 1000 patients enrolled in 15 prospective randomized controlled trials [RCTs], and more recently, Putensen and colleagues who tested 14 RCTs on different PT techniques versus ST in 973 patients) reported a significant reduction in wound infection and stoma inflammation in PT; the latter is also performed faster even if associated with increased technical difficulties, although the benefits were found in studies using the multiple dilators technique (MDT), which is now replaced by the single-step dilation tracheostomy (SSDT) technique.[11–13]

Based on the analysis of different European surveys about the use of tracheostomy in critically ill patients, a wide heterogeneity regarding techniques, timing, operator, and structures used to perform the procedure can be observed.[5]

Surgical Techniques

ST in European ICUs is less common than PT; meanwhile, elsewhere it is equally distributed.

ST is prevalent in surgical ICUs: surgeons performed 61% of STs in Germany and 44% of all tracheostomies in the Netherlands. In an Italian survey, a dedicated team involving more than one intensivist and a nurse performed 62.6% of all tracheostomies.

Most STs were performed in operating rooms. In Germany, 28% of STs were performed in the ICU, whereas in the Netherlands the percentage was lower. In 42% of French ICUs, surgeons always performed tracheostomies (in France, ST remains largely preferred).[5]

Although PT has become a common procedure in patients undergoing elective tracheostomy, in the case of long-term MV, ST remains the method of choice in selected critically ill patients presenting with distortion of neck anatomy, prior neck surgery, cervical irradiation, maxillofacial or neck trauma, morbid obesity, difficult airway, or marked coagulopathy (e.g., patients undergoing heparin treatment during extracorporeal membrane oxygenation support). ST can be also safer when anatomic landmarks are difficult to palpate, the patient presents with a malignancy at the site of insertion, or if emergency tracheostomy placement is required.

Usually physicians are more likely to perform ST to explore the airway anatomy in the operative setting and then proceed to the PT where the airway is less well visualized (some PT procedures such as the Griggs technique can be easily converted to ST in cases of difficult anatomic landmarks).

Otolaryngologists or general surgeons perform ST in the operating room in selected challenging cases involving patients presenting with complex anatomy (short neck, morbid obesity, neck stiffness, local malignancy, tracheal deviation) or coagulopathy, in addition to patients with neck, esophageal, and cardiovascular surgeries.

ST procedures can be performed under general anesthesia with propofol, fentanyl, and muscle relaxant administration. The surgical treatment of the tracheal window can be either mini-invasive similar to PT (with an open access without sutures) or invasive, realizing a true stoma and removing the anterior part of the tracheal wall with a ring flap sutured to the skin; the tracheostomy tube must be inserted between the first and third tracheal rings and fixed with two sutures: in this case, the surgical treatment involves a full dissection of the pretracheal tissues and insertion of the tracheostomy tube into the trachea under direct vision.

Because morbidity has been observed related to the transport of critically ill patients, to further reduce the rate of inadvertent mishaps, alternative techniques and surgical procedures such as ST should be considered and performed by anesthesiologists or surgeons at the bedside in the ICU.[14] Even if it can be more difficult because of suboptimal conditions of lighting, suction, sterility, and cautery, bedside tracheostomy avoids transferring the patient to the operating room, making it ideal for selected cases.

ST presents a similar risk of complications or death compared with PT, except stoma infections. The proportion of patients receiving PT or ST varies across different settings: ST is largely performed in ICUs managed by surgeons, PT is preferred in ICUs managed by intensivists, and both techniques are adopted in medical/surgical ICUs.[15–20]

Percutaneous Tracheostomy

Various PT devices have been developed to minimize risk and simplify the procedure.

Evolution in terms of technique, introduction of new percutaneous devices, and support tools such as fiber-optic bronchoscopy and ultrasound during the procedure have made this tracheostomy technique easier and safer.

Since PT was first described by Ciaglia and colleagues (using a guide wire),[1] new methods have been developed by combining the percutaneous nephrostomy multiple-dilator procedure and a variant of the vascular access described by Seldinger in 1953. In 1990 Griggs described the guide wire dilator forceps technique (GWDF) (Portex Limited, Hythe, Kent, UK), an improvement on the Rapitrach method in which the forceps was inserted along the guide wire and opened to the size of the skin incision to dilate the trachea[21,22] (Fig. 36.1). Ciaglia's initial serial MDT was revised in 1999 for use with a single tapered dilator (SSDT) with a hydrophilic coating: it allowed, in a single step, achieving complete dilation of pretracheal tissues with a technique known as the Blue Rhino technique (Cook Critical Care, Bloomington, IN, USA).[23] In 1997 Fantoni described the translaryngeal technique (TLT) (Mallinckrodt, Mirandola, Italy) in which the dilator passed from inside to outside the tracheal wall without requiring external compression of the tracheal tissues.[24] In 2003, a screwlike device was designed to open the tracheal stoma (rotational dilation technique), which was useful in case of loss of view of the tracheal lumen during bronchoscopy and to minimize the risk of posterior tracheal wall injury (PercTwist method, Rüsch GmbH, Kernen, Germany).[25]

The Ciaglia Blue Dolphin system (balloon dilatational tracheostomy method) was introduced in 2008. It represents the most recent technique derived from the Fogarty balloon embolectomy catheter used in vascular surgery. This device generates a radial force to widen the tracheostoma in a single-step dilation, minimizing bleeding and tracheal ring injury, while achieving good cosmetic results after decannulation.[26]

The success of PT rests on the expertise of the intensivist or surgeon in ICU settings (mixed medical/surgical, only medical or surgical). Moreover, the availability of different PT techniques should enable physicians to optimize the procedure and thus challenge the need for ST in clinical scenarios of primary surgical technique competence such as obesity, neurotrauma, or vascular abnormalities with high risk of bleeding.

Today we see an extensive use of PT in ICU, thanks to the easy execution of procedure at the bedside, avoiding high risk in patient transfer to the operating room.[14,27–29]

At present, there is no evidence supporting the recommendation of one PT technique over the others. A method can be selected on the basis of clinical criteria, operator experience, local practice, and availability.[30]

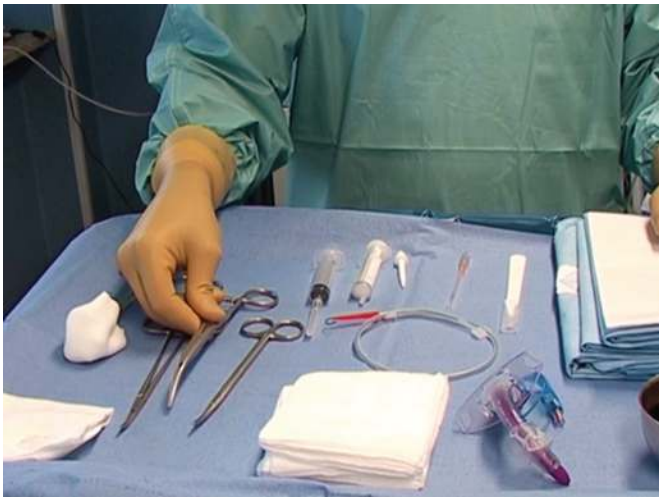

Fig. 36.1 Guide wire dilator forceps technique (Portex Limited, Hythe, Kent, UK). The operator shows the surgical forceps.

A systematic review and meta-analysis of PT in critically ill patients recently investigated the advantages of PT versus ST in relation to major and minor intraprocedural complications.[31] The review included 13 RCTs on tracheostomy in medical, neurologic, or surgical ICU settings published in the past 10 years. Results demonstrated the equivalence of all techniques in terms of incidence of side effects and rate of procedure success, except for **percutaneous** TLT, which was associated with more severe complications and a greater need to convert to another tracheostomy technique compared with GWDF and SSDT techniques.[31]

In a more recent systematic review of 14 randomized comparative studies published between 1985 and 2013, the authors suggested that the SSDT technique is less difficult and most likely associated with a greater frequency of minor hemorrhagic events, but might be preferable because clinicians have greater experience using this technique, which is the most widespread in clinical practice.[32]

Comparing ST with PT, results of the most recent meta-analysis by Putensen et al. focused on lower risks of stoma inflammation and infectious complications using PT, but as a limitation of analysis, the benefit was mostly the result of studies using the MDT, which has largely fallen out of use in favor of the SSDT technique; no advantages were found in terms of hemorrhagic complications between ST and PT.[13]

COMPLICATIONS

PT in critically ill patients is considered a relatively safe procedure, with a low frequency of major complications even in patients with severe coagulation disorders.

Complications arising from tracheostomy maneuvers based on the time between the procedure and their onset can be classified as intraoperative and postoperative (early and late complications, respectively). The frequency and severity of complications depend on tracheostomy technique, operator experience, patient anatomy, and pathophysiologic factors related to the degree of organ dysfunction, especially respiratory and coagulation deficits.

Procedure-related complications include oxygen desaturation and difficult cannula placement because of acute tracheostomy tube occlusion (generally because of the formation of a blood clot or mucus plug) or tube insertion into the wrong tract. Other early complications include hemorrhage, with bleeding controlled by local pressure or requiring exploration (with conversion from PT to another dilational technique or surgery in some cases), or desaturation because of subcutaneous emphysema with or without evidence of pneumothorax. Patients with severe bleeding should undergo bronchoscopy for suspected tracheoesophageal fistula, but this occurrence is normally characteristic of late complications.

Common adverse events in the postoperative period or later include slight bleeding, controlled by local pressure; accidental cannula removal and/or displacement (dislodged tracheal tubes within 7 days of insertion should be replaced with a tube the same size or smaller); and airway obstruction resulting from granuloma formation or stoma infection/inflammation.

Several uncontrolled case series have reported PT complications, but there are few prospective comparative studies of complications associated with PT and surgical tracheostomy or between different PT methods. A meta-analysis by Freeman and colleagues. found that, compared with surgical tracheostomy, Ciaglia's and Grigg's techniques were generally associated with lower rates of stomal bleeding, infection, and postoperative complications.[33] In a randomized trial, with double-blind follow-up comparing the outcomes and the short- and long-term complications of TLT versus surgical tracheostomy, Antonelli and colleagues demonstrated lower bleeding rates with TLT, no increase in the risk of bacteremia caused by the spread of upper respiratory tract microbes, and similar long-term effects (physical and emotional) of the two procedures.[34]

The recent implementation of extracorporeal circuits, such as venovenous extracorporeal membrane oxygenation (VV-ECMO) to improve ventilatory support, has increased the complexity of critically ill patients. ECMO circuit–blood interaction activates the coagulation cascade, with increased risk of thrombotic and hemorrhagic events. This condition might increase the risk of hemorrhagic complication during PT; however, recent retrospective data showed that PT is a safe procedure even during ECMO support when skilled operators, with careful optimization of the coagulation state, perform it.[35,36] A recent retrospective observational study reported a consistent risk of major complications (15%), which is much higher when compared with that of non-ECMO patients, where only 3% had early severe complications.[35,37,38] The most commonly described complication was major bleeding requiring blood transfusion, occurring in 11% of the studied population, and it corresponded to two-thirds of all major complications. Moreover, two posterior tracheal wall injuries, one bronchial mucosal injury, thyroid isthmus, external jugular vein injury, and one case of tension pneumothorax were described. ECMO circuit change was required in five cases because of either oxygenator failure or bleeding and circuit-related disseminated intravascular coagulation (DIC).[35] A previous retrospective study reporting data from two different German centers showed a lower incidence of major complications in five patients (4.2%) out of 118 PTs performed in a 6-year period.[36] The main difference between the two studies was the heparin management strategy: in the previous study heparin had been stopped 1 hour before PT, whereas in the more recent study it was based on the clinician's decision; as the median time of suspension of heparin was longer than 1 hour, more coagulation disorders were observed. In addition, in the previous study, clinicians performed PT earlier compared with the more recent study. However, the number of cases is too small to draw conclusions on the safety of PT during ECMO support and suggest performing PT after weaning from ECMO whenever possible.[35,36]

TIMING OF TRACHEOSTOMY

Older guidelines recommended tracheostomy after 3 weeks of endotracheal intubation only if extubation did not occur by 21 days.[39] But defining and predicting the need for prolonged MV continues to pose a major methodologic challenge. Except in emergency procedures, the timing of tracheostomy in patients requiring prolonged MV is controversial. But the real issue behind the debate is how to measure the effectiveness of early tracheostomy and its effects on outcome.

A meta-analysis published in 2005 reported that early tracheostomy shortened the duration of MV and the length of ICU stay.[40] In their study involving 1044 patients, Wang and colleagues suggested that tracheostomy timing did not significantly alter major clinical outcomes in critically ill patients.[41] Two Italian and French RCTs published by Terragni and colleagues and Trouillet and colleagues, respectively, evaluated the benefits and risks of tracheostomy and the ability to identify early patients requiring prolonged MV.[42,43] Both trials enrolled candidates for tracheostomy. In the first study, respiratory function improved in 43.3% of patients randomized to the late tracheostomy group so that tracheostomy was no longer necessary. Likewise, in the French study, only 27% of patients in the prolonged MV group underwent late tracheostomy.

The TracMan UK randomized trial analyzed survival in early versus late tracheostomy and confirmed the results of the previous trials.[44] In the early group, 91.9% of the patients enrolled received a tracheostomy, whereas only 44.9% in the late tracheostomy group underwent

tracheostomy. No significant differences in mortality or other major secondary outcomes between the two groups were found. These results convinced clinicians that routine early tracheostomy does not necessarily reduce the incidence of ventilator-associated pneumonia (VAP), shorten hospital stay, or lead to lower mortality. In general, tracheostomy should not be performed earlier than 13–15 days of OTI.[45]

Ten years after the most representative large RCT on tracheostomy timing in critically ill patients,[42] delaying the procedure for roughly 2 weeks after translaryngeal intubation is the recommended practice, and the decision is mostly influenced by the patient's overall clinical condition, prognosis, and ability to wean.

However, these trials have not strongly explored the effects of timing on mortality, which requires a large sample size.[46] Siempos Ilias and colleagues analyzed the incidence of mortality and pneumonia in 13 RCTs (2434 patients, 648 deaths) comparing early tracheostomy (within a week after OTI) with late (done any time after the first week of MV) or no tracheostomy in critically ill patients under MV.

The authors demonstrated that all-cause mortality in the ICU was not significantly lower in patients assigned to the early vs. the late or no tracheostomy group, and the incidence of VAP was lower in patients assigned to the early vs. the late or no tracheostomy group without evidence of a difference between the compared groups for 1-year mortality. Currently, if the common practice of delaying tracheostomy can be supported by the lack of effects on long-term mortality and the potential complications applying early tracheostomy timing, further studies are warranted on long-term outcomes.

Because data on patient outcomes related to the timing of tracheostomy are heterogeneous, selected patients with neurologic injury can benefit from prolonged intubation because of their limited ability to clear secretions. Prolonged intubation in traumatic brain injury, however, is associated with a high incidence of pneumonia. Conversely, early tracheostomy after trauma reduces the length of ICU stay, days on MV, and incidence of VAP. In patients with infratentorial lesions, Qureshi and colleagues suggested an aggressive policy regarding tracheostomy, which was justified by the low rate of successful extubation.[47–50] Although early tracheostomy in selected neurologic patients may reduce the length of ICU stay and pulmonary morbidity, the first 7–10 days after acute brain injury coincide with the highest incidence of intracranial hypertension; therefore the appropriate timing for tracheostomy in those patients must be related to the risk of severe intracranial hypertension.[51]

TRACHEOSTOMY AND SAFETY

Adult tracheostomy can be performed in the operating room or at the bedside in the ICU. To improve PT safety in different scenarios, suggested procedures to confirm tracheal puncture include (1) ultrasound for preoperative evaluation of the neck or during the intraoperative stage for monitoring needle progression through the trachea and (2) bronchoscopy surveillance during the procedure, which is increasingly performed by intensivists in critical care. In our experience, PT is a safe and easy procedure to perform at the bedside, even in difficult situations, by skilled intensivists with full technical support to minimize complications. For selected patients (e.g., individuals with distorted neck anatomy or history of prior neck surgery), a surgeon skilled in the conventional open technique should be readily available, even if the team is well trained in PT.[52]

Bronchoscopy

Safety during the PT procedure can be enhanced with bronchoscopy guidance to minimize complications. Several authors have recommended the use of bronchoscopy during PT because it provides direct visualization of the airway during tracheostomy tube placement. A previous retrospective study evaluating the safety and efficacy of PT procedures with or without bronchoscopy showed that the use of bronchoscopy did not give any advantage in the number of complications, except a higher conversion rate to surgical tracheostomy in the procedures performed without tracheostomy, whereas survival rate, ventilator-free days, and the length of ICU and hospital stay were similar among the analyzed trauma patients.[53] More recently an RCT showed that PT performed with fiber-optic bronchoscopy is superior to PT without bronchoscopy control by reducing the rate of major and minor complications (40% vs. 20%) and the duration of the procedure.[54]

Intraoperative endoscopic control has been shown to reduce complications associated with tracheostomy. Bronchoscopy guidance can improve safety and efficiency by monitoring placement of the tracheal puncture, the dilational procedure (preventing damage to the posterior tracheal wall and visualizing progression through the interannular membrane without breaking the tracheal rings), insertion of the tracheal cannula, and postprocedure control to detect intratracheal lesions and confirm correct endotracheal placement[55] (see Fig. 36.3).

Ultrasound and Percutaneous Tracheostomy

Although fiber-optic endoscopic control reduced some major complications during PT, in selected cases, there might be serious hemorrhagic complications because of puncturing of venous or arterial vessels in patients with aberrant vascular anatomy. Muhammad and colleagues reviewed the incidence and sequelae of bleeding events as a complication of PT.[56] They found that variations in venous (inferior thyroid vein) and arterial anatomy (thyroid artery) can lead to serious bleeding events that required investigation with diagnostic ultrasound and/or radiologic examination before proceeding with PT.

The presence of an abnormal branch of the innominate artery passing in front of the trachea near the area of a tracheostomy procedure can be detected by clinical evaluation (pulsatile swelling at the base of the neck); however, an additional ultrasound evaluation could be useful to confirm the complexity of the tracheostomy procedure and may warrant switching to a surgical approach in some cases[5] (Fig. 36.2).

Ultrasound alone cannot replace bronchoscopy. Nonetheless, it might help to identify vascular structures when evaluating the anterior neck region and guide to the best area to perform PT, avoiding major bleeding complications. Several observational studies showed the usefulness of ultrasound before tracheostomy to prevent vascular complications, and in a selected population with acute brain injury and morbid obesity, where prolonged bronchoscopy might increase intracranial pressure, ultrasound-guided PT proved successful.[57,58]

Recently, an RCT showed that ultrasound-guided PT is a safe procedure for critically ill patients and has some advantages compared with bronchoscopy-guided PT because it reduced the major bleeding complications. The trial showed that the real advantage of the ultrasound technique is the possibility of exploring the neck area to study the vascular structure; in fact, in six patients of the ultrasound–PT group, the entry location was changed after neck examination with ultrasound. The ultrasound-guided technique was performed with a transverse probe position in the out-of-plane mode to follow needle entry during puncture.[59]

In conclusion, for a safer procedure, the best option is to use ultrasound to explore the neck area to study the vascular structure and eventually to guide the percutaneous incision, but the procedure should be controlled using an optical fiber bronchoscopy, at least at the end of the procedure, to exclude any mechanical complication on tracheal structures.

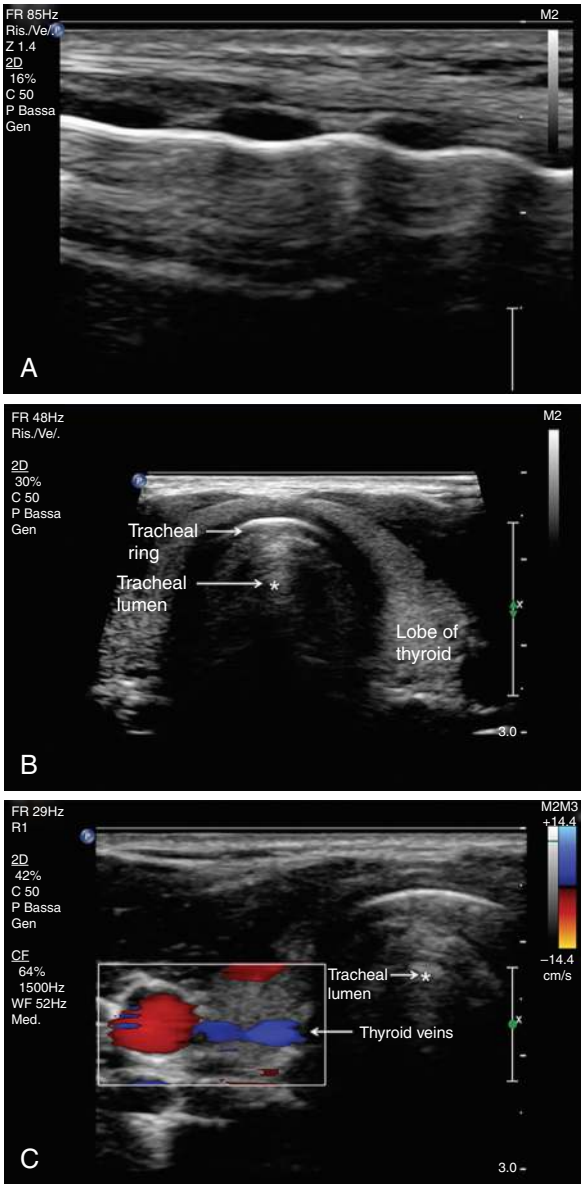

Fig. 36.2 Use of ultrasound to evaluate the anterior neck region may be a valid and economic support to improve preoperative assessment and identify potential bleeding complications during the procedure. **A,** Sagittal ultrasound image showing the upper four tracheal rings. **B,** Transverse ultrasound image showing the anterior tracheal wall, tracheal lumen shadow, and thyroid gland. **C,** Axial image of trachea and surrounding structures with vascular structures depicted (thyroid veins).

TRACHEOSTOMY IN NEUROCRITICAL PATIENTS

In patients with severe acute brain injury, tracheostomy represents an easy way to reduce the time under sedation and on MV, ICU length of stay, and to allow faster rehabilitation.[60] The decision to perform a tracheostomy in patients affected by severe acute brain injury is usually made in a phase when the prognosis is uncertain in order to give more time for a clearer prognosis to emerge.[61] A large retrospective cohort study exploring trends in tracheostomy over time conducted in the United States showed an increase from 28% to 32% over a decade. The major increase was reported in teaching and urban hospitals. After this increase in tracheostomy rate, discharge to home was relatively stable, but in-hospital mortality was significantly reduced, from 19.3% to 9.1%, whereas discharge to long-term acute facilities was increased.[62] Time to tracheostomy in patients with severe acute brain injury should be short. The limited data available from a randomized trial suggest that performing an early tracheostomy, within the first 10 days after tracheal intubation, may reduce long-term and ICU mortality and reduce the duration of MV and ICU length of stay.[63]

MANAGEMENT AND CARE OF THE TRACHEOSTOMIZED PATIENT

Another important step is the management of the tracheostomized patient. There is increasing evidence that specialist tracheostomy teams improve patient outcome and enhance the weaning process.

To improve the quality of care provided to tracheostomized patients and to support staff involved in the delivery of routine tracheostomy care, the development of a quality improvement project was performed, funded by the NHS Wales Critical Care and Trauma Network. The project consisted of formal tracheostomy teaching that was delivered by a tracheostomy team to 165 clinicians involved in tracheostomy care: 75.8% were nurses, 7.3% physiotherapists, 8.5% speech and language therapists, 7.3% medical, and 1.2% other healthcare professionals.[64]

The results of the project showed an improvement in self-assessed confidence, with knowledge and skills observed for all aspects of tracheostomy care, with greatest improvement for "methods of insertion" and "communication and swallow." Moreover, there was increased use of speaking valves to facilitate verbal communication for patients receiving ventilation. Furthermore, eating and drinking practice for patients with tracheostomy with or without MV was variable, and speech and language therapy (SLT) assessment before commencing oral intake was not occurring. After teaching sessions, all patients were assessed by SLT before commencing oral intake, and 100% of those appropriate managed to eat and drink safely during MV.[64]

In conclusion, with the increase in the number of tracheostomized patients over time, it is important to implement a program of education provided to patients and to clinical staff, to improve the management of tracheostomy and the quality of life of the patients.

TRACHEOSTOMY EMERGENCY

Emergency tracheostomy is rarely necessary because new techniques of OTI are available in critical care areas. On rare occasions, however, intubation via the oral or nasal route is unsuccessful or hazardous: foreign bodies in the larynx or extrinsic airway compression (Fig. 36.3A and B) or tracheal stenosis (more frequently as a consequence of prolonged laryngeal intubation) involving the subglottic region represent a major therapeutic challenge precluding, in some cases, OTI for establishment of an airway.

Although in laryngotracheal stenosis, surgery is considered a first-line treatment, preservation of the recurrent laryngeal nerves results in technical problems.[65]

The use of tracheal prostheses and permanent tracheostomy for establishment of an airway have been alternatives to surgery, but in recent years, the interest in endoscopic procedures such as laser-assisted endoscopy, with or without stenting, has promoted their use in subglottic stenosis to allow stabilization of the tracheal wall, with or without airways control by temporary tracheostomy (Figs. 36.4A and B and 36.5A and B).

TRACHEOSTOMY TRAINING

A learning curve for PT has been identified.[66,67] The American Thoracic Society and the European Respiratory Society recommend 5–10 procedures, whereas the American College of Chest Physicians recommends 20 procedures.

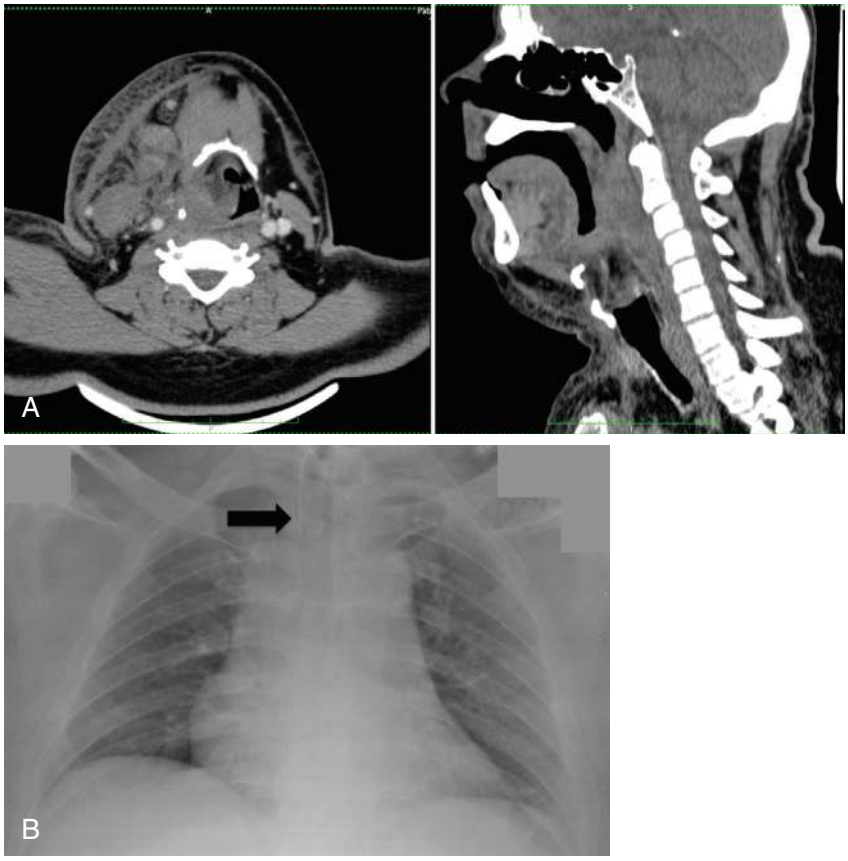

Fig. 36.3 **A,** CT scan of very severe airway obstruction as a consequence of posttraumatic oropharyngeal hematoma. **B,** Chest x-ray image after airways control by temporary tracheostomy in perioperative assessment.

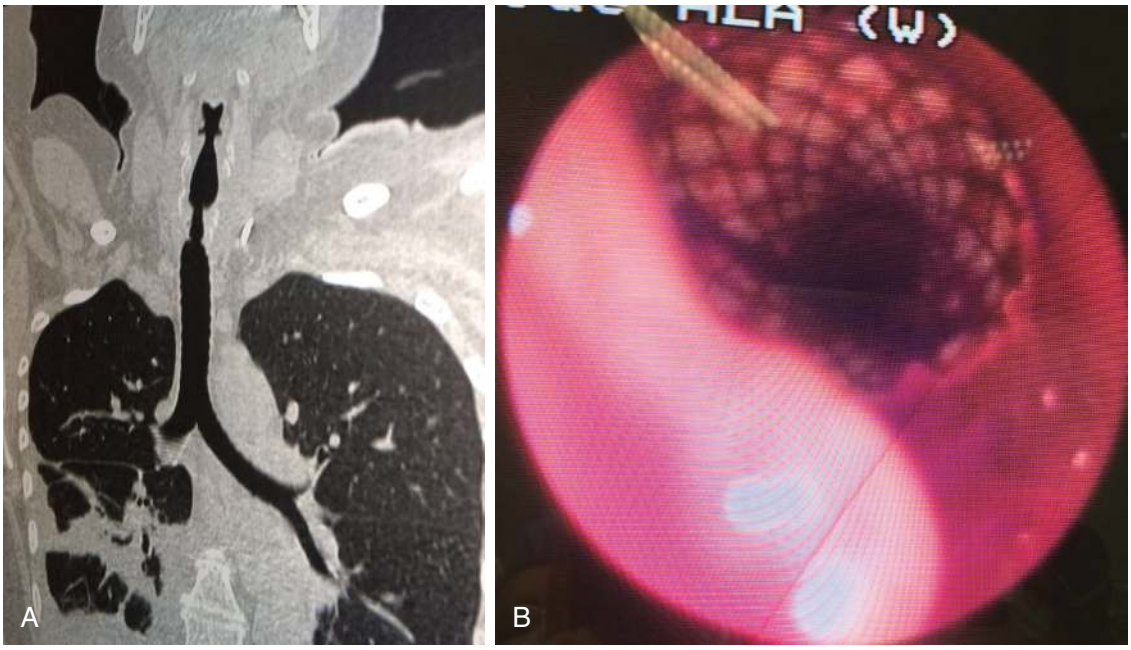

Fig. 36.4 **A,** CT scan of moderate stenosis as a consequence of prolonged laryngeal intubation involving the subglottic region. **B,** Laser-assisted endoscopy with stenting to allow stabilization of the tracheal wall without airway control by temporary tracheostomy.

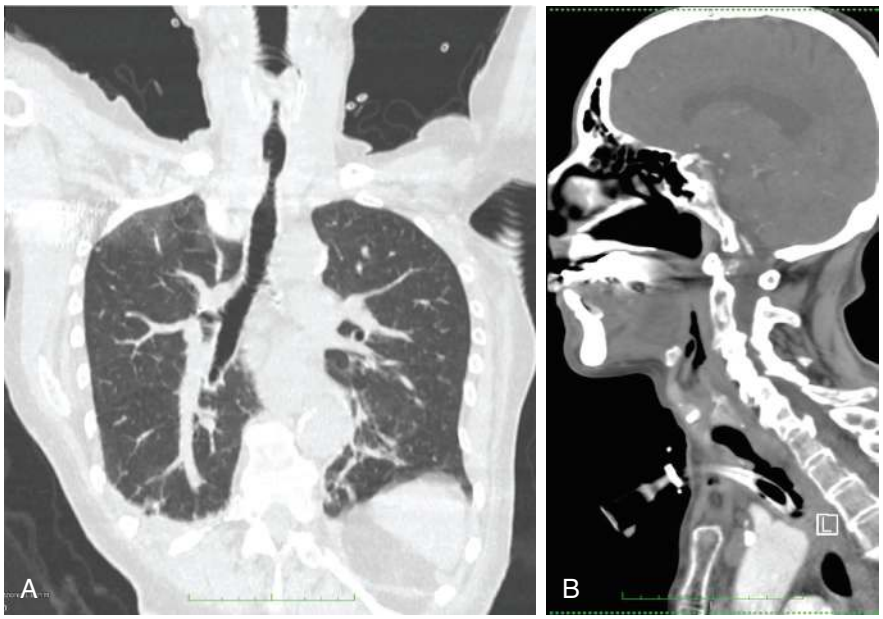

Fig. 36.5 **A,** CT scan of very severe subglottic stenosis as a consequence of prolonged laryngeal intubation in a patient after cardiac arrest because of acute airway obstruction. **B,** CT scan of airway control by temporary tracheostomy in preoperative assessment.

During initial training, practice on manikins, animal models, or biologic tissues (because of ethical and economic concerns) can improve skills and minimize complications.[68–71] The pig model may provide a more realistic approach.[72] An Italian group tested the efficacy of the porcine model in developing the skills that residents require for successful PT. The model consisted of a larynx and trachea free from perilaryngeal and peritracheal tissues. The resulting tissue block was then placed on a backing with an overlapping of sponge and plastic wrapping (simulating the skin) before being inserted into the manikin's neck.[73]

Recently a new training approach in endoscopic PT using a simulation model based on biologic tissue was performed.[71] Adult sheep heads and necks bought from the slaughterhouse were used for training (Fig. 36.6). Tracheostomy training stations for different PTs were available, with an orotracheal tube correctly positioned through the larynx of the sheep necks. The necks were cut so as to preserve all the tracheal rings. A single-use flexible video-endoscope was available in each training station to allow the participant performing PT procedures to see manipulation results and for teachers to monitor and advise as they proceeded. With the same training model, cricothyrotomy was always performed through the cricothyroid membrane.

Simulation models based on animal tissue for training in PT seem to be more realistic than manikins in terms of reality of the skin and landmark recognition. Moreover, they provide a particular "tactile feeling" in trainees and allow better monitoring of skill acquisition in endoscopic PT settings.

Fig. 36.6 Tracheostomy training station for single-step dilation tracheostomy (SSDT) with a simulation model based on biologic tissue (adult sheep neck). A detail of the Blue Rhino Ciaglia introducer (Cook Critical Care, Bloomington, IN, USA) among tracheal rings during insertion into the trachea of the sheep model.

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KEY POINTS

- Surveys on tracheostomy show wide heterogeneity in techniques (PT or surgical), timing, operator experience, and settings.
- PT continues to gain acceptance as the method of choice, though no single technique has been shown to be superior to another.
- PT has become the procedure of choice in patients undergoing elective tracheostomy; however, ST remains the method of choice in selected critically ill patients presenting with distorted neck anatomy, prior neck surgery, cervical irradiation, maxillofacial or neck trauma, morbid obesity, difficult airways, or marked coagulopathy.
- The optimal timing of tracheostomy in patients requiring prolonged MV remains controversial. After results of large RCTs in critically ill patients on tracheostomy timing, the delay of the procedure for roughly 2 weeks after translaryngeal intubation is the recommended practice, and the decision is mostly influenced by the patient's overall clinical condition, prognosis, and tolerance to weaning.
- PT is not without complications; it has a steep learning curve and requires mastery of procedural skills and extensive expertise. During initial training, practice on manikins, animal models, or biologic tissues (because of ethical and economic concerns) can improve the skills and minimize complications.

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Basic Principles of Mechanical Ventilation

Neil R. MacIntyre

Mechanical ventilatory support provides pressure and flow to the airways to help accomplish oxygen (O_2) and carbon dioxide (CO_2) transport between the environment and the pulmonary capillary bed. The overall clinical goal of mechanical ventilation is to maintain appropriate levels of O_2 and CO_2 content in the arterial blood while unloading the ventilatory muscles. An equally important goal is to provide this support without harming the lungs. Positive-pressure mechanical ventilation can be applied through either an artificial airway or a tight-fitting mask (noninvasive ventilation, discussed in detail in Chapter 55).

DESIGN FEATURES OF MODERN MECHANICAL VENTILATORS

Most modern ventilators use high-pressure gas sources to drive gas flow. Tidal breaths are generated by metering this gas flow and can be classified regarding what initiates the breath (trigger variable), what controls gas delivery during the breath (target or limit variable), and what terminates the breath (cycle variable).[1] In general, breaths can be initiated (triggered) by patient effort (assisted breaths) or by the machine timer (controlled breaths). Target or limit variables are either a set flow or a set inspiratory pressure. With flow targeting, the ventilator regulates the airway pressure to maintain a clinician-determined flow pattern. In contrast, for pressure targeting, the ventilator adjusts flow to maintain a clinician-determined inspiratory pressure. Cycle variables are a set volume, flow, or set inspiratory time. Breaths can also be cycled if pressure limits are exceeded. Using this approach, standard breath delivery algorithms from modern mechanical ventilators can be classified into five basic breath categories based upon trigger, target, and cycle criteria: (1) volume control (VC), (2) volume assist (VA), (3) pressure control (PC), (4) pressure assist (PA), and (5) pressure support (PS) (Fig. 37.1).[1]

The availability and delivery logic of the different breath types define the mode of mechanical ventilatory support. The mode controller is an electronic, pneumatic, or microprocessor-based system designed to provide the desired combination of breaths according to set algorithms and feedback data (conditional variables). The five most common modes are volume assist-control (VACV), pressure assist-control (PACV), volume synchronized intermittent mandatory ventilation (V-SIMV), pressure synchronized intermittent mandatory ventilation (P-SIMV), and standalone pressure support ventilation (PSV). It is important to note that a technique using pressure-targeted IMV set in a long inspiratory:expiratory configuration *(airway pressure release ventilation)* has often been labeled a "new mode" when it can be viewed simply as a modification of P-SIMV that extends the inflation period and allows tidal breaths superimposed on the higher pressure level.

Current ventilator designs incorporate advanced monitoring and feedback functions to allow continuous adjustments in the breath delivery patterns.[2,3] An early approach involved adding flow to the end of a pressure-targeted inflation if a target volume was not achieved *(volume-assured pressure support)*. A similar concept involves a feedback mechanism during volume-assist breaths that adds inspiratory flow to assure airway pressure does not fall below zero in the presence of vigorous inspiratory efforts.

Today, however, the most common of these feedback control mechanisms provides additional inspiratory pressure during pressure-targeted breaths to assure that the targeted average tidal volume is achieved. This mechanism makes adjustments based on previous tidal volumes and is commonly termed *pressure-regulated volume control* (pressure assist-control breaths) or *volume support* (pressure support breath). Inspiratory pressure feedback control features can incorporate additional inputs (e.g., exhaled CO_2, minute ventilation, respiratory rate) to "fine-tune" breath delivery. A more sophisticated and advanced form of these feedback control systems incorporates a minute volume target and adjusts inspiratory pressure, respiratory rate, and inspiratory:expiratory timing to minimize the calculated work per breath and avoid air trapping *(adaptive support ventilation)*.

Finally, over the last three decades, two truly novel assist modes have been introduced: proportional assist ventilation (PAV) and neutrally adjusted ventilatory assistance (NAVA).[4] The former calculates respiratory system mechanics and adjusts flow and inspiratory pressure to proportionately unload inspiratory muscles; the latter uses the diaphragmatic electromyographic (EMG) signal to adjust flow and pressure delivery in accordance with patient effort. These modes are discussed in more detail elsewhere in this text.

PHYSIOLOGIC EFFECTS OF MECHANICAL VENTILATION

Alveolar Ventilation and the Equation of Motion

Alveolar ventilation denotes fresh gas delivery to the gas-exchanging regions of the lungs. Mathematically this is expressed as:

$$VA = f \times (VT - VD)$$

where VA = alveolar ventilation per minute, f = breathing frequency, VT = tidal volume, and VD = wasted ventilation or dead space per breath. Alveolar ventilation needs to be adequate for the rates of tissue oxygen consumption (VO_2) and carbon dioxide production (VCO_2). By convention, CO_2 transport, as expressed by the relationship between VCO_2 and the steady-state arterial PCO_2, is used to quantify VA:

$$VA = 800 \times (VCO_2 \ / \ PaCO_2)$$

The difference between total ventilation (f × VT) and VA is VD.

The lungs are inflated by mechanical ventilation when a dynamic pressure increment or flow is applied at the airway opening. These applied forces interact with respiratory system compliance (both lung and chest wall components), airway resistance, and, to a lesser extent,

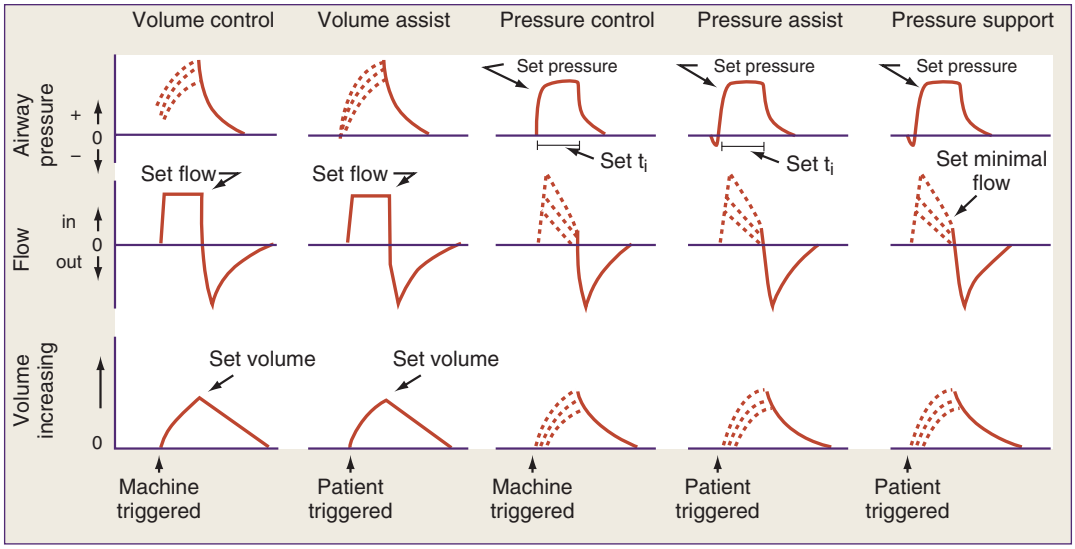

Fig. 37.1 Airway pressure, flow, and volume tracings over time depicting the five basic breaths are available on most modern mechanical ventilators. Breaths are classified by their trigger, target or limit, and cycle variables. (Adapted from MacIntyre NR. Mechanical ventilatory support. In Dantzker D, MacIntyre NR, Bakow E, eds. *Comprehensive Respiratory Care*. Philadelphia: Saunders; 1995, p. 2335.)

respiratory system inertance and lung tissue resistance to effect gas flow.[5–8] For simplicity, inertance and tissue resistance are relatively small and for clinical purposes can be ignored, so that the interactions of pressure, flow, and volume with respiratory system mechanics can be expressed by the simplified equation of motion:

$$\text{Pressure across the respiratory system in excess of the end-expiratory pressure} = (\text{flow} \times \text{resistance}) + (\text{tidal volume/compliance})$$

In the mechanically ventilated patient, this relationship is expressed as:

$$\Delta Pcir + \Delta Pmus = (\dot{V} \times R) + (VT / Crs)$$

where ΔPcir is the change in ventilator circuit pressure above baseline (peak pressure minus end-expiratory pressure: Ppeak − PEEP); ΔPmus is inspiratory muscle pressure generated by the patient (if present); $\dot{V}$ is the flow into the patient's lungs; R is the resistance of the external circuit, artificial airway, and natural airways combined; V_T is the tidal volume; and C_{RS} is the respiratory system compliance. If intrinsic or auto-PEEP (PEEPi) is present, muscle and circuit pressure must overcome this end-expiratory bias before flow and volume can be delivered, and thus PEEPi will add to the pressure requirement.

When flow is paused and pressure is held constant at end inspiration ($\dot{V} = 0$, Pmus = 0), the ventilator circuit pressure levels off at a pressure commonly referred to as the "plateau" pressure (Pplat). By use of this inspiratory hold, the components of Pcir required for flow and for respiratory system distention can be separated to describe R and Crs:

$$R = (Ppeak - Pplat)/\dot{V}$$

$$Crs = VT / (Pplat - PEEP)$$

Importantly, airway pressure measurements made under no-flow conditions are alveolar pressures and are determined by the pressure needed to distend the lung and the chest wall at that volume (Pplat at end inspiration, PEEP at end expiration). However, it is only the pressure across the lungs (transpulmonary pressure [TPP]) that affects alveolar stretch, drives regional ventilation, and maintains end-expiratory lung volume. TPP can be directly measured if an estimate of average pleural pressure (approximated by esophageal pressure) is available. Thus TPP = alveolar pressure minus pleural pressure = Paw − Ppl.[9]

In practice, because chest wall compliance (the major determinant of Ppl) is generally high, Ppl changes over the respiratory cycle are usually small, and measurements of airway Pplat and PEEP are reasonable approximations of TPP. In contrast, under conditions of very low chest wall compliance (e.g., obesity, anasarca, abdominal compartment syndrome, tight bandages), Ppl may be quite high, and thus the measured Pplat and PEEP will markedly overestimate the actual TPP.[9] This influence needs to be considered when setting the upper limits of ventilator settings in such patients and may require actual measurements of Ppl (Pes) to be safe.

In situations where spontaneous efforts occur, no-flow conditions at end inspiration are difficult to obtain, and consequently Pplat may be impossible to measure in real time. One solution to approximate Pplat under these conditions would be to deliver a controlled (i.e., passive) breath with an inspiratory pause using a similar VT and PEEP. Alternatively, there are proprietary monitors that can analyze the expiratory flow pattern during a passive exhalation to calculate respiratory system compliance and resistance and then determine a Pplat.[10]

Flow-Targeted vs. Pressure-Targeted Breaths

As noted earlier, there are two basic approaches to delivering positive-pressure breaths: flow targeting and pressure targeting. With flow targeting, the clinician sets inspiratory flow so that circuit pressure is the dependent variable. With pressure targeting, the clinician sets an inspiratory pressure target (with either time or flow as the cycling criterion) so that flow and volume are dependent variables (i.e., varying with lung mechanics and patient effort). With a flow-targeted breath, changes in compliance, resistance, or patient effort will change Pcir (but not flow); in contrast, with a pressure-targeted breath, similar changes in compliance, resistance, or effort will cause a change of tidal volume (but not Pcir).

Each strategy has advantages and disadvantages.[1,11] For flow-targeted breaths, a minimal tidal volume can be guaranteed. For pressure-targeted breaths, the rapid initial flow and subsequent declining flow of pressure targeting may enhance gas mixing and patient synchrony. As noted earlier, on modern ventilators, a variety of feedback mechanisms can combine features of flow- and pressure-targeted breaths.

Intrinsic (Auto) PEEP

PEEPi is the positive end-expiratory pressure that develops within alveoli because of insufficient expiration time, either because of inadequate time allowed between breaths by the ventilator or patient or because of increased expiratory resistance and collapse (flow limitation).[6–8,12–15] PEEPi depends on three factors: the minute ventilation, the expiratory time fraction, and the respiratory system's expiratory time constant (the product of resistance and compliance). The potential for developing PEEPi rises with increases in the minute ventilation, decreases in the expiratory time fraction, or increases in the expiratory time constant (i.e., with higher R or C_{RS} values).

The development of PEEPi will have different effects during pressure-targeted compared with flow-targeted ventilation. In flow-targeted ventilation, the constant delivered flow and volume (and thus ΔP_{cir}) means that a rising PEEPi will increase both the Ppeak and the Pplat. In contrast, in pressure-targeted ventilation, the set P_{cir} limit coupled with a rising PEEPi level will decrease ΔP_{cir} and, with it, the delivered tidal volume (and minute ventilation). Importantly, this accommodation may help limit the buildup of PEEPi.

In the patient without respiratory effort, PEEPi can be recognized in two ways. First, when an inadequate expiratory time produces PEEPi, analysis of the flow graphic will show that expiratory flow has not returned to zero before the next breath is given. Second, PEEPi in alveoli with patent airways can be quantified during an expiratory hold maneuver that permits equilibration of the end-expiratory pressure with Pcir. Note that total end-expiratory pressure is the sum of applied PEEP and PEEPi. Importantly, in patients with airway collapse, the expiratory hold maneuver will not detect the presence of PEEPi in units peripheral to the zone of closure.

In the patient with respiratory efforts, PEEPi can function as an inspiratory threshold load that produces delayed or even missed triggering of the desired breath.[12–14] In those cases with tidal flow limitation, this load can be counterbalanced with the judicious application of applied PEEP, guided either clinically or with Pes measurements.[13]

Distribution of Ventilation

A positive-pressure tidal breath must be distributed among the millions of alveolar units in the lung.[16–18] Factors affecting this distribution include regional resistances, compliances, functional residual capacities, the delivered flow pattern (including inspiratory pause), and the presence or absence of patient inspiratory efforts. In general, positive-pressure breaths will tend to distribute more to units with high compliance and low resistance and away from obstructed or stiff units (Fig. 37.2). This creates the potential for regional overdistention of healthier lung units, even in the face of "normal"-sized tidal volumes (see "Ventilator-Induced Lung Injury" later).

The flow pattern influences ventilation distribution. For example, when there are obstructive inhomogeneities, slow and constant flows will tend to distribute gas more evenly (although consequent shorter expiratory times may worsen air trapping). In addition, end-inspiratory pauses can also allow a gas shifting *pendelluft* action to help fill disadvantaged alveoli (see Fig. 37.2). In contrast, when there is parenchymal lung injury without obstructive airway inhomogeneity, initially rapid flows with subsequent deceleration (typically seen in pressure-targeted breaths) may distribute gas more evenly and will pressurize lung units rapidly, producing a higher mean inspiratory alveolar pressure for a given breath volume.

Finally, the presence or absence of patient efforts will affect this distribution. A passive positive-pressure breath without diaphragmatic contraction will distribute to more nondependent regions. In contrast, an active diaphragm will facilitate distribution of gas to more dependent zones. Importantly, in lungs with severe mechanical heterogeneity, an active diaphragm may promote regional overinflation (see "Ventilator-Induced Lung Injury" later).[19,20]

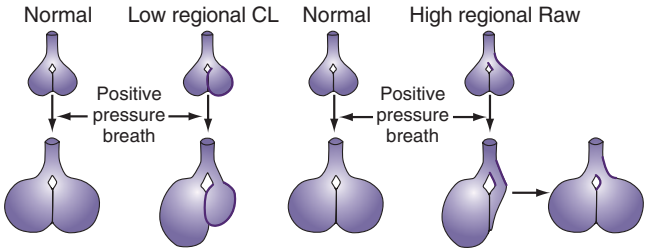

Fig. 37.2 Schematic effects of the ventilation distribution in two-unit lung models with homogeneous mechanical properties, abnormal compliance distribution, and abnormal resistance distribution. Note that in situations involving inhomogeneous lung mechanics, positive-pressure breaths are preferentially distributed to "healthier" regions of the lung and can produce regional overdistention even when a normal-sized global tidal volume is delivered. *CL,* lung compliance; *Raw,* airway resistance. (Adapted from MacIntyre NR. Mechanical ventilatory support. In Dantzker D, MacIntyre NR, Bakow E, eds. *Comprehensive Respiratory Care.* Philadelphia: Saunders; 1995, p.453)

It should be noted that more uniform ventilation distribution does not necessarily mean better $\dot{V}/\dot{Q}$ matching (i.e., more homogeneous ventilation distribution may actually worsen $\dot{V}/\dot{Q}$ matching in a lung with inhomogeneous perfusion). Because of all these considerations, predicting which flow pattern will optimize ventilation-perfusion matching is difficult, often inconsequential, and usually an exercise of empirical trial and error.

Alveolar Recruitment and Gas Exchange

Because of alveolar flooding, inflammatory exudates, and collapse, lung injury usually leads to $\dot{V}/\dot{Q}$ mismatching and intrapulmonary shunt.[21] In many (but not all) of these disease processes, substantial numbers of collapsed alveoli can be recruited during a positive-pressure ventilatory cycle. The ongoing opening and closure may be effectively countered by adequate end-expiratory pressure (PEEP or continuous positive airway pressure [CPAP]).[22–25] Alveoli prevented from collapsing, or "derecruiting," by PEEP receive several potential benefits. First, alveolar recruitment improves $\dot{V}/\dot{Q}$ matching and gas exchange throughout the ventilatory cycle. Second, as discussed in more detail later, continually patent alveoli are not exposed to the risk of injury from the shear stress of repeated opening and closing. Third, open alveoli increase generation of surfactant monolayers that improve lung compliance.

PEEP, however, can also be detrimental. Because the tidal breath is delivered on top of the baseline PEEP, end-inspiratory pressures are usually raised by the application of PEEP (although this increase may be less than the actual added PEEP because of recruitment-improved compliance). This increase must be considered if the lung is at risk for regional overdistention (see "Ventilator-Induced Lung Injury" later). Moreover, because parenchymal lung injury is often quite heterogeneous, appropriate PEEP in one region may be suboptimal in another and excessive in yet another. Optimizing PEEP is thus a balance between recruiting the recruitable alveoli in diseased regions without overdistending already recruited alveoli in healthier regions. Another potential detrimental effect of PEEP is that it raises mean intrathoracic pressure, with the potential in susceptible patients to impede venous return and compromise cardiac filling (see "Cardiac Effects" later).

Because diseased lung units require higher pressures to open than to keep open, additional recruitment can sometimes be provided by the use of recruitment maneuvers (RMs) that apply pressures in excess of the tidal values.[26–29] RMs are often performed using sustained inflations

(e.g., 30–40 cm H_2O) for up to 2 minutes. Alternative approaches use transient elevations of the PEEP–tidal volume setting and single or multiple "sigh breaths" that take the lung briefly to near-total lung capacity. Importantly, these transient pressure elevations can themselves have adverse hemodynamic consequences and, to avoid undesired patient efforts, the patient may require additional sedation (or even neuromuscular blockade).[26–29] It also must be pointed out that RMs provide initial alveolar recruitment only—the maintenance of recruitment depends on an appropriate setting of PEEP to prevent subsequent derecruitment.

Inspiratory time prolongations may also improve recruitment.[30–32] Prolonging inspiratory time, generally by adding a pause, often in conjunction with a rapid decelerating flow (i.e., pressure-targeted breath), has several physiologic effects. First, the longer inflation period may recruit more alveoli because recruitment depends not only on the pressure applied but also on its duration. Second, increased gas mixing time may improve $\dot{V}/\dot{Q}$ matching in parenchymal lung injury. Third, the development of PEEPi consequent to shorter expiratory times can have effects similar to those of applied PEEP. It should be noted, however, that the distribution of PEEPi (most pronounced in lung units with long time constants) may be less uniform than that of applied PEEP; thus the effects on $\dot{V}/\dot{Q}$ may also be different. Fourth, because these long inspiratory times significantly increase total intrathoracic pressures, cardiac output may be reduced (see "Cardiac Effects" later). And finally, inspiratory-to-expiratory ratios that exceed 1:1 (so-called inverse-ratio ventilation) are uncomfortable, and patient sedation/paralysis is often required unless a gating mechanism allows spontaneous breathing during the inflation period (airway pressure release ventilation).[31]

Mechanical Unloading

Mechanical loads describe the physical demands placed on respiratory muscles to breathe.[33,34] Loads are often expressed as the pressure–time product (PTP—the integral of pressure over time), work (W—the integral of pressure over volume), or power (W / time). Because mechanical loads correlate with inspiratory muscle oxygen demands, the concept of load is useful in considering inspiratory muscle energy requirements during spontaneous or interactive ventilatory support. More recently, the concept of mechanical loads (especially power) have been used to describe mechanical forces on the lungs that might be implicated in producing injury (see "Ventilator-Induced Lung Injury" later).[35]

Compliance and resistance, coupled with delivered flow and volume, each contribute to the magnitude of the load per breath (see "Alveolar Ventilation and the Equation of Motion" earlier). During spontaneous breaths, Pcir is zero, and integrating Pes over time or volume (in reference to the passive inflation pressure) describes the load borne by the inspiratory muscles to inflate the lungs. During a controlled passive breath, integrating Pcir over time or volume describes the load borne by the ventilator to inflate the entire respiratory system (lungs and chest wall), and integrating Pes over time or volume describes the loads imposed by the chest wall only. During interactive breaths, the load is shared between patient and ventilator.

Inspiratory muscle overload is one of the major determinants of continuing ventilator dependency and can result either from excessive mechanical loads or from inspiratory muscle dysfunction. Loads can be increased either by disease or by inappropriate ventilatory assistance (see "Patient-Ventilator Dyssynchrony" later). Inspiratory muscle dysfunction can be a result of the systemic inflammatory response syndrome, metabolic disturbances, drugs (e.g., steroids, previous use of neuromuscular blockers), malnutrition, or malpositioning (i.e., diaphragm flattening from lung overinflation).[36] Mathematically, inspiratory muscle fatigue and failure can be expected when the Pressure Time Index (PTI) exceeds 0.15[33]:

$$\text{PTI} = \text{Inspiratory pressure} / (\text{max diaphragmatic pressure}) \times (\text{inspiratory time} / \text{breath cycle time})$$

Clinically, inspiratory muscle overload is manifested by rapid, shallow breathing patterns; paradoxical abdominal motion; and patient distress.

Insufficient loading may also affect inspiratory muscles. Specifically, controlled mechanical ventilation that occurs without any patient effort, perhaps for as little as 24 hours, may produce muscle changes similar to disuse atrophy—a condition described as "ventilator-induced diaphragmatic dysfunction" (VIDD).[37–39]

ADVERSE EFFECTS OF POSITIVE-PRESSURE MECHANICAL VENTILATION

Ventilator-Induced Lung Injury

The lung can be injured when it is stretched excessively by positive-pressure ventilation. Historically, the most well-recognized injury was alveolar rupture, presenting as extraalveolar air in the mediastinum (pneumomediastinum), pericardium (pneumopericardium), subcutaneous tissue (subcutaneous emphysema), pleura (pneumothorax), and vasculature (air emboli). The risk of extraalveolar air increases as a function of the magnitude and duration of alveolar overdistention. Thus interactions of the respiratory system mechanics and mechanical ventilation strategies (e.g., high regional tidal volume and PEEP—both applied and intrinsic) that produce regions of excessive alveolar stretch for prolonged periods create alveolar units that are at risk for rupture.

Over the last half-century, it has become increasingly clear that repeatedly excessive alveolar stretch (i.e., beyond physiologic limits) can produce significant lung injury even without frank alveolar rupture (ventilator-induced lung injury [VILI])[40] Excessive stretching is induced by excessive "stress" (transpulmonary pressure) producing excessive "strain" (volume change) at end inspiration (static strain) and during tidal breath delivery (tidal strain).[40–46] A similar phenomenon occurs at the interfaces of collapsed and open alveoli when the collapsed alveoli are repetitively opened and closed. VILI may be worsened by increasing the frequency of excessive lung tidal stretching (reflected in measurements of the mechanical power to breathe) and from acceleration forces associated with rapid initial gas flow into the lung.[35] Pathologically, VILI manifests as diffuse alveolar damage and is associated with cytokine release[47,48] and bacterial translocation.[49]

VILI is often a regional phenomenon that occurs when low-resistance/high-compliance units receive a disproportionately high regional tidal volume (see Fig. 37.2) or when collapsed lung regions are repeatedly opened and closed. Importantly, vigorous spontaneous efforts, although sometimes improving ventilation distribution as described earlier, can also produce regional overdistention in severely damaged lungs. This can be especially harmful if spontaneous efforts result in excessive tidal volumes (self-induced lung injury [SILI]).[19,20]

Concern about VILI development is the rationale for using "lung-protective" ventilator strategies that include tidal volumes in the physiologic range (e.g., 4–8 mL/kg ideal body weight [IBW]), maximal end inspiratory TPP below the physiologic maximum (i.e., <25–30 cm H_2O), and PEEP strategies that minimize the collapse-reopening phenomenon without overdistending patent lung units.[25,50–52]

More recently, analyses of pressure changes during tidal volume delivery have helped "fine-tune" these recommendations. For example, the driving pressure to distend alveoli (DP = Pplat − PEEP) reflects the compliance characteristics of the lung during tidal breath delivery

(DP = VT / C).[45] From retrospective analyses of several mechanical ventilation trials, elevations in DP (e.g., >13–19 cm H_2O) would suggest either excessive regional tidal distention (in spite of an acceptable "global VT") or inadequate recruitment (in spite of acceptable gas exchange). A similar strategy analyzes the pressure profile during tidal breath delivery with a constant flow (stress index).[53] Under these conditions, an airway pressure waveform with a progressively increasing slope suggests overdistention; an airway pressure waveform with a progressively decreasing slope suggests inadequate recruitment; and an airway pressure waveform with a diagonal straight line suggests less hazardous VT and PEEP settings. Importantly, lung protective strategies may require acceptance of less-than-optimal values for pH, PaO_2, and PCO_2 in exchange for lower (and safer) distending pressures and volumes.

Cardiac Effects

In addition to affecting ventilation and ventilation distribution, intrathoracic pressure changes resulting from positive-pressure ventilation can affect cardiovascular function.[54–58] In general, as the mean intrathoracic pressure is increased, the right ventricular filling is decreased. This is the rationale for using volume repletion to maintain cardiac output in the setting of high intrathoracic pressure. In addition, lung distention can increase the right ventricular afterload, further compromising cardiac output. Conversely, elevations in intrathoracic pressure can improve left ventricular function because of an effective reduction in its afterload. Indeed, the sudden release of intrathoracic pressure (e.g., during a ventilator disconnect or spontaneous breathing trial) has the potential to precipitate flash pulmonary edema because of the acute increase in afterload coupled with increased venous return.

Intrathoracic pressures can also influence the distribution of perfusion. Although an oversimplification of the actual dynamics, the relationship between alveolar and perfusion pressures in the three-zone lung model can help explain this.[59] Specifically, the supine human lung is generally in a zone 3 (vascular distention) state. However, as the intraalveolar pressures rise, the zone 2 and zone 1 regions can appear, creating high $\dot{V}/\dot{Q}$ units. Indeed, increases in dead space (occurring in zones 1 or 2 of the lung) can be a consequence of ventilatory strategies using high ventilatory pressures or in the setting of high PEEP (either intrinsic or applied).

Positive-pressure mechanical ventilation can affect other aspects of cardiovascular function. Specifically, dyspnea, anxiety, and discomfort from inadequate ventilatory support can lead to stress-related catechol release, with subsequent increases in myocardial O_2 demands and risk of dysrhythmias. In addition, coronary blood vessel O_2 delivery can be compromised by inadequate gas exchange from lung injury coupled with low mixed venous O_2 partial pressure, resulting in part from high O_2 consumption demands by the ventilatory muscles.

Patient-Ventilator Dyssynchrony

Patients can interact with all three phases of an assisted breath: (1) trigger, (2) flow delivery, and (3) cycle.[60–62] Triggering dyssynchronies that manifest as unrecognized or delayed responses to patient effort can be attributed to insensitive or unresponsive triggering mechanisms or PEEPi. These impose a triggering load on the respiratory muscles. Premature triggering ("double triggering") may be derived from circuit motion artifacts, premature breath cycling, or the recently described "reverse" triggering observed during controlled breaths. Flow dyssynchrony occurs when the ventilator's flow delivery algorithm is not well matched to patient effort and is more likely to occur during fixed-flow breaths (i.e., flow targeted). Cycle dyssynchrony occurs when the breath cycling criteria are either inappropriately short or long for the duration of effort. Patients dyssynchronous in any phase will have unnecessary loads placed on their respiratory muscles, thereby increasing the risk of muscle fatigue. Moreover, dyssynchronous interactions produce discomfort and dyspnea.

There is no doubt that many dyssynchronies are subtle and of little clinical relevance. However, significant dyssynchronies that produce severe patient discomfort are frequently cited indications for the administration of sedatives in many intensive care units (ICUs). Therefore this may affect the duration of intubation, as high sedation usage is linked to longer ventilator use.

Managing dyssynchronies can be a significant clinical challenge. Setting trigger sensitivity to be as sensitive as possible without autotriggering is crucial. Judiciously applied PEEP in the setting of a triggering load from PEEPi can be helpful. Careful adjustments of flow magnitude, timing, and patterns (especially the use of pressure-targeted, variable-flow breaths) may help optimize flow and cycle synchrony. Finally, the newer interactive modes of PAV and NAVA described earlier may offer help to optimize synchrony in the future.

Oxygen Toxicity

Oxygen concentrations approaching 100% are known to cause oxidant injury to the airways and lung parenchyma.[63,64] The majority of the data supporting this concept, however, are derived from animal studies, and animals and humans often have different O_2 tolerances. It is unclear what the "safe" O_2 concentration or duration of exposure is in sick humans. Most consensus groups have argued that fraction of inspired oxygen (Fio_2) values less than 0.4 are safe for prolonged periods and that Fio_2 values greater than 0.8 should be avoided if possible.

Ventilator-Related Infections

Mechanically ventilated patients are at an increased risk of pulmonary infections for several reasons[2]: (1) The natural protective mechanism of glottic closure is compromised by an endotracheal tube. This permits the continuous low-grade seepage of oropharyngeal material into the airways. (2) The endotracheal tube impairs the cough reflex and in itself serves as a potential portal for pathogens to enter the lungs. This route is particularly important if the external circuit is contaminated. (3) Airway and parenchymal injury from both the underlying disease and management complications may predispose the lung to infections. (4) The ICU environment, with its heavy antibiotic use and the presence of very sick patients in close proximity, heightens risk for a variety of nosocomial infections, often from antibiotic-resistant organisms.

Preventing ventilator-associated tracheobronchitis and pneumonia is of great importance because the length of stay and mortality are heavily influenced by their development.[65–67] Handwashing and carefully chosen antibiotic regimens for other infections confer important benefits. Management strategies that avoid breaking the integrity of the circuit (e.g., circuit changes only when visibly contaminated) also appear to be helpful. Finally, the continuous drainage of subglottic secretions may be a simple way of reducing lung contamination by oropharyngeal material.

CONCLUSION

Positive-pressure mechanical ventilatory support is an essential component in the life support of patients with respiratory failure. However, it is important to note that this technology is supportive, not therapeutic, and it cannot cure lung injury. Indeed, the best we can hope for is to "buy time" by supporting gas exchange without harming the lungs.

The major goals of mechanical ventilation with positive pressure are to unload the ventilatory muscles and to optimize ventilation-perfusion matching so as to ensure adequate pulmonary gas exchange. Important complications include VILI, cardiac compromise, oxygen

toxicity, and patient discomfort. Applying ventilatory support often requires trade-offs as clinicians attempt to balance gas exchange needs with the risk of these complications. Future innovations cannot focus simply on physiologic endpoints. Rather, innovations should demonstrate benefits in clinically relevant outcomes, such as mortality, ventilator-free days, barotrauma, and costs. Only then can we properly assess the often bewildering array of new approaches to this vital life-support technology.

KEY POINTS

- Ventilator breath delivery is characterized by the trigger, target, and cycle variables.
- The interaction of a positive-pressure breath and respiratory system mechanics is summarized by the equation of motion:

Airway Pressure = (Flow × Resistance)
+ (Tidal Volume/Respiratory System Compliance)
+ PEEP

- The goal of positive-pressure mechanical ventilation is to provide adequate gas exchange while protecting the lung from overdistention and recruitment–derecruitment injuries.
- Positive-pressure mechanical ventilation in obstructive lung disease poses the additional risk of producing overdistention from air trapping.

References for this chapter can be found at expertconsult.com.

ANNOTATED REFERENCES

Beitler JR, Malhotra A, Thompson BT. Ventilator-induced lung injury. *Clin Chest Med.* 2016;37(4):633–646.
An excellent review attempting to link important data from animal studies of ventilator-induced lung injury to the clinical setting, with an emphasis on how ventilator strategies can produce both lung and systemic injury.

Briel M, Meade M, Mercat A, et al. Higher vs. lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. *JAMA.* 2010;303:865–873.
This is a meta-analysis of the three large trials conducted in the past decade examining high- versus low-PEEP strategies in the setting of low-VT ventilation. The results indicate that in acute respiratory distress syndrome (ARDS) patients, a high-PEEP strategy offers a mortality benefit. However, in the less severe acute lung injury (ALI) patients, a high-PEEP strategy trended toward a worse mortality.

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Pinsky MR, Guimond JG. The effects of positive end-expiratory pressure on heart-lung interactions. *J Crit Care.* 1991;6(1):1–15.
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Basic Principles of Renal Replacement Therapy

Eric A.J. Hoste and Floris Vanommeslaeghe

Acute kidney injury (AKI) is a common complication in critically ill patients admitted to the intensive care unit (ICU).[1–3] Epidemiologic data suggest that over 50% of ICU patients suffer from AKI, and up to 13.5% will be treated with renal replacement therapy (RRT).[1–3] Change in patient characteristics, with admission of older patients with more comorbidities such as diabetes, cardiovascular disease, and hypertension, resulted over the last decade in a marked increase of the proportion of patients treated with RRT.[4,5] RRT has therefore become an essential and often used treatment option for ICU patients, involving a spectrum of treatment modalities, with various advantages and disadvantages depending on the situation. RRT is most often delivered via extracorporeal techniques, but the COVID-19 pandemic caused renewed interest in peritoneal dialysis (PD), a technique using the peritoneum of the patient as a semipermeable exchange membrane.

TECHNICAL ASPECTS OF RRT

Extracorporeal techniques can be done with different modalities (Table 38.1). These are named according to the duration of RRT and the technique used for exchange of solutes and water: diffusion or convection.

Diffusion and Convection

Exchange of waste products over the semipermeable membrane can be via diffusion (hemodialysis) or convection (hemofiltration) (Fig. 38.1). In diffusion, blood and dialysate flow countercurrent on both sides of the semipermeable membrane of the hemofilter. The driving force that moves solutes over the semipermeable membrane is the solute concentration gradient. Uremic toxins such as blood urea nitrogen and creatinine will have high blood concentrations and are absent in the dialysate. Other factors that determine the movement of solutes from blood to dialysate are the diffusion coefficient of the membrane, its thickness, and its surface area. Diffusion is very efficient in the removal of small molecules such as potassium, ammonium, and creatinine (<500 Da); it is less efficient in the removal of larger solutes.

In hemofiltration, solutes and water are transported over the membrane by a difference in pressure between both sides of the membrane. Water and solutes are pressed from the blood compartment to the so-called effluent. The permeability coefficient of the membrane and the difference in pressure between both sides of the membrane determine the amount of fluid and solutes transported over the membrane. The effluent rate is controlled by a pump. Hemofiltration is more efficient for removal of larger molecules. In hemodiafiltration, both convection and diffusion are combined.

There are currently no data to suggest the superiority of diffusion over convection.

Duration of RRT

Intermittent hemodialysis (IHD) is a very efficient dialysis technique performed during a 3- to 4-hour period; continuous renal replacement therapy (CRRT) is less efficient, but done 24 hours a day; and hybrid techniques, alternatively termed *sustained low-efficiency daily dialysis* or *extended daily dialysis* (SLEDD or EDD), have intermediate efficacy and are used 6–12 hours per day.[6,7]

Intermittent and hybrid therapies will be performed with the use of dialysis machines that are also used for chronic dialysis patients. These monitors typically have more complicated interfaces and are therefore often managed by dialysis nurses. CRRT is most often performed with specifically designed monitors with a relatively easy interface and are managed by ICU nurses. Some centers also use these RRT machines for hybrid therapy.

Specifics Aspects of a CRRT Circuit

Fig. 38.2 shows the different aspects of CRRT performed as continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD), and continuous venovenous hemodiafiltration (CVVHDF).

Dose of RRT

The dose of CRRT is by convention expressed as the clearance of urea, a small molecule that both in hemodialysis and hemofiltration is not retained by the membrane. The effluent rate—the volume of fluid produced by hemofiltration and/or hemodialysis—therefore equals the clearance of urea, and when corrected for body weight, can be used to express the dose of CRRT: dose of CRRT = effluent rate per hour per kg body weight (mL/kg/h). For a desired dose of 25 mL/kg/h for a 60-kg patient, the effluent rate will be 25 × 60 = 1500 mL/h. This effluent needs to be partly or completely replaced by a replacement fluid; otherwise, fluid losses will be too high. The amount of effluent that is replaced will determine the fluid balance of the patient. This replacement fluid can be given prefilter (predilution), postfilter (postdilution), or in a combination of both. When given in postdilution mode, blood will concentrate while passing through the capillaries of the hemofilter. This may lead to clogging (partial clotting) and clotting of the capillaries, leading to decreased efficacy because fewer capillaries are available. To prevent this, a filtration fraction—the proportion of effluent over plasma flow—of less than 25% is advised. The filtration fraction is indicated on the dashboard of present-day CRRT machines.

In CRRT, the delivered dose should be 20–25 mL/kg/h of effluent. Two large prospective randomized studies compared this dose to a higher dose and found that outcomes were similar.[8,9] Treatment interruptions often lead to a lower delivered dialysis dose. Therefore it is advised to prescribe a dose of 25–30 mL/kg/h.[10]

TABLE 38.1 Renal Replacement Therapy Modalities

Modality	Abbreviation	Treatment Duration (per day)	Blood Flow (mL/h)	Dialysate Flow (mL/min)
Intermittent hemodialysis	IHD	2–4 h	200–450	
Hybrid techniques		6–12 h	150–200	One and a half times blood flow
• Slow low-efficiency daily dialysis	SLEDD			
• Extended daily dialysis	EDD			
• Prolonged intermittent renal replacement therapy	PIRRT			
Continuous renal replacement therapy	CRRT	24 h	100–250	
• Continuous venovenous hemofiltration	CVVH			
• Continuous venovenous hemodialysis	CVVHD			
• Continuous venovenous hemodiafiltration	CVVHDF			
Peritoneal dialysis	PD	Solution: dextrose 1.5% or glucose 1.36% to start, higher glucose concentration according to ultrafiltration needs		
• Manual exchanges	CAPD	Fill volume 1500–2000 mL		
• Automated PD (cycler)	APD	Dwell time per exchange: 2 h, consider change to 4 h once acidosis, pulmonary edema, and hyperkalemia are resolved		

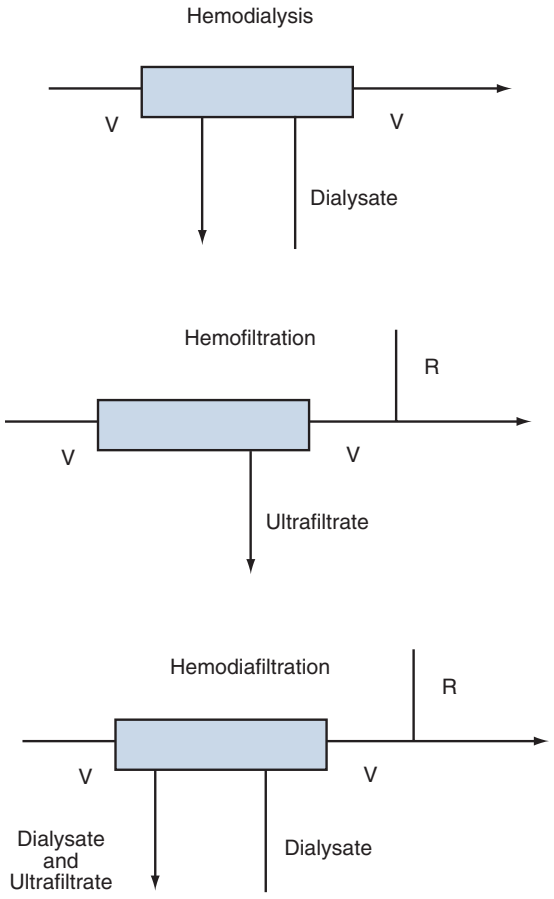

Fig. 38.1 Diffusion (as in hemodialysis) and convection (as in hemofiltration). *R,* Replacement fluid; *V,* venous blood prefilter and postfilter.

In intermittent RRT, the minimum delivered dose of dialysis should be three sessions of at least 3 hours per week, with a blood flow of >200 mL/min and a dialysate flow of >500 mL.[11]

Anticoagulation

During RRT, the patient's blood is purified by circulating it through an extracorporeal circuit containing a hemodialyzer, consisting of about 10,000 semipermeable capillary fibers. Disordered blood flow and contact of the blood with the bioincompatible material of the fibers activate the coagulation cascade, leading to clotting and subsequent blocking of the capillary fibers. This results in a reduction of the efficiency of the dialysis procedure, as fewer fibers remain available for solute exchange. When more pronounced, coagulation can even cause loss of extracorporeal blood volume by complete clotting of the extracorporeal circuit, so blood can no longer be returned to the patient.[12] Anticoagulation for RRT should be tailored according to patient characteristics and the modality chosen. Capturing the end result of the rebalanced hemostatic system in ICU patients with AKI is challenging, but new laboratory testing methods, including thromboelastography/rotational thromboelastometry (TEG/ROTEM) and thrombin generation assays, potentially yield vital information. The first technique assesses development, strength, and dissolution of clots by viscoelastic testing and does not take long before providing results. It offers information on the contribution of both enzymatic and cellular components in whole blood. Thromboelastometry analysis progressively finds acceptance in the care of patients undergoing high-risk surgery.[13] The second, thrombin generation (TG), mirrors a significant part of the overall hemostatic system, reflecting contributions of natural procoagulants and anticoagulants to hemostasis and the effect of drugs. Many semiautomated and fully automated assays are on the market today, although regrettably still lacking interlaboratory standardization.[14]

Special attention is required for nonanticoagulant strategies to avoid coagulation of the circuit. Patients with a high hematocrit are at higher risk for clotting of the extracorporeal/dialysis circuit because of the higher viscosity of the blood. Blood products should be administered separate from RRT as much as possible. Prompt reaction to pump alarms is important, avoiding interruption of the blood flow. In this regard, well-functioning vascular access is fundamental. Circuits with a lot of blood-air contact because of the use of drip chambers are especially prone to clotting. There is no evidence pointing towards the efficacy of intermittently rinsing the circuit with saline flushes to prevent clotting.[15]

No Anticoagulation Strategy

Several authors described large series of patients treated without any form of anticoagulation during RRT for AKI (in up to 50%–60%).[8,9] Especially in patients with coagulopathy, an acceptable treatment length can be reached even without anticoagulant.[16] Risking circuit clotting—in the worst case implying the loss of approximately 200 mL

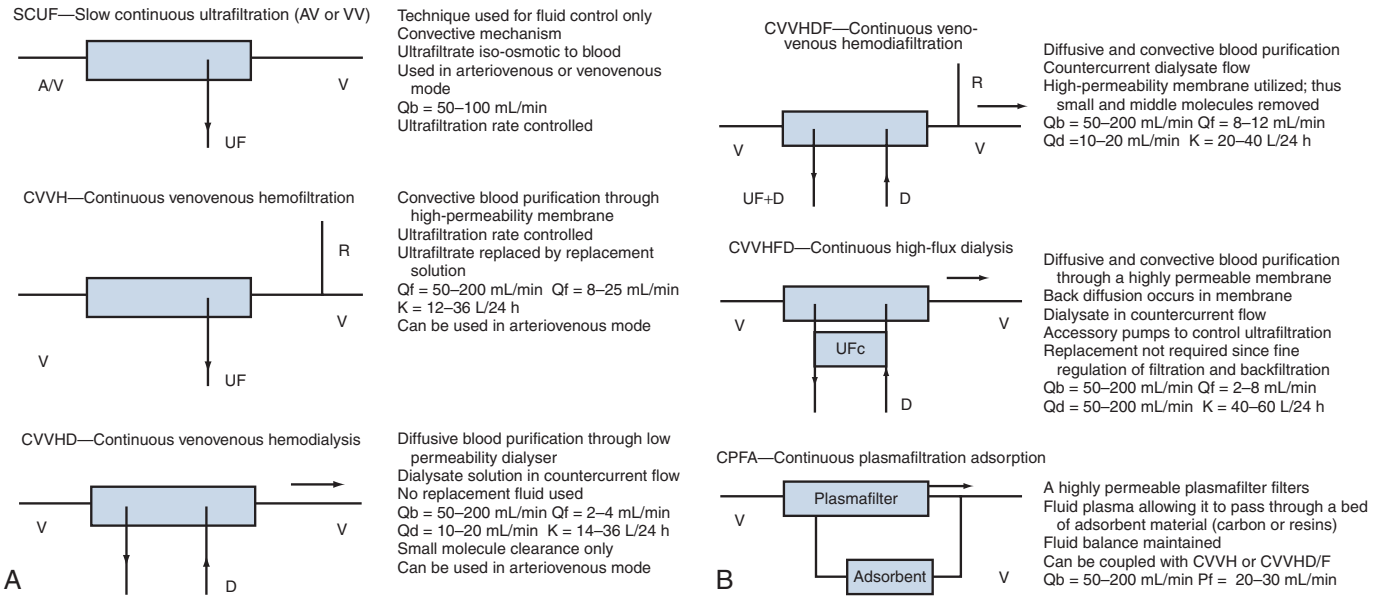

Fig. 38.2 Schematic representation and definitions of the different continuous renal replacement therapies according to standard nomenclature. Functional capabilities are described. *A,* Artery; *D,* dialysate; *K,* clearance; *Pf,* plasma filtration rate; *Qb,* arterial flow; *Qd,* dialysate flow; *Qf,* ultrafiltration rate; *UF,* ultrafiltrate; *UFc,* ultrafiltrate control pump; *V,* vein.

of extracorporeal blood and eventually also the venous access—may be defensible in patients with high bleeding risk. Neither the effect of clogging on filter performance nor the consumption of coagulation factors in RRT without anticoagulation are well studied.

Unfractionated Heparin (UFH)

Current guidelines suggest using UFH for intermittent RRT in patients without increased bleeding risk and in the case of contraindications for citrate in continuous RRT. It has a half-life between 0.5 and 3.0 hours in patients receiving dialysis.[17] It has a rapid action time of approximately 3–5 minutes. UFH acts by potentiating thrombin and inhibiting activated factor Xa. A variety of infusion schemas exists, including single dose, repeated bolus, or continuous infusion. An example of a standard dosing regimen is a bolus of 500–1000 units at the start of treatment, followed by 500–750 units/h. Other authors suggest adapting the dose to the body weight, starting with a bolus of 10–20 units/kg/h, followed by a maintenance infusion of 10–20 units/kg/h that typically would be stopped 30 minutes before the end of treatment. UFH treatment needs to be individualized according to the clinical setting. It can be monitored with routine laboratory tests as activated partial thromboplastin time (aPTT) or activated coagulation time (ACT), but many centers move to anti–factor Xa assays for monitoring UFH because it reflects the anticoagulant activity more adequately, especially during inflammatory conditions.[18,19] Anti–factor Xa level–guided anticoagulation protocols yield important potential in decreasing filter clotting.[20] If routine laboratory tests are used, typical anticoagulation targets in ICU patients are 1.5–2 times prolongation of the aPTT and 40% increase of ACT. If needed, UFH can be reversed with protamine. Heparin failure, resulting in clotting of the circuit, can be the result of antithrombin deficiency or UFH neutralization by binding to plasma proteins. During treatment, the thrombocyte count should be monitored, allowing timely detection of heparin-induced thrombocytopenia (HIT).

Low-Molecular-Weight Heparin (LMWH)

Low-molecular-weight heparins are effective and can safely be used for anticoagulation during RRT in critically ill patients.[21] LMWHs are mostly administered as a single bolus in the beginning of the dialysis, immediately after the start in the case of postfilter administration, or prefilter after 5 minutes.[22] They have a weight-based dosing and are frequently used without therapeutic monitoring in case of short treatment sessions, but especially in the setting of prolonged daily use, periodic measurement of anti–factor Xa levels is mandatory, because LMWHs are only partially cleared during hemodialysis (especially with high-flux membranes).

Citrate

The 2012 Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for Acute Kidney Injury have recommended regional citrate anticoagulation as the preferred anticoagulation modality for CRRT in critically ill patients for whom it is not contraindicated.[10] Citrate chelates calcium, an essential cofactor of many steps of the coagulation cascade. A whole range of protocols exist, applying various dialysate/replacement fluids for different RRT modalities. Prefilter infusion of citrate, either as a separate trisodium citrate solution or added to a calcium-free predilution replacement fluid, lowers the ionized calcium levels in the extracorporeal circuit to a level that achieves full blood anticoagulation (i.e., 0.3–0.4 mmol/L). In most of the protocols, the citrate dose is adapted according to the result of postfilter circuit ionized calcium measurements, although there is some concern about the reliability of blood gas analyzers at the point of care for this purpose.[23] Having a low molecular weight (198 and 258, respectively) and high sieving coefficient, citrate and citrate complexes are partially removed in the effluent. Citrate clearance is higher with dialysis than with CVVH, with extraction ratios from 20% to 60% depending on the modality and dose of the RRT. In most of the treatment protocols calcium infusion is needed to replace calcium losses and maintain systemic ionized calcium levels within the normal range. Remaining citrate is metabolized in the liver, muscle, and kidney, producing bicarbonate and eventually leading to metabolic alkalosis; therefore most of the commercially available replacement fluids contain a lowered bicarbonate concentration. In patients with impaired citrate metabolism, acidosis can ensue. Other potential

metabolic derangements include hypernatremia (metabolization of trisodium citrate), hypomagnesaemia (effluent losses in the form of citrate complexes), and hypocalcemia. Citrate accumulation can occur in patients with a profound shock or severe liver failure, although studies argued that citrate can be used safely in patients with liver dysfunction.[24] In case of citrate accumulation, there is a simultaneous increase of the total calcium and fall of the ionized calcium. The total calcium to ionized calcium ratio is the best marker for citrate intoxication. When this ratio exceeds 2.5, citrate administration must be stopped. Unintended rapid infusion of a hypertonic citrate solution, causing life-threatening hypocalcemia, is the main risk of citrate anticoagulation. In this case, it is recommended to stop the citrate infusion while continuing dialysis with a calcium-containing dialysate. In experienced hands, severe hypocalcemia-related complications seldom occur, and regional citrate anticoagulation has been shown to be safe. Treatment protocols should describe how to adjust flows under different conditions to prevent metabolic derangements. Compared with heparin, citrate is associated with lower risk of circuit loss, lower incidences of filter failure, less bleeding, and lower transfusion rates. Furthermore, citrate is a source of energy and has potential antiinflammatory effects.

UFH and Protamine

Regional anticoagulation can also be accomplished by the combination of UFH and protamine. Its use has decreased in parallel with the increasing popularity of citrate. Protamine has several side effects such as anaphylaxis, hypotension, cardiac depression, leukopenia, and thrombocytopenia. Further, there may be a risk for a rebound anticoagulant effect because of the shorter half-life of protamine compared with heparin. Regional anticoagulation with heparin-protamine is therefore no longer recommended.[10,25,26]

Platelet-Inhibiting Agents

Prostacyclin (PGI_2) and its analogue (nafamostat) inhibit platelet aggregation and adhesion. They have been used alone or in combination with heparin to improve filter survival, but several guidance documents do not recommend their use in RRT. In addition, these drugs are expensive, and there are safety concerns over hemodynamic stability with the use of prostacyclin, and anaphylaxis, agranulocytosis, and hyperkalemia with the use of nafamostat.

Dialysis Access

Central venous access is with a double-lumen catheter, preferably in the right jugular vein or a femoral vein. Use of the subclavian vein is not recommended, because contact of the catheter with the vessel wall may lead to thrombosis and ensuing stenosis, jeopardizing the possibility for an arteriovenous fistula in case there is no recovery of kidney function and the patient remains dialysis dependent. This will more likely occur when the catheter has a trajectory with angulations, such as when inserted in the left jugular vein or the subclavian veins.

For optimal blood flow rates, the tip of the catheter should be located in a large vein (i.e., the inferior or superior vena cava). For an adult, the optimal length of a catheter in the right jugular vein is therefore 12–15 cm; the left jugular vein 15–20 cm; and for the femoral approach, this is 19–24 cm. There are several different designs of dialysis catheters. At present it is not clear which design is preferable. The outer diameters of catheters vary between 11 and 14 French; larger catheter diameters will result in better blood flow rates.[27]

Temporary, noncuffed, nontunneled dialysis catheters are preferred in case of sepsis, lack of image guidance, and uncorrectable coagulopathy. However, in the absence of these contraindications, placement of a cuffed tunneled catheter may be considered immediately or after 2 weeks of using a temporary catheter.[28,29]

Like hemodialysis catheters, the insertion of Tenckhoff catheters for peritoneal dialysis can be done bedside using a Seldinger technique. In challenging cases, ultrasound or fluoroscopic guidance may be of added value. In patients with previous midline surgical scars or suspicion of intraabdominal adhesions, a surgical approach (laparoscopy or laparotomy) that offers direct vision is preferred. In experienced teams, start of peritoneal dialysis within 24–48 hours of catheter placement comes with low rates of PD fluid leaks, and rapid escalation in dwell volumes is possible. Tenckhoff catheters placed using the percutaneous technique or surgically with a purse-string suture can be removed easily, or might serve as a long-term access in case patients fail to recover from the AKI episode.

INITIATION OF RRT

The kidneys are crucial for removal of water and homeostasis of electrolytes and acid-base. Volume overload in an anuric patient and severe electrolyte and acid-base abnormalities are therefore absolute criteria for initiation of RRT (Table 38.2).[30,31] Unlike HD or CRRT, ultrafiltration and clearance cannot be exactly predicted in PD treatment. High-glucose-containing PD solutions can remove up to 1 L of fluid in 4 hours. Standard PD solutions do not contain potassium, but because solute removal is slower during PD, it may take a one day of high-volume PD to achieve serum potassium control, and later on the treatment potassium administration (intravenous or via the PD solution) may be necessary.

The exact timing of initiation of RRT in ICU patients has been the topic of fierce debates for decades. If exposure to RRT was without risks, we would not wait until occurrence of absolute criteria. But very

TABLE 38.2 Criteria for Initiation of RRT for AKI

Indication	Characteristic
ABSOLUTE CRITERIA	
Metabolic abnormality	BUN >100 mg/dL (35.7 mmol/L)
	Hyperkalemia >6 mmol/L with ECG abnormalities
	Hypermagnesemia >8 mEq/L (4 mmol/L) with anuria and absence of deep tendon reflexes
Acidosis	pH <7.15
	Lactic acidosis related to metformin use
Fluid overload	Diuretic resistant
RELATIVE CRITERIA	
Metabolic abnormality	BUN >76 mg/dL (27 mmol/L)
	Hyperkalemia >6 mmol/L
	Dysnatremia
	Hypermagnesemia >8 mEq/L (4 mmol/L)
Acidosis	pH >7.15
Anuria/oliguria	AKI stage 1
	AKI stage 2
	AKI stage 3
Fluid overload	Diuretic sensitive

AKI, Acute kidney injury; *BUN,* blood urea nitrogen; *ECG,* electrocardiogram.

Modified from Gibney N, Hoste E, Burdmann EA, et al. Timing of initiation and discontinuation of renal replacement therapy in AKI: unanswered key questions. *Clin J Am Soc Nephrol.* 2008;3:876–880.

early initiation of RRT in patients will expose these patients to potential hazards associated with insertion of the catheter (blood loss, thrombosis, catheter infection) and exposure to the extracorporeal circuit (air embolism, hypotension, etc.).[32] If RRT offers support in patients with only mild or moderate AKI, early initiation may be beneficial. However, available data suggest no benefit in, for instance, modulation of the inflammatory response,[33,34] and one study even showed harm when RRT was started very early in patients with severe sepsis or septic shock.[35]

Cohort studies on timing of RRT showed a benefit for early initiation of RRT.[36,37] However, the few small prospective randomized studies that evaluated early initiation of RRT could not show a benefit for early initiation of RRT.[31,38,39] On the other hand, cohort studies also showed that late initiation is associated with worse outcomes.[40–42] Recently, four large prospective randomized studies have addressed this in different types of cohorts. Of these, the ELAIN study, a single-center study in predominantly surgical ICU patients, found initiation at AKI KDIGO stage 2 led to reduced 90-day mortality when compared with initiating CRRT at AKI KDIGO stage 3.[43] The three other studies in general ICU and septic ICU patients could not show a mortality difference between early or accelerated initiation at KDIGO stage 2 or 3 compared with standard of care.[44–46] Moreover, they noticed that approximately 40% of patients in the standard group were not treated with RRT. Finally, the largest of the three studies, the STARRT-AKI study that included 3019 patients, found that accelerated initiation was associated with a higher proportion of patients dependent on RRT at 90 days.[46] A meta-analysis in which all prospective studies except STARRT-AKI were included showed that there is no benefit for an accelerated initiation of RRT when there are no urgent indications for RRT, and this strategy may lead to less use of RRT and thus costs.[47]

The decision to initiate RRT is therefore based on clinical criteria. These should incorporate the "demand" for RRT, which includes overload of fluid and solutes, but also severity of acute disease and chronic comorbidities.[48] Knowledge on the deterioration or recovery of kidney function within a certain period would help us in the timing of RRT, especially when there are only relative criteria for initiation of RRT (see Table 38.2). A clinical risk assessment may identify patients at greater risk for further deterioration of kidney function. This may take into account risk factors such as age, chronic kidney disease, and severity of illness of the patient. Other tools that have been explored are measurement of specific kidney biomarkers[49] such as C-C motif chemokine ligand 14 (CCL14)[50] and the furosemide stress test[51]

CHOICE OF RRT MODALITY

Since the introduction of CRRT in the mid-1980s, there has been debate on the optimal modality of RRT. Several relatively small studies and meta-analyses showed that CRRT and IHD are associated with similar patient outcomes.[52,53] However, the number of patients included in individual studies was relatively low, the baseline characteristics of patients were different, and the techniques used (modalities, dose, initiation criteria) varied between studies, making comparisons difficult. Renal outcomes may, however, be better when CRRT is used. Cohort studies and also comparison of the large prospective randomized studies on dose—the ATN and RENAL studies—suggest that CRRT is associated with better renal recovery and less end-stage kidney disease in survivors.[8,9,54–56]

CRRT is performed with a lower extracorporeal blood flow and allows removal of fluid over a longer time and a lower ultrafiltration rate, characteristics that enhance the hemodynamic tolerability of this technique. Hence, CRRT is often recommended for hemodynamically unstable patients,[10] although studies in specialized centers could not demonstrate that IHD was tolerated worse compared with CRRT in shock patients.[57]

Intermittent techniques, however, use fewer resources because they allow for several treatments with one machine per day, and dialysate and replacement fluid is produced by the dialysis machines instead of having to buy these special solutions for CRRT. It will depend on the specific setting on whether the cost of CRRT is greater than that of IHD or vice versa.[58,59] An important argument in favor of IHD and hybrid therapy is that these modalities will allow for mobilization of the patient during the off period. A recent meta-analysis suggests that hybrid therapies are associated with the same outcomes as CRRT, suggesting that increasing the length of intermittent treatment may combine the best of IHD and CRRT.[60] However, these data were compiled on a limited number of patients and most in cohort studies, making this conclusion prone to bias.

SPECIAL INDICATIONS

Heparin-Induced Thrombocytopenia

Up to 3% of heparin-exposed patients develop antibodies directed against the complex of heparin and platelet factor 4, resulting in thrombocytopenia with or without thrombosis. If HIT is likely, all heparin administration, including LMWHs, heparin-coated dialyzer membranes, and catheter locks containing heparin, must be stopped. Guidance documents recommend various options for anticoagulation during RRT in this circumstance: regional citrate anticoagulation or the use of direct thrombin inhibitors (such as argatroban or bivalirudin) or factor Xa inhibitors (such as fondaparinux).[10] Argatroban has a rapid onset of action and an elimination half-life of less than 1 hour. Its clearance is mainly hepatic (it is contraindicated in cases of severe liver failure) and independent of kidney function. Bivalirudin is renally cleared to a small extent (20%) and partially (25%) removed by dialysis.[61] Fondaparinux is excreted exclusively by the kidney[61] and can be removed using high-flux dialysis membranes.[62]

Patients with High Serum Urea Concentration

When applying acute RRT to a highly uremic patient (typically >175 mg/dL), precautions should be taken to prevent disequilibrium syndrome. This neurologic condition is characterized by nausea, vomiting, restlessness, and headache and may occasionally progress to seizures, coma, or death. The syndrome is believed to be primarily related to the decreasing osmolarity of the blood after the initiation of RRT, creating an osmotic gradient between the blood and the brain, which is compensated for by an influx of water into the brain compartment. To avoid brain edema caused by large variations in osmolality, several preventive measures can be taken, targeting a reduction in the plasma urea nitrogen of, at most, 40%. The dialysis dose can be reduced by lowering blood flow and dialysate flow, using a small dialyzer, and limiting the length of the treatment. The use of a sodium-enriched dialysate may further reduce the risk.[63]

Patients with Intracranial Hypertension or Cerebral Edema

In patients with acute brain injury, AKI requiring RRT may worsen the neurologic status in several ways. The accumulated urea and solutes diffuse from the blood compartment to the brain cells, thereby increasing water uptake by the brain cells. Dysfunction in the blood-brain barrier reinforces this process. The shift of water into brain tissue as a result of lowered tonicity of plasma with respect to the brain cells (as described in disequilibrium syndrome) may lead to increased intracranial pressure causing cerebral hypoperfusion. This is pronounced by the decreased or absent autoregulation of the cerebral blood flow and eventual hypotension during RRT. Both

hypotension and disequilibrium can be avoided by the slow progressive removal of fluids and solutes during CRRT, which in this setting is preferred over intermittent RRT. If the patient is also at increased risk for intracranial bleeding, locoregional citrate anticoagulation is recommended.[26] Gradual solute removal during peritoneal dialysis lowers the potential for disequilibrium syndrome and intracranial fluid shifts, making this a treatment modality to consider in patients with increased intracranial pressure. In case of cerebral edema because of an acute rise of ammonia, prompt RRT is mandatory. In adults, hyperammonemia is defined as a serum concentration above 50 μmol/L or 85 μg/dL, and RRT is generally indicated at ammonia levels exceeding 150 μmol/L or 255 μg/dL. When rapid ammonia clearance is needed, HD or high-dose CRRT are the preferred treatment modalities; PD is less efficient.[64,65]

Patients with Hyponatremia

If patients with severe chronic hyponatremia are treated with conventional RRT, the serum sodium concentration can be expected to increase rapidly, exposing patients to the risk of developing osmotic demyelination. High serum urea concentration may protect the brain against this.[66,67] To avoid osmotic demyelination in patients with chronic hyponatremia, the treatment during a single dialysis session has to be adjusted to provide a rate of correction that does not exceed the generally recommended rate. The easiest way to do this is to choosing low-efficiency RRT such as CVVH and to maintain sodium concentration of the replacement fluid slightly higher than the serum sodium concentration. In the routinely available dialysate/replacement solutions, the variability in sodium content is limited. Adapting the sodium concentration can be established by adding sterile water to the replacement fluid bag. Diluting replacement fluid will also result in decreased potassium and bicarbonate concentrations, and therefore may induce hypokalemia and acidosis. When applying HD treatment, one can make use of the lowest-available sodium setting (130 mmol/L), reduce the blood flow rate markedly (to 2 mL/kg/min), and shorten the dialysis time.[68]

Prevention of Contrast-Induced Nephropathy

A single dialysis session removes 60%–90% of contrast media from the blood,[69,70] and one study argued that periprocedural CRRT may be beneficial in patients with chronic kidney disease.[71] However, meta-analyses including studies in patients without severe chronic kidney disease, could not show a benefit for this strategy.[69,72] Considering the possible complications, cost, logistical difficulties, and uncertain benefit, several guidelines do not recommend RRT for the prevention of contrast-induced nephropathy.[10,73,74]

Patients with Severe Hemodynamic Instability

CVVHD, sustained low-efficiency daily dialysis, or continuous HD[10,26,73–76] seem to be equivalent treatment strategies in terms of mortality, kidney recovery, and fluid removal for hemodynamically unstable patients.[75–78] Treating those patients requires some precautions: less-aggressive ultrafiltration; increasing dialysate sodium and calcium concentrations to 145 mmol/L and 1.5 mmol/L, respectively; adapting the dialysate temperature to obtain isothermal dialysis; connecting afferent and efferent bloodlines simultaneously at the start of the procedure; and raising the blood flow slowly.

Patients with Severe Lactate Acidosis

The key issue in the management of lactic acidosis is to treat the underlying cause. CRRT can be performed in critically ill patients with severe lactic acidosis and AKI.[79] Using continuous hemodialysis with bicarbonate dialysate, lactate concentrations can be lowered and the pH can be corrected. However, no adequately powered randomized clinical trial with clinical outcome endpoints has yet evaluated RRT in this setting.[80] Severe lactate acidosis may preclude PD with lactate-buffered solutions.[81]

CONCLUSION

RRT for AKI is used in up to 10%–15% of ICU patients. Urgent indications include severe hyperkalemia and fluid overload not responsive to diuretic therapy. In the absence of urgent indications, initiation of RRT should be based on clinical judgment, which should include the demand for RRT and the capacity of the kidneys. Early initiation of RRT at AKI stage 2 or 3 does not offer a survival benefit. The modality of RRT chosen will be determined by the availability of modalities, the expertise of the team in handling these, and patient characteristics that may change during the course of illness. Continuous therapies are the most used modality in many ICUs. Intermittent hemodialysis can cause hemodynamic instability and is so preferably used in hemodynamically stable patients. Specialized units also use intermittent hemodialysis and hybrid therapies for hemodynamically unstable patients. PD is used in low- and middle-income countries as a first-choice therapy but can be used also in specific patients in case of a capacity surge, such as during the COVID-19 pandemic. Extracorporeal therapies can be performed without anticoagulation. Anticoagulation strategies most often used are regional citrate anticoagulation, UFH, and LMWHs. For continuous RRT a delivered dose of 20–25 mL/kg/h is recommended. To account for downtime, a prescribed dose of 25–30 mL/kg/h is advised.

KEY POINTS

- Urgent indications for initiation of RRT for AKI include severe hyperkalemia and fluid overload not responsive on diuretic therapy.
  - In the absence of urgent indications, early initiation of RRT does not offer a survival benefit.
  - In the absence of urgent indications, RRT is started on clinical judgment and the balance between the capacity of the kidneys to remove fluid and metabolites and the demand of the patient, which includes comorbidities, severity of acute illness, and retention of fluid and metabolites.
- The choice of the modality of RRT will be determined by the availability of modalities, the familiarity of the team to handle these, and patient characteristics. In hemodynamically unstable patients, continuous therapies will be used more often.
- RRT can be performed without anticoagulation in patients with impaired coagulation or increased bleeding risk. Citrate, UFH, and LMWHs are the most often used anticoagulation strategies.

References for this chapter can be found at expertconsult.com.

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39

Target Temperature Management in Critically Ill Patients

Filippo Annoni, Lorenzo Peluso, and Fabio Silvio Taccone

DEFINITIONS

Hypothermia is defined as a core body temperature lower than 36°C, regardless of the cause.[1] Within hypothermia we can still distinguish mild (i.e., between 35°C and 32°C), moderate (i.e., between 32°C and 28°C), severe (i.e., between 28°C and 24°C), and profound (i.e., <24°C) hypothermia.[2]

The concept of target temperature management (TTM) includes the use of induced hypothermia (i.e., cooling procedures initiated to provide brain and/or organ protection in different clinical scenarios), followed by or combined with an active control of temperature (i.e., normothermia and avoidance of fever) after hypothermia over a defined period.[3]

PHYSIOLOGY AND PATHOPHYSIOLOGY

Hypothermia has been considered over decades as a potential therapeutic strategy for different purposes, including pain management, hemorrhagic control, tetanus treatment, and neuroprotection; however, its applicability remained limited by the difficulties in achieving and maintaining a given temperature threshold (in particular for nonsedated patients) and in managing related adverse effects. As a matter of fact, only "moderate hypothermia" was initially considered to be effective[4]; nevertheless, in the last few decades, the report of beneficial effects of "mild hypothermia" in some clinical settings, together with the advances in medical technologies providing adequate temperature management, has significantly contributed to spread the research and implementation of TTM worldwide.

Most studies have focused on the effects of hypothermia/TTM on the brain, considering its high sensitivity to ischemic injury. When the brain temperature is reduced, its metabolic rate slows down by 6%–10% for each degree, thereby diminishing oxygen consumption and carbon dioxide (CO_2) production and the reperfusion injury.[5] Indeed, after a period of blood flow reduction, a complex cascade of events triggered by the reperfusion starts within minutes and can persist up to 72 hours, increasing the degree of ischemic injury.[6] These mechanisms include (1) an increase of the inflammatory response accompanied by increased cerebral blood flow (hyperemic phase); (2) an increase in cellular Ca^{2+} influx that is responsible, along with the cellular metabolic failure, for mitochondrial dysfunction; (3) a decrease in intracellular pH; (4) the release of glutamate in the extracellular space in the brain, determining a state of persistent neuronal hyperexcitability; (5) blood-brain barrier disruption with augmented permeability; (6) augmented production of free radicals; and (7) increase in programmed cell death (apoptosis).[4] Moreover, hyperthermia, which is either caused by the inflammation after reperfusion or by direct hypothalamic damage, which is involved in the tight temperature regulation in humans, occurs frequently in the postreperfusion phase; as hyperthermia is independently associated with worse outcome[7] and can also exacerbate the magnitude of the secondary brain damage,[8,9] it sounds logical to control body and brain temperature in brain-injured patients.

In particular, hypothermia can mitigate several of these phenomena, thus limiting the installation of a vicious circle by which the organ damage can further progress despite optimal medical treatment. In particular, in the acute phase (i.e., first minutes to hours), hypothermia would contribute to reducing reperfusion injuries by reducing the cerebral metabolic rate[10] and the release of excitatory amino acids,[11] decreasing free radical production[5] and inflammation,[12] and attenuating pro-apoptotic signals.[13] Subsequently, in the subacute phase, hypothermia can counteract the occurrence of brain edema[14] (i.e., hours to days), and it can favor neuronal repair[15] (i.e., following days and weeks). As body temperature is a major determinant of all biochemical reactions and interactions in the human organism, inducing hypothermia modifies the entirety of the biologic processes thorough the body (Table 39.1).

The first effect triggered by the temperature drop is the appearance of shivering, which generally manifests as the core temperature becomes lower than 35.5°C[4]: that is, one degree below the vasoconstriction threshold.[16] Shivering is the physiologic attempt to restore core temperature by causing an increase in heat production by involuntary movements, but also determines increase in work of breathing, heart rate, and myocardial oxygen consumption.[17] These effects could complicate the induction phase of hypothermia (i.e., prolonged time to target temperature) and should be treated promptly to avoid an undesired increase in the metabolic rate in injured organs.[5] Several options could be considered, including pharmacologic therapy and direct surface counter-warming,[18] as summarized in Table 39.2.

The induction of hypothermia can induce some cardiovascular alterations, including an increase in cardiac systolic function associated with a mild impairment in diastolic function despite a reduction in heart rate.[19] However, the cardiovascular effects of hypothermia could be different in critical illness: In survivors after cardiac arrest, cooling to 33°C has been shown to increase contractility[20] and improve recovery from cardiac arrest–related dysfunction when applied for more than 48 hours.[21] Pulmonary effects of TTM are tightly related to the decrease in oxygen demand and CO_2 production by the entire body. These variations must be taken into account to adequately adjust ventilatory parameters in order to avoid deleterious shifts in arterial partial pressure of CO_2 (PCO_2) or pH.[5] Several aspects of the immunologic response are also modified by hypothermia, raising concerns about a higher incidence of infections.[22] Fortunately, large trials using mild TTM did not show any difference in the rate of infections.[23–25] Nevertheless, perioperative hypothermia has been associated with an increased risk for surgical wound infection when compared with normothermia.[26] Also, platelet count and function appear to be decreased

when core temperature decreases below 35°C, whereas coagulation appears to be affected significantly only for temperatures below 33°C.[5,27] Reassuringly, despite these alterations no significant increase in spontaneous bleeding or hemorrhage rate has been found in large trials on the use of mild TTM in comatose survivors after cardiac arrest[23] or after traumatic brain injury (TBI).[28,29] Hypothermia can induce electrolyte abnormalities and increase the sensitivity to them. Specifically, potassium, magnesium, and phosphate depletion could cause serious adverse effects, including life-threatening arrhythmias, both during the induction and the rewarming phase and must then be monitored closely.[30] Hyperglycemia, caused by decreased insulin sensitivity occurring during hypothermia, is common particularly in the induction phase and is associated with poor neurologic outcome,[31] whereas hypoglycemia caused by increased insulin sensitivity may occur during the rewarming phase, especially if the rewarming rate is too fast.[5] The overall changes in enzymatic (i.e., liver) and tubular (i.e., kidney) functionality can reduce the blood clearance of several medications during hypothermia[32]; thus when TTM is applied, possible alteration in drug pharmacodynamics must be taken into account. Lastly, TTM can slow bowel and gastric function, promoting ileus and delayed gastric emptying,[33] which in turn must not be considered a contraindication to nasogastric feeding when indicated.

TABLE 39.1 Main Physiologic Effects of Mild Hypothermia

Physiologic Variables	Observed Effect
Cerebral metabolism	Decreased
Cerebral blood flow	Decreased
Fat metabolism	Increased
Lactate production	Increased
Oxygen consumption and carbon dioxide production	Decreased
Insulin secretion and sensitivity	Decreased
Inflammatory response	Decreased
Shivering	Increased
Cutaneous vasoconstriction	Increased
Renal electrolyte excretion (Mg, K, P)	Increased
Heart rate (if euvolemia)	Decreased
Myocardial contractility	Increased
Myocardial sensitivity to mechanical manipulation	Increased
Response to antiarrhythmic drugs	Decreased
Platelet function	Decreased
Drug clearance	Decreased
Bowel function	Decreased

CLINICAL APPLICATION OF HYPOTHERMIA/TTM IN CARDIAC ARREST

Experimental Evidence

Experimental evidence in different animal models has shown that body temperature may play a critical role in determining the extent of brain injuries after transient global ischemia.[34–36] Specifically, induced hypothermia was associated with a protective effect on brain damage, whereas hyperthermia or fever was associated with a deleterious effect.[35,37,38] In a recent comprehensive systematic review and meta-analysis of TTM in animal cardiac arrest models, TTM was found to be beneficial in most experimental conditions for all outcomes, despite the fact that the majority of the studies were conducted in small

TABLE 39.2 Therapeutic Options to Treat Shivering During Hypothermia (Not Exhaustive)

Drug or Strategy	Pros	Cons
Passive cutaneous counter-warming (i.e., blanket, room temperature)	Inexpensive, widely available	Unprecise, might require time to be effective
Active cutaneous counter-warming (i.e., heated forced-air blanket)	Relatively cheap, fast, evidence supported	Requires specific material
Selected cutaneous counter-warming (i.e., face, hands)	Fast; the patient remains accessible all the time	Unprecise, may be less effective than full-body surface counter-warming
Acetaminophen	Well tolerated, widely available	Liver toxicity; might mask fever Limited usefulness to treat shivering
Magnesium sulfate (IV)	Well tolerated, efficient with surface cooling technique	Risks of hypermagnesemia
Serotonin modulators (i.e., buspirone, ondansetron)	Effective for shivering prevention	Often ineffective for moderate and severe shivering
Opioids (i.e., morphine, sufentanil, meperidine)	Widely available, often already part of the treatment in patients requiring TTM	Might increase the risk of seizures, respiratory depression, dependency
Alpha-agonists (i.e., dexmedetomidine, clonidine)	Fast acting, widely available, effective for mild and intermittent shivering	Bradycardia, hypotension
Ketamine	Effective as bolus to prevent and treat shivering	Hypertension, lack of evidence for continuous infusion, hallucinations
Sedatives (i.e., propofol, midazolam, thiopental)	Widely available, often part of the treatment in patients requiring TTM	Risk of hypotension and propofol-related infusion syndrome Increased delirium incidence (midazolam) Long-lasting sedation (thiopental, midazolam)
Neuromuscular blockers	Effective for moderate and severe shivering, widely available	Increase necessity for sedation, prolonged ICU stay Increase risk of ventilator-associated pneumonia

ICU, Intensive care unit; *IV*, intravenous; *TTM*, target temperature management.

animals (i.e., rodents) and not entirely replicated in all species, were profoundly heterogeneous (i.e., intra-arrest cooling vs. early/delayed cooling), and many were biased by small cohorts or not clinically relevant outcomes (i.e., histologic effects on dying neurons or apoptosis, circulating biomarkers of brain injury, short-term survival).[39] The difficulty in translating experimental results into clinical practice is common to other fields of research and is further increased by the profound differences in etiology, comorbidities, and recovery capacities along different life periods in humans, requiring an even greater amount of scientific evidence.

Newborns

Neonatal encephalopathy (NE) is a clinically defined syndrome of impaired neurologic function in the earliest hours/days of life in infants born at or beyond the 35th week of gestation.[40] Among different causes of NE, hypoxic ischemic encephalopathy (HIE) is a subtype caused by the limitation of oxygen delivery in the newborn and is responsible for high mortality and neurodevelopmental impairment.[41,42] It remains challenging for the clinician to diagnose and classify the severity of NE in newborns[43,44]; the Sarnat staging system (and its modified version, excluding heart rate) is a neurologic physical examination–based tool useful to classify newborns with suspected HIE into three categories of severity (i.e., mild, moderate, and severe).[45] In moderate and severe HIE, therapeutic hypothermia administered for 72 hours at a core temperature of 33°C–34°C was associated with reduced brain injury and improved survival in several clinical trials,[46–50] providing clear long-term neurocognitive benefit.[51] Time to initiation of TTM in newborns appears to be of critical importance, meaning the highest benefit is to be expected with the earliest initiation.[52] Whether the treatment should be applied also to neonates of more than 6 hours of age remains disputable.[53,54] Given the large amount of evidence available, TTM at 33°C–34°C initiated within 6 hours of age and continued for 72 hours is now considered the standard of care for moderate to severe HIE in newborns with at least 36 weeks of gestation, but it remains controversial in more premature infants or in mild HIE.

Pediatric

Evidence extrapolated from neonatal HIE or adult studies may not fit with the heterogeneous pediatric population. Peculiar characteristics such as the respiratory rather than the etiology of cardiac arrest in children and the different comorbidities might shift the balance of applying TTM after global ischemic brain injury to harm, and hence it needs to be studied in a specific manner.[55,56] Recently, two large randomized controlled trials (RCTs) addressing both the population of out-of-hospital cardiac arrest (OHCA) and in-hospital cardiac arrest (IHCA) did not find a benefit in survival with good neurologic outcome at 1 year between TTM maintained for 48 hours at 33°C compared with therapeutic normothermia (i.e., 36.5°C target temperature) in children of age between 2 days and 18 years.[57,58] In a recent meta-analysis evaluating available evidence for TTM 32°C–36°C compared with no target or other different temperature targets in comatose children after the return of spontaneous circulation (ROSC) including eight observational cohort studies and one pilot study, no clear benefit or harm could be identified.[59] The evidence to support the use of TTM in comatose children after ROSC remains inconclusive, and its application remains largely derived from adult evidence.

Adults

Mild hypothermia (i.e., 32°C–34°C) was implemented globally following the publication of two RCTs regarding OHCA comatose survivors of presumed cardiac origin with initial shockable rhythm conducted in Australia and Europe, which showed significant benefit on survival and neurologic outcome when TTM was continued for 12–24 hours,[60,61] when compared with standard of care. In 2013 the TTM trial showed that two different "doses" of TTM (i.e., 33°C or 36°C for 24 hours) resulted in similar mortality and neurologic outcome when applied to comatose survivors resuscitated from OHCA of presumed cardiac origin, irrespective of the initial rhythm.[23] Since then, several centers around the globe have adopted 36°C as the target core temperature in the postresuscitation phase; however, this shift from mild hypothermia to controlled normothermia has often produced greater difficulties in maintaining optimal target temperature, resulting in a higher incidence of early fever and potentially in a reduced probability of good neurologic recovery.[62,63]

Recently, in a mixed population of OHCA and IHCA patients with an initial nonshockable rhythm and mainly hypoxic causes of arrest, mild hypothermia at 33°C was found to significantly increase the number of patients with favorable neurologic outcome when compared with normothermia at 36.5°C–37.5°C,[25] in particular within the IHCA group. However, a large randomized trial involving more than 1800 patients reported that hypothermia at 33°C for 24 hours did not result in improved survival or neurologic outcome when compared with normothermia (i.e., 37.5°C), although half of normothermic patients required a specific device to actively maintain body temperature within this value.[64]

All these results suggest the following statements: (1) TTM is not effective in all comatose survivors after cardiac arrest; (2) TTM at 33°C might be used in nonshockable rhythms, in particular in the presence of "respiratory" causes or occurring in the hospital; and (3) subgroup analyses to understand which patients might benefit from this intervention are necessary.

Moreover, because animal experiments showed an even greater benefit of TTM when it was started during resuscitation maneuvers, intra-arrest cooling was studied with large amounts of cold fluid and failed to provide any additional benefits in humans, while decreasing the ROSC rate in patients with initial shockable rhythm.[65] Conversely, transnasal evaporative intra-arrest cooling appeared to be feasible and safe and was associated with a positive trend of increased favorable neurologic outcome in OHCA with initial shockable rhythm.[66] More studies are necessary to demonstrate the effectiveness of this approach in large patient cohorts.

OTHER CLINICAL APPLICATIONS OF HYPOTHERMIA/TTM IN BRAIN INJURY

Traumatic Brain Injury

Increased intracranial pressure (ICP) is a common complication of TBI because of the mass effect of the hemorrhage), the inflammatory edema accompanying the blood-brain barrier disruption, and the disturbed cerebrospinal fluid drainage. A rise in ICP often results in a decrease in cerebral perfusion pressure, coupled with the disturbed autoregulation of the cerebrovascular system, and this can lead to secondary ischemic damage and thus worsen prognosis.[67]

One large study evaluated the use of TTM as first-line treatment for elevated ICP (i.e., vs. osmotic therapy) and found a higher mortality rate and worse neurologic outcome than in the control group; hence the study was prematurely stopped.[28] Another recently published RCT investigated the use of early prophylactic TTM for 72 hours at 33°C in association with slow rewarming and did not find any difference in favorable neurologic outcomes.[29] At this stage, the widespread use of TTM is not indicated in the early phases of severe TBI, but can remain effective to reduce ICP in case of refractory

intracranial hypertension.[68] Of note, the control group in all these studies was kept at "strict normothermia" (i.e., 37°C), which should be therefore considered "standard of care" in this setting.

Intracerebral Hemorrhage and Subarachnoid Hemorrhage

In patients suffering from intracerebral hemorrhage (ICH), increased ICP caused by cerebral edema and hematoma expansion can represent a life-threatening complication; in addition, early brain edema or delayed cerebral ischemia after subarachnoid hemorrhage (SAH) might result in secondary ischemic brain damage. In a series of patients with large intracerebral hemorrhage (>25 mL), long-lasting mild TTM (35°C for up to 10 days) has shown promising results in terms of neurologic outcome and decrease in peri-hemorrhagic edema when compared with an historical cohort.[69] Similar results were observed with hypothermia in a series of 100 patients with persistently elevated ICP after ICH.[70] More recently, excellent outcome was described in a small case series of patients with severe vasospasm and elevated ICP treated with TTM after SAH, although there was no control group.[71] Hence, TTM should only be considered an adjunct therapy in cases of refractory ICP in this setting and should be further evaluated in clinical trials. Although unproven, "strict normothermia" (i.e., 37°C) should be considered the standard of care in ICH and SAH patients with severe neurologic impairment and/or elevated ICP.

Ischemic Stroke

Ideally, the neuroprotective role of TTM could limit the extension of the core ischemic area after an acute ischemic stroke and therefore limit the burden of neurologic disability. Evidence to support the use of TTM is based on relatively small and heterogeneous trials with different TTM strategies, indications, and outcome assessment.[72] One large randomized ongoing trial, the IcTUS2/3 trial (NCT01123161), is actually investigating whether the combination of thrombolysis and TTM is superior to thrombolysis alone. However, the EuroHYP-1 trial, which enrolled 98 patients, showed no benefit from mild TTM plus medical treatment on the functional outcomes of ischemic stroke patients treated with the best-available medical care.[73]

OTHER POTENTIAL APPLICATIONS

In acute myocardial infarction, therapeutic hypothermia has been investigated in both experimental and clinical settings with the purpose to limit ischemia reperfusion injuries and thereby reduce the infarct size.[74] No consistent findings were found in a series of small randomized trials and their pooled data analysis, despite a promising possible application of TTM for infarction with a large myocardium at risk and localized within the anterior wall of the left ventricle.[75]

In spinal cord injury, TTM has been not studied by any RCTs yet, despite some experimental evidence and some clinical reports of possible beneficial effects.[76]

In the context of hepatic liver failure and hepatic encephalopathy, TTM was used as an adjunctive therapy in the case of increased ICP for patients who were subsequently transplanted, with beneficial effects on both hemodynamic variables and ammonia levels[77]; however, because of the weak evidence available, it is not considered yet the standard of care.

In mechanically ventilated patients with septic shock, induced hypothermia (target 32°C–34°C for 24 hours) followed by 48 hours of normothermia (i.e., 36°C–38°C) resulted in a similar overall mortality rate than a control normothermic group; moreover, in the hypothermia group, 30-day mortality was higher (44.2% vs. 35.8%) than the normothermic group.[78] Hence, induced hypothermia should not be used in patients with septic shock. Whether normothermia might improve hemodynamics and outcome in these patients when compared with no fever control remains to be evaluated.[79]

PRACTICAL ASPECTS

Three different phases can be identified in the process of applying TTM (induction, maintenance, and rewarming), during which several "phase-specific" physiologic phenomena could be observed in response to a decrease in body temperature. A practical algorithm for the application of TTM is provided in Fig. 39.1. Ideally a rapid induction, a precise target temperature during maintenance, and a slow and constant rewarming should be achieved to provide the most effective treatment and avoid side effects at best.[80]

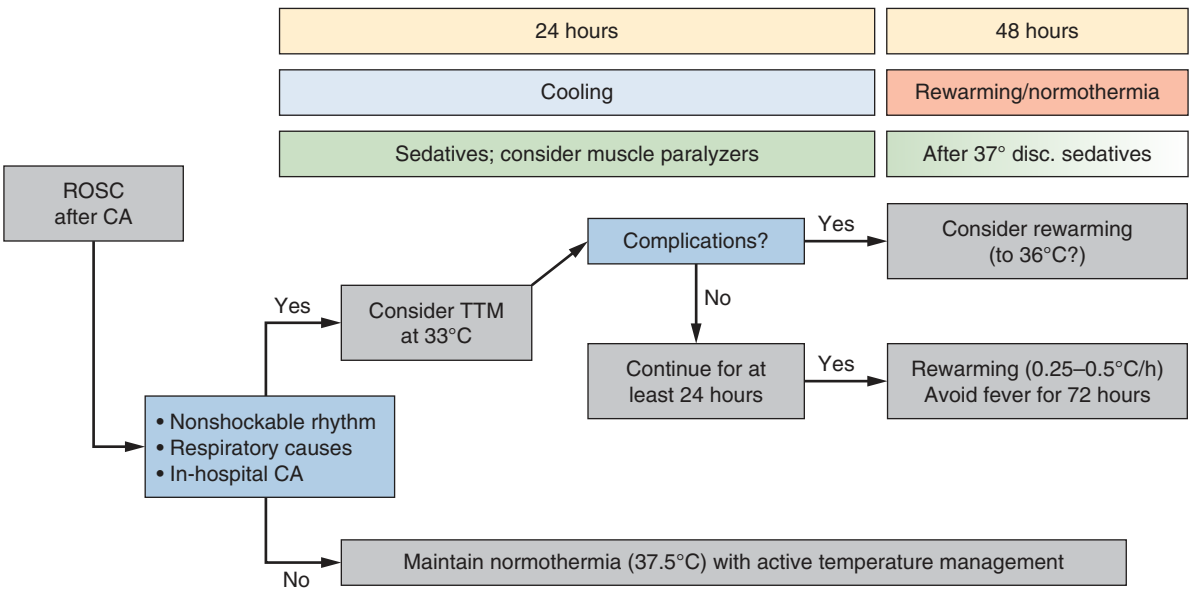

Fig. 39.1 Example of TTM Algorithm in Cardiac Arrest Patients. Consider TTM at 33°C if the arrest is associated with nonshockable rhythm, in particular for respiratory causes and if developed in hospital. *CA,* Cardiac arrest; *ROSC,* return of spontaneous circulation; *TTM,* target temperature management.

Initiation of TTM should be started as soon as possible, in particular after cardiac arrest, and maintained for a minimum period of 24 hours or longer, according to the underlying disease. As soon as the decision to apply TTM is made, a continuous measurement of the core temperature by an intravascular, bladder, or esophageal probe should be started to ensure an optimal temperature management. The appropriate device to induce and maintain the selected temperature is also of importance: several methods exist, including ice packs, cold fluids, cold blankets, automated skin pad systems, intravascular devices, and intranasal gas cooling devices; consistent differences exist among them, which are outlined in Table 39.3. Moreover, automated temperature feedback systems, both intravascular and external, were associated with better neurologic outcomes[81] and should therefore be considered, at least for cardiac arrest patients. Adverse secondary effects, including shivering, electrolyte disorders, ventilatory adjustments, and the presence of life-threatening hemorrhage, should be promptly recognized and treated.

The subsequent rewarming phase should be slow (0.15°C–0.25°C/h) to minimize adverse events and potentially minimize the burden of secondary brain damage.[82,83] Sedation must be titrated wisely according to the comfort of patients, their hemodynamic status, and the need to perform a comprehensive neurologic assessment.

TABLE 39.3 Different Cooling Methods

Drug or Strategy	Pros	Cons
IV fluids	Easily feasible in different locations Not expensive Low workload for healthcare providers	Difficult to maintain constant temperature Not specific to brain cooling Slow induction No feedback control Risk of fluid overload
Surface devices without temperature feedback	Easily feasible in different locations	Difficult to maintain temperature Not specific to brain cooling Slow induction No feedback control Risk of skin lesions Expensive
Surface devices with temperature feedback	Precise temperature induction and maintenance Fast induction Presence of feedback control Low workload for healthcare providers	Only feasible in ICU setting Not specific to brain cooling Risk of skin lesions Expensive
IVC	Precise temperature induction and maintenance Fast induction Presence of feedback control Low workload for healthcare providers	Only feasible in ICU setting Not specific to brain cooling Risk of infections and/or thrombosis Expensive
TNEC	Easily feasible in different locations Specific to brain cooling Very few side effects	Difficult to maintain temperature Slow induction No feedback control Risk of fluid overload

ICU, Intensive care unit; IV, intravenous; *IVC,* intravascular catheter; *TNEC,* transnasal evaporative cooling.

CONCLUSIONS

The application of TTM during critical illness remains controversial and still associated with unanswered issues, such as which patient populations might benefit the most. Clinically relevant effects of hypothermia have been observed in newborns suffering from HIW and in some—at the moment poorly characterized—adult cardiac arrest survivors. Future research is needed to clarify the exact role of TTM after cardiac arrest and other critical illnesses.

KEY POINTS

- TTM has been shown to minimize or reduce the severity of cerebral damage in different models of experimental brain injury, in particular of anoxic origin.
- When hypothermia is used, several side effects, including shivering, altered diastolic ventricular function, moderate immunosuppression, reduced platelet function, electrolyte imbalance, and hyperglycemia, may occur. All these phenomena should be adequately monitored and treated whenever necessary.
- In newborns suffering from HIE, the use of TTM at 33°C for 72 hours is recommended as the standard of care in the management of such patients.
- In cardiac arrest in pediatric patients, there is no evidence for a beneficial effect of TTM.
- In adult victims of cardiac arrest, the use of TTM remains extremely controversial; if the application of hypothermia at 33°C should not be considered standard of care any more in such patients, there are some patients (i.e., nonshockable rhythms, in particular if of respiratory origin and/or occurring in hospital) who might still benefit from such intervention.
- In traumatic brain-injured patients, hypothermia at 33°C should be avoided as first-line therapy; its role as "salvage therapy" in the case of refractory intracranial hypertension is still accepted in current recommendations.
- In other forms of brain injury, the benefits of TTM remain poorly demonstrated; however, in severe patients, aiming at normothermia appears the most widely used approach.
- There is no indication for regular use of hypothermia or strict normothermia in other critically ill patients

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ANNOTATED REFERENCES

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Extracorporeal Membrane Oxygenation (Venovenous and Venoarterial ECMO)

Ali B.V. McMichael, Mehul A. Desai, Melissa E. Brunsvold, and Heidi J. Dalton

INTRODUCTION

Use of extracorporeal life support (ECLS) for respiratory and/or cardiac failure continues to increase, with almost 500 Extracorporeal Life Support Organization (ELSO) centers worldwide and almost 100,000 patients now added to the ELSO registry.[1] In actuality, ECLS use is likely much higher, as many centers do not report data to ELSO or any other international registry. The survival rate for ECLS varies significantly by indication for support and age.[2] Table 40.1 lists the survival rates reported to ELSO for neonates, pediatric, and adult patients. ECLS complications continue to be common and are most frequently the result of bleeding or clotting. As ECLS technology improves and global experience increases, the indications for ECLS continue to expand.

MODES OF ECMO

Extracorporeal membrane oxygenation (ECMO) modes are conventionally named for the sites from which the blood is drained and returned. Fig. 40.1 depicts typical cannula placement for neonates, pediatric, and adult patients. There are two major technical types of ECLS: venoarterial (VA) and venovenous (VV). Hybrid modes that incorporate VA and VV together are also used in specific circumstances.

Venoarterial Cannulation

In the VA mode, deoxygenated blood is removed from the venous system and pumped to a membrane lung, which removes carbon dioxide and adds oxygen. Oxygenated blood is then returned to the patient via the arterial system. Use of the venous and arterial vessels depends on the patient size and condition and is divided into peripheral and central cannulation.

Venous drainage in older children and adults is either from the internal jugular or femoral vein. As femoral vessel size limits the adequacy of venous and arterial cannulation in neonates and small children, usually up to the age of 2 years, the right or left internal jugular vein is most commonly accessed. Oxygenated blood is usually returned to the patient via the carotid or femoral artery. The femoral artery is the preferred method in adolescents and adults to prevent need to repair or sacrifice the carotid artery at the time of decannulation. An increase in adverse neurologic events resulting from restricted cerebral blood flow secondary to loss of the right carotid artery and from emboli returning from the ECMO circuit to the left carotid are also reasons why carotid access is often avoided.[3] Cerebral venous congestion from internal jugular cannulas is also theorized to add to the risk of neurologic events, although there are no definitive studies that have adequately researched this. Some neonatal centers advocate placement of a distal jugular bulb drainage cannula (also known as a *cephalad cannula*), which is then Y'ed into the ECMO venous drainage line to increase venous flow and decrease intracranial venous pressure. This technique, however, is rarely described in adult care.[4] If the femoral artery is used, a reperfusion cannula may need to be employed to provide adequate perfusion distal to the cannula site and thereby mitigate limb ischemia.[5] Continuous noninvasive monitoring by pulse oximetry or near-infrared spectroscopy on lower extremities during femoral VA access may help with earlier identification of limb ischemia if changes in blood flow and oxygenation develop post-cannulation.[5–7] A side-graft on the femoral artery can also be placed that does not totally occlude distal blood flow, but this process cannot be accomplished via a percutaneous approach and requires surgical intervention. Other arterial access possibilities include cannulation of the subclavian and innominate vessels, facilitated by advances in cannula technology and growing experience. If these arteries are cannulated, care must be taken to avoid either hyperemia of the distal limb (which may require a ligature to restrict distal blood flow) or ischemia that develops after occlusion of distal flow. Side grafts have also been used in subclavian arterial access.

Hypoxemia Differential

In patients with severe respiratory failure who are cannulated via the femoral artery, development of differential oxygen saturation of the upper and lower extremities can occur because of competing native cardiac output and returning ECMO circuit flow directed retrograde up the aorta. Where the native cardiac output, which is likely desaturated in patients with severe pulmonary gas exchange problems, meets the oxygenated ECMO return flow is often termed the "mixing zone." Higher native cardiac output and lower ECMO return will move the mixing zone more distal in the aorta, whereas increased ECMO flow may push oxygenated blood farther up the aorta. If desaturated blood from the left heart is primarily perfusing the upper body, including the brain and coronaries, this results in a cyanotic upper body with a well-perfused lower body, a condition for which the terms "harlequin" or "north-south" syndrome is used. Methods to improve upper body oxygenation include placing another venous cannula into the right atrium (RA) which is Y'ed into the arterial ECMO return to direct some oxygenated blood to the RA and improve cardiac oxygen delivery. Care must be taken to ensure that both ECMO return cannulas—especially the femoral cannula—achieve adequate flow to prevent stasis and thrombosis.

TABLE 40.1 Survival to Decannulation and Discharge or Transfer for Neonatal, Pediatric, and Adult Extracorporeal Membrane Oxygenation (ECMO)

	Total Runs	Survival to Decannulation, *N* (%)	Survival to Hospital Discharge or Transfer, *N* (%)
NEONATAL			
Respiratory	32,634	28,627 (87)	23,860 (73)
Cardiac	8993	6216 (69)	3899 (43)
ECPR	2080	1463 (70)	883 (42)
PEDIATRIC			
Respiratory	10,549	7636 (72)	6347 (60)
Cardiac	12,836	9271 (72)	6854 (53)
ECPR	5086	3032 (59)	2159 (42)
ADULT			
Respiratory	25,631	17,832 (69)	15,741 (60)
Cardiac	27,004	16,117 (59)	11,891 (44)
ECPR	8558	3582 (41)	2549 (29)

ECPR, Extracorporeal pulmonary resuscitation. Data from the ELSO International Registry Report, July 2020.

For patients cannulated via the femoral artery, use of pulse oximetry or arterial blood gas data from the right hand or use of cerebral near-infrared spectroscopy (NIRS) may help follow oxygen saturation levels. Although there is controversy as to when adequate oxygen is reaching the upper body and brain, most centers use as guidelines the achieving of arterial saturations >80% (sometimes lower) or, conversely, avoidance of signs of inadequate oxygenation, such as mental confusion, electrocardiogram (ECG) changes of ischemia, or high blood lactate levels. These help to determine whether the cannulation strategy needs to be altered to improve upper body oxygenation. If unable to adequately provide respiratory and cardiac support with this configuration, movement of the femoral artery cannula to an upper body site or central cannulation should be established.

Central Cannulation

Central cannulation is accomplished via a median sternotomy with cannulation of the RA as the venous drainage and ascending aorta as the arterial return. Advantages of central VA-ECMO include increased venous drainage and antegrade return of oxygenated blood flow to the proximal aorta. Central cannulation is most commonly used for postcardiotomy patients but may benefit septic shock patients when higher flow is required. Disadvantages to central cannulation include increased risk of bleeding and infection and decreased patient mobility.

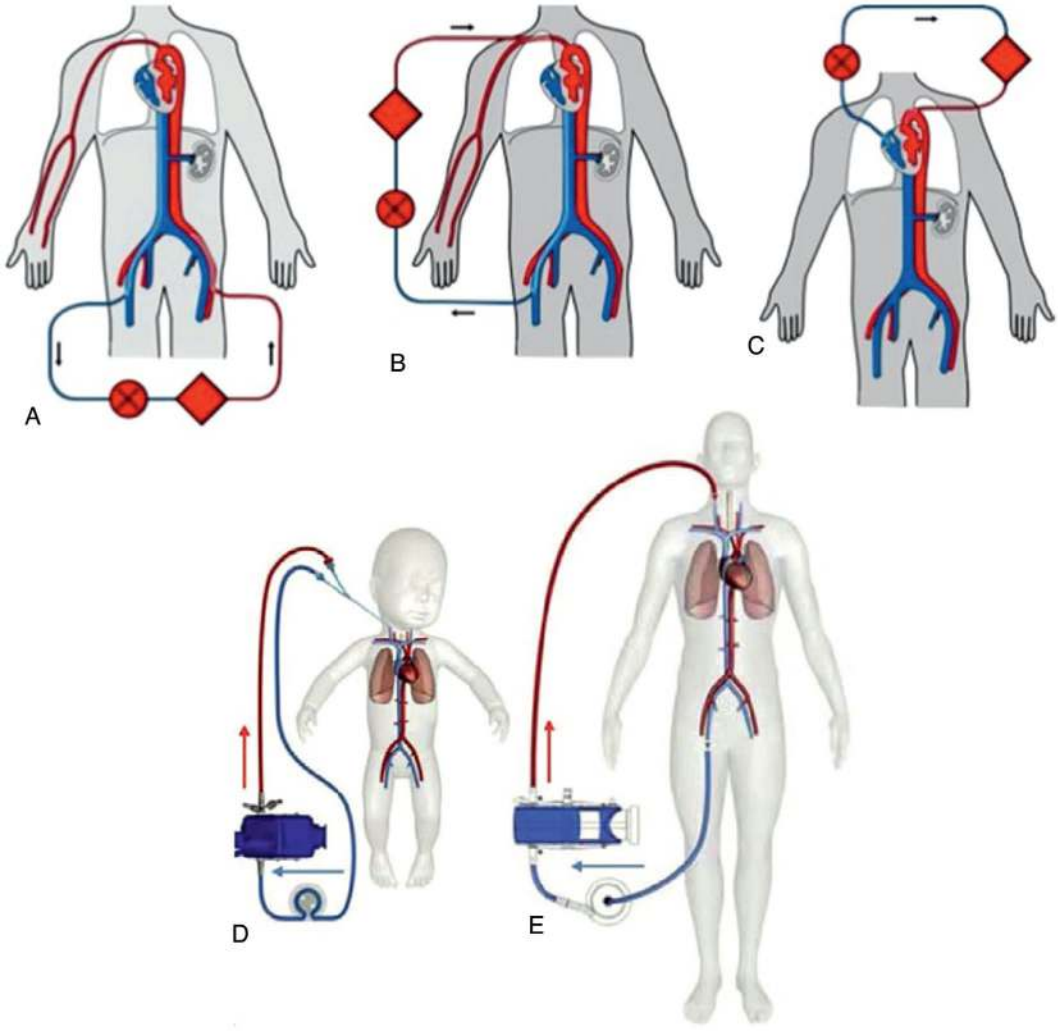

Fig. 40.1 Schematic of possible venoarterial **(A–C)** and venovenous **(D, E)** ECMO circuit configuration. **(A)** VA, peripheral, femorofemoral. **(B)** VA, peripheral, femoro-axillary cannulation. **(C)** VA, central cannulation. **(D)** VV, single, double-lumen cannula. **(E)** VV, two single-lumen cannulas. *ECMO,* Extracorporeal life support; *VA,* veno-arterial; *VV,* venovenous. (Adapted from Sangalli F, Patroniti N, Pesenti A. *ECMO—Extracorporeal Life Support in Adults.* New York: Springer; 2014: Figs. 3-9 and 6-6.)

Venovenous Cannulation

In the VV mode, deoxygenated blood is removed from the venous system and sent via an external pump to the membrane lung where oxygen is added and carbon dioxide removed. Oxygenated blood is then returned to the venous system. As the native heart must deliver oxygenated ECMO flow to the systemic circulation, VV requires adequate cardiac function. Venous blood is externally diverted from the patient, commonly by the inferior vena cava (IVC) and usually via the femoral vein, and then reinfused to the RA after gas exchange via the internal jugular vein. The drainage cannula is optimally placed in the hepatic IVC/RA region, as the largest volume of flowing blood for drainage exists here, and this vessel is less prone to collapse than those farther down in the abdomen. The internal jugular reinfusion cannula should be placed in the RA. The two cannulas should be separated by a few centimeters to reduce recirculation of ECMO return being drained back into the ECMO intake circuit without traversing the systemic circulation. Dual-lumen cannulas now exist that drain both the IVC and superior vena cava (SVC) and reinfuse oxygenated blood into the RA. When placed properly, these catheters direct oxygenated return through the tricuspid valve and into the right ventricle, thus reducing recirculation. As it is somewhat difficult to achieve proper placement of the dual-lumen cannula, placement under fluoroscopic or echocardiographic guidance is recommended. Unfortunately, dual-lumen cannulas appropriate for neonates are not readily available; those that are available have concerns regarding cardiac perforation or placement, which limit their use.[8]

In patients cannulated for respiratory failure via VV-ECMO, sudden right ventricular failure can occur, often after days to a week on ECMO support. Although causation of such events is unclear, etiologies may include development of progressive pulmonary fibrosis and associated increased pulmonary vascular resistance, pulmonary emboli, fluid overload, or failure of the right ventricle from constant exposure to the relatively high-pressure jet returning from the ECMO circuit. Deterioration can occur rapidly, and if not medically managed successfully or the patient is not transitioned to VA support, right ventricular failure may lead to cardiac arrest.[9] Periodic echocardiographic evaluation of right ventricular function coupled with clinical examination aimed at detecting venous distention or other evidence of right heart failure are advisable.

PHYSICAL SYSTEMS FOR ECMO

The ECLS circuity is composed of cannulas, a pump, an oxygenator (which is also referred to as the *membrane lung*), and tubing. Several technologic changes have been made to the ECLS circuit, including creation of centrifugal pumps with streamlined circuity and decreased priming volume; advancements in artificial membrane technology; and integrated systems that allow for ongoing assessment of venous saturations, blood gas values, temperature, hemoglobin, ECMO flow, ECMO pressures, and alarms. Newer systems also have enhanced portability and improved safety.[10,11]

Two pump types exist for ECLS: centrifugal and roller-head. With the advent of newer centrifugal systems that are not associated with the severe hemolysis and plasma leakage issues of the past, most centers now use centrifugal pump and hollow-fiber/polymethylpentene membrane lung systems. Roller-pump devices generate high return pressure that poses justified concern for circuit rupture. Given this hazard and their dependence on gravity for venous drainage, many centers now have abandoned them. Centrifugal systems are also easier to set up, require less priming volume, may be safer, are easier to move, and facilitate patient mobility. In addition, centrifugal systems tend to require less immediate bedside technician monitoring, which reduces staffing needs and costs.[11–13] Moreover, newer systems are thought to minimize the hemolysis encountered with earlier versions of centrifugal pumps.[14] At this writing, newer centrifugal and membrane lung systems are appearing on the market, each with potential advantages and more miniaturization; however, whether these innovations truly affect outcome is yet unknown. Of interest, use of roller-pump devices continues in the United States for neonatal patients, whereas the rest of the world has changed to centrifugal setups. Several reports of an increase in hemolysis, hyperbilirubinemia, renal injury, and a decrease in survival in children with centrifugal pumps compared with roller devices have appeared, although whether these events are related to lack of experience with centrifugal systems or to other factors is unclear.[15–17]

Much like the pumps, oxygenator technology has improved over time. Use of the silicone membrane lung, the workhorse for ECMO for many years, provided good gas exchange but was cumbersome to prime, stimulated a large inflammatory response because of its large surface area, and promoted thrombosis which required replacement. Its use has almost disappeared, and most centers have transitioned to microporous hollow-fiber oxygenators that employ polymethylpentene fiber technology. Hollow-fiber oxygenators are also advantageous because of their lower priming volume, smaller surface area, and improved gas exchange. These devices now exist in a variety of sizes, which makes them applicable to patients of varying size—neonates through adults.

Most ECMO systems also incorporate measurement of flow, revolutions per minute, pressure and alarm limits, and a variety of other indicators. Devices to measure flow, blood gases, and other parameters can also be placed on the circuit noninvasively. These even afford remote monitoring and adjustments in flow, which may allow multiple patients to be managed at distant sites. One new recently Food and Drug Administration (FDA)–approved system by Abiomed provides an oxygen concentrator, which obviates need for an external oxygen source, and a battery life of 3 hours, which may allow ambulation and facilitate care of patients outside the intensive care environment.

MANAGEMENT OF ANTICOAGULATION AND BLOOD TRANSFUSION

During ECMO initiation, a massive inflammatory response occurs because of contact of patient blood with the foreign ECMO circuit, upregulating the coagulation system. Both activation and consumption of platelets occur, which induce changes in the coagulation cascade and promote a prothrombotic state.[18–20] Anticoagulation is administered during cannulation and is continued throughout the ECMO run to mitigate the risk of thrombosis in both the circuit and the patient. Unfractionated heparin (UFH) remains the standard anticoagulant for ECLS patients, although newer anticoagulants, including direct thrombin inhibitors such as bivalirudin and argatroban, have been used successfully as well. No randomized trial exists currently to compare UFH with these newer anticoagulants to demonstrate if the anticoagulants are equivalent or if one approach is better than another. In a pilot single-center adult study, use of an algorithm-based heparin titration based on activated partial thromboplastin time (aPTT) was compared with a weight-dosed arm of 10 units/kg/hour with no titration for 10 patients on VV-ECMO. No differences were noted in need for circuit exchange, bleeding events, or amount of transfused blood.[21] Other case series in patients with high risk for bleeding, including trauma or postcardiotomy, have shown that low-dose or no heparin during ECMO may be safe, but continuous monitoring of the circuit for thrombus formation is warranted.[22] Other means of reducing platelet activation, aggregation, and circuit thrombosis such as surface coatings on the ECMO tubing, administering nitric oxide across the

membrane lung, and use of antiplatelet agents, are areas of clinical and bench research.

Laboratory monitoring for UFH on ECLS varies among centers, and no single test or combination of tests has been found to be superior to another regarding bleeding or thrombosis. Although much effort and research have occurred and continue to try to define the optimal anticoagulation testing regimen for patients receiving ECLS, the answer is not currently known. Activated clotting time (ACT) is historically the most common laboratory test for monitoring UFH, but other tests, such as anti–factor Xa and viscoelastic assays, are being employed at many ECLS institutions. ACT is a whole-blood test that measures the time of whole blood to form a fibrin clot. It can be performed at the bedside and is simple to do, but its accuracy is affected by several factors, including thrombocytopenia, platelet dysfunction, hemodilution, hypofibrinogenemia, temperature, and technical factors. Anti–factor Xa assay is a chromogenic assay that measures the UFH inhibition of the factor Xa activity, and thus should be a better test for providing information specific to heparin effect. Viscoelastic testing methods such as thromboelastography (TEG) and rotational thromboelastometry (ROTEM) are whole-blood tests that measure the viscoelastic properties of a clot, including time to initiate clot formation, extent of fibrin formation, clot strength, and clot lysis. Although viscoelastic tests seem to provide a more comprehensive view of the quantity and function of coagulation factors, platelets, and fibrinogen, there currently are minimal data to support their use in ECLS, although more data are emerging. Bedside viscoelastic testing is now available at many centers, but it is currently unknown if it will improve anticoagulation management or if it will decrease the incidence of thrombotic or bleeding events. An understanding of what each anticoagulant test measures and its limitations is crucial to manage ECMO anticoagulation. Many studies suggest that a combination of probes, including a clotting time test such as ACT or TEG/ROTEM, plus a plasma-based test such as anti–factor Xa or aPTT, present a more comprehensive picture of the coagulation status and anticoagulant effect in ECLS patients.[23]

Blood product transfusion thresholds vary based on patient age and type of ECLS (VV versus VA). Table 40.2 displays common transfusion thresholds recommended by ELSO. Other more detailed manuscripts on this topic are included in the references.[24,25] Adult patients tend to have lower hemoglobin goals than children, although reasons for this are unclear. Red blood cells are transfused with the primary goal to increase oxygen-carrying capacity and augment tissue oxygenation, but study results vary as to whether increasing hemoglobin improves clinical status or if the potential adverse effects of transfusion outweigh any potential benefit.[26–31] Similar issues with adverse effects of platelet transfusion to achieve goal platelet count have been documented in ECMO patients.[28,32,33] One common agreement regards the mandate to maintain normal fibrinogen levels during ECMO.

TABLE 40.2 Transfusion Thresholds for Blood Products in Adults and Children

	Adult	Pediatric
Hemoglobin	7 g/dL	8–10* g/dL
Platelet	Nonbleeding patients: >50–100,000 cells/mm^3 Bleeding patients >100,000 cells/mm^3	Nonbleeding patients: >50–100,000 cells/mm^3 Bleeding patients >100,000 cells/mm^3
FFP	>1.5–2.0 if bleeding	>1.5–2.0 if bleeding
Fibrinogen	<100–150 mg/dL	<100–150 mg/dL

FFP: Fresh frozen plasma.
*Consider higher hemoglobin goal for cyanotic congenital heart disease.

COMPLICATIONS

Among the most common complications for ECLS patients are hemorrhage and thrombosis. A summary of the most frequent complications reported to the ELSO registry are listed in Tables 40.3 and 40.4. Development of secondary infection while being supported by ECMO, need for a long duration of support, mediastinal cannulation, lack of correction in lactate or pH over the first 24 hours of support, and quantity of administered blood products are all factors that have been associated with outcome.[34,35]

Several neurologic complications, including seizures, ischemic stroke, intracranial hemorrhage, and brain death, may occur during ECMO.[36,37] The cause of neurologic injury during ECMO is complex and likely multifactorial. Predispositions include patient pre-ECMO factors such as hypoxia, acidosis, low cardiac output, impaired cerebral autoregulation, and alterations in cerebral blood flow.[38] Cannulation site can increase the risk of neurologic complications; ligation of the carotid artery is associated with the highest risk of injury.[39] Noninva-

TABLE 40.3 Common Complications for Adult and Pediatric Patients Placed on ECMO for Primary Respiratory Indication

	Adult (%)	Neonatal (%)	Pediatric (%)
Mechanical pump malfunction	1.5	1.6	2.2
Mechanical oxygenator failure	9.1	5.7	10.6
Cerebral infarct	2	6.8	4.2
Intracranial hemorrhage	3.9	7.6	6.4
Pulmonary hemorrhage	6.1	4.5	8.1
Cannula site bleeding	13.2	7.9	18.3
Surgical site bleeding	10.5	6.3	12.6
Infection	17.5	5.8	16.8

Adapted from the 2016 ELSO Registry International Report.

TABLE 40.4 Common Complications for Adult and Pediatric Patients Placed on ECMO for Primary Cardiac Indication

	Adult (%)	Neonatal (%)	Pediatric (%)
Mechanical pump malfunction	0.8	1.5	1.8
Mechanical oxygenator failure	6.6	6.1	7.2
Cerebral infarct	3.8	3.4	5.0
Intracranial hemorrhage	2.2	11.3	5.3
Pulmonary hemorrhage	3.1	5.2	5.3
Cannula site bleeding	18.5	10.7	15.6
Surgical site bleeding	20.2	29.3	28.9
Infection	13.0	7.1	11.0

Adapted from the 2016 ELSO Registry International Report.

sive monitoring, including NIRS, transcranial Doppler, and electroencephalogram (EEG), may help detect acute brain injury.[40–42] Initial studies employing multimodal neurologic monitoring are promising, but further study and standardization are needed.[43,44]

Vascular complications are also common and occurred in 29% of patients in a systematic review of 6583 adult ECMO patients.[45] Access of the femoral artery for VA-ECMO can lead to lower extremity ischemia, pseudoaneurysm formation, dissection, and retroperitoneal bleeding. As mentioned previously, a distal perfusion cannula can be placed to mitigate limb ischemia. In addition, at the time of decannulation, a repair of the femoral artery can be performed to prevent arterial stenosis.[46] Dissection and retroperitoneal hematoma may occur during cannulation, but the risk can be minimized by using ultrasound guidance during percutaneous access of the femoral vessels. Thromboembolism and pseudoaneurysm are usually late vascular complications that occur in approximately 6% and 1.3% of patients, respectively.[45] Pseudoaneurysms present with a pulsatile, palpable bulge and if small generally can be managed with injection of thrombin. If large or rapidly expanding, however, these defects will usually require surgical intervention.[47] Because injury to the right ventricle, coronary sinus, and hepatic vein can occur during placement of dual-lumen VV-ECMO cannulas, their placement under fluoroscopy is recommended.

Although pump or circuit failure is an uncommon event, sudden deterioration of performance can result in lack of adequate patient support, leading to adverse events or fatality. Air embolus in centrifugal pumps can also occur, and centers transitioning from roller-head to centrifugal systems often see a rise in air events, as the "suction" provided by the centrifugal pump can rapidly pull air from any open stopcock. For this reason, most centers limit any access on the "negative" or prepump head side of the ECMO circuit, and systems that can stop forward flow of air bubbles are often employed. Centrifugal pumps require a thorough understanding of how patient physiology affects them, as they are very sensitive to "preload" (adequate venous drainage) and "afterload" that may impede forward ECMO flow from the pump.

ECMO FOR RESPIRATORY FAILURE

Use of ECLS for respiratory failure is supported by the rationale that ECLS provides time for lung recovery while simultaneously allowing implementation of effective lung protective ventilation. The ELSO guidelines for acute respiratory failure consider ECLS as a rescue therapy for hypoxic respiratory failure with high mortality risk, hypercarbia despite plateau pressures >30 cm H_2O, severe air leak syndrome, need for intubation for a patient on a lung transplant list, or immediate cardiac or respiratory collapse.[48] Each center may develop their own criteria, but these general rules exist. Use of scoring systems to predict ECMO outcome or candidacy are appearing but require further refinement. Descriptions of these scores, including PRESET, PRESERVE, and RESP, can be found in the references.[49–52] Table 40.5 lists the most common adult respiratory indications for ECLS.

ARDS

Severe acute respiratory distress syndrome (ARDS) continues to have a high associated mortality rate, in spite of the use of lung protective strategies that include ventilation with relatively low tidal volumes and pressures.[53–55] Per ELSO guidelines, ECLS should be considered for patients in hypoxic respiratory failure if the mortality risk exceeds 50%, and ECLS is indicated if risk of death is 80% or greater.[48] Mortality of 50% is associated with a PaO_2/FiO_2 <150 mm Hg on FiO_2 of 90% and/or a Murray score of 2 to 3. Mortality rates of ~80% are associated with a PaO_2/FiO_2 <100 on FiO_2 >90% and/or a Murray score of 3 to 4.

TABLE 40.5 Adult, Neonatal, and Pediatric Respiratory Failure Indications From the ELSO International Registry

	N (%)
ADULT*	
Viral pneumonia	926 (17)
Bacterial pneumonia	1362 (24)
ARDS	1298 (23)
ARF, non-ARDS	1984 (36)
NEONATAL#	
CDH	1851 (32)
MAS	1393 (24)
PPHN	1233 (21)
Respiratory distress syndrome	71 (1)
Sepsis	256 (4)
Other	1035 (18)
PEDIATRIC#	
Acute respiratory failure	730 (22)
Chronic lung disease	98 (3)
Sepsis	281 (3)
Congenital heart disease	152 (5)
Bronchiolitis	329 (10)
Pneumonia (viral, bacterial, aspiration, and other)	652 (17)
Pertussis	69 (2)
Asthma	91 (3)
Other	910 (27)

Adapted from the Pediatric ELSO Registry Report 2016 and Extracorporeal Life Support Organization Registry International Report 2016.
ARDS, Acute respiratory distress syndrome; *ARF,* acute respiratory failure; *CDH,* congenital diaphragmatic hernia; MAS meconium aspiration PPHN persistent pulmonary hypertension.
*Adult patients include total patients reported to the ELSO registry from 1989 to 2016.
#Neonatal and pediatric include total patients reported to the ELSO registry from 2009 to 2015.

Two recent randomized controlled trials that evaluated ECLS in adult ARDS patients are CESAR and EOLIA. In the CESAR trial, 180 adult patients with refractory ARDS were randomized 1:1 to transfer to a ECMO center for VV-ECMO consideration versus conventional care using a lung protective strategy.[56] Respiratory support of patients in the conventional arm who were not transferred to the ECMO center was suggested to follow general lung protective guidelines, but specific ventilator management was not mandated. Of the 90 patients transferred to the ECMO center, 68 (75%) received ECMO and 57 (63%) survived to 6 months without disability, compared with the 41 (47%) patients who survived to 6 months and received conventional management. Although these results seem to demonstrate the efficacy of ECMO, limitations to data interpretation include the fact that 22 of the patients randomized for transfer to the ECMO center did not receive ECMO and 5 patients died during transport.[57] Critics of the study noted that the major finding was that care in an ECMO-capable center was associated with improved outcome, not necessarily the use of ECMO. The EOLIA trial was undertaken to overcome some limitations noted in the CESAR trial. This randomized controlled trial

included 240 adult patients randomized by center and length of mechanical ventilation to VV-ECMO or conventional ventilator treatment according to the published Express trial of positive end-expiratory pressure (PEEP) that used a tidal volume of 6 mL/kg and PEEP set so as to not exceed a plateau pressure of 28–30 cm H_2O.[58] Early use of neuromuscular blocking agents and prone positioning were also recommended. The primary endpoint was 60-day mortality. Although there was no significant difference in mortality rate between groups (35% in the ECMO groups versus 46% in the control group, $P = .09$), patients in the most severe group of respiratory failure based on PaO_2/FiO_2 did experience benefit from ECMO. Further, if data of patients who suffered a sudden cardiac arrest that necessitated the VA-ECMO were excluded from the analysis, ECMO also appeared to confer benefit. Last, the study was powered to see a reduction of 20% in mortality in the ECMO group. As mortality in the control group was less than expected, this may have contributed to the inability to detect a statistically significant difference between groups. Despite not having definitive evidence favoring ECMO for acute respiratory failure, it should be considered for severe ARDS patients but requires judicious patient selection, early initiation of ECLS, and use of lung protective strategies while on ECMO.

ECMO Use in Lung Transplantation

The number of lung transplants in the United States per year is increasing. In 2018 2562 lung transplants were performed in the United States. However, despite this increase, 365 adult lung transplant candidates remained who died or became too sick to undergo transplant.[59] The mortality rate for waitlisted patients with acute end-stage exacerbations persists as high as 50%. If patients do not require support for oxygenation but do need decarboxylation, extracorporeal carbon dioxide removal ($ECCO_2R$) can be employed. In one report of 121 patients who underwent ECMO (VA, VV, and central ECMO) as a bridge to lung transplant, 70 (59%) received a transplant and 64 (91%)) survived to discharge. One predictor of successful bridge to transplant was the ability to rehabilitate to ambulation (odds ratio, 7.579; 95% confidence interval, 2.158–26.615; $P = .002$).[60] As a result of ECMO support, 82 (68%) patients were able to achieve ambulation. Therefore any lung transplant candidate who requires so much support that it interferes with rehabilitation, such as prone positioning or paralysis, should be considered for ECMO as a bridge to transplant. Contraindications to ECMO as a bridge to transplant include severe second organ dysfunction, sepsis, and removal from transplant listing.

For patients with primary graft dysfunction (PGD) after transplantation, ECMO can be used to support patients until lung recovery.[61] Although survival is improved by ECMO, the long-term graft outcomes may be negatively affected, as patients with PGD who require ECMO have been found to have impaired maximum allograft function compared with those who do not require ECMO.[62]

ECMO Use in Refractory Hypercapnia

For patients with severe hypercapnia with obstructive lung disease, including asthma and chronic obstructive pulmonary disease (COPD), ECLS and a similar technique that is directed at mainly carbon dioxide removal ($ECCO_2R$) may be considered. Although ECLS and $ECCO_2R$ are applied to patients on conventional mechanical ventilation with hypercarbia, they may simultaneously offer advantages over unassisted mechanical ventilation by reducing ventilator-associated lung injury risk, including oxygen toxicity and hyperinflation. As membrane lungs are highly efficient at removing carbon dioxide, much less flow is needed to achieve decarboxylation than is required for oxygenation. This allows for use of smaller drainage cannulas, single dual-lumen cannulas, and even systems where the patient's own cardiac output provides flow without need for an ECMO pump in the system. During $ECCO_2R$, blood is removed from a venous drainage cannula and pumped via an ECMO pump or the patient's own cardiac output through a membrane lung where carbon dioxide is removed via diffusion and then returned to the body. Employing either $ECCO_2R$ or ECMO can rapidly reverse acidosis related to acute hypercapnia. If acidosis is detrimental to cardiac or neurologic performance, ECMO or $ECCO_2R$ can reduce risk of death. As many acutely hypercapnic states (such as severe asthma) are self-limited, providing support may require very short ECMO/$ECCO_2R$ runs. Use of these techniques has also been employed before intubation as a means of avoiding intubation and sedation.

A systematic review of 142 adult $ECCO_2R$ patients from six studies demonstrated a reduced need for endotracheal intubation but no improvement on outcomes, including duration of mechanical ventilation, intensive care unit (ICU) length of stay, and mortality.[63] Several trials are currently ongoing to further evaluate $ECCO_2R$ in adult respiratory failure, and new devices that require flow rates of <500 mL/min are also in clinical trials.

ECLS IN HEART FAILURE

The use of VA extracorporeal support for heart failure has increased, motivated by the ongoing improvements in technology and management. The reversibility of the etiology of heart failure is key to survival, unless the patient is under consideration for destination therapy, short-term ventricular assist device (VAD) placement, or transplant. Commonly held contraindications for VA-ECMO in heart failure include uncontrollable bleeding, irreversible neurologic or end-organ impairment, incurable malignancy, and end-stage cardiac disease when not a candidate for transplant or destination therapy of VAD. VA-ECMO can be considered for a variety of cardiogenic shock states, some of which are highlighted here. Table 40.6 demonstrates the most common adult cardiac indications for ECLS.

Postoperative Cardiogenic Shock

ECMO may be considered postoperatively as a temporary support for patients unable to wean from cardiopulmonary bypass. Whereas approximately 50% of postoperative cardiogenic shock patients can be weaned off of ECMO, survival to hospital discharge only approximates 30%. Predictors of adverse outcome associated with mortality include advanced age (>70 years old), prolonged ECMO support, renal failure, high EuroSCORE, diabetes mellitus, obesity, and lack of improvement of lactate while receiving ECMO assistance.[64] Duration of ECMO support compared with other ECMO indications is generally shorter, and if cardiac recovery has not occurred within 48–72 hours, some institutions recommended transition to more durable assist devices.[65] Early evaluation of residual repairable lesions should be undertaken by means of ECG or cardiac catheterization laboratory investigation.

Acute Myocardial Infarction

Although implementation of ECMO after acute myocardial infarction (AMI) is rare, its use has increased significantly over the last two decades.[66] VA-ECMO may benefit patients with AMI with refractory cardiogenic shock in order to prevent further end-organ injury and potentially facilitate percutaneous coronary intervention. Patients with severely depressed left ventricular function should also undergo continuous evaluation for need for venting or unloading of the left ventricle (LV). Many centers have developed "shock teams" to identify patients in a timely fashion who require device or interventional procedures, often using algorithms for the deployment of ECMO, stents, intraaortic balloon pump (IABP), Impella, and other aspects of care to aid in rapid decision making.[67,68]

TABLE 40.6 Adult, Neonatal, and Pediatric Cardiac Failure Indications From the ELSO International Registry

	N (%)
ADULT*	
Shock	2083 (61)
Cardiomyopathy	704 (21)
Myocarditis	227 (7)
Congenital defect	420 (12)
NEONATAL#	
Congenital heart disease	2301 (81)
Cardiac arrest	41 (1)
Cardiogenic shock	57 (2)
Cardiomyopathy	44 (2)
Myocarditis	38 (1)
Other	368 (13)
PEDIATRIC#	
Congenital heart disease	2010 (52)
Cardiac arrest	128 (3)
Cardiogenic shock	175 (5)
Cardiomyopathy	317 (8)
Myocarditis	204 (5)
Other	1016 (26)

*Adult patients include total patients reported to the ELSO registry from 1989 to 2016.
#Neonatal and pediatric include total patients reported to the ELSO registry from 2009 to 2015.
Adapted from the Pediatric ELSO Registry Report 2016 and Extracorporeal Life Support Organization Registry International Report 2016.

Acute Fulminant Myocarditis

Acute fulminant myocarditis (AFM) is characterized by a refractory and rapid onset of severe hemodynamic compromise and usually is secondary to a viral illness. Patients with AFM require aggressive pharmacologic therapy and often mechanical circulatory support until native cardiac function recovers. Although transplant or VAD may be required, myocarditis is one cardiac entity in which recovery with ECMO may occur even after several weeks. In a multiinstitutional review of 57 adult patients with AFM, 43 (75%) patients recovered function in 9 days (standard deviation [SD] ± 10.6) and 41 (72%) patients survived to discharge.[69]

LEFT VENTRICULAR UNLOADING

Because of the higher risk of bleeding and infectious complications with open surgical access, percutaneous cannulation is preferred for VA-ECMO. As mentioned previously, the most common cannulation method remains femoral access, which introduces retrograde flow to the aorta. The presence of retrograde flow introduces variable afterload that can potentially impair recovery of the LV. In the absence of LV recovery, rising left atrial pressures may result in pulmonary vascular congestion and pulmonary hemorrhage. Impaired oxygenation by the native lung may then result in ejection of hypoxemic blood into the aortic root and arch, resulting in coronary ischemia and cerebral ischemia, respectively. These events increase the risk of death. Although universal agreement on when to employ ventricular offloading does not exist, most centers use a pulse pressure of <10 mm Hg, development of pulmonary edema, and echocardiographic evaluation of aortic outflow as markers for intervention. Pulmonary artery catheter data, which are infrequently available these days, may be informative. Although low-dose inotropes or afterload reduction can sometimes be helpful, the impact of increasing calciotropic support on a failing ischemic heart may accentuate harm. An akinetic or hypokinetic heart in the presence of high afterload can produce inadequate ventricular contraction with a relatively immobile aortic valve. Thrombi mat, then form above the valve or within the LV, despite therapeutic anticoagulation. Upon recovery of cardiac function, this can place the patient at risk for coronary or cerebral infarction. Similarly, in patients with a mechanical mitral valve, the presence of low flow and pressure can potentiate clot formation. This vicious cycle places the heart at risk of impaired recovery, remodeling, and progressive heart failure.

Several observational studies have demonstrated decreased mortality with LV unloading in patients on VA-ECMO for cardiogenic shock.[70] LV unloading options currently consist of surgical techniques (surgical LV vent), transaortic LV unloading (cannula or peripheral VAD such as Impella), transseptal venting (atrial septostomy or percutaneous transseptal atrial vent), indirect LV unloading (via IABP), and use of positive inotropic agents. The decision for mode of LV unloading requires understanding of the myocardial physiology, valvular function, and potential for recovery. Because of the dynamic environment and potential implications on recovery, constant assessment and evaluation are required to determine the optimal method and timing of initiating LV unloading.

ECPR

Extracorporeal pulmonary resuscitation (ECPR) continues to be a rescue therapy for cardiac arrest refractory to conventional cardiopulmonary resuscitation (CPR). A review of over 1700 adult patients who had received ECPR from 2003 to 2014 in the ELSO registry found that the survival to hospital discharge had remained stagnant over the 12-year period at 27%–30%.[71] The use of ECPR during that same period significantly increased from 35 to over 400 cases per year. Although survival had not significantly improved, the same review found that ECLS-related complications, including acute renal failure, pulmonary hemorrhage, surgical site bleeding, and nosocomial infections, have decreased over time. Neurologic complications continue to be common, but in comparison with conventional CPR, ECPR has a higher favorable neurologic outcome.[72–74]

Most studies have found that a longer interval from CPR onset to establishment of ECLS is associated with poorer results, including unfavorable neurologic outcomes. Delay varies with location (out-of-hospital versus in-hospital arrest), age, adequacy of CPR, and etiology of arrest.[75–79] In a single-center review of 55 out-of-hospital-cardiac-arrest (OHCA) patients with coronary artery disease and an initial rhythm of ventricular fibrillation or ventricular tachycardia, a protocolized resuscitation strategy including mechanical CPR, initiation of ECLS upon arrival to hospital followed by coronary angiography, and percutaneous coronary intervention (if appropriate) demonstrated survival to discharge with good neurologic outcome in 36 (42%) patients, compared with 26 (15%) in a historical control group.[80] This review highlights both the importance of the initial rhythm on survival outcome and need for a dedicated multiprofessional team of first responders, ECLS, and interventional cardiologists. The CHEER study, a single-center prospective observational study of 26 OHCA and in-hospital-cardiac arrest (IHCA) adult patients, employed a

multipronged resuscitation protocol using a mechanical CPR device, therapeutic hypothermia, and two-physician percutaneous femoral vein and artery cannulation.[81] Time from cardiac arrest to ECMO initiation was notably quick, with a median time of 56 minutes for all patients and 40 minutes for survivors. Nonsurvivors had a longer time to ECMO initiation, with a median time of 70 minutes, highlighting the importance of decreasing time to ECMO initiation. Fifty-four percent of patients survived to hospital discharge, with all survivors having good neurologic outcomes. A recent study, ARREST, randomized 30 adults with OHCA and refractory ventricular fibrillation to standard ACLS treatment or ECMO. The phase II open-label, single-center trial found that 6 of the 14 patients (43%) treated with ECMO survived to discharge, compared with only 1 of 15 (7%) patients treated with standard ACLS.[82] However, whether ECPR should be employed for all OHCA patients is still controversial, given the significant barriers to out-of-hospital ECPR implementation that include cost and resource availability. A recent large registry study showed that ECPR did not improve mortality or outcome.[83] ECPR may be more successful in OHCA for patients with a shockable rhythm, who receive immediate bystander CPR, and have a CPR duration less than 60–90 minutes. Improving center outcomes for all ECPR patients should focus on appropriate patient selection and quality of CPR and team training (including simulation if able), with the primary goal of minimizing time to cannulation.[84,85]

NEW INDICATIONS

The emergence of the COVID-19 pandemic created a new indication for respiratory ECLS in the setting of overwhelmed ICUs and diminishing supply of protective personal equipment. As the knowledge of the respiratory virus continues to evolve, recommendations were created by ELSO to help guide decision making for provision and clinical management of COVID-19 ECLS patients. Data from the ELSO COVID dashboard currently show 3668 adult COVID-19 patients treated with ECMO from January to November 2020, with a mortality rate of 45% for patients with a final disposition of hospital discharge or death.

A disturbance in the coagulation pathway for COVID-19 patients has now been well described in the literature that is characterized by increased risk of arterial and venous thromboembolism. Consequently, higher levels of anticoagulation may be required.[86] However, some ECMO patients may have an increased risk of bleeding later in the ECMO course because of transition from a procoagulant state to an anticoagulant state secondary to a disseminated intravascular coagulation (DIC)–like picture, decreased platelet adhesion, and hyperfibrinolysis.[87] The increased rate of thrombosis but a concomitant increased potential for later bleeding adds to the general confusion regarding anticoagulation during ECMO. Use of viscoelastic testing in this population may be especially useful. One intriguing new finding from the international COVID Consortium noted that use of prone positioning during ECMO in COVID patients was associated with improved outcome. More study in this area is clearly required.

WEANING FROM ECMO

Weaning from ECLS depends on the mode. For VV mode, the extracorporeal gas flow should be reduced stepwise to zero and then gas flow clamped off from the membrane lung with close monitoring of the patient's arterial oxygenation and carbon dioxide levels. Initially, circuit flow is continued. The patient is generally monitored for several hours to a few days while monitoring hemodynamic parameters and signs of adequate tissue oxygenation such as lactate. Ventilator support may need to be increased while still keeping below injurious setting guidelines that address tidal volume, airway pressures, ventilation frequency rate, and fraction of inspired oxygen. Note that many patients with respiratory failure will have return of adequate oxygenation before the ability to maintain adequate ventilation. Monitoring of respiratory rate and work of breathing during the trial off ECMO are important aspects. In patients who remain intubated, use of end-tidal CO_2 monitoring may identify rapid increases in $PaCO_2$ during weaning or trial off support. Although reduction of blood flow is not mandatory during VV ECMO weaning as blood is leaving and entering the same side of the heart, most centers do reduce blood flow to 1–2 L/min before decannulation.

For VA patients, the ECMO blood flow is reduced either over a predetermined time frame set by the clinical team or fairly rapidly with echocardiographic guidance at the bedside. Often referred to as a "ramp trial," reduction of flow is lowered to 1 L/min or 40–50 cc/kg in pediatric patients and cardiac patients while performance is assessed via hemodynamics, gas exchange, and echocardiographic evaluation. Length of time spent at low flow should be carefully considered, because of the risk of thrombus formation. If the patient tolerates lower flow, assessed by stable hemodynamics with minimal need to increase vasoactive support and maintenance of stable oxygenation and ventilation, then consideration for decannulation may be appropriate. Especially in infants and children, even the low flow provided during this phase may be enough to maintain clinical stability; when all support is removed, however, some patients rapidly fail. Thus to adequately assess if the patient can tolerate the absence of ECMO support, clamping of both circuit cannulas is required. To prevent clotting from stasis in the cannulas, they should be opened and flushed every 10–15 minutes. Adult patients may not require total clamping of the circuit if they exhibit good performance at low flow. Alternatively, patients who are recovering but not yet able to independently maintain adequate unassisted hemodynamic support may be transitioned to other devices such as Impella until full recovery occurs.

PEDIATRIC ECMO

According to the most recent ELSO registry report from July 2020, the number of neonatal and pediatric patients in the registry who received ECLS is 72,178, with an overall survival rate to hospital discharge of 61%.[88] Historically, ECLS was used mainly as a rescue therapy for neonatal respiratory and cardiac failure. As the indications for ECLS have expanded in older groups, an increase in pediatric cases, especially cardiac, has simultaneously occurred. Improvements in perinatal and neonatal care have reduced the need for ECMO in the newborn.

The most common indication for neonatal respiratory ECLS is congenital diaphragmatic hernia, which also has the lowest associated rate of survival. Infectious lung disease, including bronchiolitis, pneumonia, and pertussis, is the most common etiology for pediatric respiratory failure[89] (see Table 40.5). VV cannulation use had increased substantially over the last decade. However, given current lack of appropriate VV cannulas for neonates, there has been a relative recent decline in VV-ECMO.

Table 40.6 lists the most common cardiac etiologies for neonates and pediatric patients. A recent review from the Pediatric Cardiac Critical Care Consortium (PC[4]) registry described the epidemiology and outcomes for pediatric ECLS cardiac patients.[90] That review of over 14,000 hospitalizations found that pediatric cardiac ECLS was used most often for systemic circulatory failure and cardiac arrest. Surgical patients were more likely to need ECMO postoperatively if they were younger, had been sicker preoperatively, had longer operative bypass time, or required more complex repairs. Surgical patients had a slightly lower in-hospital mortality rate of 49% compared with

63% for medical patients. Mortality rate for patients who received ECPR was 83% for medical patients and compared with a mortality rate of 50% for medical patients.

The most common complications for neonatal and pediatric ECLS stem from mechanical issues or bleeding and thrombotic events. Neurologic complications continue to contribute to significant morbidity and mortality, with 5%–11% of neonatal and pediatric patients suffering from an intracranial hemorrhage. Many recent reviews of neonatal and pediatric ECLS have highlighted the importance of long-term follow-up after hospital discharge with neurodevelopmental screening to assess for any neuropsychologic deficiencies that may impair learning, communication, and behavior.[91]

Similar to adult ECMO, scoring systems have been developed to predict mortality for pediatric ECLS patients. Several scores composed of different variables have been created for neonatal and pediatric respiratory patients. A score system by Barbaro and colleagues based on ELSO registry data divides patients into neonatal (neo-RESCUERS) and pediatric (ped-RESCUERS).[92,93] Maul and colleagues developed the neonatal respiratory score PIPER (Pittsburgh Index for Pre-ECMO Risk), as a tool to compare neonatal VA respiratory patients.[94] Lastly, the P-PREP score for patients aged 7 days to less than 18 years with respiratory failure by Bailly and colleagues was also derived from the ELSO registry and then externally validated.[95] These scores should not be used as selection tools to deny ECLS to individual patients or for management, but rather to help counsel families of the possible mortality risks and for research and quality improvement.[96] Further refinement and validation of these scores are needed. Detailed pediatric ECMO information is also provided within the references.

ETHICAL CONSIDERATIONS

As the number of centers that provide ECLS and the indications for ECLS continue to increase, there are several ethical considerations confronting its use. The final goal for any ECLS patient should be recovery or transplantation, for which ECLS serves as a temporizing bridge. For some patients, recovery or transplant prove not achievable, requiring withdrawal or limitation of ECLS support. Clear communication before initiation of ECLS regarding risk of complications, possible failure, overall goals of care, and limitations of ECLS can help mitigate some of the family distress in the event that withdrawal is deemed necessary by the caregivers. Palliative care teams can help with these difficult conversations, facilitating alignment of goals of the family and care team. In times of pandemic situations such as COVID-19, lack of available staff, equipment, and hospital beds and lack of in-person family discussions also raise new ethical concerns of how best to triage patients, provide ECMO care, establish appropriate informed consent when emergent discussions are held over the phone, and provide understanding of the patient's clinical course without family bedside presence. The ability to maintain ECMO over months with newer technology also raises issues of when to withdraw or limit care. All these challenges will require careful conversation and thought as the field moves forward.

FUTURE CONSIDERATIONS

Given the rapid extension of ECMO to many clinical settings previously excluded or unexplored, it is likely that the use of this modality will continue to rise. How, when, and where to offer it to well-qualified patients will remain key issues to resolve. How to assure access to such care is also problematic, especially in resource-poor environments or in regions with no nearby ECMO center. Guidelines for credentialing for ECMO centers and providers also need further discussion. Use of telemedicine or remote monitoring systems to augment patient management may assist in care. The continued evaluation of quality of life after ECMO, risk/benefit, and healthcare expenditures are also areas of mandatory research. With recent reports that ECMO techniques may improve outcome in cardiac arrest and can be effectively applied outside the hospital environment, the question of how this innovation will affect emergency care is another discussion likely to become a focal point in the near future. Only with well-intentioned collaboration among clinicians, researchers, and administrators will we improve ECMO outcomes at the center, regional, national, and international levels.

KEY POINTS

- There are two modes of ECMO: venovenous and venoarterial. Venovenous ECMO is used for isolated respiratory failure, whereas venoarterial ECMO provides both respiratory and cardiovascular support.
- Venovenous ECMO is used for diverse pediatric and adult indications, including severe ARDS, refractory hypercapnia, bridging to lung transplantation, and severe PGD after lung transplant.
- Venoarterial ECMO is used for certain cardiogenic shock states, including postoperative cardiogenic shock, AMI, and acute myocarditis. This methodology also serves as a bridge to deploying a VAD or heart transplantation.
- ECPR can be used for refractory cardiac arrest, but high rates of morbidity and mortality in this setting continue to require judicious patient selection.
- Anticoagulation is necessary during most ECMO runs to prevent patient and circuit clotting. Management of anticoagulation continues to be challenging, and more research is needed to define optimal laboratory testing and anticoagulation strategies.
- Complications occur commonly during ECMO and include infection, bleeding, clotting, and cerebrovascular events such as ischemic stroke and hemorrhage.

References for this chapter can be found at expertconsult.com.

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Brunetti MA, Gaynor JW, Retzloff LB, et al. Characteristics, risk factors, and outcomes of extracorporeal membrane oxygenation use in pediatric cardiac ICUs: a report from the Pediatric Cardiac Critical Care Consortium Registry. *Pediatr Crit Care Med.* 2018;19:544–552.
This review is the first multicenter study describing outcomes of pediatric cardiac patients requiring ECMO. Data were obtained from the Pediatric Cardiac Critical Care Consortium (PC⁴) registry. Of 449 ECMO runs, the mortality rate was 49% in the surgical group and 63% in the medical group. High-risk subgroups were identified among both medical and surgical cohorts to create or improve quality initiatives that affect patient outcome.

Combes A, Hajage D, Capellier G, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *N Engl J Med.* 2018;378:1965–1975.
The EOLIA trial followed the CESAR trial and attempted to determine if early initiation of ECMO for severe ARDS patients reduced 60-day mortality. No statistical difference in mortality was seen between the control group who received conventional mechanical ventilation and the ECMO group. The power calculation was based on a high expected mortality of 60%, which was a major critique of the study.

Lorusso R, Gelsomino S, Parise O, et al. Neurologic injury in adults supported with veno-venous extracorporeal membrane oxygenation for respiratory failure: findings from the Extracorporeal Life Support Organization Database. *Crit Care Med.* 2017;45:1389–1397.
This observational study of 4988 VV-ECMO adult patients describes the neurologic complications reported to ELSO from approximately 350 centers.

Neurologic complications occurred in 7% of the patients, with intracranial events being the most common (181 of the 426 complications, 42.5%). This review emphasizes that the mortality rate for patients with neurologic complications was high, with 76% of patients dying compared with 38% of patients who did not have neurologic complications.

Nasr VG, Raman L, Barbaro RP, et al. Highlights from the Extracorporeal Life Support Organization Registry: 2006-2017. *ASAIO J.* 2019;65: 537–544.

This report published on behalf the ELSO Registry Scientific Oversight Committee gives a brief summary of 16 articles that were picked by the committee to have a potential important impact on clinical ECMO practice. Included in this report are two reviews of adult and pediatric ECPR, outcome data of prolonged ECMO for adult respiratory failure, validation of pedRESCUERS, and a retrospective study highlighting bleeding and thrombosis associated with complications and affecting survival.

Oliver WC. Anticoagulation and coagulation management for ECMO. *Semin Cardiothorac Vasc Anesth.* 2009;13:154–175.

This review describes the normal coagulation process and how the extracorporeal circuit disturbs the hemostatic balance, leading to contact activation and consumption of procoagulant and anticoagulant components. The role of anticoagulation and a description of common laboratory tests used to manage anticoagulation are also discussed.

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41

Nutritional Support

Arthur R.H. van Zanten

Critically ill patients typically have anorexia and are frequently unable to take oral diets. Therefore micronutrients and macronutrients should be prescribed as enteral or parenteral nutrition.[1]

The catabolic response of critical illness is characterized by inflammatory and endocrine stress responses that may induce variations in resting energy expenditure (REE) and urinary nitrogen excretion.[2]

Nutritional intake may be insufficient and lead to accumulated energy and protein deficits. This can result in a reduction of the lean body mass (LBM) to an extent of 1 kg per day.[3] Low-admission LBM, severe skeletal muscle wasting, and intensive care unit (ICU)–acquired weakness are all associated with a prolonged need for mechanical ventilation and increased infectious morbidity and mortality rates.[4,5]

Anorexia is likely a temporary adaptive response, as animal and human studies have shown trophic effects of enteral nutrients on gut mucosa integrity and improved outcomes.[6]

Nutritional support for adult ICU patients aims at reducing energy and protein deficits without inducing overfeeding, providing sufficient micronutrient intake, and preserving gut integrity. Several large nutrition trials with high-quality data have led to some consensus. However, many controversies persist.[6,7]

NUTRITIONAL RISK ASSESSMENT

Most nutritional assessment instruments, such as the MNA, SGA, SNAQ, NRS-2002, and MUST scores, have not been developed for ICU patients and rarely have been specifically validated.[8]

The (modified) NUTrition Risk in the Critically ill (mNUTRIC score) has been made available.[9] A conceptual model links starvation, inflammation, nutritional status, and outcomes. Low scores (0–4) predict a low malnutrition risk, and high scores (5–9) identify patients with increased ventilation duration and mortality that are most likely to benefit from nutrition therapy (Table 41.1).

Patients with a higher body mass index (BMI; kg/m^2) demonstrate better ICU and hospital survival because of poorly understood mechanisms.[10] Low skeletal muscle area, as assessed by computed tomography (CT) scan, is a risk factor for mortality in ventilated patients independent of gender and APACHE-II score. Moreover, muscle mass was a primary predictor of mortality, whereas BMI was not.[11] Preserving LBM is a primary target of nutritional therapy.

REFEEDING SYNDROME

Refeeding syndrome refers to biochemical and clinical symptoms, in addition to metabolic abnormalities caused by shifts in electrolytes and fluid imbalance in malnourished patients undergoing refeeding by oral, enteral, and/or parenteral feeding.[12]

It is characterized by low concentrations of predominantly intracellular ions: phosphate, magnesium, and potassium, in addition to abnormalities in glucose metabolism, sodium levels, and water balance associated with morbidity and mortality.[13] Thiamine deficiency can also occur.[14]

The incidence of refeeding syndrome can be up to one-third of patients in longer-ventilated ICU patients when a nutrition-induced drop in plasma phosphate levels <0.65 mmol/L is used as the definition.[15] Plasma electrolytes—in particular phosphate—and glucose should be measured before feeding and any deficiencies corrected during feeding. Whenever marked hypophosphatemia occurs after the start of feeding, intake should be reduced to 500 kcal per day for 48 hours.[16,17]

ENTERAL NUTRITION

Tube feeding, or enteral nutrition (EN), is administered as a special liquid food mixture containing proteins, carbohydrates, fats, vitamins, and minerals through a tube into the stomach or small bowel.

Feeding Tubes

Nasogastric or nasoenteral tubes are placed into the stomach or bowel through the nose. To prevent sinusitis or nasal decubital ulceration, orogastric and oroenteral tubes are also used. A tube placed directly through the skin into the stomach or bowel is called a *gastrostomy* or *jejunostomy*.

Nasogastric tubes may be used depending on composition: polyvinyl chloride (PVC) tubes up to 10 days, polyurethane (PUR) up to 6–8 weeks, and silicone tubes for 6 weeks to 3 months.

Blenderized Tube Feeds

Low-cost blenderized tube feeds ("home brew") are used in some parts of the world. Macronutrient content is usually highly variable, often conflicting with daily recommendations.[18] Moreover, there is a high contamination risk, physical and chemical instability, and high osmolarity and viscosity, potentially enhancing intolerance.

Commercially Available Tube Feeds

Tube feeds are available as canned powder to dissolve, liquid-containing glass bottles, or self-collapsible packages. Closed feeding systems involve the use of sterile feeding containers that are spiked with feeding sets. Closed feeding systems use connectors that prevent a connection to intravenous lines and reduce the contamination risk, and the hanging time can be increased up to 24 hours. Higher contract price and increased waste of closed systems lead to higher daily costs. However, after adjusting for nursing time and feed contamination costs, the total costs are lower.[19]

TABLE 41.1 Modified* NUTRIC Score Variables

The NUTRIC score is designed to quantify the risk of critically ill patients developing adverse events that may be modified by aggressive nutrition therapy. The score of 1–9 is based on five variables that are explained here.

Variable	Range	Points
Age (years)	<50	0
	50 to <75	1
	>75	2
APACHE-II score (points)	<15	0
	15 to <20	1
	20 to 28	2
	>28	3
SOFA score (points)	<6	0
	6 to <10	1
	>10	2
Number of comorbidities	0 to 1	0
	>2	1
Days from hospital to ICU admission	0 to <1	0
	>1	1

*Interleukin-6 (IL-6) was part of the original scoring system (acute inflammation); however, it was often not routinely available, as it contributed very little to the overall prediction of the NUTRIC score. The modified score is depicted.

From Heyland DK, Dhaliwal R, Jiang X, et al. Identifying critically ill patients who benefit the most from nutrition therapy: The development and initial validation of a novel risk assessment tool. *Crit Care*. 2011;15(6):R268.

Compositions of Tube Feeding

Nutrient concentrations of formulas vary from 1.0 to 2.0 kcal/mL. Calorically dense formulas are used in patients requiring fluid restriction. Polymeric high-protein formulas have higher protein to nonprotein energy ratios and aid in achieving protein requirements in obese patients while preventing energy overfeeding. There is no evidence that hydrolyzed protein (peptide-based) formulas are superior with respect to tolerance, absorption, or outcome.[20]

Fibers

There are feeds with and without fibers. Sources of fiber in EN include soluble and insoluble fibers. Soluble fibers (e.g., pectin and guar) are fermented by colonic bacteria and enhance colonic sodium and water absorption to treat EN-associated diarrhea. Insoluble fibers (e.g., soy polysaccharide) increase fecal weight and peristalsis and decrease the fecal transit time.[21] Frequently, mixtures of fibers are used.

Disease-Specific Feeding Formulas

Renal formulas have lower protein concentrations and lower potassium and phosphate levels. Hepatic formulas have increased amounts of branched-chain amino acids (e.g., valine, leucine, and isoleucine) and reduced amounts of aromatic amino acids (e.g., phenylalanine, tyrosine, and tryptophan). Diabetic formulas have lower carbohydrate, higher fat content, and variable types of carbohydrates (e.g., oligosaccharides, fructose, cornstarch, and fiber). In pulmonary formulas, some carbohydrate calories are substituted with fat calories to limit carbon dioxide (CO_2) production and improve ventilation. Acute respiratory distress syndrome (ARDS) formulas combine antioxidants with borage and fish oils to supplement gamma-linoleic acid (GLA), and eicosapentaenoic acid (EPA).

In patients with chyle leakage, low-fat or medium-chain triglycerides (MCTs) or enriched feeds are recommended. MCTs do not require lymphatic transport.

Overall, for all disease-specific feeding formulas, strong evidence to improve outcome is lacking.[22]

Allergies

The majority of adverse reactions to foods are nonimmunologic in origin, with lactose intolerance being the most common. Documented food allergies in adults are likely lower than 8%–10%, and most enteral feeds are gluten-free. For specific allergies, soy-free, casein-free, whey-free, and egg-free feeds are available.

Contraindications to Enteral Nutrition

In general, EN is safe when contraindications are carefully reviewed (Table 41.2). They are related to obstruction, bowel perforation, and ischemia. Many critically ill patients are at risk of splanchnic hypoperfusion caused by circulatory redistribution. It is essential to provide adequate fluid therapy before commencing EN. There is no definition of hemodynamic stability associated with safe enteral feeding. Retrospective data show that early EN in patients on vasopressor treatment is safe and improves outcome.[23] However, aggressive feeding up to target in the phase of shock resuscitation induces bowel ischemia.[24] Patients should have stable blood pressures without the need to increase vasopressors, with acceptable central venous oxygen saturation ($ScVO_2$) and/or plasma lactate levels or other indicators of adequate blood flow. For most patients this will be within 12–24 hours after admission, still meeting the window of early EN (24–28 hours).

Timing of Initiation

By definition, early EN is initiated within the first 24–48 hours after hospital admission. Admission is considered to be the starting moment for ICU patients. Observational studies show that early EN is superior to late initiation (>48 hours) and is therefore recommended in the guidelines.[25] The practical inability to initiate early EN may reflect the severity of illness.

Trophic or Permissive Underfeeding Versus Full Enteral Nutrition

The optimal dose of nutritional support is heavily debated. Permissive underfeeding, trophic, trickle, and hypocaloric feeding are frequently used and confusing.

Permissive underfeeding suggests a lower nutritional intake (e.g., calories, proteins, and micronutrients) is acceptable. Hypocaloric feeding implies that only energy intake is lower. Trophic feeding has no clear definition, although it is accepted to represent an enteral intake of 10–20 mL/h or 500–1000 kcal/day.

Recent trials on trophic, permissive underfeeding and full nutritional support did not demonstrate benefits of either strategy, suggesting that trophic feeding or permissive underfeeding (PERMIT trial)could be sufficient; however, gastrointestinal tolerance was better in the trophic feeding arm in the EDEN trial.[26–28] Most studies included relatively young, well-nourished (high BMI) patients with low nutritional risk (NUTRIC score <5). In the only trial with a higher nutritional risk, trophic feeding was associated with more infections. Functional outcomes in all studies were not investigated, although long-term outcomes have been shown to be associated with feeding adequacy.[29]

Energy-Dense Versus Routine Enteral Nutrition

In 3957 patients undergoing mechanical ventilation, the rate of survival at 90 days associated with the use of an energy-dense formulation

TABLE 41.2 Recommendations to Start and Delay Early Enteral Nutrition

Recommendations	Rationale
Recommendation 1: Start early enteral nutrition in all critically ill patients within 48 hours, preferably within 24 hours when there is no reason to delay enteral nutrition (see the following recommendations).	Early enteral nutrition is associated with lower risk of infections and preserves the gut function, immunity, and absorptive capacity.
Recommendation 2: Delay early enteral nutrition in case of enteral obstruction.	Feeding proximal of an obstruction will lead to blow-out or perforation.
Recommendation 3: Delay early enteral nutrition in case of compromised splanchnic circulation such as uncontrolled shock, overt bowel ischemia, abdominal compartment syndrome, and during intraabdominal hypertension when feeding increases abdominal pressures.	Absorption of nutrients demands energy and oxygen. In states of low flow or ischemia, forcing feeding into the ischemic gut may aggravate ischemia and lead to necrosis or perforation.
Recommendation 4: Delay early enteral nutrition in case of high-output fistula that cannot be bypassed.	Enteral feeding will be spilled into the peritoneal space or increase the fistula production.
Recommendation 5: Delay early enteral nutrition in case of active gastrointestinal bleeding.	Enteral feeding will limit the visualization of the upper gastrointestinal tract during endoscopy.
Recommendation 6: Delay early enteral nutrition in case of high gastrointestinal residual volume (> 500 mL in 6 hours).	This threshold is associated with poor gastric emptying and may increase the risk of aspiration. Prokinetics and postpyloric feeding can circumvent this problem.

From Van Zanten ARH, De Waele E, Wischmeyer PE. Nutrition therapy and critical illness: Practical guidance for the ICU, post-ICU, and long-term convalescence phases. *Crit Care*. 2019;23(1):368.

(1.5 kcal/mL) for enteral delivery of nutrition was not higher than that with routine EN (1.0 kcal/mL). Higher calorie delivery did not affect survival time, receipt of organ support, number of days alive and out of the ICU and hospital or free of organ support, or the incidence of infective complications or adverse events.[30]

Stoppages

Interruptions in enteral feeding for various reasons are frequent, resulting in intakes less than the prescribed amounts. Administering target volumes over 20 hours to circumvent this problem or to increase the infusion rate after stoppages can be recommended.[31]

Gastric Residual Volume

The increased gastric residual volume (GRV) amount aspirated from the stomach after administration of feed represents feeding intolerance. Risk factors for delayed gastric emptying include gastroparesis, diabetes mellitus, gastric outlet obstruction, (postoperative) ileus, trauma, or sepsis, and medications affecting gastric motor function (e.g., opioids). Aspiration of gastric contents should be prevented, although the GRV thresholds are non–evidence based. Recommendations have gradually increased up to 500 mL in 6 hours and GRV can be reinfused or discarded. Discarded GRV reduces feeding efficacy.

Proton pump inhibitors reduce gastric secretions.[32] Prokinetic medications are used to improve gastric emptying, such as metoclopramide (e.g., 4 × 10 mg and erythromycin 2 × 200 mg) either alone or combined. They are safe when QTC intervals are monitored and used for up to 7 days, and tachyphylaxis is common.[33] Two trials demonstrated that the omission of GRV measurement does not increase the aspiration incidence. Moreover, allowing a large GRV increases the amount of feeding administered. To abandon the GRV measurement is debated, and if all strategies fail, a postpyloric feeding tube can be inserted as often as small intestinal functions are normal.[34]

Postpyloric Feeding

Immediate postpyloric feeding may facilitate the early increase of EN, although evidence of superiority is lacking. However, reduced aspiration risk has been clearly demonstrated.[35] Postpyloric tubes are placed by duodenal endoscopy or disposable tubes with fish-eye lenses, using electromagnetic tube placement or self-advancing nasal-jejunal devices. Selection of modality, timing, and success of positioning are related to patient factors, operator experience, and logistics. Criteria to monitor postpyloric feeding are provided (Box 41.1), as monitoring jejunal feeding is complex.

Complications of Enteral Nutrition

Most complications associated with EN are minor, but some can be serious. Complications can be categorized into problems encountered during the placement of tubes (e.g., tracheal/pulmonary misplacement and epistaxis) and during delivery: clinical and metabolic problems (e.g., refeeding syndrome, high GRV, vomiting, aspiration, diarrhea, azotemia, hypernatremia, and dehydration or hyperglycemia), and nutritional problems (e.g., tube obstruction and bacterial contamination).

Aspiration

There is no consistent relationship between GRVs and aspiration. Aspiration may occur with low GRV; it occurs significantly more often when the volumes are high.[36] Head-of-bed elevation can be recommended, although whether 45 degrees head-of-bed elevation is superior to 25 to 30 degrees elevation remains unproven.

Routine GRV monitoring in ventilated patients to prevent aspiration is debatable, as omitting measurements does not transfer into higher ventilator-associated pneumonia rates.[37]

Diarrhea

Critically ill patients may develop diarrhea for various reasons (Box 41.2). During the first 14 ICU days, at least 1 day of diarrhea was observed in 14% of patients. Delivering >60% of the energy target by EN, antibiotics, and antifungal drugs are risk factors.[38] Of the diarrhea episodes, 89% last 4 days or less. EN per se was not a risk factor, although anecdotal improvements have been reported when using fiber-enriched nutrition or hydrolyzed protein formulas.[39]

Constipation

The prevalence of lower gastrointestinal tract paralysis leads to an increased fecal transit time; >5 days is common, and in some series up to 90% is seen. Opioid administration is associated with delayed defecation. Prophylactic or therapeutic laxatives and/or fiber-enriched EN (prebiotics) is recommended. Both lactulose and polyethylene glycol are more effective in promoting defecation than the placebo. Early defecation is associated with a shorter length of stay.[40]

Box 41.1 Monitoring Postpyloric Feeding*

Monitor
GRV volume and aspect
Abdominal distention
Fecal transit time
Intraabdominal pressure (optional)

Criteria to Stop Postpyloric Feeding
Major feeding admixture in gastric aspirate suggesting backflow (NB: gastric aspirate without tube feed admixture is not a reason to stop irrespective of volume)
Major abdominal distention
Uncontrolled vomiting
Obstruction ileus
Intraabdominal pressure >20 cm H_2O
Severe diarrhea

GRV, Gastric residual volume.
*Before starting postpyloric feeding, check for general recommendations to delay enteral nutrition (see Table 41.2).

BOX 41.2 Common Causes of Diarrhea in Critically Ill Patients

Medication
Antibiotics
H_2-recepter antagonists, antacids
Drugs: significant amounts of sorbitol, magnesium, or hypertonic medications
Laxative use (unintended)

Gastrointestinal Dysfunction
Gastric or small bowel resection
Inflammatory bowel disease
Pancreatic insufficiency
Radiation enteritis
Sprue
Protein-losing gastroenteropathies
Bowel impaction (paradoxical)

Malnutrition
Hypoproteinemia
Micronutrient deficiencies

Enteral Nutrition–Associated
Excessive feeding rate, concentration, volume, or osmolality
Adaptation in malnourished patients or those whose gastrointestinal tract has not been used recently
Intolerance or allergy to feeding formula

Infection
Clostridium difficile enterocolitis
Opportunistic gastrointestinal infection
Significant amounts of contaminated feeding formula
Altered gastrointestinal flora

Endocrine Dysfunction
Diabetes mellitus
Hyperthyroidism
Hypocortisolism

Protocols

Evidence-based nutrition protocols designed to improve enteral feeding have been shown to improve feeding adequacy and outcome.[41,42] Developing a protocol is recommended (Fig. 41.1).

PARENTERAL NUTRITION

Total parenteral nutrition (TPN) supplies all daily nutritional requirements by the parenteral route (via a central venous catheter or venous peripherally inserted central catheter [PICC] line). Partial or supplemental parenteral nutrition (SPN) aims to close the gap in the intake when EN does not reach the targets.

Composition

The optimal PN composition depends on the clinical situation, energy, and protein needs, in addition to electrolyte abnormalities and the risk of fluid overload.

The liquid food mixture of standard PN comprises amino acids (apart from glutamine for reasons of stability), carbohydrates (e.g., dextrose/glucose), and lipid emulsions (e.g., soybean oil–, olive oil–, or fish oil–based) and is infused from multichamber or single-chamber sterile infusion bags.[43] Trace elements are added to meet daily recommended allowances. In the absence of EN, vitamin K supplementation, among other vitamins, is important. In the case of hepatic complications (hyperbilirubinemia) interruption of lipid emulsion is recommended, and the optimal lipid emulsion still is debated. The omega-3 fatty acids in fish oil have antiinflammatory effects, omega-9 fatty acids in olive oil have neutral immune effects, and omega-6 fatty acids in soybean oil are proinflammatory. Soybean-based emulsions should be avoided.[6]

Timing of SPN Initiation

Nutrition guidelines present divergent advice regarding the timing of SPN, ranging from early SPN (<48 hours after admission) to postponing SPN until day 8 after ICU admission. Others have studied starting SPN after 3 days (timely; Fig. 41.2).

One randomized controlled trial (RCT) found a higher percentage of living ICU discharge at day 8 in the late SPN group, but there were no differences in ICU and in-hospital mortality. No other RCT found differences in ICU or in-hospital mortality rates. Contradicting results were found for ICU and hospital length of stay, infection rates, nutrition targets, duration of ventilation, glucose control, duration of renal replacement therapy, muscle wasting, and fat loss.

It is reasonable to assume that there are no clinically relevant benefits of early SPN. Considering infectious morbidity and potential slower organ failure resolution and higher acquisition costs, the early administration of SPN cannot be recommended.[44]

In severely malnourished patients, early SPN should be considered, and initiation can be delayed for 5–8 days in others.[25,45]

Complications

Several complications are related to PN use (Box 41.3), and most can be prevented by catheter sepsis prevention and the close monitoring of glucose and electrolytes, fluid status, triglycerides, and liver and renal laboratory tests.[46]

Parenteral Nutrition Versus Enteral Nutrition

EN was considered to be superior to PN. The CALORIES trial that compared 2400 patients randomized into EN or PN changed this assumption.[47] No differences in infections and mortality were found, and less vomiting and hypoglycemia were observed during PN. No differences in caloric intake were found to be the result of the

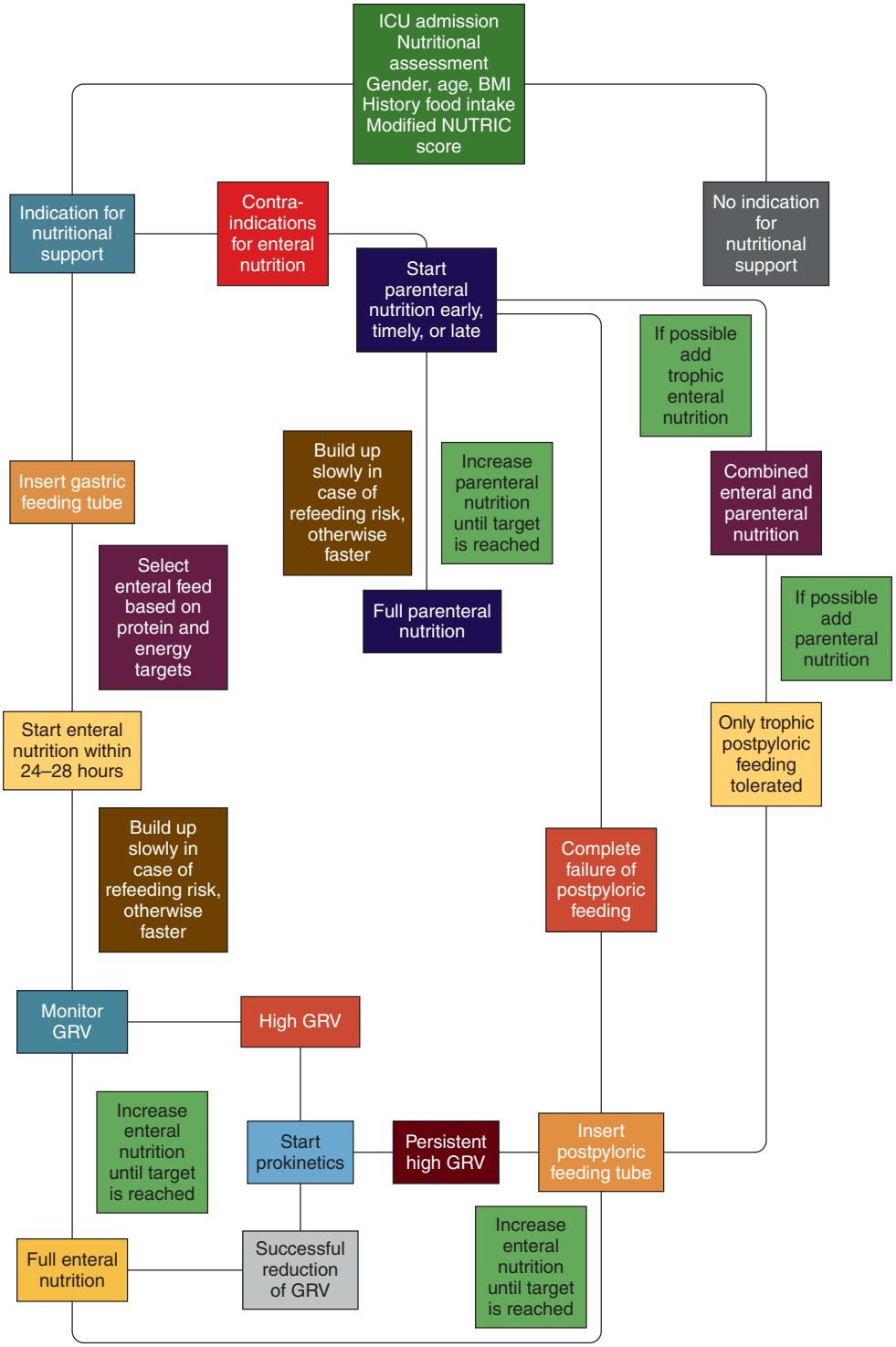


Fig. 41.1 Nutritional support flow chart. *BMI*, Body mass index; *GRV*, gastric residual volume; *ICU*, intensive care unit.

buildup of parenteral intake. Possibly because of better glucose control, preventing overfeeding, and better central catheter care, complications were similar to EN. EN remains a first-line therapy, but in cases where targets cannot be reached, it is safe to commence PN.

CALORIC REQUIREMENTS

Energy requirements in critical illness are unknown. Underfeeding (<80% of energy target) and cumulative energy deficit and overfeeding (>110% of target) are associated with increased morbidity (e.g., infections) and mortality. An optimum energy intake is estimated at 70%–85% of the REE target.[25,48] This lower optimum may result from endogenous energy production that cannot be abolished by providing energy.

Formulas to Estimate Energy Expenditure

Energy requirements are estimated based on patient characteristics before admission. However, requirements differ for each patient and day and should be preferably adjusted according to indirect calorimetry,

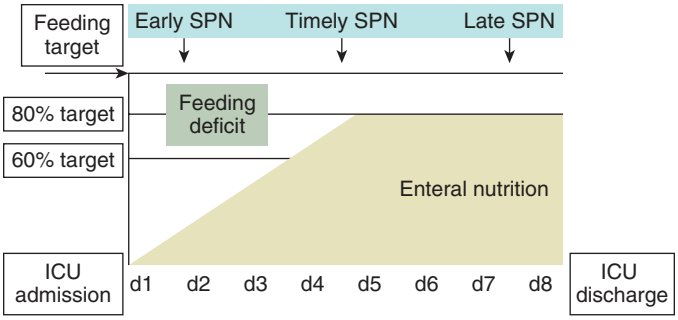


Fig. 41.2 Timing of supplemental parenteral nutrition (*SPN*) to prevent feeding deficit in the intensive care unit (*ICU*).

BOX 41.3 Complications of Parenteral Nutrition

Catheter-Related
Bleeding
Pneumothorax
Central line–associated bloodstream infection
Obstruction
Thrombosis, embolism

Metabolic
Refeeding syndrome
Overfeeding
Glucose abnormalities (hyperglycemia or hypoglycemia)
Hyperlipidemia (hypertriglyceridemia)
Liver dysfunction (increased transaminases, bilirubin, and alkaline phosphatase)
Hepatomegaly
Hyperammonemia
Abnormalities of serum electrolytes and minerals
Vitamin and mineral deficiencies
Elevated BUN

Circulatory
Volume overload

Adverse Reactions
Dyspnea
Cutaneous allergic reactions
Nausea
Headache
Back pain
Sweating
Dizziness

Gallbladder-Associated
Cholelithiasis
Gallbladder sludge
Cholecystitis (acalculous)

BUN, Blood urea nitrogen.

although not widely available and often technically difficult or impossible to apply. Data from 160 variations of 13 predictive equations compared with indirect calorimetry measurements demonstrated 38% underestimated and 12% overestimated energy expenditure (>10%). Differences from −43% to 66% above indirect calorimetry values in individual patients were observed.[49]

Guideline Recommendations for Daily Energy Intake

International societies have recommended intakes ranging from 20 to 25 kcal/kg per day in the acute phase and from 25 to 30 kcal/kg in the recovery phase. Additionally, it was suggested to prescribe hypocaloric feeding in critically ill obese (BMI >30 kg/m^2) patients, 60%–70% of the target energy requirements, or 11–14 kcal/kg of the actual body weight or 22–25 kcal/kg of the ideal body weight.[1,25,50]

Indirect Calorimetry

Using a metabolic cart, REE can be measured with indirect calorimetry by measuring oxygen consumption (VO_2) and carbon dioxide production (VCO_2). Every liter of oxygen consumed is equivalent to 5 kcal. Weir introduced an equation to calculate REE:

$$\text{REE} = [\text{VO}_2\ (3.941) + \text{VCO}_2\ (1.11)]\,1440\ \text{min/day}$$

REE provides better energy targets than formulas, and the respiratory quotient (RQ) (CO_2 production/O_2 consumption) is indicative of substrate use. RQ is 1.0 when the fuel is a carbohydrate, 0.8 for protein, and 0.7 for fat; normal RQ is 0.80–0.85. RQ >1.0 may indicate overfeeding. Inaccuracies can arise from air leaks (e.g., circuit or pneumothorax). As O_2 sensors are inaccurate at the higher fraction of inspired oxygen (FiO_2) levels (>0.6–0.7), application in pulmonary failure is limited. Additionally, high positive end-expiratory pressure (PEEP) levels of circuit compressibility cause volume changes and measurement errors.

The evidence that strategies of energy provision based on indirect calorimetry results in improved outcomes is limited.[50] However, the application of indirect calorimetry is now recommended.[25]

Nonnutritional Calories

Typically, nutritional calories are evaluated; however, some calories may go unnoticed. Glucose- and dextrose-containing infusions and drugs, propofol (lipid-based), and trisodium citrate used for extracorporeal circuit anticoagulation during renal replacement therapy provide nonnutritional caloric intake, potentially inducing overfeeding.[51]

PROTEIN REQUIREMENTS

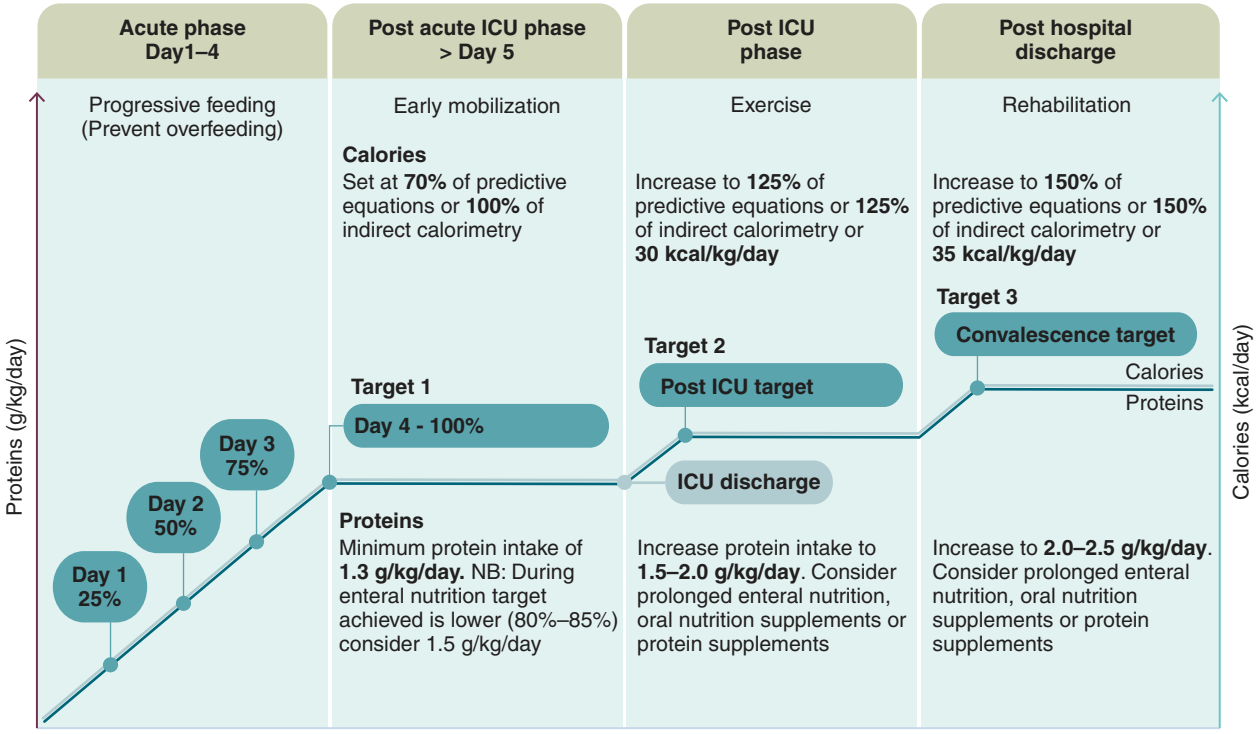
Critical illness causes increased protein turnover and the loss of LBM. There is growing evidence demonstrating the importance of protein and amino acid provisions, and it is likely that nutritional proteins have an impact on the preservation of muscle mass, resulting in better patient outcomes.[48]

Guideline Recommendations for Daily Protein Intake

Several nutritional societies provide slightly different recommendations; however, they can be summarized as to provide at least 1.3 g/kg per day or 1.2–2.0 g protein/kg if the BMI is <30 kg/m^2, 2.0 g/kg ideal body weight if the BMI is 30–40 kg/m^2, and 2.5 g/kg ideal body weight if the BMI is >40 kg/m^2.[1,21,25] Recent studies have suggested that early (day 1–3) very high protein administration may confer harm.[52,53] Therefore gradual progression to protein targets is recommended over 3–4 days.[25,54]

RECOMMENDATIONS FOR CALORIES AND PROTEINS DURING DISEASE AND RECOVERY PHASES

In the early phase, gradual progression of calories and proteins to target is recommended while monitoring phosphate for refeeding hypophosphatemia.[54] During the further patient journey, more calories and



Recommendations			
	Adjust caloric intake for nonnutritional calories from glucose, propofol, and citrate	Patients are at risk for reductions in caloric intake after cessation of enteral nutrition	Patients are at risk for prolonged reduced caloric intake; consider the use of oral nutrition supplements
	When feeding is reduced to prevent overfeeding due to nonnutritional calories, use very-high protein feeds or protein supplements	Patients are at risk for reductions in protein intake after cessation of enteral nutrition and feeding tube removal	Patients are at risk for prolonged reduced protein intake; consider the use of oral nutrition supplements
Monitoring			
Monitor phosphate. Stay at 25% of caloric for 48 h when phosphate drops	Indirect calorimetry (every 48 h) and adjust target accordingly	Monitor oral intake; do not remove feeding tube early	Monitor oral intake and oral nutrition supplement intake
Prevent very early high protein intake	Consider to monitor nitrogen balance	Consider use of muscle ultrasound, BIA, DEXA or CT for body composition	Consider functional muscle tests and follow-up of body composition

Fig. 41.3 Practical Approach to Provide Proteins and Calories During the Phases of Critical Illness and Convalescence. During the first 3 days, calories and proteins are gradually progressed to target 1 on day 4 in steps of 25% daily increase. Target 1 is 1.3 g/kg/day for proteins and for calories, 70% of calculated targets, or 100% of the target when measured by indirect calorimetry. Target 2 should be met during chronic critical illness and after intensive care unit (*ICU*) discharge on general wards. For target 2, calories are increased to 125% of predictive equations or indirect calorimetry, or 30 kcal/kg/day, and for proteins 1.5–2.0 g/kg/day should be targeted. After hospital discharge, target 3 recommends a higher caloric target (150% of predictive equations or 35 kcal/kg/day) and a higher protein intake of 2.0–2.5 g/kg/day. *BIA,* Bioelectrical impedance analysis; *CT,* computed tomography; *DEXA,* dual-energy x-ray absorptiometry; *g/kg/day,* grams of proteins per kilogram per day; *kcal/day,* total kilocalories per day. (From Van Zanten ARH, De Waele E, Wischmeyer PE. Nutrition therapy and critical illness: Practical guidance for the ICU, post-ICU, and long-term convalescence phases. *Crit Care.* 2019;23[1]:368.)

proteins should be prescribed (Fig. 41.3). Even after ICU and hospital discharge, increased levels of calories and proteins are necessary to recover, probably for prolonged periods.[54]

SPECIFIC MACRONUTRIENTS

Enriched or supplemented (par)enteral nutrition with supposed immune-modulating macronutrients (e.g., glutamine, arginine, and fish oil) have frequently been studied.[37] Pharmaconutrition suggests that specific nutritional components may exert pharmacologic effects to modulate the immune response.

Contrasting earlier international recommendations, the MetaPlus trial demonstrated no effect of a cocktail of macronutrients (e.g., glutamine and fish oil) and micronutrients (e.g., selenium, vitamins C and E, and zinc) on the primary endpoint of infections.[53] Moreover, increased long-term mortality among medical patients was observed.

In the REDOXS trial, no clinical benefit of glutamine and antioxidants was found and a trend toward increased mortality at 28 days, in addition to significant increases in in-hospital and 6-month mortality in glutamine-supplemented patients, were found.[55]

Since then, the safety of immune-modulating ingredients has been questioned. Benefits are limited or absent, and potential harm is involved. Use of unbalanced compositions is not recommended.[56]

Glutamine

Glutamine is the most abundant plasma amino acid. In critical illness, plasma levels can be low. However, this is not always the case. Nonessential amino acids can be synthesized from other amino acids. Low levels in ICU patients are considered to be conditionally deficient, too low for the actual condition or disease state. As low-admission plasma glutamine was associated with increased mortality, supplementation was considered.

Positive effects are based on results from older, smaller, and mainly single-center studies. Recent studies have challenged the conditional deficiency hypothesis, both in mechanistic studies and in recent randomized trials (MetaPlus and REDOXS). Low levels could potentially reflect an adaptive response. Glutamine supplementation may only be considered while monitoring plasma levels and should be avoided, as serious safety issues are involved.[57]

Arginine

Another amino acid considered to be conditionally deficient is arginine. Data from 30 trials in 3000 patients after major surgery exhibited reduced infectious morbidity of arginine supplementation and a reduced length of stay. Before surgery, 5–7 days of arginine (12–15 g/day) may be beneficial. However, harm was observed in severe sepsis patients. Excessive nitric oxide production increasing mortality risk was the suggested mechanism. For sepsis patients, arginine-supplemented EN should be avoided.[39]

Fish Oil

There is a lack of studies showing associations of low baseline EPA and docosahexaenoic acid (DHA) levels and outcome. Smaller studies combined borage and fish oils (GLA/EPA) with antioxidants in ARDS, suggesting a benefit.[22] The large OMEGA-EN trial (e.g., omega-3 fatty acids, EPA, DHA, GLA, and antioxidants) in ARDS patients was prematurely terminated for not reducing ventilator-free days and a higher 60-day in-hospital mortality trend ($P = .054$).[58] At present, based on a meta-analysis, the effect of fish oil seems limited or absent.[59]

SPECIFIC MICRONUTRIENTS

The exact recommended daily allowances (RDAs) for antioxidants, trace elements, and vitamins in ICU patients are not known. Many patients have low admission plasma levels. During the ICU stay, this may worsen, as RDAs are only available in 1500 mL (or 1500 kcal) of EN, and many patients have lower intakes. In PN, trace elements and vitamins must be added. However, whether supraphysiologic dosages should be prescribed is inconclusive.

Antioxidants and Trace Elements

A meta-analysis of 21 RCTs on combined antioxidant supplementation showed significant reductions in mortality, ventilation duration, and a trend toward reduction in infections with no effect on ICU or hospital length of stay. Most of the included RCTs were small studies (<100 patients), which were inadequate to detect important effects on mortality. The positive signal emerges only after statistically aggregating these smaller trials.[60]

Vitamins

Few data are available via vitamin supplementation in ICU patients; however, whether low plasma levels reflect deficiency is not known. Hyperlactatemia may reflect thiamine deficiency, and supplementation is recommended.[57] Supplementation may also be indicated in case of history of alcohol abuse, severe malnutrition, or refeeding hypophosphatemia.

Although initial studies on high-dose supplementation with vitamins C, D, and B_1 (and steroids) were promising, recent RCTs were unable to show benefits concerning relevant clinical endpoints.[61–65]

There is a lack of dose-finding studies for most vitamins in critically ill patients. Moreover, we do not know whether normalizing plasma levels translates into a better outcome.[57]

PREBIOTICS AND PROBIOTICS

The World Health Organization has defined probiotics as "live microorganisms, which confer a health benefit on the host."[66] Prebiotics (fibers) are food for probiotics that are nondigestible by humans. Prebiotics stimulate the growth of beneficial bacteria. Symbiotic supplements contain both probiotics and prebiotics.

Critical illness leads to alterations of the gut microbiota, leading to a loss of commensal flora and the overgrowth of potentially pathogenic bacteria. Probiotics restore the microbiota bacterial balance and improve the immune function, in addition to the gastrointestinal structure and function.[67]

Bacterial translocation of probiotics has been reported anecdotally. Since the PROPATRIA trial,[68] which showed increased mortality among probiotic-treated pancreatitis patients because of gut ischemia, safety concerns have been expressed.

A meta-analysis of 13 RCTs did not demonstrate a reduction in the ventilation duration or lower ICU or hospital mortality rates. However, a reduced incidence of ICU-acquired pneumonia and ICU length of stay was found.[69] In a recent Cochrane analysis, the effect on pneumonia was questioned because of the low-quality studies that were included.[70] Identification of which ICU patients could benefit from probiotics is unclear.

SPECIAL PEDIATRIC CONSIDERATIONS

This chapter has been written from the perspective of the adult ICU patient. However, with respect to many aspects, considerations for children are similar. Clinical nutritional support in children must minimize tissue loss, optimize tissue repair, and minimize metabolic overloading. Patients in the pediatric intensive care unit (PICU) should undergo detailed nutrition assessment within 48 hours of admission. Furthermore, as patients are at risk of nutrition deterioration during hospitalization, which can adversely affect clinical outcomes, it has been suggested that the nutrition status of patients be reevaluated at least weekly throughout hospitalization.[71,72]

Pushing nutritional intake beyond recommended levels may create additional metabolic stress. Also for children, indirect calorimetry is recommended to target the energy settings, as predictive equations have been shown to be unreliable. Overall, the pediatric critical care population is heterogeneous, and a nuanced approach to individualizing nutrition support with the aim of improving clinical outcomes is necessary. On the basis of evidence from RCTs and as supported by observational cohort studies, a minimum protein intake of 1.5 g/kg per day is recommended.[71,72]

EN support is generally considered the preferred route for nutrition; however, parenteral nutrition may be necessary to meet the needs of some critically ill children. Based on large cohort studies, early initiation

of EN (within 24–48 hours of PICU admission) and achievement of up to two-thirds of the nutrient goal in the first week of critical illness have been associated with improved clinical outcomes.[71,72]

In the recent PEPANIC trial it was clearly demonstrated that early SPN may induce harm in children. Early parenteral nutrition should be avoided in the early phase (first week) of critical illness unless the enteral route cannot be used.[73] The complexity of pediatric disease and the wide range of ages and body conditions, in addition to the multiple options for nutrient delivery, necessitate close collaboration between physicians and pediatric dietitians who are familiar with children's nutrition requirements during critical illness. In children, immunonutrition is not recommended.

KEY POINTS

- ICU admission LBM and cumulative protein and energy deficit are associated with outcome.
- Refeeding syndrome, as identified by hypophosphatemia occurring after resuming nutrition, should lead to caloric restriction for 2 days and gradual introduction of calories, while supplementing electrolytes and thiamine.
- Enteral feeding is preferred over parenteral nutrition and should be initiated early (24–48 hours after ICU admission) to preserve gut condition.
- Absolute contraindications for EN are intestinal obstruction, perforation, and ischemia.
- Hemodynamic instability is only a temporary contraindication for enteral feeding; feeding can commence when stable vasopressor infusion is achieved.
- In well-nourished patients, trophic feeding or permissive underfeeding is associated with similar outcomes as full nutritional support.
- Higher calorie delivery by energy-dense feeding is associated with similar outcomes as routine enteral feeding.
- Measuring GRV reduces feeding efficiency; therefore it should be abandoned, or high GRV up to 500 mL in 6 hours should be accepted.
- Critical care nutrition protocols improve feeding adequacy.
- Gastrointestinal symptoms such as diarrhea are common during an ICU stay; however, they are frequently the result of causes other than enteral feeding.
- There are no clear benefits of SPN within 5 days of ICU admission.
- Formulae to estimate energy expenditure are inaccurate; therefore indirect calorimetry is recommended.
- Caloric overfeeding should be prevented; therefore nonnutritional calories from propofol, dextrose, and citrate infusion should be considered as an energy source.
- Protein intake should be at least 1.3 g/kg per day (1.5 g/kg per day in children), with higher recommendations in patients with greater BMI and protein loss resulting from renal replacement therapy. Gradual progression to target over several days is recommended.
- Based on contradictory results from clinical trials, pharmaconutrition with glutamine, arginine, and fish oil cannot be recommended.
- RDAs for vitamins and trace elements in critical illness are unknown; however, supplementation should be considered in patients on parenteral nutrition or EN intake below 1500 kcal/day.
- High-dose supplementation of vitamins B_1, C, and D has not improved outcomes of critical illness.
- Although prebiotics and probiotics seem to be safe in most ICU patients, proven benefits in targeting gut microbiota with these strategies are lacking.

References for this chapter can be found at expertconsult.com.

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Van Zanten ARH, De Waele E, Wischmeyer PE. Nutrition therapy and critical illness: practical guidance for the ICU, post-ICU, and long-term convalescence phases. *Crit Care*. 2019;23(1):368.
Practical and extensive overview of guideline recommendations translated into daily recommendations to feed critically ill patients during the ICU treatment phase, after discharge from the ICU in general wards, and even after hospital discharge based on the assumption that long-term outcomes are dependent on optimal nutrition therapy throughout all these phases.

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Advanced Bedside Neuromonitoring

Jovany Cruz Navarro, Samantha Fernandez Hernandez, and Claudia S. Robertson

INTRODUCTION

Little can be done to reverse the primary brain damage caused by an insult; however, one of the major factors influencing outcome in patients with acute brain injury is the additional brain damage that occurs from secondary brain injury processes.[1] These secondary insult processes entail a combination of inflammatory, biochemical, and excitotoxic changes,[1,2] making it challenging for the clinician to detect which processes are most important to monitor in order to obtain the most favorable outcome.[3] In addition, secondary ischemic insults of extracerebral origin (e.g., arterial hypotension, hypoxemia) can be prevented or treated before they become severe enough.[4] The main purpose of advanced monitoring of the brain in the intensive care unit (ICU) is to detect these secondary insults, allowing for a more informed, individualized approach to treatment.[3–5]

MONITORING NEUROLOGIC STATUS

The clinical approach to a patient with a neurologic problem requires the physician to have a specialized anatomic and physiologic knowledge of the nervous system. Daily evaluation of neurologic and mental status should be included in the neuromonitoring protocol. Neuromonitoring should include the Glasgow Coma Scale (GCS) score, function of pyramidal and extrapyramidal systems, status of cranial nerves, function of the cerebellum and spinal cord whenever possible, and any changing trend in the neurologic status. In critically ill patients, such a complete neurologic evaluation can sometimes be unreliable or impossible because of the use of sedatives and the need for intubation and ventilatory support as part of the medical treatment of the neurologic problem. However, in the nonsedated patient, the Full Outline of UnResponsiveness (FOUR) score, which measures ocular and limb responses to commands and pain, pupillary responses, and respiratory pattern,[6] may provide a more complete assessment of brainstem function. The FOUR score has been shown to perform equally well as the GCS in critically ill patients after brain injury,[7] possessing a similarly predictive power of outcome and the capability of being assessed in intubated patients.[8,9] Current evidence suggests that both the GCS and FOUR score provide useful and reproducible measures of neurologic state and can be routinely used to chart trends in clinical evaluation.

Pupillary evaluation is a strong predictor of outcome that must be integrated into the daily GCS evaluation. However, poor interrater reliability exists among practitioners when it comes to pupillary assessment. Devices like the handheld pupillometer provide objective measurement of pupillary response and diameter, but more clinical experience is needed to determine if they should be included as a standard of care.[10]

Along with neurologic examination, information about vital signs and key laboratory values should be immediately available in a 24-hour record sheet or electronic medical record. Assessment of pain and sedation can be challenging in the context of brain injury. Evidence recommends the use of validated and reliable scales such as the Sedation-Agitation Scale (SAS) and Richmond Agitation-Sedation Scale (RASS),[11] as these provide workable solutions in some patients.

"Wake-up tests" in patients with intracranial hypertension pose significant risks[12] and show no proven benefits in terms of duration of mechanical ventilation, length of intensive care unit (ICU) and hospital stay, or mortality rate in patients with neurologic disorders.

The Glasgow Outcome Scale (GOS) has been the standard outcome tool for neurocritical care. However, other tools, such as the Neurological Outcome Scale for TBI (NOS-TBI), have been adapted for traumatic brain injury (TBI) patients from the National Institutes of Health Stroke Scale (NIHSS).[13] This scale has demonstrated adequate predictive validity and sensitivity to change compared with gold-standard outcome measures and may enhance the prediction of outcome in clinical practice and research.[14]

INTRACRANIAL PRESSURE AND CEREBRAL PERFUSION PRESSURE

The threshold that defines normal or raised intracranial pressure (ICP) is uncertain, but normal resting ICP in an adult is considered to be less than 15 mm Hg, and a sustained ICP >20 mm Hg is considered pathologic.[3,15] In the 2016 Guidelines for the Management of Severe TBI, an ICP threshold >22 mm Hg was adopted as a level IIb recommendation to initiate treatment to reduce ICP in order to reduce mortality.[16] The necessity of ICP monitoring was questioned by the BEST-TRIP trial[17]: the researchers found no significant difference in outcome when management of patients with severe TBI was guided by either (1) ICP monitoring or (2) neurologic examination and imaging. However, the results of this trial are research oriented and highlight the necessity for further studies and may not be generalizable to other populations. First, the study was conducted on two developing countries where prehospital resuscitation might be less developed, resulting in higher episodes of secondary insults such as hypotension and hypoxia, and severely injured patients may not survive long enough to reach the hospital. Thus the study population may have had less severe brain injury than comparable ICUs in developed countries. Finally, 6-month survival was confounded by increased mortality after ICU discharge, possibly related to limited resources to receive rehabilitation and prolonged medical care.[18] In the most current Brain Trauma Foundation Guidelines (BTFG) for severe

TBI, monitoring of ICP is recommended in the management of severe TBI patients to reduce in-hospital and 2-week postinjury mortality, and the previous 2007 BTFG recommendations are no longer valid because of lack of supporting evidence.[16] Moreover, the Milan consensus does not recommend ICP monitoring in a comatose patient in the setting of normal imaging.[19] Treatment of ICP is important, and in circumstances where adequate resources are available, such treatment is advised.

Cerebral perfusion pressure (CPP) is the difference between the mean arterial blood pressure (MAP) and ICP. Under normal physiologic conditions, a MAP of 80–100 mm Hg and an ICP of 5–10 mm Hg generate a CPP of 70–85 mm Hg.[20] Cerebral blood flow (CBF) is determined by both CPP and cerebrovascular resistance (CVR) according to the formula CBF = CPP / CVR.

Under normal circumstances, the brain is able to maintain a relatively constant CBF of approximately 50 mL per 100 g/min over a wide range of CPP (60–150 mm Hg).[21] After injury, the ability of the brain to pressure autoregulate can be impaired, and CBF is often dependent on CPP.

The recommendations for an adequate CPP have changed over time and may in part be associated with the variability in how MAP is measured[22] and the autoregulatory function status. The 2007 BTFGs recommend targeting CPP values within the range of 60–70 mm Hg.[16] CPP values <60 mm Hg increase the risk of cerebral ischemia and hypoperfusion, whereas therapies required to maintain CPP >70 mm Hg such as intravenous fluids administration have been associated with an increased risk of acute respiratory failure.[16]

INTRACRANIAL PRESSURE MONITORING DEVICES

The current gold standard for ICP monitoring is the ventriculostomy catheter, or external ventricular drain (EVD), which is a catheter inserted in a lateral ventricle, usually via a small right frontal burr hole. This ventricular catheter is connected to a standard pressure transducer that must be maintained at a specific level. The reference point for ICP is the foramen of Monro, although in practical terms, the external auditory meatus is often used as a landmark.[23] Advantages of EVDs include the ability to measure global ICP and to perform periodic in vivo external calibration and therapeutic cerebrospinal fluid (CSF) drainage and sampling. However, intraventricular catheters are also associated with the highest rate of infection among the ICP monitors.[1] Several microtransducer-tipped ICP monitors are available for clinical use (e.g., Camino ICP monitor, Codman microsensor, Hummingbird ICP, and Neurovent-P ICP monitor). These catheter-based transducers can measure pressure directly in the brain parenchyma. Although there are fewer risks of infection and intracranial hemorrhage with these catheters,[1] the main disadvantage of these probes is that they cannot be calibrated in vivo. Also, after preinsertion calibration, they may exhibit zero drift (degree of difference relative to zero atmospheres) over time.[24]

Noninvasive ICP monitoring devices have been developed to reduce the risk associated with invasive monitors. Such technologies include displacement of the tympanic membrane,[25] optical detection of cerebral edema,[26] transcranial Doppler pulsatility index, and magnetic resonance of the optic nerve sheath, among others.[23] So far, none of these methods has provided sufficient accuracy to replace invasive monitors.

ICP WAVEFORMS

The normal ICP waveform consists of three arterial components superimposed on the respiratory rhythm. The first arterial wave is the percussion wave, which reflects the ejection of blood from the heart transmitted through the choroid plexus in the ventricles. The second wave is the tidal wave, which reflects brain compliance, and the third wave is the dicrotic wave that reflects aortic valve closure. Under physiologic conditions, the percussion wave is the tallest, with the tidal and dicrotic waves having progressively smaller amplitudes. When intracranial hypertension is present, cerebral compliance is diminished. This relationship is reflected by an increase in the peak of the tidal and dicrotic waves exceeding that of the percussion wave (Fig. 42.1).

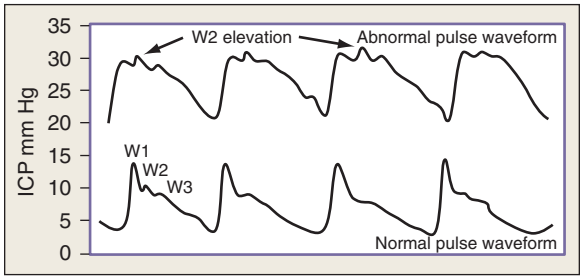

Fig. 42.1 *(Upper tracing)* Normal intracranial pressure (*ICP*) waveform and its components: W1 (percussion wave), W2 (tidal wave), and W3 (dicrotic wave). *(Bottom tracing)* As ICP increases, distinctive waveform changes occur (e.g., elevation of the second pulse wave and "rounding" in the ICP waveform).

COMPLICATIONS

Among the complications related to ICP monitoring, intracranial hemorrhage and infections are the most common.[1,23] Less frequent complications are malfunction, malposition, and obstruction. Although these complications generally do not produce long-term morbidity in patients, they can cause inaccurate ICP readings and may increase hospitalization costs by requiring replacement of the monitor.

The incidence of infection is reported to range from 0% to 22%,[27] depending on the type of device. Several other factors have been identified that may affect the risk of EVD infection: the use of prophylactic parenteral antibiotics, the presence of other concurrent systemic infections, the presence of intraventricular or subarachnoid hemorrhage (SAH), duration of monitoring, open skull fracture (including basilar skull fractures with CSF leak), leakage around the ventriculostomy catheter, and repeated flushing of the EVD.[28] Prophylactic antibiotic-impregnated catheters may be used in order to reduce EVD-associated infections; however, more trials should be conducted to evaluate the beneficial effect on clinical outcome. Placement of ICP monitors should be done under the most sterile possible conditions, minimizing excessive manipulation and flushing. The second most common complication related to ICP monitoring is postprocedural intracerebral hemorrhage (<1%).[27]

JUGULAR VENOUS OXYGEN SATURATION

Placement of a jugular venous oxygen saturation ($SjvO_2$) catheter involves retrograde insertion into the internal jugular vein of a catheter equipped with an oxygen sensor at the tip. The catheter is similar to the type used for CVP monitoring but is directed cephalad into the jugular bulb.[29] The tip of the catheter must be placed above the C1–C2 vertebral bodies to avoid contamination with blood coming from the facial vein. Correct positioning of the catheter can be confirmed with a lateral skull x-ray (Fig. 42.2). The incidence of complications related to the $SjvO_2$ catheter is low but includes carotid artery puncture, hematoma formation, infection, thrombosis, and increased ICP that may arise during catheter insertion or with prolonged monitoring.

SIDE OF JUGULAR CATHETERIZATION

The International Consensus on Multimodal Monitoring in Neurocritical Care recommends that the catheter site placement be based on the diagnosis, the type and location of brain lesions, and technical

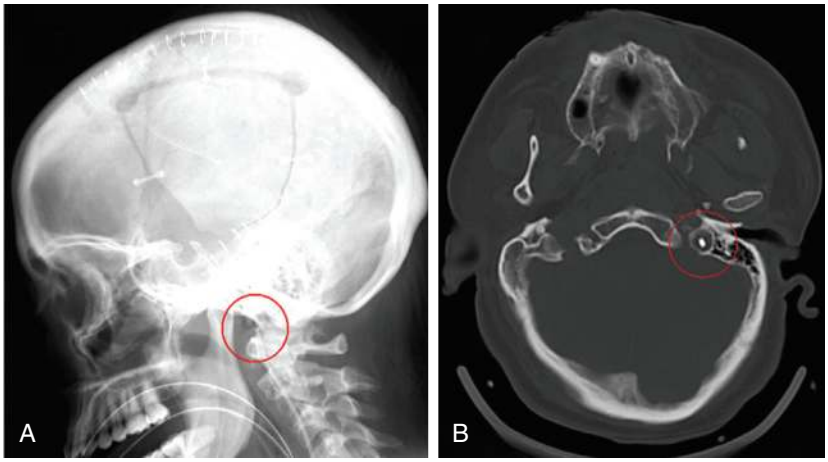

Fig. 42.2 A, Lateral skull x-ray confirming adequate $Sjvo_2$ catheter placement at the C1–C2 level. **B,** Head computed tomography scan showing the catheter tip correctly placed at the jugular venous bulb level.

feasibility.[30] If the strategy is to use $SjvO_2$ as a monitor of global oxygenation, then cannulating the dominant jugular vein is logical because it is most representative of the whole brain. The dominant internal jugular vein is the larger of the two internal jugular veins, as determined by ultrasound imaging.

NORMAL JUGULAR VENOUS OXYGEN SATURATION

$SjvO_2$ reflects the global balance between cerebral oxygen delivery (supply) and the cerebral metabolic rate of oxygen (demand). When arterial oxygen saturation, hemoglobin concentration, and the hemoglobin dissociation curve remain stable, $SjvO_2$ generally parallels changes in CBF. Normal $SjvO_2$ values range from 55% to 75%,[31] and jugular venous desaturation has been associated with worse outcomes post-TBI.[1] Current guidelines recommend maintaining $SjvO_2$ >50% in order to improve outcomes in the TBI population (level III recommendation),[16] acknowledging the fact that $SjvO_2$ >75% has also been associated with poor neurologic outcomes.[1,31] $SjvO_2$ provides only information of a global state of cerebral oxygenation, and focal ischemic areas are not evaluated with this technique. Multiple pathologic clinical scenarios may cause an increase or decrease in $SjvO_2$ values (Table 42.1).

TRANSCRANIAL DOPPLER FLOW VELOCITY AND FLOW VOLUME

Transcranial Doppler (TCD) ultrasonography is a noninvasive monitoring technique that measures blood flow velocity in one of the major arteries at the base of the brain. A 2-MHz pulsed ultrasound signal is transmitted through the skull (usually through the temporal bone) and, using the shift principle, measures red cell flow velocity. Flow volume is directly proportional to flow velocity and can be calculated by multiplying the velocity by the cross-sectional area of the vessel insonated. Cerebral vasospasm after aneurysmal SAH and traumatic SAH is a major cause of disability, with a similar incidence among both groups.[32] Angiography remains the gold standard for diagnosing posttraumatic vasospasm,[33] but TCD ultrasonography gives a noninvasive alternative for daily bedside monitoring of the CBF dynamics. Current literature suggests a high level of suspicion for posttraumatic vasospasm when velocities are above 200 cm/sec per TCD examination.[33] The Lindegaard ratio (middle cerebral artery–to–extracranial internal carotid artery flow velocity ratio) helps in differentiating vasospasm from hyperemia; vasospasm is considered to be present if the Lindegaard ratio index is greater than 3, and severe vasospasm when it is greater than 6.[34] In hyperemia, the flow velocity for both intracranial and extracranial vessels increases, whereas in vasospasm, high-flow velocity is seen only in intracranial vessels, resulting in a high ratio.

Vasospasm after TBI or SAH has an impact on morbidity and mortality. Frequently, the first clinical sign is a deterioration in the neurologic examination, which occurs too late to reverse the process. TCD ultrasonography may identify changes in flow velocity that can precede these clinical findings and may lead to further diagnostic assessment and therapy. The major drawback of TCD ultrasonography is that it is operator dependent, though color-coded TCD provides improved accuracy of measurement.

TCD studies have high specificity as a supporting tool for the diagnosis of brain death.[35] Brief systolic forward-flow spikes with reversed or absent diastolic flow found bilaterally or in three different arteries are accepted TCD criteria to support the diagnosis of brain death. TCD should not be used as a sole brain death diagnostic tool.[36]

TABLE 42.1 Clinical Conditions Associated With Alterations in $SjvO_2$ Values

Increased $SjvO_2$	Restricted oxygen diffusion or extraction resulting from neuronal infarction or inflammation Decreased cerebral metabolism Hyperemia
Decreased $SjvO_2$	Local or systemic hypoperfusion (e.g., intracranial hypertension, shock or prolonged hypotension, vasospasm) Decreased systemic oxygen supply (e.g., low PaO_2) Increased cerebral metabolism or oxygen extraction (e.g., seizures, fever) Anemia

BRAIN TISSUE OXYGEN PARTIAL PRESSURE

A major limitation of $SjvO_2$ technology is that regional ischemia cannot be identified. After TBI, regional differences in CBF are commonly seen. Brain tissue oxygen partial pressure ($PbtO_2$) is a tool that measures local brain oxygen partial pressure levels. It has proven to be the most reliable cerebral oxygenation monitoring technique to date.[1]

$PbtO_2$ is measured using a polarographic Clark-type electrode at the tip of a catheter placed in the brain parenchyma. The Clark electrode polarographic probe has a semipermeable membrane covering two

electrodes. In the presence of dissolved oxygen crossing the membrane, an electric current is generated and then transferred to a monitor for interpretation. Temperature is also needed to calculate the oxygen tension—brain temperature rather than core temperature is preferred for this purpose, as a sensor is incorporated into the $PbtO_2$ catheter.[37]

Normal values for $PbtO_2$ range from 20 to 40 mm Hg[1,5,30,38]; levels below 20 mm Hg are indicative of compromised brain oxygen, and intervention should be considered. The likelihood of poor outcome after severe TBI increases with long periods of $PbtO_2$ below 20 mm Hg. It has been reported that low $PbtO_2$ values after a severe TBI are present within the first few days postinjury in up to 70% of patients.[38]

Correct probe placement and depth into the region of interest are key for successful monitoring of $PbtO_2$. Two general strategies have been used for placement of this probe. Some recommend placement of the probe into relatively normal brain tissue so that the PO_2 values reflect global brain oxygenation.[5] Changes in $PbtO_2$ correlate well with changes in $SjvO_2$ when the sensor is inserted into noncontused areas of the brain. Others recommend placement of the probe into penumbra tissue so that PO_2 values reflect oxygenation in the most vulnerable areas of the brain.[1] Regardless of the strategy used, the $PbtO_2$ values must be interpreted with the understanding that the values measure only the local tissue surrounding the catheter. $PbtO_2$ monitoring is safe and provides accurate data for up to 10 days and can be used to guide pharmacologic, hemodynamic, or respiratory therapy.[30] Along with ICP monitoring, $PbtO_2$ assessment has been incorporated into an overall management strategy of patients suffering from severe TBI. A recently completed two-arm, single-blind, prospective, randomized controlled multicenter phase II trial (BOOST-II) showed that ICP + $PbtO_2$–guided management in severe TBI compared with ICP alone was associated with reduced mortality and improved outcomes 6 months postinjury.[38] BOOST-II demonstrated that ICP + $PbtO_2$–guided management is not only safe but nonfutile, laying the foundation for BOOST-3, which is a phase III trial that will assess the impact of ICP + $PbtO_2$–guided management in severe TBI on neurologic outcome.

Treatment for a reduced $PbtO_2$ should be first directed at any underlying causes of inadequate cerebral oxygen delivery. Such corrections might include increasing CPP (reducing ICP, increasing MAP), improving arterial oxygenation, transfusions for a low hemoglobin concentration,[1,5] reducing fever, or treating subclinical seizures. If an underlying cause for the low $PbtO_2$ is not found, or if $PbtO_2$ remains low after optimizing oxygen delivery, obtaining a follow-up computed tomography (CT) scan of the head might be considered to assess whether a delayed hematoma or hemorrhagic contusion has developed. A sustained (>30 min) $PbtO_2$ of 0 mm Hg and no response to oxygen challenge are consistent with brain death,[39] although care related to interpretation in this regard is needed, depending on the location of the probe or potential probe malfunction.[40]

NEAR-INFRARED SPECTROSCOPY

Near-infrared spectroscopy (NIRS) is based on the fact that light in the near-infrared range (700–1000 nm) can pass through skin, bone, and other tissues with relative ease. After the light has penetrated, it will either be scattered or absorbed. Tissues such as bone and skin will scatter the light, whereas oxygenated and deoxygenated hemoglobin, possessing a different absorption spectra, will mostly absorb it and have a lower scattering effect.[41] Changes in the absorbance of near-infrared light as it passes through these compounds can be quantified using a modified Beer-Lambert law, which describes optical attenuation. The main advantage of NIRS is that it is a noninvasive method for estimating regional changes in cerebral oxygenation.[1] Some studies have reported its potential utility in the prehospital management of severe TBI.[42] However, its clinical use is limited by an inability to differentiate between intracranial and extracranial changes in blood flow and oxygenation; lack of standardization between commercial devices; and confounded saturation signals because of the presence of epidural, subdural, or intracranial hematomas.[42] Given the latter limitation, Brogan and colleagues conducted a systematic review and meta-analysis on the use of NIRS as a possible diagnostic tool to detect traumatic intracranial hematomas. The authors found NIRS to have a low cross-study sensitivity and negative predictive value (NPV) for intracranial hematomas, making it inadequate for use as a diagnostic tool.[41] Currently, there are no studies providing evidence that NIRS use alone can influence outcomes in adult neurocritical care.

ELECTROENCEPHALOGRAM

An electroencephalogram (EEG) depicts the spontaneous electrical activity of the cerebral cortex and is generated mainly by the summation of excitatory and inhibitory postsynaptic potentials of cortical neurons. It does not reflect activity in subcortical levels, cranial nerves, or the spinal cord. The electrical signal is amplified, filtered, and then displayed as either 8 or 16 channels (8 channels per hemisphere) to give an accurate representation of electrical activity throughout the cortex. EEG activity is usually interpreted in terms of frequency, amplitude, and location (focal or generalized activity).

EEG is the most frequently used electrophysiologic technique in the ICU. It offers information about brain electrical activity and is essential to detect clinical and subclinical seizures. The presence of seizures, including duration and response to therapy, may predict outcome after coma, with or without known acute brain injury in the ICU setting.[30] After TBI, a cascade of neurometabolic disruptions (i.e., release of excitatory neurotransmitters, neuroinflammation) unfold, adversely affecting cerebral physiology and leading to posttraumatic seizures (PTSs) and secondary brain injury.[5,43] PTSs can occur in up to 40% of TBI patients, with the vast majority of these being nonconvulsive seizures (NCSs) or nonconvulsive status epilepticus (NCSE).[43] Continuous EEG (cEEG) in comatose TBI patients admitted to the ICU has been recommended in order to monitor subclinical seizures, as routine noncontinuous EEG could not capture these events.[44]

A low threshold for obtaining a continuous EEG must be considered in patients with acute brain injury and unexplained alteration of consciousness. It is also urgently needed in patients with convulsive status epilepticus who remain unresponsive after 1 hour of administering adequate antiepileptic treatment.[30,44] cEEG is strongly recommended in patients undergoing therapeutic hypothermia and within 24 hours of rewarming to exclude NCS in all comatose patients after cardiac arrest.[45]

In recent years, a more invasive form of cerebral electrical activity monitoring has been studied in humans: intracranial EEG using either subdural strip electrodes or intracortical depth electrodes.[1,46] This invasive form of EEG has been shown to be superior at identifying certain forms of seizures not detected by standard scalp EEG, in addition to slowing potential changes that move across the cortex, called *cortical spreading depolarizations (CSDs)*.[46,47] CSDs (or just spreading depressions) have been described in animal models by Leão since the 1940s.[48] CSDs have been identified in up to 70% of TBI patients through intracranial EEG and are associated with secondary insults and worsening of clinical outcomes.[1,47,49,50] Currently, observational studies are underway to better elucidate the application and effect of CSD monitoring on TBI patients, such as the "Spreading Depolarizations in Traumatic Brain Injury" trial, a substudy of the TRACK-TBI consortium.

MICRODIALYSIS

Microdialysis is a technique used to sample the extracellular fluid of cerebral tissue. This method is based on the diffusion of water-soluble substances through a semipermeable membrane, which can sample small molecules (<20 kDa) such as glucose, glycerol, glutamate, lactate, and pyruvate and larger ones (>100 kDa) such as cytokines. The degree of permeability of the membrane determines the molecular weight of the substances that can cross it. Although the recovery of larger molecules has been better studied in the past decade, 100-kDa catheters are not yet Food and Drug Administration (FDA) approved as of the time this manuscript was created.[51]

The concentration of substances in the dialysate depends on the flow rate and chemical composition of the perfusate, the length of the dialysis membrane, the type of dialysis membrane, and the diffusion coefficient of the tissue. The recovery of a particular substance is defined as the concentration in the dialysate divided by the concentration in the interstitial fluid. If the membrane is long enough and the flow slow enough, the concentration in the perfusate will be the same as that in the interstitial fluid (i.e., 100%).

The technique of cerebral microdialysis allows continuous and online monitoring of changes in brain tissue chemistry. As with brain tissue oxygenation monitoring, microdialysis also involves inserting a fine catheter (diameter 0.62 mm) into the brain. Catheter location will vary depending on the site and type of injury and the goals of treatment.[51] The dialysate, which is collected in vials that are exchanged every 10–60 minutes, is then analyzed using sensitive assays.

The key substances measured by microdialysis that have proven to be clinically significant because of their representation of brain chemistry are glucose, lactate, pyruvate, glutamate, and glycerol.[1,51] The clinical value of these substances can be described in a tiered fashion (with tier 1 being the most clinically significant) as follows:
Tier 1: Lactate:pyruvate (LP) ratio and glucose
Tier 2: Glutamate
Tier 3: Glycerol

Lactate:Pyruvate Ratio

An elevated LP ratio has been associated with worse outcomes. If the LP ratio is elevated in the presence of low pyruvate, it signifies ischemia. If, however, the LP ratio is elevated in the presence of normal or high pyruvate, it indicates mitochondrial dysfunction.

Glucose

Studies have shown that both low brain glucose (<0.8 mM) and high brain glucose are associated with worse outcomes; however, a definitive normal range has not been established yet.

Glutamate

Glutamate is an excitatory neurotransmitter that is released during seizures and ischemia; it is also associated with worse outcomes after TBI.

Glycerol

Glycerol, a marker of oxidative stress, has limited specificity for brain injury and/or ischemia; it is influenced by systemic concentrations, and no association with outcomes after TBI has been found yet.

Metabolite variations over time can help with clinical management and are not limited to identification of ischemia, but allow monitoring of energy metabolism in the brain as well.

Cerebral microdialysis has a very low complication rate; nonetheless, there are a number of limitations regarding its clinical use, including its focal measurement and the fact that it discloses different metabolite concentrations when inserted into pathologic versus preserved brain areas. Consequently, microdialysis results should be interpreted based on the location of catheter insertion, confirmed by postinsertion CT.[30]

Microdialysis, when used with multimodality monitoring, may enhance the understanding of cerebral physiology and pathophysiology and guide management and individualized therapy.[51,52] Future research studies should focus on assessing the effectiveness of microdialysis-guided management as part of a multimodal monitoring approach in acute brain injury.

KEY POINTS

- Evaluation of neurologic and mental status should be included in the monitoring protocol whenever possible.
- The ventriculostomy catheter remains the preferred device for monitoring ICP and is the standard against which all new monitors are compared.
- The two major complications of ICP monitoring are ventriculitis and ICH.
- The simplest measure of cerebral perfusion is CPP. For equivalent levels of CPP, cerebral perfusion is impaired more by decreases in blood pressure than by increases in ICP.
- TCD ultrasonography is a noninvasive monitor that provides indirect information about CBF in one of the major arteries at the base of the brain. In the absence of vessel stenosis, vasospasm, or changes in arterial blood pressure or blood rheology, pulsatility reflects the distal cerebrovascular resistance.
- The Lindegaard (hemispheric) index is the ratio of flow velocity in the middle cerebral artery and the internal carotid artery. The mean hemispheric index in normal individuals is 1.76 ± 0.1, and pathologic values suggestive of vasospasm are generally above 3.
- Normal values for $PbtO_2$ are 20–40 mm Hg, and critical reductions are below 20 mm Hg.
- The use of EEGs in the ICU to detect early subclinical seizures may help reduce mortality and morbidity in status epilepticus. Invasive EEG has been proven to be the only monitoring modality in detecting spreading depolarizations, which have been associated with worse outcomes after TBI.

References for this chapter can be found at expertconsult.com.

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43

Coma

Melissa B. Pergakis and Wan-Tsu W. Chang

COMA

Disorders of altered consciousness present a diagnostic dilemma to the clinician in the critical care setting. They represent a wide of range of pathology that can be systemic in nature or the result of structural or nonstructural intracranial pathology. Immediate evaluation and accurate diagnosis leading to lifesaving interventions are of paramount importance, as some causes of coma are irreversible. However, this can be a difficult task in critically ill patients. As such, the clinician must have an understanding of underlying disorders of consciousness and coma, the anatomy and pathophysiology leading to this disease state, a systemic approach in history taking and examination, and a rapid approach to workup and early therapeutic interventions.

DEFINING DISORDERS OF CONSCIOUSNESS

Consciousness is defined as a state of full awareness of one's self and relationship to the environment and is composed of content and arousal.[1,2] Whereas arousal is akin to one's wakefulness and alertness, content of consciousness includes higher cerebral functional activity and awareness of one's relationship to self and environment. As one might expect, content of consciousness is not possible without a certain level of arousal.[1]

Coma is defined as a state of unresponsiveness. The patient lies in the bed with eyes closed without any purposeful response to external stimuli.[1] Motor responses to deep painful stimuli may include flexor or extensor posturing, but comatose patients will not have any meaningful or purposeful movements, including localization.

Several other pathologic states of consciousness often referred to in the critical care setting demonstrate variable levels of arousal and awareness. These include *lethargy, obtundation, stupor, clouding of consciousness,* and *delirium. Lethargic* patients are severely somnolent, although they can be awoken by minimal stimuli; however, they will drift off to a state of drowsiness when continuous stimuli are not applied. *Obtunded* patients are similar to lethargic patients but have even less interest in their surroundings and slower responses to any sort of stimulation. These patients often exhibit more somnolence than lethargic patients. *Stuporous* patients require vigorous stimulation to be kept awake and if not stimulated will quickly fall into a state of unresponsiveness, and thus represent a state between awareness and coma.[1,3,4]

In contrast to patients requiring minimal or more extreme forms of stimuli for wakefulness, patients can also have *clouding of consciousness, confusional state,* and *delirium. Clouding of consciousness* refers to an altered state of consciousness that is defined by inattention and reduced wakefulness, whereas a *confusional state* tends to be more extreme and includes disorientation and inability to follow commands. *Delirium* and *confusional state* are often used interchangeably; however, *delirium,* by definition of the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edn (DSM-V) is defined as altered consciousness with shifting attention or inability to focus and fluctuating course.[5]

As one can imagine, these terms can be nebulous, oftentimes overlap, and are not always used in the appropriate clinical context to accurately describe a patient's level of consciousness. Consequently, standardized scales have been developed to aid providers in measuring level of consciousness in patients. These scales serve as important tools when communicating with other healthcare providers. The scale most often used is the Glasgow Coma Scale (GCS)[6] (Table 43.1), which was initially used in trauma patients. The GCS measures three different criteria—eye opening, motor response, and verbal response—with lower scores indicating a poor examination. Typically, a score of 8 or below is indicative of coma.[6] It is important to note that it is not possible to assess verbal response in intubated patients. Brainstem reflexes, an essential aspect of the examination in a comatose patient, are also not accounted for in GCS. With these shortcomings in mind, Wijdicks and colleagues developed the Full Outline of UnResponsiveness (FOUR) score (Table 43.2).[7] This scale includes eye response, motor response, brainstem reflexes, and respiratory patterns. The FOUR score provides more specific neurologic subtleties and consequently allows the clinician to differentiate between stages of herniation.[7]

DIFFERENTIAL DIAGNOSIS

Though the etiology of coma encompasses a wide range of causes, the differential diagnosis of coma is, in contrast, quite limited. Differentiating between coma and the following diagnoses requires an eloquent understanding of neuroanatomy in addition to precise and careful neurologic examination, differentiating between disorders of consciousness, and an appropriate time course for the specified disease process.

Locked-in syndrome results from damage to the ventral pons and the corticobulbar, corticospinal, and corticopontine tracts. The clinical presentation includes quadriplegia and anarthria with *retained* level of consciousness. Locked-in syndrome at times mimics as coma if a focused but thorough neurologic examination is not performed. In this case, careful inspection of the eye movements would reveal preservation of vertical eye movements when asking the patient to "look up." However, failure to do so may result in an inaccurate diagnosis of coma. The causes of locked-in syndrome are numerous, including ischemic, hemorrhagic, traumatic, neoplastic, metabolic (central pontine myelinolysis), demyelinating (multiple sclerosis), and infectious; consequently, appropriate and swift diagnosis allows for timely therapeutic intervention if possible.[8]

Persistent vegetative state refers to patients who have had a prolonged disorder of consciousness for longer than 1 month. Over time, patients may appear to have their eyes open, but remain unresponsive and unaware of external stimuli. The term *persistent vegetative state*,

TABLE 43.1 Glasgow Coma Scale[8]

Eye Opening Response	
Spontaneous	4
To verbal stimuli	3
To pain only	2
No response	1
Verbal Response	
Oriented	5
Confused, but able to answer questions	4
Inappropriate words	3
Incomprehensible speech	2
No response	1
Motor Response	
Obeys commands	6
Purposeful movement to noxious stimuli	5
Withdrawal to noxious stimuli	4
Flexion to noxious stimuli	3
Extension to noxious stimuli	2
No response	1
Total Score	**3–15**

TABLE 43.2 Full Outline of Unresponsiveness Score[7]

Eye Response	
Eyes open, tracking, or blinking to command	4
Eyes open but not tracking	3
Eyes closed but open to loud voice	2
Eyes closed but open to pain	1
Eyes remain closed with pain	0
Motor Response (Upper Extremities)	
Thumbs-up, fist, or two fingers	4
Localizing to pain	3
Flexion in response to pain	2
Extension in response to pain	1
No response to pain or generalized myoclonus status	0
Brainstem Reflexes	
Pupil and corneal reflexes present	4
One pupil wide and fixed	3
Pupil or corneal reflexes absent or fixed	2
Pupil and corneal reflexes absent	1
Absent pupil, corneal, and cough reflexes	0
Respiration Pattern	
Not intubated, regular breathing pattern	4
Not intubated, Cheyne-Stokes breathing pattern	3
Not intubated, irregular breathing	2
Breathes above ventilatory rate	1
Breathes at ventilator rate or apnea	0
Total Score	**0–16**

which can be pejorative, has been replaced by *unresponsive wakefulness syndrome*,[9] which more specifically describes the patient's clinical presentation. Typically, these patients have widespread cerebral structural injury and will have significant cerebral atrophy over time.[10]

Akinetic mutism was first described by Cairns and colleagues in the 1940s as a state in which the patient does not move or speak; in the first case report, it was the result of an epidermoid cyst in the third ventricle.[11] Since that time, akinetic mutism has been reported in bifrontal dysfunction or mesencephalic damage. Akinetic mutism is also associated with Creutzfeldt-Jakob disease and is one of the diagnostic criteria.[12] In contrast to coma, patients with akinetic mutism are in fact aware and alert but are apathetic.

Brain death is death because of *irreversible* damage of the brain.[13] Coma is one of the prerequisites for brain death, and neuroimaging must be consistent with irreversible brain injury. Additionally, all other confounding factors must be eliminated, including medication side effects, electrolyte imbalances, acid-base disturbance, endocrine abnormalities, hypothermia, and hypotension.[14] Given that coma and brain death are intimately intertwined, it is essential to know when the comatose patient meets the prerequisites and criteria for brain death. In addition to the aforementioned prerequisites, the patient must have an examination consistent with brain death, including absent brainstem reflexes and absent motor response in all four limbs to noxious stimuli. Apnea testing must also be done. In certain circumstances, ancillary testing may be needed if components of the clinical examination or apnea testing cannot be performed, such as with massive facial trauma or hemodynamic instability. Ancillary testing includes four-vessel cerebral angiography, nuclear brain perfusion scan, electroencephalogram (EEG), and transcranial Doppler.[14]

Psychogenic unresponsiveness or *functional coma* is a diagnosis of exclusion and is described as a state of unresponsiveness with preservation of brainstem reflexes. It can present in patients who have a history of depression, factitious disorders, or conversion disorders. Though a diagnosis of exclusion, the neurologic examination may alert the clinician to the fact that coma may not be organic in nature. Physical signs include resistance to eyelid opening and looking to the ground when turned on one side, termed "eye gaze sign."[15] Patients may not appear to have a normal vestibulo-ocular reflex (VOR), as they are able to fixate on a particular point with head turn. However, caloric stimulation with the instillation of cold water in the ear of a patient with psychogenic coma would cause eye deviation to the ipsilateral ear with contralateral horizontal nystagmus. This examination finding would be in contrast to organic coma, in which the VOR would be abnormal. Typically in psychogenic coma, EEG frequencies are consistent with patients in the awake state.

ANATOMY AND PHYSIOLOGY

Discussion regarding the anatomy of consciousness would be remiss without briefly delving into the pivotal experiments of the 1930s and 1940s that helped synthesize understanding of the anatomic basis of consciousness. Constantin Von Economo studied patients during the epidemic of encephalitis lethargica and suggested that the upper brainstem and posterior hypothalamus controlled arousal.[16] Bremer, while transecting the brains of cats, showed that transection through the midbrain caused a state of persistent sleep and EEG findings consistent with slow wave sleep; conversely, transection at the level of the cervicomedullary junction did not have any effect on arousal or sleep/wake cycles.[17] Moruzzi and Magoun extrapolated on this premise further by showing that stimulating cholinergic neurons in the pontine tegmentum caused a state of arousal that was independent of the sensory pathways, including the medial lemniscus and spinothalamic tract.

Destruction of the lesions in the reticular formation did not disrupt sensory pathways; disruption of sensory pathways did not cause a state of unarousal.[18]

As such, the idea arose that two separate ascending pathways existed: ascending sensory pathways and an ascending reticular activating system (ARAS). Though the ascending sensory pathways and the ARAS terminate in the cerebral cortex (more specifically, in the primary sensory cortex and diffusely throughout the cortex, respectively), these ascending pathways synapse in different thalamic nuclei.[2] The long ascending pathways synapse in the ventral posteromedial and ventral posterolateral nuclei, whereas the ARAS synapses in the intralaminar, midline, and reticular thalamic nuclei, also known as the *nonspecific thalamic nuclei.*[19–21] As evidenced earlier, the ARAS either communicates or is located at multiple levels of the neuroaxis, including the afferent sensory pathways, the reticular formation in the brainstem, the thalamus, and the cerebral cortex. Pathology anywhere along this neuroaxis could contribute to alterations of consciousness.

Though underlying physiology is not entirely understood, neurons in the rostral pons and caudal midbrain have been implicated as major contributors to the pathways of the ARAS. Cholinergic nuclei in the pontine-midbrain junction that project to the thalamocortical neurons also modulate wakefulness. Additionally, norepinephrine in the locus coeruleus and serotonin in the raphe nuclei contribute to increasing levels of arousal.[22,23] These neurotransmitters of wakefulness and arousal are modulated by GABAergic and galaninergic inputs from the ventrolateral preoptic nucleus of the hypothalamus promoting onset of sleep.[24,25]

ETIOLOGY

With a more thorough understanding of the anatomic basis of coma, it is clear that coma arises from dysfunction of the bilateral cerebral hemispheres, the diencephalon, or the brainstem. Taking this into account, there are both nonstructural and structural causes of coma. Swift and accurate diagnosis allows for timely management that in fact may be vastly different. Therapeutic interventions can range from neurosurgical intervention to correction of electrolyte abnormalities in order to reverse the cause of coma or mitigate downstream injury.[26]

Nonstructural

Nonstructural causes of coma comprise about two-thirds of unresponsive patients presenting to the emergency department.[27] Nonstructural causes include systemic disease states causing diffuse neuronal dysfunction, including toxic, metabolic, endocrine, or nutritional etiology. *Toxic* causes include barbiturate, alcohol, or opioid overdose and carbon monoxide poisoning. *Metabolic* causes include hyponatremia and hypocalcemia in addition to renal failure, hepatic failure, hyperammonemia, or acidosis. Case reports of D-lactic acidosis seen after small bowel resection or intestinal bypass can also progress to severe encephalopathy and eventually coma.[28] Hypoglycemia, Addison disease, or myxedema coma constitute endocrine causes of coma.[29] *Nutritional deficiency* such as niacin deficiency[30] or, more specifically, Wernicke encephalopathy, usually presenting with ataxia, ophthalmoplegia, nystagmus, and encephalopathy, can rarely present as coma.[31] Vitamin B_{12} deficiency typically presents with subacute combined degeneration of the spinal cord, and dementia can also present with encephalopathy that can progress to coma.[32] Hypothermia often presents as coma and even mimics brain death at times.[33]

In the case of nonstructural causes of coma, onset is not typically abrupt but may fluctuate and evolve, with depressed level of mentation worsening over time. This is not always the case, especially in toxic ingestion or overdose, where conversely onset may be abrupt. Given that the underlying pathophysiology includes bi-hemispheric cerebral and/or brainstem depression because of toxic or metabolic causes, the neurologic examination should be grossly nonlateralizing. A focal neurologic deficit should alert the clinician to initiate search for an underlying structural cause of coma.

Structural

In contrast to nonstructural causes of coma, structural lesions account for about one-third of patients presenting with altered mental status to the emergency department.[27] The brain sits within an enclosed space in the skull along with cerebrospinal fluid (CSF) and blood, all of which has a fixed volume. Mass effect from abscess, tumor, meningitis, cerebral or cerebellar edema from stroke, obstruction of CSF flow, or disruption of venous drainage from a venous sinus thrombosis can cause compression by displacement of structures, specifically the ARAS, bilateral thalamus, or bilateral cerebral hemispheres, and subsequently cause coma.

Structural lesions are either *supratentorial* or *infratentorial* and associated with herniation syndromes, with accompanying clinical findings (Table 43.3). *Central* or *transtentorial herniation* is a type of supratentorial herniation in which the diencephalon and midbrain herniate through the tentorium. There are four stages of herniation. In the diencephalic state, pupils are small and sluggish. Gaze is conjugate or minimally skewed with impaired upgaze. Motor examination may be within normal limits, though extensor toes, or Babinski sign, may be seen. Cheyne-Stokes respirations are seen, or there may only be sighing or yawning. If central herniation is not reversed at this point, the midbrain–upper pontine stage occurs next. Pupils are midline, dilated or irregular in shape, and fixed. Gaze is typically disconjugate, and the oculocephalic reflex (OCR) is impaired. Motor response is decerebrate, which is extension of all four limbs and the trunk. Cheyne-Stokes respirations or hyperventilation is seen. It will then progress to the lower pontine stage where pupils remain midline, fixed, and dilated with absent OCR and a flaccid motor examination. Tachypnea and shallow breathing mark this stage. At this point, the prognosis is usually irreversible. The final stage is the medullary stage in which pupils are fully dilated and fixed, respirations are ataxic, pulse is irregular, and the patient is hypotensive. This stage is fatal.

The second supratentorial herniation syndrome is *uncal herniation,* which is medial displacement of the uncus and hippocampal gyrus across the edge of the tentorium cerebelli compressing the third cranial nerve and midbrain. Given the anatomic landmark of the medial temporal lobe, an expanding or edematous tumor or stroke within that region should alert the clinician that uncal herniation syndrome may be imminent. As with central herniation, uncal herniation also has four stages as the third cranial nerve (CN III) and brainstem become compressed over time in a rostral–caudal progression. The first stage is the early CN III stage in which the pupil may be dilated or sluggish ipsilateral to the lesion, with or without ptosis. Gaze is variable, either normal or disconjugate. Motor examination may not show any abnormality. Next is the late CN III stage where the ipsilateral pupil is widely dilated and fixed with ptosis. Usually at this stage, OCRs of the ipsilateral eye are impaired. Motor examination shows weakness ipsilateral to the intracranial lesion. This is due to the Kernohan notch phenomenon, where the contralateral cerebral peduncle of the midbrain compresses against the tentorium. In the midbrain–upper pontine stage, both pupils become fixed and dilated with extensor posturing. The final stage is the same as the aforementioned medullary stage in central herniation, which is terminal.

Infratentorial lesions tend to develop rapidly. The stages seen in supratentorial herniation are typically not seen in infratentorial herniation. Infratentorial herniation is typically the result of tonsillar

TABLE 43.3 Herniation Syndromes

Herniation Syndrome	Etiology	Mechanism	Clinical Findings
Supratentorial			
Transtentorial or central herniation	Frontal, parietal, occipital lobe lesions; seen with diffuse brain swelling	Downward displacement of the brainstem from supratentorial structures	
		Diencephalic stage: preservation of red nuclei; loss of sympathetic output from hypothalamus	Pupils are pinpoint, roving eye movements; conjugate or mildly skewed gaze; motor examination may be normal or may have hemiplegia contralateral to the lesion with ipsilateral paratonia; bilateral hyperreflexia or Babinski sign; Cheyne-Stokes breathing pattern, or sighing and yawning
		Midbrain–upper pontine stage: red nucleus becomes affected with preservation of the reticulospinal nucleus of rostral pons	Pupils are midline and dilated, but can be irregularly shaped; gaze is disconjugate; oculocephalic reflex (OCR) is impaired; extensor posturing is seen; Cheyne-Stokes respirations or hyperventilation
		Lower pontine stage	Pupils remain dilated, fixed, and midline; OCRs and oculovestibular reflexes are impaired; motor examination is flaccid; bilateral Babinski sign; tachypnea
		Medullary stage	Pupils fixed and dilated; ataxic respirations, irregular pulse, hypotension; apnea; finally, death
Uncal herniation	Supratentorial lesions, but specifically those of the temporal lobe	Medial displacement of the uncus and hippocampal gyrus across the edge of the tentorium cerebelli causing compression of midbrain and third cranial nerve (CN III)	
		Early CN III stage: medial temporal lobe begins to exert pressure on CN III	Pupil may be dilated or sluggish ipsilateral to the lesion with or without ptosis; gaze is variable but can be disconjugate; motor examination does not show any abnormality
		Late CN III stage: midbrain becomes further compressed with compression of the contralateral cerebral peduncle against the tentorium	Ipsilateral pupil is widely dilated and fixed with ptosis; OCRs may be impaired; weakness ipsilateral to side of lesions because of Kernohan notch phenomenon
		Midbrain–upper pontine stage	Both pupils become fixed and dilated with extensor posturing
		Lower pontine–medullary stage	Pupils fixed and dilated; ataxic respirations, irregular pulse, hypotension; apnea; finally, death
Infratentorial			
Tonsillar herniation	Posterior fossa mass or lesion	Cerebellar tonsils herniate through the foramen magnum	
		Medullary compression; increased pressure and tension from dura around cerebellar pressure cone	Stiff neck/nuchal rigidity
		Compression of bilateral corticospinal tracts	Flaccid quadriplegia
		Compression of medulla	Cardiovascular and respiratory collapse
Cerebellar/upward herniation	Posterior fossa lesions or ventriculostomy	Cerebellum and mesencephalon travel up through the tentorium	
		Posterior fossa becomes displaced across tentorium into the middle cranial fossa; compresses midbrain, thalami, and bilateral superior cerebellar arteries	Rapid decline in mentation and progression to comatose state; apnea
		Third ventricle enlargement with obstruction of cerebral aqueduct	Parinaud syndrome (impaired upgaze, convergence-retraction nystagmus, eyelid retraction, impaired pupillary light reflex with intact accommodation); diabetes insipidus because of damage on pituitary stalk

herniation, cerebellar herniation, or midbrain–pontine reticular formation compression. In *tonsillar herniation*, the cerebellar tonsils herniate through the foramen magnum, marking a fatal descent as the patient suffers from cardiovascular and respiratory failure. *Cerebellar herniation* is an upward herniation syndrome in which the cerebellum and mesencephalon travel up through the tentorium. Coma results from increased intracranial pressure because of venous congestion or noncommunicating hydrocephalus.

The clinical presentation of comatose patients presenting with nonstructural causes of coma because of global cerebral neuronal dysfunction can vary greatly from comatose patients with a structural lesion who often have a lateralizing examination. Parsing out supratentorial from infratentorial lesions may be slightly more nuanced and challenging in the critical care setting, where many patients may have both systemic and structural causes at play, but the earlier framework lends several neuroanatomic clues to aid in diagnosis.

APPROACH TO A PATIENT WITH COMA

History

The history may be the first piece of information that alerts the clinician to the underlying cause of coma. A bystander who witnessed the event is an extremely useful asset. Additionally, friends, family members, emergency service personnel, and first responders to the scene may provide the most substantial information. Once the patient has arrived at the hospital, use of the electronic medical record also provides vital information. If the patient is already admitted to the hospital, the hospital course and complications up to that point provide invaluable information.

A report of sudden onset of loss of consciousness would be expected in a massive intracranial hemorrhage either from a ruptured cerebral aneurysm causing subarachnoid hemorrhage or parenchymal hemorrhage. Ischemic brainstem stroke from basilar artery occlusion would also likely be sudden in onset. Conversely, altered sensorium over a period of hours to days suggests an underlying toxic-metabolic cause of coma. Trauma may be observed by a bystander. Bystanders may be able to give information regarding toxic exposures such as herbicides or intoxication resulting from opioids, inhalants, MDMA (ecstasy), or other dissociative agents.[34]

The patient's past medical history is also important in considering underlying causes of coma. Patients with diabetes mellitus may be hypoglycemic or hyperglycemic and in diabetic ketoacidosis or hyperosmolar hyperglycemic state (HHS). HHS more often causes mental status changes, given that serum osmolality has the most effect on mental status.[35] A history of epilepsy may suggest seizure. A recent diagnosis of brain tumor could suggest hemorrhage secondary to tumor, tumor expansion, or worsening edema, though the time course of these three entities may be quite different. If the patient is on anticoagulation, one should consider coagulopathic intracranial hemorrhage or other bleeding diathesis causing hypotension or shock. If the patient is immunosuppressed, one should consider infectious etiology, either the result of meningitis, encephalitis, or systemic infection as causes of septic shock. Additionally, knowledge of the patient's medication list could assist if there are concerns for neuroleptic malignant syndrome or serotonin syndrome.

When gathering the clinical history, the clinician should take care not to prematurely close the diagnosis. Some disease states may coexist, and as such, the clinician should not become anchored on one diagnosis. For example, in ethanol intoxication, subdural hemorrhage and hypoglycemia can occur together.[36] Reconsidering one's initial hypothesis as to the underlying cause of coma may change over the course of the patient's evaluation as new data become available.

Physical Examination

Physical examination should start with a general systemic examination to assess for clues suggestive of an underlying etiology. Hypertension may indicate hyperadrenergic response from intracranial hemorrhage, whereas hypotension may indicate septic or cardiogenic shock. Hypothermia or hyperthermia suggests underlying infection. Hypothermia could also be seen in an endocrine abnormality such as hypothyroidism or Addison disease. Hyperthermia could additionally suggest neuroleptic malignant or serotonin syndrome. Hypertension and hyperthermia may be seen in a variety of drug intoxications, including cocaine, amphetamines, or phencyclidine. A thorough examination of the skin may show a rash suggestive of meningitis, cutaneous findings of endocarditis, or hematomas suggestive of coagulopathic state. Cutaneous bullae are often seen in barbiturate poisoning. Periorbital ecchymosis, or "raccoon eyes," or postauricular bleeding ("Battle sign") may be seen on inspection of the head, indicating basilar skull fracture. Fundoscopic examination can show papilledema suggesting increased intracranial pressure because of a multitude of causes. Point-of-care ultrasound can be used to assess optic nerve sheath diameter, which has been found to correlate with intracranial pressure.[37] Nuchal rigidity is seen in meningoencephalitis or subarachnoid hemorrhage. Jaundice and ascites suggest underlying liver disease and possible hepatic encephalopathy or, more worrisome, cerebral edema because of liver failure. Finally, the breath may be fruity in ketoacidosis, musty in acute hepatic failure, smell like onion in paraldehyde toxicity, or like garlic in organophosphate toxicity.[38]

The neurologic examination, though limited, serves as an important indicator for localization of intracranial pathology as the underlying cause of coma. The clinician is also able to follow the neurologic examination over time to detect signs of improvement or deterioration. As previously mentioned, the important aspects of the neurologic examination in coma include motor response, pupillary response, eye movements, and respiratory patterns in assisting with localization. Motor response is one of the measured examination findings in both the GCS and FOUR score. Flexor or decorticate posturing localizes to the bilateral cerebral hemispheres or thalamic dysfunction. Extensor or decerebrate posturing localizes to the red nucleus in the midbrain. As mentioned, asymmetric motor examination suggests focal intracranial pathology. Abnormal movements such as asterixis may be seen in toxic-metabolic encephalopathy, whereas a combination of asterixis and myoclonus can be seen in uremic encephalopathy. Severe myoclonus is often seen after cardiac arrest and in lithium intoxication, cephalosporin intoxication, or with pesticides.[38] It is important to distinguish between myoclonus and shivering or rigor, which may lead the clinician to a separate underlying cause entirely. Movements that are rhythmic in nature can indicate seizure and warrant further investigation.

Pupillary response in toxic-metabolic coma may be small and sluggish without any other brainstem reflex abnormalities. Unilateral or bilateral dilated and fixed pupils should alert the physician to a structural cause of coma and compression of the brainstem. The detailed discussion earlier regarding herniation syndromes outlines the pupillary abnormalities found in these syndromes.

Oculomotor findings, though often confusing, can be helpful in localization of coma, as they are located in the brainstem where the centers for arousal are located. When the ocular reflex is present in a comatose patient, it indicates preserved function of the brainstem. Posterior fossa and brainstem lesions cause skew deviation. Forced gaze deviation of the eyes to one side suggests a lesion or seizure in the frontal eye fields or a lesion in the parapontine reticular formation. In the case of a stroke in the frontal eye field, one would expect that the gaze deviation would be toward the stroke and away from the side of hemiparesis. Gaze deviation in seizure is opposite of this, as the frontal eye fields drive gaze away from the area of epileptic activity. Gaze deviation toward the side of hemiplegia is seen in a pontine stroke or lesion. Pontine lesions can also cause ocular bobbing, which is a rapid downward jerk of the eyes.[39] Roving eye movements are typically seen in toxic-metabolic coma or bi-hemispheric coma. Ping-pong gaze and ocular dipping can be seen in bi-hemispheric dysfunction.[38] Ping-pong gaze is conjugate horizontal eye movements that move from one extreme to the other at 2–4 Hz.[40] Ocular dipping constitutes a slow downward phase followed by rapid upward movement.[41]

Respiratory patterns can often be difficult to interpret if not assessed in the context of the entire clinical picture. For example, Cheyne-Stokes breathing can be seen in patients with congestive heart failure, elderly patients, or patients with bi-hemispheric lesions.[27] The Cheyne-Stokes respiratory pattern is defined by periods of apnea with increasing and subsequent decreasing of tidal volumes.[42] Ataxic

respirations may be seen in patients with medullary dysfunction. Tachypnea can be seen in patients with severe acidosis, whereas bradypnea is seen in opioid intoxication. It is important to take caution that many of these breathing patterns can be masked by mechanical ventilation.

DIAGNOSTIC EVALUATION

Laboratory testing likely ensues in the midst of the first few minutes of initial encounter and should include a basic set of tests, including complete blood count, chemistry panel, finger stick blood glucose, coagulation panel, liver function panel, ammonia, thyroid function tests, arterial blood gas, and serum osmolality. In cases of suspected intoxication, a drug screen should be sent along with any specific toxicology testing. If the patient is febrile, an infectious evaluation should be initiated. Calculation of the anion gap in metabolic acidosis would account for methanol, salicylates, ethanol, or paraldehyde ingestion. An increased osmol gap would be seen with atypical alcohols.

In regard to neuroimaging, patients who rapidly improve with treatment of underlying hypoglycemia or other measures are unlikely to need neuroimaging. Any patients with suspected traumatic brain injury (TBI) or a localizing neurologic examination should have a noncontrast computed tomography (CT) of the brain as the initial test. CT of the brain will show intracranial hemorrhage such as epidural, subdural, intraparenchymal, or subarachnoid hemorrhage or gross abnormalities such as infarct or mass. In the case of trauma with suspected vascular injury, CT angiography should also be obtained if it is readily available. Additionally, in patients with a normal noncontrast CT of the brain in whom basilar artery occlusion is suspected, CT angiography should also be obtained. Suspicion of cerebral venous sinus thrombosis as a cause of intracranial hypertension necessitates a venogram. Brain magnetic resonance imaging (MRI) shows greater anatomic detail of the cortical and subcortical structures of the brain. In cases of suspected posterior fossa stroke and impending obstructive hydrocephalus, brain MRI should be obtained to further visualize these structures, given that brain CT is poor at visualizing structures of the posterior fossa. MRI is also a particularly useful tool in assessment of hypoxic-ischemic injury and to aid in prognostication after cardiac arrest.

EEG is a useful diagnostic tool for convulsive or nonconvulsive status epilepticus. However, more often than not in patients with diffuse cerebral dysfunction, diffuse slowing or triphasic waves are seen. It is important to note that even patients with structural injury can have an EEG that appears slow or have triphasics. As such, the clinician should not rely heavily on the EEG, and caution should be taken in these cases.

Lumbar puncture (LP) should be performed to rule out central nervous system (CNS) infections. In a comatose patient, noncontrast brain CT is done before LP. Opening pressure should be measured. Studies sent from the CSF should include cell count, protein, glucose, differential, CSF culture, cryptococcal antigen, and viral polymerase chain reaction (PCR). The clinician should note appearance of the CSF, whether it is clear, cloudy, xanthochromic, or bloody.

MANAGEMENT

The recommendations that follow should be completed within the first hour of a patient presenting with altered consciousness.[38] As with any patient on initial evaluation, the airway should be secured and attention to breathing and circulation addressed at first encounter in order to ensure adequate oxygenation and ventilation. In cases of severe facial trauma, intubation is indicated for airway protection. Intravenous (IV) or central access should be established as indicated for suspected underlying cause. If the patient is hypotensive and not responsive to fluid resuscitation, start vasopressors to avoid cerebral hypoperfusion. In cases of trauma, the cervical spine should be immobilized until it can be cleared.

If the patient is hypertensive, consider beta-blockers and calcium channel blockers such as nicardipine or clevidipine for strict blood pressure control, especially in intracranial hemorrhage or acute ischemic stroke. Avoid sodium nitroprusside and nitroglycerin if there is clinical suspicion for raised intracranial pressure because of the risk of worsening intracranial pressure through cerebral vasodilation. If the patient had a cardiac arrest, therapeutic hypothermia should be initiated, regardless of whether the patient had a shockable or nonshockable rhythm.[43] In cases of hypothermia, warm the patient with a warming blanket, and, conversely, hyperthermic patients should be placed on cooling blankets. Some have suggested the use of a "coma cocktail" consisting of IV thiamine, glucose, naloxone, flumazenil, or physostigmine; however, it is safer to take a more targeted approach in management.[34,44] Use of flumazenil is controversial, as it can precipitate seizures in patients with underlying seizure disorder or who also present with tricyclic antidepressant intoxication.[38] The risk of seizure outweighs its empirical use for suspected benzodiazepine overdose and limits it to a highly select population of patients presenting with coma.[45] Acute hyponatremia should be treated with 3% hypertonic saline. Emergent hemodialysis may be needed for toxin removal, and bicarbonate may be used to alter pH for salicylate or tricyclic antidepressant overdoses. Endocrine emergencies, including myxedema coma, should be treated with thyroid hormone and supportive measures to correct hypothermia and hyponatremia[29]; and diabetic ketoacidosis (DKA) with fluids, electrolyte repletion, and insulin.[46] Finally, if infectious etiology is suspected, broad coverage with antibiotics is recommended. If there is suspicion for meningoencephalitis, empiric treatment should be started at dosing adequate for CNS penetration with concomitant administration of dexamethasone.

In the event of structural brain injury because of intracranial hemorrhage or mass, neurosurgery should be consulted for appropriate interventions, including ventriculostomy or surgery if necessitated. Emergent treatment for intracranial hypertension, if suspected, should be initiated by raising the head of the bed at or above 45 degrees, maintaining the head midline and in a neutral position to facilitate intracranial venous drainage, avoiding hypoxia, and maintaining normotension and normothermia. If needed, 0.5-1 g/kg of 20% mannitol or 2.5-5 mL/kg of 3% hypertonic saline may be given as IV bolus over 15-20 minutes. Hyperventilation for a goal partial pressure of carbon dioxide ($PaCO_2$) of 30–35 mm Hg should only be used as a bridging measure to definitive therapies. If basilar artery occlusion is identified on CT angiogram, stroke and neurointerventional specialists should be consulted immediately for possible IV tissue plasminogen activator and/or mechanical thrombectomy.

PROGNOSIS

Prognosis of coma is dependent on the underlying etiology. Most patients with coma regain consciousness, and very few persist into a prolonged minimally conscious state.[47] In general, several overarching principles portend a poor prognosis. Any injury that causes massive hemispheric swelling, a clinically deteriorating examination with loss of brainstem reflexes, basilar artery occlusion without recanalization of the vessel, TBI with corpus callosum and brainstem injury, and

pontine hemorrhage with thalamic extension are all likely to have a poor prognosis.[47]

Regarding *TBI,* as a general principle most patients who are elderly tend to have a worse prognosis. Young patients who have TBI can have a variable outcome.[47] Otherwise, the structures involved, concomitant association with cerebral edema, and time to treatment have important prognostic influence on outcome. Use of biomarkers as both diagnostic and prognostic tools is on the forefront in the hopes that these biomarkers are used in the development of therapy.[48] Likewise, the prognosis after *stroke* reaches beyond the scope of this chapter and is in part determined by a myriad of factors, including hemorrhagic versus ischemic stroke, the size of the infarct, patient characteristics and comorbidities, intervention performed, time to intervention, and a variety of other factors.

Perhaps the best prognostication studies for coma come from patients suffering from *cardiac arrest*. Before the era of targeted temperature management, Levy and colleagues[49] found that patients with postanoxic encephalopathy had several clinical examination findings portending poor outcome. Poor outcomes were associated with absent pupillary response and absent corneal reflexes. Additionally, no movement or extensor posturing to noxious stimuli predicted poor outcome.[49] With the advent of therapeutic hypothermia, these prognostic predictors have not held up, likely because of different reasons, including prolonged effects of sedating medications and paralytics used during targeted temperature management. More recent data have shown that pupillary reactivity continues to be a robust predictor of outcome, though corneal reflexes and motor response have fallen out of favor.[50] Other promising tools include EEG to assess for patterns of reactivity, somatosensory-evoked potentials, and neuroimaging.[51] Though prospective studies are needed to help guide the prognostic utility of these tools, likely a multimodal approach is best. As a general rule, the clinician should wait at a minimum 72 hours before withdrawal of any life-sustaining measures, except if the patient is brain dead, and in some cases it may take even longer for drug clearance in the age of therapeutic hypothermia.[50]

In cases of *meningitis,* patients who present with a low GCS or FOUR score are likely to have a poor outcome.[47,52] In a study by Lucas and colleagues on patients presenting with bacterial meningitis, approximately 3% presented with a GCS of 3. The GCS could in part be explained by hydrocephalus, seizures, or cerebral edema.[52] Thus poor prognosis in meningitis usually is the result of intracranial and systemic complications of the disease.

CONCLUSION

Coma is often seen in the critical care setting because of a variety of underlying pathologies. Accurate and timely diagnosis allows for rapid medical or surgical decision making regarding therapeutic intervention and management. Ultimately, treatment and prognosis are disease specific.

KEY POINTS

- Coma is a state of unconsciousness in which patients do not respond to any external stimuli. Scales to measure coma include GCS and FOUR score.
- Coma arises from dysfunction of the bilateral cerebral hemispheres, the diencephalon, or the brainstem.
- Nonstructural causes of coma include toxic-metabolic disorders, endocrine disorders, and nutritional deficiencies and comprise about two-thirds of patients presenting with coma to the emergency department. The other one-third of patients are found to have structural lesions, which are classified as supratentorial or infratentorial.
- The neurologic and physical examination helps the clinician differentiate the stages of herniation syndromes and identify any lateralizing deficit.
- The management of nonstructural and structural causes of coma is vastly different, but both require timely recognition and swift treatment.
- The mainstay of initial evaluation includes airway, breathing, and circulation.
- A detailed and thorough history may give the clinician important clues to the underlying cause of coma, and details should be obtained from family, friends, and bystanders.
- Noncontrast CT of the brain is readily available and thus is the initial diagnostic test of choice for suspicion of structural intracranial lesions. Additionally, CT angiogram and CT venogram can be obtained for evaluation of vessel abnormality such as thrombus.
- Prognostication in coma is dependent on the underlying cause of coma, though most patients regain consciousness, with few progressing to a persistent vegetative state.
- In cases of cardiac arrest, withdrawal of any life-sustaining measures should not be done before 72 hours, especially in the age of therapeutic hypothermia.

References for this chapter can be found at expertconsult.com.

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Use of Brain Injury Biomarkers in Critical Care Settings

Marie-Carmelle Elie-Turenne, Zhihui Yang, J. Adrian Tyndall, and Kevin K.W. Wang

Brain injury represents a constellation of both well- and ill-defined neurologic conditions that are the sequelae of both traumatic and nontraumatic illness, including stroke, anoxic-ischemic events, and sepsis. Traditionally, computed tomography (CT), magnetic resonance imaging (MRI), and electroencephalography (EEG) have been the diagnostic standards for differentiating brain injury from other forms of encephalopathy. In addition, these studies have been used as adjuncts to the clinical assessment in order to monitor progression, response, and resolution of neurologic disease. However, these modalities present both diagnostic and logistical challenges. In cases of clinical instability, transportation of patients to facilitate these diagnostic studies may be delayed by hours or days. Moreover, imaging and EEG may lack sensitivity in mild cases of brain injury that manifest more subtly.

The emergence of biologic fluid–based biomarkers of brain injury has great potential for aiding in diagnostics, monitoring disease, and providing therapeutic applications in neurointensive care. Specifically, brain injury biomarkers such as neuron-specific enolase (NSE) have already demonstrated some prognostic utility in patients after cardiac arrest and have potential uses in a variety of intensive care unit (ICU)–relevant central nervous system (CNS) insults such as traumatic brain injury (TBI) and stroke.[1] In this chapter, we use TBI as a prototype disease to demonstrate how brain injury biomarkers could complement conventional diagnostic and monitoring tools in ICU management.

BIOFLUID-BASED BIOMARKERS FOR DETECTING BRAIN INJURY IN THE ICU

A biomarker is defined as a "biologically based parameter that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention."[2] During brain injury, a variety of cellular changes can occur, including degeneration, protease activation, oxidative stress, and metabolic disturbances. These changes result in the shedding of specific proteins into the cerebrospinal fluid (CSF) or serum that can be identified and studied for their association with disease presence, outcome, and progression. These biofluid-based biomarkers reflect the earliest changes that occur in the cells before the evidence of injury appears on images. Therefore the use of biomarkers could offer a rapid, noninvasive, and cost-effective tool for the diagnosis of brain injury and determination of the subsequent need for additional diagnostic testing, monitoring, or therapeutic intervention.

Most biofluid-based markers of CNS injury to date are proteins or protein fragments. In the context of basic research, several brain injury biomarkers, including NSE, glial protein *S-100B*, glial fibrillary acidic protein (GFAP), and myelin basic protein (MBP), have been shown to have great utility in TBI specifically. Alpha-II spectrin protein and its breakdown products (SBDPs) are potential biomarkers of necrosis and apoptosis after TBI. The cleaved form of the axonally located microtubule binding protein tau (c-tau) has been identified as a new biomarker in mouse and rat TBI models. In addition, inflammation markers such as neurofilament-H are promising axonal injury biomarkers of various forms of acute brain damage in experimental TBI models.

Proteomics is the large-scale study of proteins, particularly their structures and functions. This field includes the study of changes in protein expression patterns as related to diseases and environmental conditions. The search for biomarkers of TBI has been approached by integrating biofluid and tissue information. This new approach takes advantage of functional synergy between certain biofluids and tissues with the potential for clinically significant findings. Using differential neuroproteomic methods, a systematic assessment has successfully identified additional protein biomarkers for TBI, such as ubiquitin C-terminal hydrolase-L1 (UCH-L1) and microtubule-associated protein 2 (MAP2), with relevant animal models.[3]

The application of basic scientific discoveries to the clinical setting remains a challenge. Systems biology (the computational and mathematical modeling of complex biologic systems) is an approach to building a holistic, systematic, and unbiased understanding of the structural and behavioral elements of biologic networks. Translating these findings into the clinical, data-driven development cycle and data-mining steps for discovery, qualification, verification, and clinical validation are needed. Data mining techniques used in this field extend beyond the level of data collection to an integrated scheme of animal modeling, instrumentation, and functional data analysis. In the context of TBI proteomics, systems biology tools can be incorporated in several ways to overcome many of the limitations of simple proteomics.[4]

CURRENT BIOMARKER CANDIDATES AND THEIR PROPERTIES

Although neurobiomarkers are not yet Food and Drug Administration (FDA) approved for clinical use, considerable research into protein biomarkers for TBI has produced several putative diagnostic and prognostic markers. Table 44.1 describes the most studied potential TBI biomarkers and reflects the current state of the art. Other possible markers include neurofilament proteins MAP2 (2A, 2B), fatty acid binding protein-H (H-FABP), brain-derived neurotropic factor (BDNF), and autoantibodies to brain antigens. But more studies are required for further clinical utility verification and biomarker characterization.

TABLE 44.1 Potential TBI Protein Biomarkers That Could Have Critical Care Utility

TBI Protein Biomarker	Full Protein Name	Origin	Human Severe TBI Data	Human Moderate-to-Mild TBI or Concussion Data
GFAP (and BDPs)	Glial fibrillary acidic protein (and its breakdown products)	Astroglial injury	Yes	Yes
UCH-L1	Ubiquitin C-terminal hydrolase-L1	Neural cell body injury	Yes	Yes
Tau (P-tau)	Microtubule-associated tau protein (phosphorylated tau protein)	Axonal injury; neurodegeneration	Yes	Yes
S100B	*S100B* protein	Astroglia/BBB	Yes	Yes
SBDPs (SBDP150, 145, and 120)	αII-spectrin breakdown products of 150, 145, and 120 kDa	Axonal injury; brain cell necrosis-apoptosis	Yes	?
MBP	Myelin basic protein	Demyelination	Yes	—
NSE	Neuron-specific enolase	Neural cell body injury	Yes	—
NF-L, NF-H	Neurofilament protein-light and -heavy	Axonal injury	Yes	—

TBI, Traumatic brain injury.

The first listed biomarker is *GFAP*. It is an astrocyte-specific intermediate filament protein known as a marker of astrocyte activation. Eight different isoforms of this protein are expressed across numerous subsets of astrocytes. Measurements of GFAP and its breakdown products have provided promising data on injury pathways, focal versus diffuse injuries, and prediction of morbidity and mortality. It has also been studied in both CSF and serum of patients with severe TBI.[5–10] Serum GFAP levels in severe and moderate TBI with Glasgow Coma Score (GCS) <12 are associated with unfavorable outcome at 6 months.[11] New enzyme-linked immunosorbent assay (ELISA) for GFAP and its breakdown products detected both mild-to-moderate TBI[12] and the full spectrum of TBI (TRACK-TBI cohort)[13] in two independent studies. Similarly, Metting and colleagues demonstrated that serum GFAP was increased in patients with an abnormal CT after mild TBI.[14] Another follow-up study using the TRACK-TBI cohort demonstrated that the combination of UCH-L1 with GFAP/BDP further improves its diagnostic utility.[15] A recent paper also found that a caspase-6–generated form of GFAP is elevated at 72 hours after cardiac arrest, but did not predict outcome.[16]

UCH-L1 is a deubiquitinating enzyme highly expressed in neuronal cells. It is one of the few markers identified using proteomic methods. In addition, its high brain specificity and abundance in brain tissue make it an attractive candidate marker. CSF and serum UCH-L1 levels were found to be elevated in patients with severe TBI, correlating with the severity and outcome of injury.[17,18] Increased levels of UCH-L1 post-TBI are proposed to be secondary to blood-brain barrier (BBB) dysfunction.[19] Several other studies also report the detectability of UCH-L1 in blood after mild TBI and with UCH-L1 levels correlating with traditional clinical assessments.[12,20] However, the utility of UCH-L1 in mild TBI with respect to its sensitivity and specificity requires further clinical assessment.

In the ALERT-TBI trial (1959 participants), UCH-L1 and GFAP assays in combination were found to discriminate those with CT abnormalities defined clinically with mild to moderate TBI when measured within 4 hours postinjury.[21] These findings in part led to US FDA clearance for testing of this combination among the mild TBI cohort.[22]

Tau is an intracellular MAP with a molecular mass of 48–67 kDa that is highly enriched in axons. TBI was found to cause the cleavage of tau protein, with elevated levels of c-tau in CSF and serum. c-tau possesses many desirable characteristics of a biochemical marker and is associated with both disruption of the BBB and postinjury cleavage of tau protein.[23] Other studies from two groups have demonstrated the significance of tau/c-tau in predicting outcome in severe TBI patients.[24,25] Similarly, several studies report the utility of tau or c-tau in the prediction of outcome in mild TBI.[26,27] However, other studies have reported the poor ability of tau protein to predict outcome and postconcussion syndrome in mild TBI.[28] Recently, two ultrasensitive assay platforms were developed to enable the robust detection of tau (and a phosphorylated form of tau) in serum from acute-phase TBI patients with various levels of TBI severity.[29]

S100B is a glia-specific calcium-binding protein. Elevated *S100B* levels accurately reflect the presence of neuropathologic conditions, including TBI or neurodegenerative diseases linked to astroglial injury. More importantly, *S100B* levels are reported to rise before any detectable changes in intracranial pressure, neuroimaging, or neurologic examination findings. *S100B* is considered a prognostic biomarker of BBB permeability and CNS injury. Several studies have reported that S100B protein might detect brain death after severe TBI.[30,31] Another study showed that serum and urine levels of *S100B* after TBIs have prognostic significance for survival and disability.[32] A similar study on serum S100B measured 24 hours after injury reported that it predicts unfavorable outcome (i.e., Glasgow Outcome Scale [GOS] score <4 or death at 3 months after injury in severe TBI patients).[33] *S100B* elevation has also been found after mild TBI.[34] Although *S100B* remains promising as an adjunctive marker, the main limitation toward its use is the lack of specificity for brain trauma; this is likely, given that *S100B* can be released by cells other than astrocytes.

αII-spectrin is a cytoskeletal protein enriched in neuronal axons and presynaptic terminals. *SBDPs* are produced by the breakdown of αII-spectrin by calpain and caspase, which are activated in the brain after TBI. SBDPs thus reflect axonal damage. SBDP150 and SBDP145 are indicative of calpain activation, often associated with acute necrotic neuronal cell death, and SBDP120 is generated by the action of caspase-3 and is associated with delayed apoptotic neuronal death. αII-spectrin has been studied primarily in the context of severe TBI. Elevation of SBDP150 and/or SBDP145 levels in CSF was reported as a possible outcome predictor in patients with severe TBI versus initial CT diagnosis with Marshall grade. SBDPs, especially CSF SBDP150, may be useful as a differential diagnostic biomarker for its ability to distinguish between focal and diffuse injury in the acute phase of TBI.[35,36] Whereas αII-spectrin is present in various nucleated cells and most tissues, its high abundance and enrichment in brain and the fact that SBDPs are injury generated make SBDPs potentially useful TBI biomarkers, especially in combination with other more brain-specific markers.

MBP is one of the most abundant proteins in white matter, composing 30% of the myelin protein. It is important in the myelination of nerves. As a constituent of the sheath, MBP is essential for normal myelination and axonal signal conduction. Several studies on severe TBI patients have reported that MBP levels could track the occurrence of post-TBI hypoxia, predict the outcome, and prompt adequate treatment.[8,37] Serum MBP is elevated in the majority of children with acute TBI, including well-appearing children with TBI from child abuse in whom the diagnosis might otherwise have been missed.[38] Most recently, a review by Kochanek and colleagues suggests that MBP is a potential biomarker for pediatric TBI.[39] Because MBP lacks clinical sensitivity, the interest in MBP as a biomarker for TBI is lower than that of *S100B*, NSE, and GFAP. One possible explanation for this lack of sensitivity is that MBP undergoes extensive fragmentation/degradation after TBI, thus complicating its robust detection by traditional sandwich ELISA.

NSE is a glycolytic enzyme that is present in central and peripheral neurons and neuroendocrine cells, with serum levels rising after cell injury. NSE is passively released into the extracellular space only under pathologic conditions during cell destruction. Acute post-TBI levels of NSE and MBP were correlated with outcome in children, particularly those under 4 years of age.[40,41] In the setting of diffuse axonal injury in severe TBI, levels of NSE at 72 hours after injury have shown an association with unfavorable outcome.[42] However, in very early studies, serum or CSF NSE was considered of limited utility as a marker of neuronal damage.[43,44] A limitation of NSE is the occurrence of false-positive results that occur because NSE is also present at high levels in red blood cells.

Neurofilament (NF) proteins are the key intermediate filaments in neurons and a major component of the axonal cytoskeleton. The major neuronal filaments in the CNS are those assembled from NF triplet proteins: neurofilament light (NF-L; 61 kDa), medium (NF-M; 90 kDa), and heavy (NF-H; 115 kDa). After TBI, calcium influx into the cell contributes to a cascade of events that activates calcineurin, a calcium-dependent phosphatase that dephosphorylates neurofilament side-arms, presumably contributing to axonal injury. Phosphorylated NF-H (pNF-H) was found to be elevated in the CSF of adult patients with severe TBI compared with controls.[45] Similarly, hyperphosphorylated NF-H has also been shown to significantly correlate with neurologic deficit in severe TBI children.[46] More recently, phosphorylated NF-H was shown to stratify lower grades of injury, with significant rises in pNF-H seen up to 3 days after mild TBI. pNF-H levels in CSF are also elevated in amateur boxers. Although pNF-H is showing promise as both a sensitive and specific marker of axonal injury after TBI, consideration of other NF isoforms is needed to stratify injury severity in TBI patients. For example, amateur boxers also have elevated CSF levels of NF-L.[27]

TBI is a complex injury: primary injury occurs at the moment of trauma, when tissues and blood vessels are stretched, compressed, and torn; secondary injury then follows. Secondary injury events include damage to the BBB, release of factors that cause inflammation, free radical overload, excessive release of the neurotransmitter glutamate (excitotoxicity), influx of calcium and sodium ions into neurons, and dysfunction of mitochondria. We thus anticipate a growing list of putative TBI biomarkers with different cell or subcellular origins and different diagnostic and prognostic properties. Such findings are also very likely for other relevant CNS insults in neurointensive care. Preclinical and clinical studies suggest the potential alteration of the following proteins in some cases of TBI: neurite degeneration markers, MAP2, amyloid β peptide (Aβ1-40, Aβ1-42), neuroinflammatory markers (microglial ionized calcium-binding adapter molecule 1, inflammasome proteins-caspase-1, Nacht leucine-rich-repeat protein-1 (NALP-1), apoptosis-associated speck-like protein containing a caspase recruitment domain (ACS),[47,48] biofluid levels of neurotropic markers (BDNF, nerve and growth factor, and heart-type fatty acid—binding protein).[49–51] Last, autoimmune markers (autoantibodies to brain antigens such as GFAP) have also been reported as potential biomarkers for subacute or chronic phases of TBI.[52] However, future work is required for their clinical utility verification and biomarker characterization.

POTENTIAL USES OF BRAIN BIOMARKERS FOR TBI PATIENT MANAGEMENT

Severe TBI

TBI severity is assessed immediately upon presentation and subsequently monitored serially using clinical examination, GCS, and cranial imaging. CT scans are useful for identifying hemorrhage, swelling, or skull fracture and direct localization information that guides possible surgical intervention. Lesions contributing to increased intracranial pressure (ICP) or intracranial hemorrhage frequently require decompressive craniectomy, ventriculostomy, or treatment to increase cerebral perfusion pressure with the objective of restoring energy and oxygen supply. During the acute phase of severe TBI, protein biomarkers are thought to be released into the CSF and/or into the circulation by passing through the disrupted BBB. These body fluid–based biomarkers represent the extent of damage to neurons or astrocytes and reflect a great diversity in outcomes, ranging from immediate death to full recovery. Thus far, no single protein biomarker can describe the complete profile of TBI pathology, which involves a complex cascade of pathophysiologic events, subsequent degeneration of various brain cell types (neurons, glia, oligodendrocytes), and deterioration of brain micro- and macrostructures and functions. Brain function relies not only on intact neurons and astrocytes but also on intact network connectivity. Thus ideally, we should use a combination of complementary TBI biomarkers that originate from different cell types or subcellular structures that are vulnerable to TBI (see Table 44.1). This approach will likely allow us to assess the extent of cellular and structural damage and, eventually, the recovery process of the brain as a whole at different stages after the initial TBI event (Fig. 44.1). Thus by serial monitoring of biofluid levels (CSF, blood) for a panel of protein biomarkers, we can gain information regarding the severity of the injury, the progression of the injury, possible occurrence of secondary insult, and prognosis of TBI patients, and may even be able to formulate personalized therapeutic strategies (Fig. 44.2).

In conclusion, we have described the importance of biofluid-based protein biomarker detection after severe TBI germane to neurointensive care. We also propose a possible logistic workflow where the use of TBI biomarker assays may be integrated into clinical practice for acute TBI patients in the critical care setting. We described several TBI protein biomarkers with potential utility in the diagnostic and management approach of TBI. A limitation at present is the lack of real-world utility, as these tests are not universally available. Establishing a point-of-care device (POC platform) that can readily provide biomarker results within minutes would serve as a potential adjunct for prompt bedside evaluation in hemodynamically unstable or critical patients. Another challenge is to determine whether we already have the optimal biomarkers for formulating the best possible biomarker panel for TBI or if we need to continue to search for more ideal candidates. The next 5–10 years promise to be an exciting time for witnessing how the implementation of TBI biomarker–based diagnostics will change medical practice regarding critical care TBI patient management and, ultimately, for the full spectrum of patients in the neurointensive care setting.

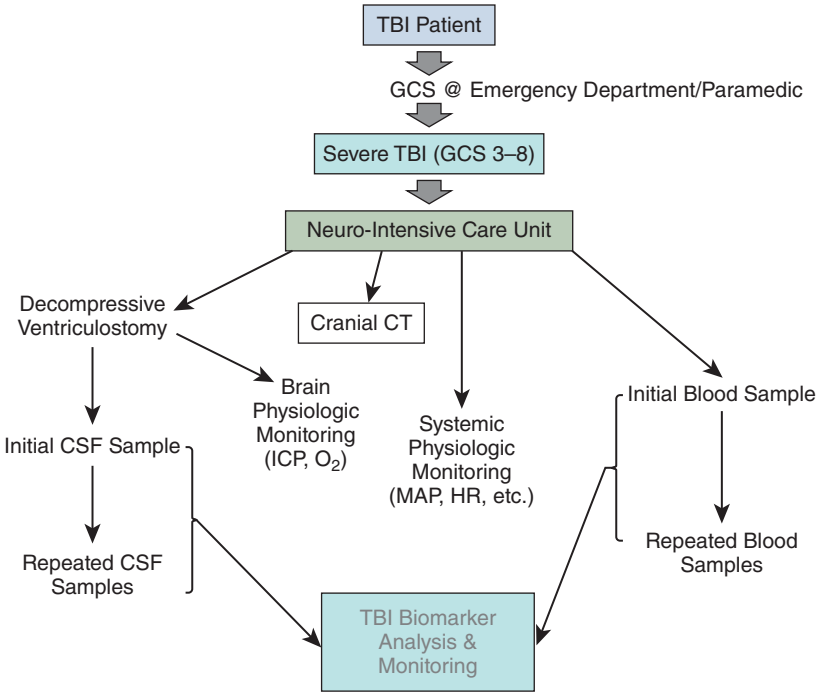

Fig. 44.1 Envisioned uses of brain biomarkers for severe traumatic brain injury *(TBI)* patient management. *CSF,* Cerebrospinal fluid; *CT,* computed tomography; *GCS,* Glasgow Coma Scale; *HR,* heart rate; ICP, intracranial pressure; *MAP,* mean arterial blood pressure.

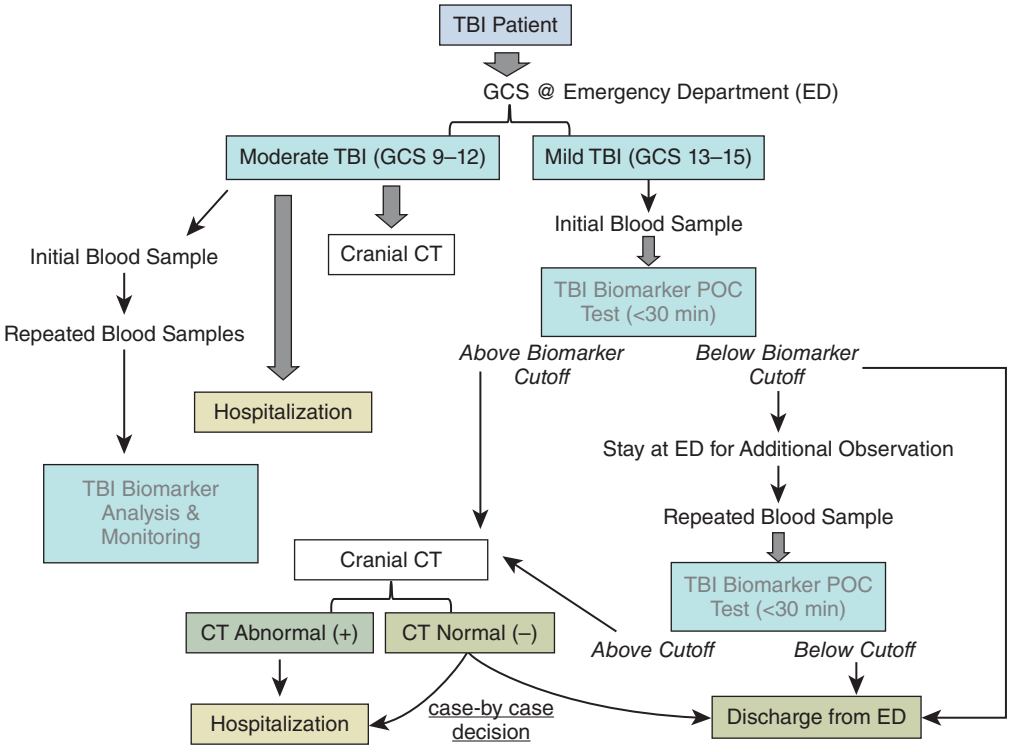

Fig. 44.2 Envisioned uses of brain biomarkers for mild-to-moderate traumatic brain injury *(TBI)* patient management. *CT,* Computed tomography; *ED,* emergency department; *GCS,* Glasgow Coma Scale; *POC,* point-of-care.

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KEY POINTS

- Serum biomarkers of brain injury are being developed for multiple purposes and applications in a wide variety of patients in the neurointensive care setting, including (1) prognostication, (2) injury severity stratification, (3) detection in occult presentations of brain injury in ICU patients, and (4) to monitor treatment effects.
- GFAP is a marker of brain injury derived from astrocytes and is showing promise for clinical translation.
- Two neuronal markers, namely UCH-L1 and NSE, also have potential to identify brain injury. NSE is currently used in some centers for prognostication after cardiac arrest.
- MBP is an emerging marker of white matter damage that is being assessed in clinical studies.
- The MAP tau is an emerging biomarker that is implicated as an initiator of chronic neurodegenerative disease, including chronic traumatic encephalopathy.

References for this chapter can be found at expertconsult.com.

ANNOTATED REFERENCES

Diaz R, Wang KK, Papa L, et al. Acute biomarkers of traumatic brain injury: Relationship between plasma levels of ubiquitin C-terminal hydrolase-L1 and glial fibrillary acidic protein. *J Neurotrauma.* 2014;31(1):19–25.
In a multicenter observational study 206 patients with traumatic brain injury combining serum levels of UCH-L1 and GFAP rendered superior sensitivity and specificity (area under the curve [AUC] 0.94) for diagnosing TBI than when evaluated in isolation (AUC 0.87 and 0.91 for UCH-L1 and GFAP, respectively).

Goyal A, Failla MD, Niyonkuru C, et al. S100b as a prognostic biomarker in outcome prediction for patients with severe traumatic brain injury. *J Neurotrauma.* 2013;30(11):946–957.
In a study of injured patients with severe TBI, researchers evaluated the temporal profile of S100B as a prognostic biomarker in both CSF ($n = 138$ subjects) and serum ($n = 80$ subjects) samples across a 6-day time course. Whereas serum S100B levels were increased post-TBI in the first 6 days, the correlation of CSF and serum levels diminished over time.

Papa L, Lewis LM, Falk JL, et al. Elevated levels of serum glial fibrillary acidic protein breakdown products in mild and moderate traumatic brain injury are associated with intracranial lesions and neurosurgical intervention. *Ann Emerg Med.* 2012;59(6):471–483.
In this prospective study of brain-injured patients presenting with Glasgow Coma Scale of 9–15, GFAP-BDP was detectable in serum within an hour of injury and was associated with injury severity, GCS score, CT lesions, and in predicting a neurosurgical intervention.

Wijdicks EF, Hijdra A, Young GB, et al. Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: Prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* 2006;67(2):203–210.
This is a systematic review of several studies of comatose patients after cardiac arrest Among other clinical and diagnostic study findings, serum neuron-specific enolase higher than 33 μg/L predicted poor outcome.

Yan EB, Satgunaseelan L, Paul E, et al. Hypoxia is associated with prolonged cerebral cytokine production, higher serum biomarker levels, and poor outcome in patients with severe traumatic brain injury. *J Neurotrauma.* 2014;31(7):618–629.
In a study of TBI patients, eight cytokines were measured in the CSF and serum over 6 days and classified as hypoxic and normoxic. Patients were divided into Hx ($n = 22$) and Nx ($n = 20$) groups. Markers of neuroinflammation, including granulocyte macrophage-colony stimulating factor (GM-CSF), interferon (IFN)-γ, and tumor necrosis factor (TNF), were prolonged in the CSF of hypoxic patients 4–5 days post-TBI. In addition, S100B, MBP, and NSE were significantly higher in Hx patients with unfavorable Glasgow Outcome Scale Extended, suggesting these markers could be used in the acute setting to detect the occurrence of post-TBI hypoxia.

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Cardiopulmonary Cerebral Resuscitation

Joshua C. Reynolds

Cardiopulmonary arrest occurs as the endpoint or consequence of many diseases. The mechanism is often unknown when treatment is initiated, and an algorithmic approach titrated to real-time monitoring is used. When the cause is known or suspected, individualized therapy can be directed at that cause. In all cases, management has two priorities: (1) rapid restoration of cardiopulmonary function and (2) minimization of ischemic damage to end organs, especially the brain. Restoration of circulation is composed largely of mechanical, pharmacologic, and electrical treatment. In contrast, treatment of brain and other organ injury primarily involves prevention of reperfusion-mediated and secondary cellular and molecular events using specific and detailed intensive care. Meaningful survival is unlikely without detailed attention to the longitudinal scope of this disease.

From the first introduction of closed-chest compressions until 2000, there was little change in long-term survival after cardiac arrest.[1,2] However, subsequent regional efforts to improve resuscitation practices at multiple levels, including emergency response and post–cardiac arrest care, have yielded significant improvements in meaningful survival.[3,4] Specific patterns of physiologic changes after cardiac arrest have been described, and there is accumulating evidence about which aspects of post–cardiac arrest management influence final outcomes.[5–7] Improving outcomes further requires an integrated approach to immediate resuscitation, subsequent intensive care management, and post–intensive care recovery. This chapter reviews the epidemiology of cardiac arrest, the initial approach for reversing cardiopulmonary arrest, modifications of this approach appropriate for specific disease states, and post–cardiac arrest intensive care oriented around minimizing secondary brain injury.

EPIDEMIOLOGY

In industrialized countries, heart disease is the overall leading cause of death, with an incidence of cardiopulmonary arrest outside the hospital ranging from 55 to 120 events per 100,000 people per year.[8–11] Median survival after out-of-hospital cardiac arrest is estimated at 10.6%,[8] but the range varies regionally from less than 2%[12,13] to 16% in certain exemplary systems.[11] The incidence of cardiac arrest in hospitals is about 0.17 events per hospital bed per year.[14] For inpatients experiencing cardiac arrest, median survival to hospital discharge is about 20%.[15] Almost half of in-hospital cardiac arrests occur in an intensive care unit (ICU) setting, where survival is higher than that in an unmonitored unit.[15] Respiratory insufficiency is the most common preexisting condition for in-hospital cardiac arrest,[15] and as many as 17% of episodes of respiratory compromise in hospitals progress to cardiac arrest.[16]

Although out-of-hospital cardiac arrest is more common in men than in women, both outside[10] and inside hospitals,[14] the incidence of cardiac arrest is higher in women (6%) than in men (4.4%) who are admitted to a hospital for acute myocardial infarction (MI).[17] Cardiac arrest outside a hospital affects blacks and Latinos more than Caucasians or Asians,[10,12,18] and rates are higher in neighborhoods composed of minority and lower-socioeconomic-status populations. These groups are also more likely to have a cardiac arrest, less likely to have bystander cardiopulmonary resuscitation (CPR), and less likely to survive.[19,20] Although sudden death can affect patients of all ages, the mean age for sudden cardiac arrest is between 65 and 70 years in most studies.[10,11,14]

Most mortality after cardiac arrest is attributable to cardiopulmonary collapse or brain injury. Only one-third to one-half of patients who collapse outside a hospital and only 44% of patients who collapse in a hospital have restoration of circulation long enough to be admitted to the ICU.[14] Approximately two-thirds of patients who are admitted to a hospital after an out-of-hospital collapse[21] and 60% of patients who are resuscitated from cardiac arrest in a hospital[14] die before discharge from the hospital. Variation around this estimate differs between academic medical centers and tends to be higher in hospitals with higher case volume, higher surgical volume, and greater availability of invasive cardiac services.[8] Postischemic brain injury is the most common reason for in-hospital death after out-of-hospital cardiac arrest,[14,22] whereas multiple organ failure is more common after in-hospital cardiac arrest.[23] Failure to awaken contributes to withdrawal of life-sustaining treatment for about 61% of out-of-hospital cardiac arrest patients.

RESTORING CIRCULATION

Acute treatment of cardiac arrest consists of two concurrent, goal-directed activities: (1) artificial circulation of oxygenated blood to the heart and brain and (2) electric shock to terminate ventricular fibrillation (VF) and other unstable tachydysrhythmias (Fig. 45.1). Continuous, uninterrupted, high-quality chest compressions are the cornerstone of resuscitation,[24] whereas electrical rescue shocks are used only when appropriate.[25] The organization of an electrocardiogram (ECG) and the presence of a pulse will prompt appropriate selection of therapy. The recommended division of time and prioritization of activities to accomplish these goals is depicted in Fig. 45.2. All other treatments, including medications and advanced airway maneuvers, are designed to supplement these two core activities, and their optimization necessitates minimal interruption. Focused bedside ultrasound evaluation can aid in the assessment of critically ill patients and identify reversible causes only if performed without interrupting resuscitation.[26] The American Heart Association and European Resuscitation Council provide consensus scientific statements about the acute management of cardiac arrest, including a detailed review of specific drugs and procedures.[27] The following sections provide an overview of airway management, circulation support, rescue shock for defibrillation, and drug therapy.

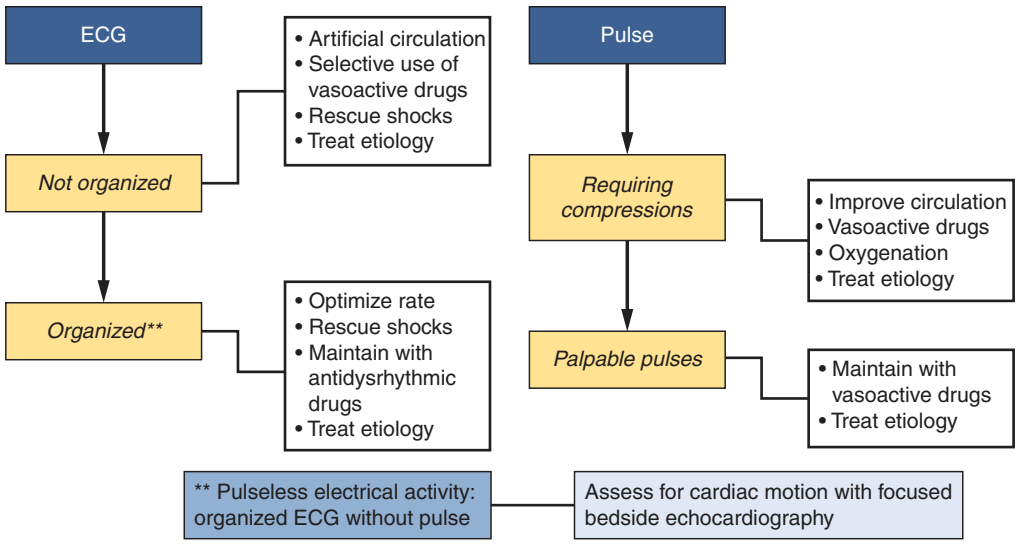

Fig. 45.1 Continuous reassessment of the patient during cardiac resuscitation relies on an electrocardiogram (ECG) and on the presence of cardiac mechanical activity (pulses). If an organized ECG is not present, interventions should be undertaken to restore an organized ECG. If mechanical cardiac activity is not present, interventions should be undertaken to improve mechanical cardiac activity. Achieving both goals results in return of circulation.

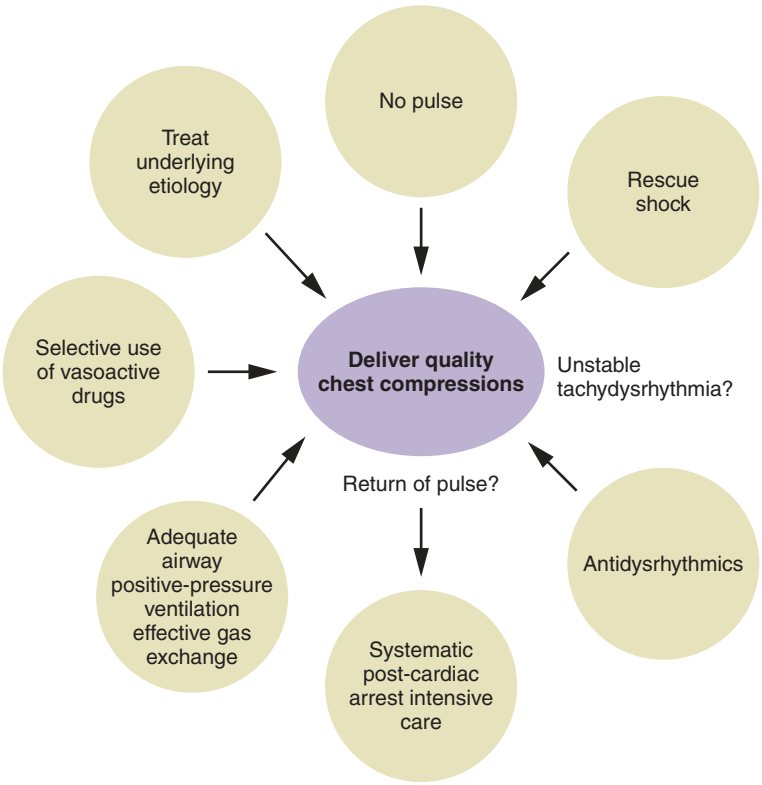

Fig. 45.2 Prioritization of activities must occur during cardiac resuscitation. *Central circle* emphasizes that core activity of chest compression should be interrupted only to provide rescue shocks when appropriate or when restoration of circulation occurs. All drugs, airway devices, and other interventions are designed to augment either artificial circulation or defibrillation. None of these adjuncts should interrupt or detract from providing artificial circulation. *VF,* Ventricular fibrillation.

Airway and Gas Exchange

Obstruction of the airway occurs in patients with impaired consciousness, including cardiac arrest, preventing oxygenation and ventilation.[28] Agonal respiration occurs after acute cardiac arrest for an additional 1–2 minutes,[29] which may confuse lay people and delay the recognition of cardiac arrest. Although associated with survival, it is unclear whether agonal respiration generates sufficient ventilation to support life.[30] Regardless, artificial ventilation is required for patients requiring more than momentary resuscitation efforts.

Simple maneuvers to open the airway include extension of the neck (head tilt) and forward displacement of the mandible (chin lift or jaw thrust). Insertion of an oropharyngeal or nasopharyngeal airway can displace the tongue from the posterior pharynx. Positive-pressure ventilation using mouth-to-mouth or bag-valve-mask (BVM) ventilation with as little as 400 mL in adults (6–7 mL/kg) delivered over 2–3 seconds will cause the chest to rise.[31] Minute ventilations smaller than those required for long-term support probably provide adequate gas exchange during cardiac arrest. Conversely, hyperventilation or hyperexpansion of the chest can impair venous return and decrease circulation during resuscitation.[32]

The need for gas exchange must be balanced against the fact that even brief interruptions in chest compressions reduce coronary perfusion pressure (CPP) (Fig. 45.3).[33] In swine, comparison of different chest compressions to ventilation ratios suggests that two breaths per 50 or more chest compressions are optimal for resuscitation.[34] One innovative practice to reduce interruptions in compressions is to provide chest compressions without any artificial ventilation[35] or with passive insufflation of oxygen.[36] Accounting for anatomic dead space, chest compressions alone probably do not generate significant ventilation in humans.[28,37] As a compromise, some systems deliver uninterrupted chest compressions and asynchronous positive-pressure breaths. A large, randomized trial comparing continuous compressions with positive-pressure ventilation to interrupted compressions at a ratio of 30 compressions per two ventilations found no meaningful difference in survival or short-term favorable neurologic recovery.[38] Regardless of ratio, the duration of any pause to deliver breaths must be minimized.

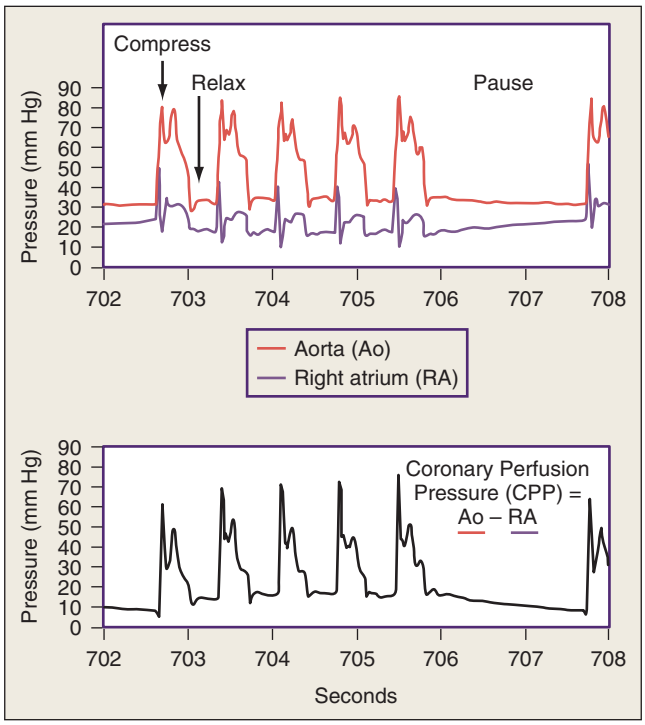

Fig. 45.3 Chest compressions provide coronary perfusion by creating a pressure gradient between the aorta (***Ao***) and the inside of ventricles (approximated by the right atrium [***RA***]). The gradient between sites is the coronary perfusion pressure (*CPP*). During chest compression, pressure increases in both Ao and RA. During relaxation, pressure persists in Ao more than in RA. Thus myocardial blood flow is most related to CPP during the relaxation phase of chest compressions. Note that CPP declines within 1–2 seconds when compressions pause for ventilation. (Unpublished laboratory data.)

Waveform capnography can confirm ventilation and monitor adequacy of circulation. During cardiac arrest, end-tidal CO_2 is related to cardiac output and pulmonary blood flow.[39] Therefore CO_2 levels may be very low (<10 mm Hg) at the onset of resuscitation. Adequate artificial circulation will cause CO_2 levels to increase, and these levels may be used as a feedback to improve or modify chest compressions. An end-tidal CO_2 level greater than 15–16 mm Hg is associated with successful cardiac resuscitation.[40,41] Conversely, end-tidal CO_2 less than 10 mm Hg after 20 minutes of resuscitative efforts can confirm failure of resuscitation.[42] Common resuscitation drugs disrupt the association between capnography readings and pulmonary blood flow: epinephrine infusion reduces CO_2 levels, and sodium bicarbonate infusion produces a transient elevation of CO_2 levels. An abrupt increase in end-tidal CO_2 levels, usually to levels over 35 mm Hg, may be useful in recognizing the return of circulation, without interrupting chest compressions for pulse checks (Fig. 45.4).

Airway Devices

The most common ventilation device used by rescue personnel, paramedics, and other healthcare providers is a self-inflating bag attached to a face mask (BVM), which requires adequate training and practice for ventilation success by a single provider. Two providers achieve more reliable airway management. BVM ventilation also pushes air into the stomach,[43] which can promote emesis and abdominal distention, impair venous return, and reduce lung compliance.[44] Normal esophageal resistance to air entry into the stomach (15–20 cm H_2O)[45] declines with loss of muscle tone during cardiac arrest (5–8 cm H_2O).[46]

Tracheal intubation with a cuffed tracheal tube secures the airway definitively and protects from emesis. However, laryngoscopy typically requires an interruption in chest compressions. Observational studies found extremely long interruptions in chest compressions during "uncomplicated" tracheal intubation.[47] Conversely, supraglottic airway adjuncts such as laryngeal tubes (e.g., King LT) or laryngeal mask airways can temporarily secure the airway during resuscitation.[48,49] These devices have the advantage of blind insertion within seconds without laryngoscopy or associated interruptions in chest compressions.[43]

Three randomized trials of out-of-hospital cardiac arrest subjects conducted in different emergency response systems with ranges of intubation success (52%–98%) compared various advanced airway strategies with BVM.[50–52] Subjects randomized to BVM were subject to variable durations of BVM while preparing for device insertion. One trial explicitly allowed crossover between interventions at the discretion of providers. Even in settings with high tracheal intubation success rates, an advanced airway (supraglottic airway or tracheal intubation) did not improve survival or neurologic outcome compared with BVM. The rationale for transitioning from BVM to advanced airways is contingent on clinical context, patient anatomy, aspiration risk, and oxygenation and ventilation success. If an advanced airway is required, providers should select a device (supraglottic airway or tracheal intubation) based on the clinical context and their individual skill set.

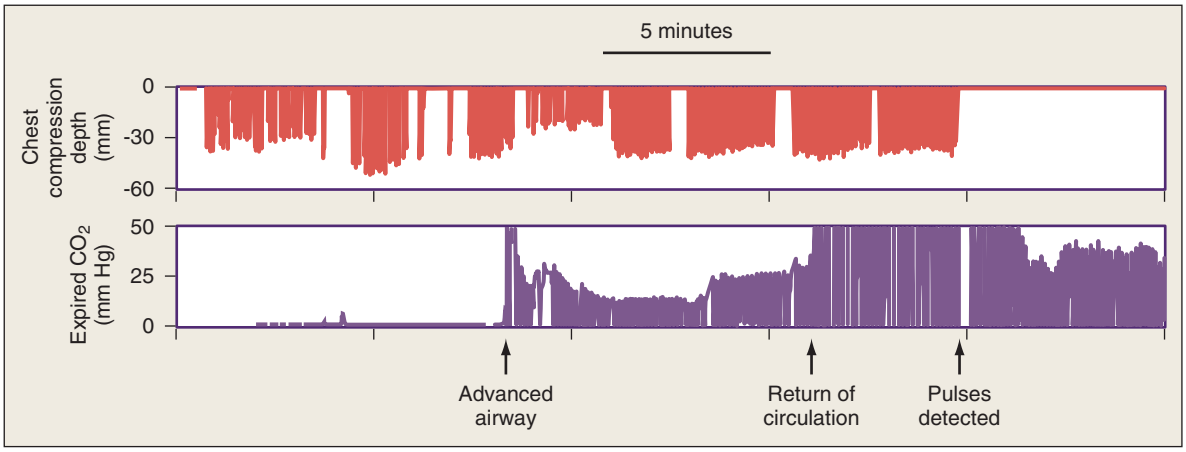

Fig. 45.4 End-tidal CO_2 changes during resuscitation. Tracings from monitor-defibrillator with an accelerometer to measure chest compression depth *(top trace)* and waveform capnography to measure exhaled CO_2 *(bottom trace).* Exhaled CO_2 confirms correct placement of an advanced airway. Note frequent interruptions in chest compressions before placing an advanced airway. More continuous chest compressions are followed by an abrupt rise in exhaled CO_2, corresponding to a return of circulation, including pulmonary circulation. Chest compressions continue for 2–3 minutes until providers detect a palpable pulse.

Ultimately, resuscitated patients with coma or continued respiratory failure will require tracheal intubation.

Artificial Circulation

In patients without a pulse, compression of the heart and chest by repetitive depression and release of the sternum circulates blood. The critical parameter for restoring myocardial energy stores, and thus spontaneous circulation, is the development of adequate CPP. CPP is the pressure gradient between the aorta and the inside of the ventricles at the end of diastole or during the relaxation phase of chest compressions. Most blood flows through the ventricular walls during diastole or during the relaxation phase of chest compressions, when ventricular pressure is the lowest (see Fig. 45.3). CPP is highly correlated with myocardial perfusion and consequently with the likelihood of resuscitation.[53] In humans, return of circulation requires that the developed CPP exceeds 15–20 mm Hg.[53]

Peak arterial pressure or palpable pulses measured during chest compressions do not necessarily represent CPP because ventricular pressures are simultaneously elevated. Consequently, palpation of pulses and systolic pressures developed by chest compressions may be misleading. It is most useful to follow the "diastolic" or relaxation-phase arterial pressure. If unable to follow any of these pressures, the clinician must rely on indirect evidence of myocardial perfusion, such as improved electrical and mechanical activity or increased pulmonary CO_2 excretion.

Even brief interruptions in chest compressions decrease CPP, and interruptions are inversely associated with restoring circulation and survival.[24] When chest compressions are measured during actual resuscitations by paramedics or hospital providers, interruptions and pauses are frequent.[54,55] Some monitor-defibrillators now have features to measure and record chest compressions and to provide real-time feedback about depth and rate to providers.[56] These features have no detectable effect on survival.[57] The chest compression fraction is one metric of compression continuity that is emphasized as a component of high-quality resuscitation[24] (Fig. 45.5), and many clinicians feel that the real-time and automated feedback is a useful safety and quality improvement mechanism to enhance total system performance.

Until the 1960s, thoracotomy was the standard approach for treatment of sudden cardiac arrest, but this procedure has now been supplanted by closed-chest compressions. Direct cardiac compression is more effective than external chest compressions, producing roughly a threefold increase in CPP.[58–60] This approach also allows recognition of cardiac tamponade, treatment by pericardiotomy, direct visualization of mechanical activity and fibrillation, and direct electrical defibrillation or pacing. In the setting of cardiopulmonary collapse resulting from exsanguination, thoracotomy also allows for aortic compression to shunt blood to the heart and brain and to direct control of intrathoracic bleeding. It should be considered in specific clinical circumstances, such as patients with traumatic cardiac arrest or recovering from recent cardiac surgery.

To improve delivery of uninterrupted chest compressions, a variety of mechanical devices have been developed.[24,33,61–63] Some of these devices exploit circumferential compression or active compression/decompression of the chest. A Cochrane review of mechanical versus manual chest compressions for cardiac arrest found no evidence of benefit of mechanical compressions in the return of spontaneous circulation or survival to hospital admission, and a subsequent pragmatic randomized trial found no improvement in 30-day survival.[63,64] Although no current device is superior to well-conducted manual compressions, these devices may play a role in providing chest compressions in settings where manual compressions are difficult or impossible (e.g., during ambulance transport, under the fluoroscopy arm, or when multiple providers are not available) or as a bridge to recovery and/or definitive treatment of the suspected etiology (e.g., extracorporeal circulatory support, percutaneous coronary revascularization, fibrinolysis of massive pulmonary embolism).

Extracorporeal Circulation

Extracorporeal perfusion for restoration of circulation (ECPR) can be used to resuscitate subjects for whom chest compressions have failed.[65–67] However, this approach requires specialized technical skill, system commitment, and increased costs and risks. Logistical issues include limited availability of perfusion equipment, setup time for circuit priming, and delays in establishing adequate venous and arterial access. Portable cardiopulmonary bypass devices that can be

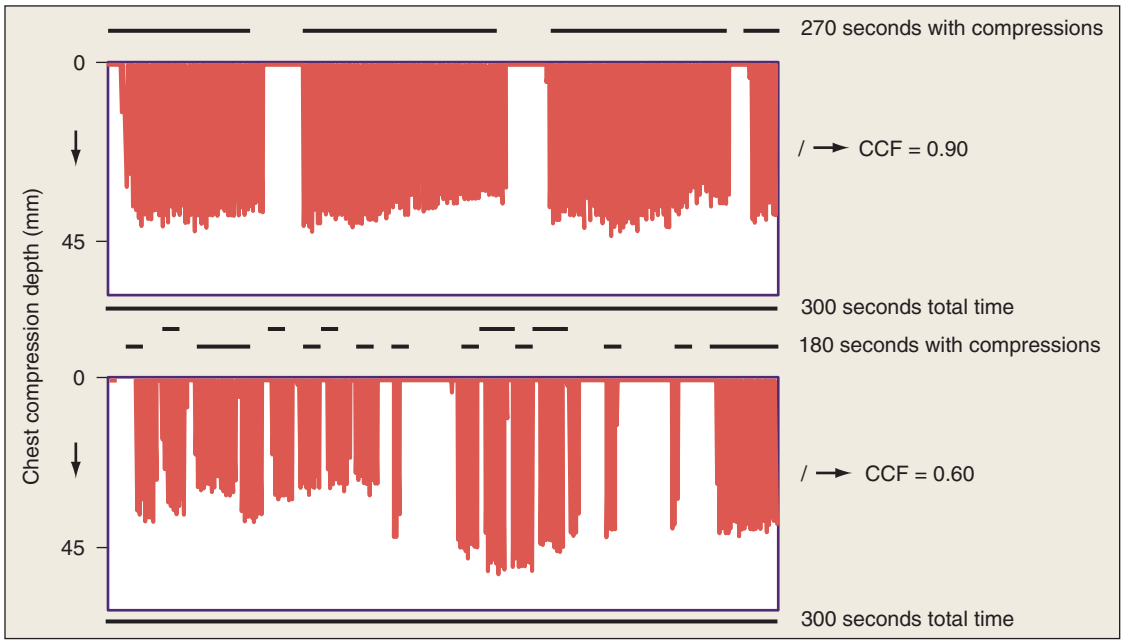

Fig. 45.5 Chest compression fraction (***CCF***) describes the continuity of chest compressions during resuscitation. Tracings of chest compressions detected by the accelerometer of a monitor-defibrillator can be used to calculate the proportion of time when chest compressions are occurring. In the *top tracing*, there are few pauses, and CCF is 0.90. In the *lower tracing*, frequent interruptions for breaths or procedures result in a CCF of 0.60.

primed quickly, along with improved techniques for rapid vascular access, have broadened the use of ECPR.

Multiple observational studies demonstrate the operational feasibility of ECPR and suggest the possibility of improved clinical outcomes, but it remains critical that ECPR be used for appropriately selected patients.[68] The ideal candidate is young with a witnessed cardiac arrest from a shockable rhythm, with a presumed cardiac (or other reversible) etiology, who receives immediate CPR and who has a brief interval until successful cannulation and commencement of extracorporeal resuscitation.[69] Examples of selection criteria from three centers are given in Table 45.1.

The timing of ECPR is equally important because irreversible myocardial and neurologic injury can preclude survival despite mechanically restoring circulation. Conventional resuscitation is clearly

TABLE 45.1 Sample Selection Criteria for Extracorporeal Perfusion for Restoration of Circulation (ECPR)

	Surugadai Nihon University Hospital Tokyo, Japan	Sharp Memorial Hospital San Diego, California	Alfred Hospital Melbourne, Victoria, Australia
Inclusion criteria	Age 18–74	Persistent cardiac arrest	Age 18–65
	Witnessed cardiac arrest	Shock refractory to standard therapies	Suspected cardiac etiology
	Presumed cardiac etiology		Any CPR within 10 minutes of collapse
	EMS arrival ≤15 minutes		Initial rhythm of ventricular fibrillation
	Defibrillation by AED or EMS personnel		30 minutes of persistent cardiac arrest
	Persistent cardiac arrest on arrival to ED		
Exclusion criteria	Presumed noncardiac etiology	Initial rhythm of asystole	Known preexisting significant neurologic disability
	Successful ROSC ≤10 minutes of arrival to ED	Any CPR not initiated ≤10 minutes of cardiac arrest	Known significant end-stage comorbidities
	Core body temperature <30°C on arrival to ED	Estimated EMS transport time >10 minutes	Terminal illness because of malignancy
	Pregnancy	Total arrest time >60 minutes	
		Suspicion of sepsis or hemorrhage	
		Preexisting severe neurologic disease	

Sample selection criteria for extracorporeal life support (ECLS) in out-of-hospital cardiac arrest (OHCA).
AED, Automatic external defibrillator; *CPR,* cardiopulmonary resuscitation; *ED,* emergency department; *EMS,* emergency medical services; *ROSC,* return of spontaneous circulation.

preferred when patients have early recognition, early high-quality chest compressions, and early defibrillation. However, increasing the duration of treated cardiac arrest decreases the odds of functionally favorable survival (as low as 1%–15%, depending on case features, initial cardiac rhythm, witnessed collapse, and bystander CPR).[70] Observational data of ECPR candidates treated with traditional resuscitation suggest the therapeutic window for conversion to ECPR occurs after 10–20 minutes of professional resuscitation.[71] Several randomized trials of ECPR are in progress.

Electrocardiogram Monitoring

Continuous three-lead ECG monitoring is essential for guiding resuscitation. A practical approach is to divide rhythms into organized and nonorganized. Organized rhythms include supraventricular rhythms or ventricular tachycardia (VT). Nonorganized rhythms include VF and asystole. Nonorganized rhythms cannot support cardiac output, regardless of volume status, cardiac muscle state, or vascular integrity. Therefore restoring cardiac electrical activity to an organized rhythm is an essential step in resuscitation. Organized rhythms can support cardiac output unless they are too slow (<30–40 complexes/min) or too fast (>170–180 complexes/min). An organized rhythm in the absence of a palpable pulse is termed *pulseless electrical activity* (PEA).

As the incidence of PEA as the initial cardiac rhythm increases, with a relative decrease in the incidence of VF,[10,72–74] PEA is an area of increased study and focus. Point-of-care echocardiography during resuscitation allows for more nuanced assessment of PEA. PEA may be subdivided into an organized rhythm in the absence of palpable pulse with or without echocardiographic motion ("true PEA" vs. "pseudo-PEA"). In cases of pseudo-PEA, pausing compressions and administering vasopressors may aid in restoring circulation.[75] Alternatively, cases of pseudo-PEA with insufficient cardiac output from a tachydysrhythmia and dwindling preload should be corrected by rescue shock.

The absence of perfusion with slow organized electrical activity may result from primary myocardial injury (e.g., massive MI) or from uncoupling of electrical and mechanical activity (e.g., prolonged circulatory arrest). The rate of complexes may be used to monitor resuscitation efforts. With increasing ischemia, energy depletion will occur in the electrical system and the rate of PEA will slow down. If resuscitation improves the energy state of the heart, the rate of PEA will accelerate. Narrow complexes reaching rates of 80–100 beats per minute often herald the return of a pulse. Falling rates reflect unsuccessful resuscitation efforts.

VF and asystole lie along a continuum of not-organized ECG. Arbitrary peak-to-peak amplitude of the ECG is usually used to distinguish asystole (amplitude <0.1–0.2 mV) from VF (amplitude >0.2 mV).[76] However, VF also exhibits temporal structures that may be absent in asystole.[77] VF is a chaotic electrical activity formed by multiple interacting waves of activation within the heart.[78] VF emerges from broken wavefronts that result from areas of ischemia (e.g., MI), areas of prolonged refractoriness (e.g., drug-induced or inherited prolonged QT intervals), or too-rapid succession of activation potentials (e.g., tachycardia or an "R on T" premature beat). As the organization and amplitude of these waves decline because of ischemia or hypoxemia, the amplitude of the ECG also declines. Reperfusion of the heart in asystole may restore VF. Furthermore, the amplitude and organization of the VF increases with reperfusion, providing a marker of adequate artificial perfusion.

Rational Use of Rescue Shocks for Defibrillation

Delivery of immediate transthoracic electric rescue shocks to patients in VF can convert VF into an organized cardiac rhythm. Rescue shocks are highly effective when VF is for a very brief duration (<1–2 minutes). These shocks may work by depolarizing the heart, canceling the original wavefronts, or prolonging the refractory periods.[78] Although rescue shocks can successfully restore an organized rhythm, repeated shocks may directly damage the myocardium.[79] Optimal therapy should provide rescue shocks at the lowest effective energy while minimizing the number of unsuccessful rescue shocks.

In the out-of-hospital setting when the collapse is not witnessed by paramedics, only 9%–12% of rescue shocks restore an organized ECG,[80,81] and most shocks convert VF into asystole.[82] Even after successful defibrillation, VF may recur because of incomplete depolarization by the shock, heterogeneous areas of refractoriness, or persistent foci of chaotic activity.[83] Multiphasic shock waveforms are more effective for depolarization of individual myocytes and require less energy than monophasic waveforms.[78] Consequently, most available defibrillators deliver biphasic waveforms. Increasing pressure of paddles from 0.5 kg to 8 kg on the chest decreases transthoracic impedance by as much as 14% and increases delivery of current to the heart.[84,85] This advantage of paddles must be weighed against the increased safety and convenience afforded by hands-free self-adhesive defibrillation pads, which are now used in most settings. In the past, multiple shocks would be delivered in rapid succession to decrease chest impedance. However, repetitive shocks decrease chest impedance by about 8% or less in actual patients,[84,86,87] which does not justify the interruption of artificial circulation to deliver "stacked" shocks. Reducing the interruption in chest compressions before and after a rescue shock is associated with greater resuscitation success,[88] which led to the coining of the term *perishock pause*. Duration of the perishock pause is inversely associated with survival to hospital discharge.[89] Specific techniques to reduce the perishock pause include continuing chest compressions while the defibrillator is charging, only stopping at the last moment before shock, and eliminating the postshock pulse check. Alternatively, manual compressions may be continued during rescue shocks if the rescuer is using Class 1 electrical insulating gloves complying with International Electrotechnical Commission (IEC) standards and modern self-adhesive defibrillation pads. In this scenario, the risk of shock to rescuers from touching a patient during defibrillation is small.[25]

For VF that has lasted more than 3–4 minutes, preclinical data suggest that delaying rescue shocks until after a few minutes of chest compressions will improve success.[90–93] To date, two clinical studies in out-of-hospital cardiac arrest patients have found that either 90 seconds or 3 minutes of chest compressions before delivery of the initial rescue shock improved resuscitation rates for subjects with VF outside a hospital, particularly when rescuer response intervals were longer than 4 minutes.[2,94] However, a third study found no difference in outcome with 5 minutes of chest compressions before shock,[95] and a fourth study found no difference in outcome with 3 minutes of chest compressions before shock.[96] Finally, a large multicenter trial comparing immediate rescue shock to 3 minutes of chest compressions before rescue shock stopped enrollment, finding no difference between groups.[97] Taken together, the clinical data suggest that the first rescue shock for VF should be delivered as soon as possible within 3–5 minutes as long as chest compressions are started immediately but that there is no reason to intentionally delay the rescue shock.

Quantitative analysis of the VF waveform can distinguish early VF from late VF and may be useful in estimating the likelihood of rescue shock success.[98] Larger amplitude of VF[99] in addition to frequency-based measures and nonlinear dynamic measures of VF organization[100–103] are associated with a higher probability of rescue shock success. Future generations of defibrillators may provide real-time, semiquantitative estimates of the probability that a rescue shock will succeed in restoring an organized rhythm. It is unknown if these quantitative measures will be clinically useful for titrating resuscitation.

Beta-blockade with a short-acting agent such as esmolol represents another therapeutic option for VF. Beta-activation (e.g., systemic epinephrine) increases myocardial oxygen requirements, worsens ischemic injury, lowers the VF threshold, and worsens postresuscitation myocardial function.[104–106] Blocking beta-receptors may terminate the electrical storm responsible for refractory VF.[104–108] Esmolol is a favorable agent given its ultra-short half-life.[109] Low-certainty observational evidence suggests that beta-blockade is associated with improved clinical outcomes, primarily restoration of circulation, and short-term survival.[110]

Drug Therapy

Drug therapy in cardiac arrest can be divided into three categories: pressors, antidysrhythmics, and metabolic drugs. Pressors are used during resuscitation and include epinephrine and vasopressin. Both of these drugs can increase CPP via the alpha-adrenergic (epinephrine) or vasopressin receptors (Fig. 45.6).[111,112] Epinephrine is usually administered in 1-mg (~0.015 mg/kg) increments. In laboratory studies, the pressor effects of epinephrine during cardiac arrest were brief (~5 minutes). Vasopressin is administered as 40-unit boluses (~0.5 units/kg) and produces a longer-lasting increase in CPP (~10 minutes).

Epinephrine consistently improves return of circulation and survival, but its effects on neurologic recovery are less certain. Older clinical trials testing moderate (7 mg vs. 1 mg) and higher (15 mg vs. 1 mg) initial boluses of epinephrine found higher rates of pulse restoration and admission to hospital, but overall survival was not significantly different.[113–115] Accumulated beta-adrenergic toxicity likely increases myocardial oxygen consumption, ectopic ventricular arrhythmias, hypoxemia from pulmonary arteriovenous shunting, and postarrest myocardial dysfunction.[116] However, higher doses of epinephrine may impair cerebral circulation, a detrimental effect that may offset any benefit from increasing rates of restoration of circulation.[117,118] A massive, population-based, matched cohort study found that prehospital epinephrine was associated with restoration of circulation but with lower probability of 1-month survival and favorable functional outcome.[119] Taken together, these data raised the worrisome possibilities that when epinephrine is required to restore cardiac activity, severe brain injury has already occurred or that it contributes to brain injury.[117] Two randomized trials comparing epinephrine with placebo in out-of-hospital cardiac arrest consistently demonstrated superior return of circulation, survival to hospital admission, and survival to hospital discharge.[120,121] One trial noted additional survivors with worse neurologic outcome at hospital discharge in the epinephrine arm, but also improved survival to 3 months without statistical difference in favorable or unfavorable neurologic outcomes.[121] The net increase in survivors constituted those with both favorable and unfavorable neurologic outcomes. Of note, neurologic status of initially comatose cardiac arrest survivors can improve for up to 6 months.[122]

The optimal dosing and timing of epinephrine remain an active area of investigation. Both drugs should ideally be titrated to improvement in clinical indicators (ECG waveform, mechanical activity, changes in end-tidal CO_2 or diastolic arterial pressure as a surrogate for CPP). Rote, repeated administration is unlikely to result in meaningful outcome improvements. Titrated epinephrine infusions may balance the positive and negative physiologic effects, but this approach has not yet been explored clinically. The concept of goal-directed cardiac arrest resuscitation is an emerging paradigm within resuscitation science supported by preclinical and preliminary clinical work.[123,124]

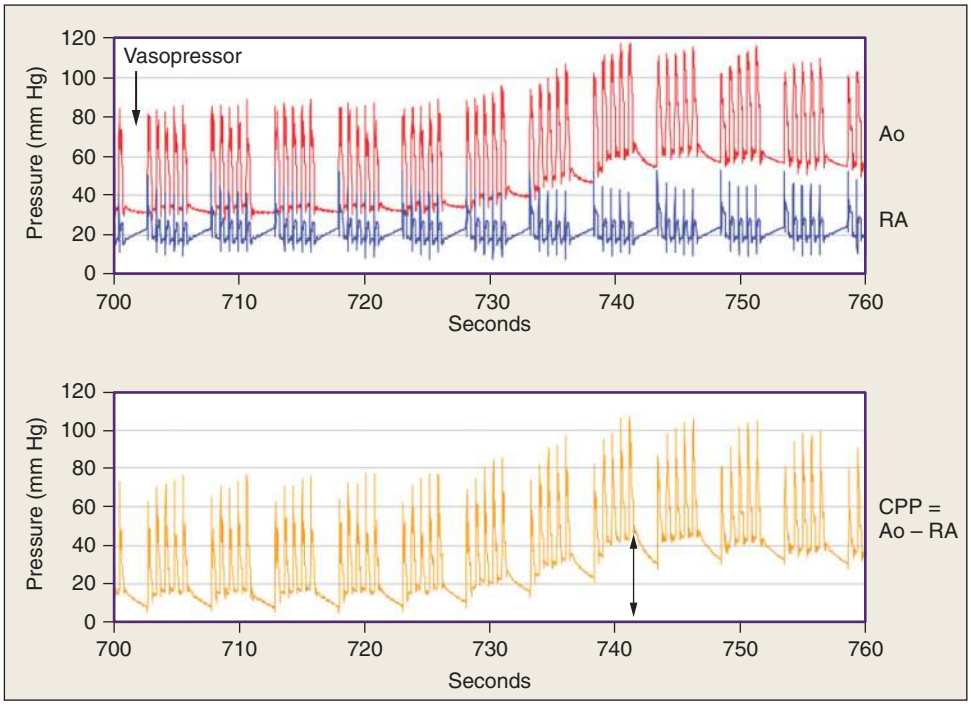

Fig. 45.6 Administration of a vasoactive drug can increase coronary perfusion pressure (*CPP*) produced by chest compressions. Note that CPP generated by chest compressions alone is below the 15–20 mm Hg believed necessary for restoration of circulation. However, aortic pressure (*Ao*) and thus CPP increase above this threshold 40–60 seconds after drug administration *(arrow)*, whereas right atrial (*RA*) pressure remains unchanged. When treating cardiac arrest, it is reasonable to expect the vasoactive drug will act after 60 more seconds of chest compressions. (Unpublished laboratory data.)

Vasopressin can increase CPP without complicating beta-adrenergic effects. Resuscitation rates and survival are identical for patients resuscitated with vasopressin and standard doses of epinephrine after in-hospital[125] or out-of-hospital cardiac arrest.[126] Some post hoc analyses suggest vasopressin may be superior for resuscitation and survival of patients whose first ECG rhythm is asystole and for those subjects requiring multiple doses of vasopressors.[126] Subsequent trials of the combination of epinephrine with vasopressin versus epinephrine alone found no difference in outcome with the different combinations of drugs.[127,128] Given its lack of clear advantage over epinephrine, vasopressin is typically excluded from treatment guidelines and algorithms in the interests of simplification.

The role of antidysrhythmic drugs during cardiac arrest is equivocal.[129,130] Atropine may relieve bradycardia when it is vagally mediated. However, nervous system influences on the heart are largely eliminated after more than 1–2 minutes of circulatory arrest. Therefore there is little expectation that atropine will improve resuscitation from asystole or PEA. Lidocaine, procainamide, and bretylium have a long history of use in the treatment of VF. Once VF is established, lidocaine can increase the electrical energy required to defibrillate by more than 50%.[131] Other classes of antidysrhythmics without sodium channel blockade do not alter defibrillation energy requirements. For example, amiodarone (5 mg/kg) is superior to placebo[132] and to lidocaine[133] in terms of restoring the pulse in out-of-hospital patients with VF that is not terminated by three rescue shocks. A large clinical trial comparing amiodarone, lidocaine, or placebo for shock-refractory VF found no overall difference in survival.[134] However, both lidocaine and amiodarone were superior to placebo in the subgroup of witnessed VF.

Empiric treatments of metabolic disturbances with bicarbonate or other buffers may improve acidemia resulting from ischemia, but do not necessarily translate into improved clinical outcomes.[135,136] Originally proposed as an antagonist of adenosine released during ischemia, two prospective studies of aminophylline in subjects with PEA or asystole found no improvement in resuscitation.[137,138] Use of dextrose-containing fluids versus dextrose-free fluids did not alter outcome for out-of-hospital cardiac arrest patients.[139] Other metabolic therapies, including calcium and magnesium, also lack supporting data.[140,141] However, it is appropriate to consider specific use of these agents to correct known abnormalities that are contributing to cardiac arrest, such as hyperkalemia, calcium channel blocker overdose, torsades, or hypomagnesemia.

Taken together, the data support a simple pharmacologic approach to the treatment of cardiac arrest: epinephrine can augment CPP generated during chest compressions, antidysrhythmic drugs may be useful for maintaining organized rhythms in witnessed shock-refractory VF, and all other drug therapies should be based on the clinical situation and the response of the patient.

ASPECTS OF CARDIAC ARREST IN SPECIFIC SITUATIONS

If the original etiology of cardiac arrest is available, treatment and prognosis can be individualized to the specific patient. Among out-of-hospital patients, as many as 66% have primary cardiac disturbances.[142] For in-hospital patients experiencing cardiac arrest, dysrhythmia and cardiac ischemia account for 59% of events.[14] This section reviews unique features of cardiac arrest resulting from both cardiac and noncardiac causes.

Primary Cardiac Events

Primary dysrhythmia or cardiogenic shock is the most common proximate cause of cardiac arrest.[142,143] Patients undergoing angioplasty have a 1.3% incidence of cardiac arrest, and survival in these patients resembles survival in other populations.[144] Among patients admitted to a hospital with acute MI, cardiac arrest occurs in 4.8%.[17] Dysrhythmias are common during the hours after reperfusion therapy,[144] although reperfusion therapy reduces the overall risk of cardiac arrest.[145] During acute MI, cardiac arrest is most likely to occur in patients with lower serum potassium levels, more than 20 mm of total ST elevation, and a prolonged QTc interval during the first 2 hours of their event.[145] Some 3.3% of subjects surviving acute MI suffered sudden cardiac death.[146] Abnormalities of the heart are present in most cases of cardiac arrest, with coronary artery disease present in at least 65% of autopsies.[147] Taken together, these data suggest that most patients with cardiac arrest will have contributing cardiovascular disease.

When angiography was performed on consecutive patients resuscitated from cardiac arrest, acute coronary artery occlusion was identified in 48%–58% of the patients.[148,149] Similarly, 51% of initially resuscitated outpatients exhibited an elevation in cardiac enzymes or ECG evidence of acute MI.[150] In one series, troponin T was elevated in 40% of out-of-hospital patients undergoing CPR.[151] The direct myocardial injury from defibrillation and CPR may cause spurious elevations of creatine kinase that are unrelated to cardiovascular disease.[152] However, elevation in cardiac troponin levels are believed to reflect acute MI rather than injury from electric shocks.[153] Thus the 40% of subjects undergoing CPR with elevated troponin probably suffered myocardial injury before collapse. Unless a clearly noncardiac etiology for cardiac arrest is evident, acute coronary angiography may reveal an indication for angioplasty, thrombolysis, or other reperfusion therapy. Primary revascularization is safe in comatose patients undergoing hypothermia treatment.[154,155]

Primary ventricular tachydysrhythmias are rapidly reversible and are the initially recorded rhythm in 23%–41% of out-of-hospital cardiac arrest patients[10,11,156] and in 25% of in-hospital cardiac arrest patients.[14] Long-term antidysrhythmia treatment should be considered for patients who survive sudden cardiac arrest. At a minimum, treatment should be considered for patients with depressed left ventricular function or primary dysrhythmia without a reversible etiology.[157] Importantly, subjects surviving a life-threatening ventricular dysrhythmia have a 15%–20% risk of death during a mean of 16 months of follow-up, even when a reversible cause of the dysrhythmia such as electrolyte disturbance or hypoxia is identified.[158] Implantable defibrillators are superior to antidysrhythmic drugs for reducing the risk of subsequent death.[159] This benefit is primarily in subjects with a left ventricular ejection fraction (LVEF) less than 35%.[160] Implantable defibrillators were not better than antidysrhythmic drugs in a European trial that enrolled subjects resuscitated from cardiac arrest secondary to ventricular dysrhythmia without regard to LVEF.[161] Nevertheless, these devices offer significant hope of preventing sudden cardiac death, and identification of patients that they may benefit is an active area of research. At present, implantable defibrillators should be discussed for patients who recover from coma with LVEF less than 0.35 or who survive a ventricular arrhythmia in the absence of clearly reversible causes.

Asphyxia

Asphyxia causes transient tachycardia and hypertension, followed by bradycardia and hypotension, progressing to PEA or asystole. This period of blood flow with severe hypoxemia before cardiac arrest may worsen central venous hypoxemia and subsequent oxygen debt, rendering asphyxiation a more severe injury than VF or other rapid causes of circulatory arrest.[162] Brain edema is more common on computed tomography (CT) scans after resuscitation when cardiac arrest is caused by pulmonary rather than cardiac etiologies.[163] During cardiac arrest, pulmonary edema develops from redistribution of blood into the pulmonary vasculature,[164] worsening oxygenation in the asphyxiated

patient. Attention to the primary cause of asphyxia, in addition to maneuvers that will increase oxygenation, may be necessary.

Pulmonary Embolism

Pulmonary emboli may occur in postsurgical patients and in medical patients with impaired mobility.[165] In two series, pulmonary emboli were present in 10% of both in-hospital deaths[166] and out-of-hospital deaths.[167] Pulmonary emboli can result in rapid cardiopulmonary collapse and should be considered as a possible etiology of cardiac arrest in the proper clinical setting or when collapse is preceded by sudden shortness of breath, hypoxemia, and/or pleuritic chest pain.

Pulmonary emboli cause cardiac arrest from hypoxemia or when a large thrombus obstructs right ventricular outflow into the pulmonary arteries. This situation results in a dilated, distended right ventricle and an empty left ventricle, which can be seen on a transthoracic echocardiogram. Circulation cannot be restored unless this obstruction is relieved. Because the primary disturbance is hypoxemia and decreased cardiac output, cardiac arrest from pulmonary embolism often presents with an initial rhythm of PEA or asystole.

Administration of a bolus of fibrinolytic drugs such as tenecteplase has been used with reported success in nonrandomized trials during resuscitation of undifferentiated patients,[168] but failed to demonstrate benefit in a larger randomized trial of undifferentiated patients in cardiac arrest.[169] Likewise, a randomized trial of tissue plasminogen activator to undifferentiated patients with out-of-hospital cardiac arrest and an initial rhythm of PEA failed to demonstrate any benefit.[170] Observational studies and subgroup analyses from randomized data report varying degrees of association between intra-arrest systemic fibrinolysis and survival. The potential effects on longer-term outcomes are unknown. Low-certainty evidence suggests that this treatment increases overall risk of bleeding (including any intracranial hemorrhage), but not necessarily risk of major bleeding (including symptomatic or major intracranial hemorrhage).[27] Case series report the feasibility of surgical embolectomy and percutaneous mechanical thrombectomy.[171–173] When logistically feasible, ECPR is a reasonable bridge to recovery or definitive therapy in cases of cardiac arrest from known or highly suspected massive pulmonary embolism.

Electrolyte Disturbances

Potassium disturbance is the most likely electrolyte disturbance to result in cardiac arrest. In cardiac patients, hypokalemia has been linked to the incidence of VF after MI.[174,175] Hypokalemia may also account for the increased incidence of sudden death in patients taking large doses of diuretics. VF is rare in patients where serum potassium is maintained over 4.5 mEq/L. Conversely, hyperkalemia can prolong repolarization, increasing the likelihood of VF initiation. Hyperkalemia may also suppress automaticity in the myocardial electrical system, leading to bradycardic PEA or asystole. Interestingly, cardiac arrest occurring during hemodialysis is not associated with high or low potassium levels but is more common after patients are dialyzed against a low (0 or 1 mEq/L) potassium dialysate.[175] These data suggest that rapid changes in potassium rather than the absolute value are important triggers of cardiac arrest in this population. Derangements of calcium and magnesium may produce similar or synergistic changes in cardiac conduction.

The clinical setting of cardiac arrest or widened ventricular complexes with repolarization abnormalities on ECG may suggest a primary electrolyte disturbance. If hyperkalemia is suspected, the usual acute resuscitation maneuvers can be supplemented by a bolus injection of calcium carbonate (1 g), bicarbonate (1 mEq/kg), and perhaps insulin (0.1 units/kg) with glucose (0.5–1 g/kg). These drugs may improve cardiac electrical stability, facilitating restoration of circulation.

Poisoning

Cardiac arrest can result from drug overdose. Therapy does not change except when specific antidotes or countermeasures to the poison are available. For example, calcium channel blocker overdose may be countered by administration of intravenous (IV) calcium.[176] Beta-blocker toxicity may require large doses of inotropic agents[177] or may respond to glucagon.[178] Digoxin overdose may respond to digoxin-binding antibodies.[179] In the case of narcotic-induced respiratory depression, subsequent cardiac arrest is usually a specific case of asphyxia rather than specific cardiotoxic effects. Intravenous lipid emulsion is typically recommended to treated life-threatening local anesthetic toxicity (including cardiac arrest) and has been used for other lipid-soluble poisonings.[180,181] In cases of refractory cardiac arrest, both IV lipid emulsion and ECPR are reasonable therapeutic considerations.[182,183] Poisoned patients are often younger, with few comorbidities, and may recover well once the poison is eliminated. This potential for a better outcome may justify longer and more aggressive efforts at resuscitation. A cohort study of recreational drug overdose-related cardiac arrest found that overdose-related patients who survived to hospital discharge were more likely than other cardiac arrest patients to have a favorable discharge disposition.[184]

Sepsis

Cardiac arrest developing from sepsis may involve direct myocardial depression from humoral factors.[185,186] Vasodilation also results in apparent hypovolemia. Finally, impaired oxygen extraction, shunting, and mitochondrial depression can produce cellular hypoxia. Because pump and vascular failure are the principal physiologic derangements, the most common initial ECG rhythm would be expected to be a rapid PEA that slows to asystole with ischemia. Large doses of inotropes, vasoconstrictors, and volume may be needed to restore circulation. Acute volume resuscitation may require 100 mL/kg of isotonic fluids or more and must be titrated to physiologic endpoints (for example, central venous oxygen saturation, CVP, or urine output). Because the underlying sepsis physiology will still be present when the pulse is restored, these patients may prove exceedingly unstable during the subacute recovery period and have a reduced chance of survival.[30,187–189]

Trauma/Hemorrhage

Hypovolemic cardiac arrest occurs after severe trauma, gastrointestinal hemorrhage, or other blood loss. Absence of venous return results in an empty heart that cannot produce cardiac output despite a normal inotropic state and vascular tone. As with sepsis, this situation would most likely present with a rapid PEA that slows to asystole, but VF can develop in response to global ischemia. Because cardiac function and vascular function are initially normal, inotropes and vasoconstrictors are unlikely to benefit hypovolemic cardiac arrest. Likewise, during hypovolemic cardiac arrest, the empty cardiac ventricles render external chest compressions ineffective. As such, there is no physiologic justification to employ the same resuscitation measures that are used for more traditional cases of cardiac arrest. Instead, attention should be turned toward emergent procedures to control hemorrhage, intravascular volume expansion with crystalloid fluids or blood products,[190] and mobilization toward definite surgical repair. After restoration of circulation, patients with hemorrhagic cardiac arrest are likely to develop multisystem organ failure.[190]

If blood loss is ongoing or if massive volume replacement cannot be rapidly instituted, thoracotomy allows clamping or compression of the aorta, perhaps retaining sufficient blood in the proximal aorta to perfuse the coronary and cerebral arteries. This procedure has reported success in the treatment of penetrating traumatic injuries[191] but

not in blunt trauma.[192] Survival is better if thoracotomy occurs in the operating room after a brief loss of pulse and best if the penetrating injury has created a cardiac tamponade that is directly relieved by pericardiotomy. Clearly, restoration of circulation must be accompanied by repair of the site of hemorrhage.

Hypothermia

Hypothermia represents an important situation where prolonged resuscitative efforts are justified by the greater tolerance of the cold heart and brain to ischemia. Survival with favorable neurologic recovery has been reported after cold water submersion or exposure, with cardiac arrest, and resuscitation efforts lasting several hours.[193,194] Subjects in whom circulatory arrest occurs because of hypothermia appear to be more salvageable than subjects who asphyxiate or have circulatory arrest before becoming cold.[195]

Treatment should be based upon the initial temperature of the patient. For temperatures between 32°C and 37°C, no change in drug or electrical treatment is required, and this level of hypothermia may be beneficial for resuscitation of both brain and heart.[196,197] For temperatures between 29°C and 32°C, cardiac activity may be preserved, and external warming (warm air, heating lights, warm blankets) and warm IV fluids should accompany the usual resuscitation efforts. The likelihood of generating sufficient perfusion to rewarm the body declines as temperatures decrease from 32°C to 29°C, and more invasive warming should be considered if external warming fails to elicit a rapid response. Mechanical and electrical activity of the heart is disrupted at temperatures below 28°C, and patients may exhibit PEA, VF that is refractory to defibrillation attempts, or asystole. Repetitive rescue shocks in such patients are not justified and may be detrimental; instead, rescue shocks should be reserved until the patient has been rewarmed in the setting of ongoing circulatory support. The efficacy of most resuscitation drugs may be impaired.

Active rewarming during resuscitation of victims of severe hypothermia can include arterial and venous access for partial or complete cardiopulmonary bypass. Extracorporeal circulation is particularly useful because it can provide artificial circulation and warming, simultaneously.[195,198,199] Another option is the placement of thoracostomy tubes and lavage of the chest with warm fluids.[200] Thoracostomy is intuitively preferable to peritoneal lavage because the heart is directly warmed. Warm air forced over the body surface provides the least heat exchange.[201] In any case, it is difficult to determine whether circulation can be reestablished in profoundly hypothermic patients until near-physiologic core temperatures (32°C–36°C) are restored.

Other Medical Conditions

Comorbidities have a tremendous influence on the outcome of patients with cardiac arrest.[143,202,203] In some cases, cardiac arrest may be an expected progression of the patient's disease. For example, no survivors were reported among cancer patients with expected cardiac arrest.[203] Therefore it may be appropriate to set limits on resuscitation efforts in certain medical conditions before cardiopulmonary collapse. Ideally, discussion about the expectations for resuscitative efforts should be held with the patient, his or her family, or the patient's representatives before cardiac arrest. If those discussions did not occur before the first cardiac arrest, they should promptly follow any initially successful resuscitation.

POST–CARDIAC ARREST CARE TO MINIMIZE BRAIN INJURY

Post–cardiac arrest syndrome is a defined clinical entity, consisting of brain injury, myocardial dysfunction, systemic ischemia/reperfusion, and the persistent precipitating pathology that caused the cardiac arrest.[7] Management of this syndrome in patients after restoration of circulation directly affects their ultimate outcome. For example, survival varies for comparable patients treated by a single ambulance service who are delivered to different hospitals with institutional differences in in-hospital management.[5,6] The American Heart Association and European Resuscitation Council now incorporate guidelines for the treatment of post–cardiac arrest syndrome into their consensus scientific statement.[27] This section will highlight a bundled post–cardiac arrest care package, designed to mitigate primary injury and prevent secondary brain injury.

Brain injury after ischemia is an active process that develops in successive phases (e.g., ischemic injury, reperfusion injury, and secondary injury) over hours to days after resuscitation.[204] Multiple cellular and molecular mechanisms contribute to this brain injury.[204–210] Protein synthesis is inhibited at the level of translation initiation for several hours.[208] Ischemic injury is characterized by energy failure, anoxic depolarization, loss of ion gradients, dysregulation of calcium and glutamate, and disruption of the blood–brain barrier. Reperfusion injury is characterized by release of excitatory amino acids, generation of free radicals and reactive oxygen species, reactive hyperthermia, no-reflow phenomenon, and cerebral edema.[209] Secondary injury is characterized by failure of autoregulation, cerebral hypoperfusion, ongoing cerebral ischemia, additional oxidative injury, cerebral edema, seizure, and hyperpyrexia. Ultimately, activation of specific proteases between 24 and 72 hours after reperfusion is associated with the appearance of histologic signs of neuronal death.[210] Despite detailed knowledge of the mechanisms involved with brain ischemia, no monotherapy drug to date has demonstrated a clear benefit in human trials. Randomized trials have examined thiopental, the calcium channel blocker lidoflazine, magnesium, and diazepam.[211–213] One explanation for this failure is that multiple mechanisms contribute simultaneously to the process of ischemic neuronal death. Antagonizing one pathway leading to neuronal death may leave other backup mechanisms unaffected. Less specific therapies, such as reducing brain temperature with or without general anesthesia, may prove more effective. For example, multiple prospective randomized clinical trials found that controlling body temperature for 12–24 hours after resuscitation improved survival and neurologic recovery.[196,214,215] Preliminary clinical trials suggest that inhaled xenon combined with induced mild hypothermia mitigates neuronal white matter injury and myocardial injury.[216,217] Confirmatory randomized trials are in progress. Whether temperature reduction itself confers benefit or merely served to prevent deleterious hyperthermia, it is important to note the success of this type of systemic therapy.

Opportunities to mitigate secondary brain injury require attention to other organ systems and physiologic processes. Observational data also support coronary revascularization and meticulous avoidance of hyperthermia, hypotension, hypocarbia, hypoxia, and hyperglycemia.[5,218–220] Taken together, systematic brain-oriented intensive care is more likely to improve outcome rather than a single therapeutic drug or intervention (Table 45.2).

Coronary Revascularization

Given the prevalence of acute coronary occlusions and high-risk coronary artery disease in this population, appropriate treatment of ST elevation MI (STEMI) should be promptly initiated, regardless of initial level of consciousness.[221] Historically, this has been extrapolated to patients without STEMI because acute coronary ischemia is such a common precipitant of cardiac arrest. Repeated observational studies have highlighted immediate coronary angiography with concomitant coronary intervention as an independent predictor of survival and favorable neurologic outcome, irrespective of the presence or absence of STEMI on the initial ECG.[221] But this evidence base was subject to a

TABLE 45.2 Post–Cardiac Arrest Intensive Care

Temperature	Targeted temperature management 33°C–36°C for at least 24 hours
	Rewarm slowly (<0.25°C/h)
	Avoid fever for 72 hours or until awake
Cardiovascular	Mean arterial pressure >80 mm Hg during the first day (inotropic and vasopressor support as needed; invasive monitoring as needed)
	Reperfusion therapy for STEMI, regardless of concurrent coma or treatment with hypothermia
	Reperfusion therapy for acute coronary syndromes without STEMI if hemodynamically or electrically unstable
	Medical management for acute coronary syndromes (antiplatelet drugs, anticoagulation)
Pulmonary	Avoid hyperventilation
	Avoid hypoxia or unnecessary hyperoxia
	Pneumonitis is common
Gastrointestinal	Usual care
	Consider early refeeding (after hypothermia) to reduce translocation
Fluids/ Electrolytes	Monitor CVP and urine output with hypothermia/rewarming
	Monitor potassium/electrolytes during temperature changes
	Keep potassium ≥3.5 mEq/L
	Monitor glucose frequently, normal treatment of hyperglycemia >180 mg/dL
Infection	Pneumonia is common
	Prophylactic antibiotics are of unproven benefit
	Treat infections as they are identified
	Antipyretics are reasonable
Neurologic	CT scan to exclude intracranial lesions
	Sedation and muscle relaxation as needed for targeted temperature management
	Monitor for seizures with continuous EEG
	Suppress malignant EEG patterns with antiepileptic therapy
	Serial clinical examinations for prognosis
	Examinations may change dramatically over first 72 hours (or longer with hypothermia treatment)
	EEG, SSEP, and MRI with DWI can supplement clinical examination for prognosis
	Consider pharmacologic stimulation in patients with intact SSEP but persistent coma

CT, Computed tomography; *CVP,* central venous pressure; *DWI,* diffusion-weighted imaging; *EEG,* electroencephalogram; *MRI,* magnetic resonance imaging; *SSEP,* somatosensory evoked potential; *STEMI,* ST elevation myocardial infarction.

high degree of selection bias that likely favored treating patients with a presumed better prognosis. Factors typically associated with a higher probability of emergency cardiac catheterization include male sex, younger age, shockable initial cardiac rhythms, witnessed collapse, and bystander CPR.[221]

Although emergency cardiac catheterization is still recommended for patients with STEMI, the requisite timing of cardiac catheterization for those with suspected acute coronary syndrome, but without STEMI, is an active area of clinical investigation. The first trial to randomize patients after out-of-hospital cardiac arrest from an initially shockable rhythm without STEMI or ongoing shock to coronary angiography performed immediately or in a delayed fashion after neurologic recovery was neutral for survival and neurologic recovery.[222] This neutral finding may be from the mitigation of selection bias or differing patient populations. Although nearly two-thirds of patients enrolled had coronary artery disease, the vast majority constituted stable lesions, and few patients had unstable lesions or thrombotic occlusions. Of note, half of the patients in the delayed angiography group with acute thrombotic occlusions manifested cardiac deterioration and crossed over to receive urgent intervention. A second trial randomizing out-of-hospital cardiac arrest patients without STEMI to immediate coronary angiography or intensive care with potential for delayed coronary angiography reported preliminary pilot data that did not detect prohibitive concerns with feasibility or safety.[223] A culprit lesion was identified and revascularized in approximately one-third of subjects randomized to immediate coronary angiography, and 15% of subjects randomized to intensive care crossed over to early coronary angiography for subsequent manifestations of ischemia. Multiple additional randomized trials are in progress.

Further complicating the interpretation of available data, the majority of nonsurvivors after resuscitation from cardiac arrest die from neurologic complications or iatrogenic withdrawal of life-sustaining therapies because of perceived poor neurologic prognosis. Even among randomized trials of coronary angiography, death from neurologic injury was three times as frequent as death from a cardiac etiology. Multiple scores and rubrics have been developed to risk stratify patients with respect to death from neurologic injury when selecting patients for coronary angiography, but none has been rigorously tested in a prospective fashion.

Until additional randomized data are available, a reasonable approach is to pursue emergency coronary angiography and revascularization for patients resuscitated from cardiac arrest with STEMI regardless of initial level of consciousness. Patients without STEMI but suspected of acute coronary syndrome fall along a continuum of risk. Those with an initial shockable rhythm or ongoing hemodynamic or electrical instability are at higher risk for acute coronary lesions and are more likely to benefit from definition of coronary artery anatomy, revascularization, or percutaneous mechanical circulatory support, all of which can be facilitated by left heart catheterization. Whereas for patients without these "STEMI-equivalents," it may be reasonable to delay coronary angiography in lieu of optimizing other aspects of critical care and estimating the trajectory of neurologic recovery.

Targeted Temperature Management

Meticulous temperature control is important during the first 24–48 hours after ischemic brain injury. Bacteremia and spontaneous fever are common in resuscitated patients, making active prevention of hyperthermia mandatory.[224,225] Fever prevention is beneficial to the injured brain after traumatic brain injury, stroke, and cardiac arrest.[218,226,227] Mechanistically, temperature probably affects more than the brain metabolic rate (manipulations of temperature that improve neurologic recovery in laboratory studies produce no effect on jugular venous lactate or oxygen uptake).[228] Instead, a variety of signaling pathways and cellular responses are sensitive to relatively small (1°C–2°C) changes in brain temperature.[211,212] Also, lowering brain temperature can reduce intracranial pressure[229] and vulnerability to seizures.[230]

For nearly 20 years, mild induced hypothermia (32°C–34°C) for 12 or 24 hours has been the cornerstone of post–cardiac arrest intensive care. Two randomized trials published in 2002 found a 24%–30% reduction in relative risk for death or poor neurologic outcome[231] and

significant improvement in the odds of survival and good neurologic outcome for subjects resuscitated from VF cardiac arrests.[196,214] A subsequent large, prospective, randomized trial comparing a targeted temperature of 33°C with 36°C found that both groups had similar mortality and neurologic outcome at 180 days.[215] The most notable difference between the 2002 trials compared with the subsequent trial was that the earlier studies did not adequately control temperature in the control arm. Temperatures greater than 37°C commonly occurred in subjects for both control groups, whereas tight control at 36°C was followed in the subsequent trial. Additionally, the subsequent trial used a blinded neurologic assessment along with regimented decisions about prognosis. Finally, patients in the 33°C versus 36°C trial had very high rates of witnessed cardiac arrest, bystander CPR, initial shockable rhythm, and very brief intervals from collapse until start of basic life support.[215] It is possible that subgroups of patients with greater post–cardiac arrest illness severity may benefit from a specific target temperature or from titrated use of temperature.

Current recommendations are to keep all comatose post–cardiac arrest patients at a constant target temperature ranging between 32°C and 36°C. This differs from reactive treatment of fever, which is an active area of investigation in an ongoing randomized trial. It is erroneous to assume that selection of 36°C as a target temperature is synonymous with not managing temperature or fever prevention without active controls. Active measures require thermostatically controlled devices, of which there are many. Importantly, there is no clinical situation where, at minimum, active control of temperature at 36°C is contraindicated.

There is no biologic basis to believe that the neurologic benefit of temperature management is specific to patients with one type of cardiac rhythm. Patients with all rhythms were included in the largest clinical trial.[215] Multiple case series report successful application of induced hypothermia for patients after out-of-hospital and in-hospital cardiac arrest with all initial rhythms.[3,232,233] One randomized trial specifically comparing a targeted temperature of 33°C with 37°C in comatose patients resuscitated from cardiac arrest with nonshockable rhythms found a 5% absolute increase in 90-day favorable neurologic outcome.[234] At the time of resuscitation, most patients are already mildly hypothermic, with core temperatures between 35°C and 35.5°C.[197,214,215] This spontaneous cooling results from mixing of core and peripheral blood compartments during circulatory arrest, but patients typically rewarm within a few hours after restoration of circulation unless specific interventions are instituted.[215,235]

The maximum delay in achieving target temperature has been tested in several randomized trials of prehospital induction of temperature management with both rapid infusion of cold crystalloid fluid after return of spontaneous circulation and transnasal evaporative cooling with perfluorocarbons before return of spontaneous circulation.[236–240] Although subgroups treated with transnasal evaporative cooling suggest potential for efficacy, these trials have been mostly neutral. Of note, more instances of re-arrest and pulmonary edema requiring diuresis were observed after undifferentiated prehospital administration of cold IV fluid boluses.[236–238] This intervention is likely best used in a hospital-based critical care setting with adequate monitoring and resources.

The optimal duration of temperature management is an active area of investigation. Laboratory studies suggest that secondary brain injury occurs for several days after restoration of circulation, manifesting as cerebral energy failure, metabolic stress, edema, and seizures.[241] Although statistically neutral, one trial randomizing patients to a target temperature of 33°C for 24 or 48 hours suggests the potential for improved survival and neurologic recovery with longer durations of lower temperature. A subsequent trial testing assorted durations of targeting 33°C between 6 and 72 hours is in progress.

Laboratory studies suggest that rewarming should be performed slowly (<0.25°C/h). Until additional data are available, a regimen similar to the largest clinical trial (at least 24 hours of temperature management targeting 33°C–36°C, followed by meticulous fever suppression for at least 3 days) is reasonable.[215]

After cardiac arrest, temperature management can be achieved by a variety of techniques, including surface cooling with ice packs, cooling blankets, or endovascular devices.[242–251] Initial studies using surface cooling alone suggested that it is slow and may require 4–6 hours to reach 34°C.[243–246] However, neuromuscular blockade and sedation to prevent shivering greatly accelerate surface cooling.[246] There are few direct comparisons of surface cooling and endovascular cooling; however, endovascular catheters may provide more stable control of temperature over time.[246,247] Local cooling of the head is unlikely to produce brain hypothermia when there is adequate perfusion by warm core blood,[248] although the head can be an effective site for removing heat from the body.[251]

Rapid infusion of 30 mL/kg cold (4°C) crystalloid fluid produces a rapid decrease in core temperature in post–cardiac arrest patients.[249,250] Cold fluid boluses must be administered quickly into the central circulation (via a central line or under pressure infusion via a peripheral line). The volume required may limit this intervention in some patients. Cold IV fluids only produce a transient decrease in core temperature, requiring that a maintenance technique (endovascular or surface cooling device) be in place after the infusion.[242,251]

Induction of cooling can result in peripheral vasoconstriction, with an apparent reduction in vascular volume, rise in CVP, and diuresis.[252,253] Rewarming causes vessels to dilate, CVP to fall, and the patient to appear relatively hypovolemic. Inattention to these fluid shifts was cited as a pitfall in trials of therapeutic hypothermia for traumatic brain injury.[254] Hypokalemia, hypophosphatemia, and hypomagnesemia also occur during cooling, followed by hyperkalemia during rewarming.[255,256] Frequent monitoring and correction of electrolytes are warranted.

Primary angioplasty is safe in patients undergoing hypothermia treatement.[154,155] Mild hypothermia greater than 30°C does not interfere with defibrillation. Cooling from 37°C to 31°C has a positive inotropic effect, increasing stroke volume to a greater extent than it decreases heart rate.[252] Clinical data report a transient 18% decline in cardiac index with cooling to 33°C.[253]

Although mild hypothermia can inhibit platelet function and coagulation,[257] these changes are of a small magnitude, leading to few bleeding complications, even in subjects with concurrent trauma or administration of heparinoids and glycoprotein IIb/IIIa inhibitors.[197,226] Bleeding after hypothermia and cardiac catheterization was reported in 6.2% of post–cardiac arrest patients.[258] However, mild hypothermia may inhibit antiplatelet medications (ticagrelor, prasugrel, and clopidogrel). Early studies of post–cardiac arrest patients treated with mild hypothermia and percutaneous coronary intervention found a high incidence of stent thrombosis (11%–31%), but it was impossible to distinguish between the relative contributions of post–cardiac arrest syndrome and iatrogenic mild hypothermia.[259] Subsequent large observational studies comparing post–cardiac arrest subjects with and without mild hypothermia found no difference in stent thrombosis (~4%).[260] Mild hypothermia seems to disproportionately affect platelet inhibition by clopidogrel compared with other antiplatelet medications, and more stent thrombosis has been observed in patients treated with clopidogrel compared with ticagrelor.[261,262]

Infections may become more common when patients are cooled for 24 hours or longer.[214,263] Elevation in pancreatic enzymes has been reported in cooled patients, but these changes resolve with rewarming.[214]

Creatinine clearance and platelet count may fall during cooling, but both parameters normalize with rewarming.[214]

Hemodynamic Management

Myocardial function declines transiently after cardiac arrest.[264] Oxidative stress or other triggers can lead to myocyte damage after reperfusion.[265] Clinically, some vasoactive and/or inotropic drug support is necessary in most patients resuscitated from cardiac arrest, with expected hemodynamic recovery over the subsequent 24–48 hours.

During the first day after resuscitation from cardiac arrest, patients exhibit increased cerebral vascular resistance[266] and absent or right-shifted cerebral autoregulation, such that brain perfusion declines when mean arterial pressure (MAP) declines below 80–120 mm Hg.[267,268] When blood pressure is maintained, clinical positron emission tomography (PET) studies suggest that regional perfusion remains matched to metabolic activity after cardiac arrest,[269,270] yet microvascular dysfunction can still lead to regions of no-reflow. The brain is particularly sensitive to hypotension and may require a higher MAP than normal during the first hours to days after cardiac arrest. Periods of hypotension after circulation is restored add further secondary ischemic brain injury and are associated with death and poor neurologic recovery.[219,271] Higher MAP is associated with survival and better neurologic recovery.[272,273] Conversely, broad indiscriminate application of higher MAP targets may worsen vasogenic edema or oxidative injury in the subset of patients with intact autoregulation. Invasive monitoring of cerebral oxygenation and blood flow to titrate hemodynamic parameters to patient-specific optimal cerebral perfusion pressure is an active area of investigation.[204]

For most patients, relative hypertension (MAP of 80–100 mm Hg), if tolerated by the heart, should be considered using inotropes and/or pressors to prevent brain hypoperfusion. Hemodynamic management strategies are not well defined in most post–arrest care implementation studies,[274] and no specific choice of pressors has been demonstrated to be superior. Dopamine (5–20 μg/kg/min), norepinephrine (0.01–1 μg/kg/min), and/or epinephrine (0.01–1 μg/min) are all potential agents. Dopamine has the disadvantage of inducing tachydysrhythmias. Epinephrine has more positive inotropy than norepinephrine but can prolong lactic acidosis. Thus norepinephrine is a common first-line agent. Additional inotropic support (dobutamine 2–15 μg/kg/min; milrinone 50 μg/kg/min loading dose followed by 0.375–0.75 μg/kg/min infusion) may be necessary in cases of ongoing shock despite adequate MAP and hemoglobin (as assessed by severe hypokinesis, low venous oxygen saturation [SvO_2], oliguria, and/or failure to clear serum lactate). Ultimately, the choice and doses of these agents must be titrated to individual patients.

Mechanical circulatory support should be strongly considered for patients with persistent shock despite optimization of medical management. Historically, the intraaortic balloon pump was frequently used for hemodynamic support, but multicenter randomized trials have failed to demonstrate a mortality reduction in patients with STEMI and cardiogenic shock.[275] An alternative approach is utilization of a temporary left ventricular assist device that augments left ventricle-to-aorta blood flow via an axial pump.[276] It provides up to 3.5 L/min of blood flow when placed percutaneously and up to 5 L/min of blood flow when placed surgically.[277] Extracorporeal circulatory support with a venous-to-arterial circuit may be preferred in patients with ongoing cardiopulmonary resuscitation, right heart failure, or those without sufficient gas exchange. Ultimately, the means of mechanical support selected depends on the patient's hemodynamics, the expected hemodynamic impact of the device, the ease and rapidity of insertion, underlying comorbidities or contraindications, and the ultimate goals of support.

Oxygenation and Ventilation

Oxygenation must be balanced to avoid both cerebral hypoxemia and additional oxidative stress. Multiple observational studies note that post–cardiac arrest hyperoxia (partial pressure of oxygen [PaO_2] ≥300 mm Hg) is associated with higher inpatient mortality than normoxia.[278,279] These studies speculate that high oxygen concentration increases oxidative free radical damage. One multicenter cohort study found a linear, dose-dependent relationship between levels of oxygen tension and inpatient mortality but could not identify a single threshold for harm.[280] Few randomized data are available, and several large prospective randomized trials testing different oxygen titration strategies are in progress.[281] In the absence of evidence to support a specific FiO_2 goal for patients, it is reasonable to titrate fraction of inspired oxygen (FiO_2) to the lowest values sufficient to maintain a normal arterial oxyhemoglobin saturation (94%–98%).

Although cerebral autoregulation is frequently impaired, carbon dioxide (partial pressure of carbon dioxide [$PaCO_2$]) remains a major regulator of cerebral blood flow.[268] Observational studies note that both hypocapnia ($PaCO_2$ ≤30 mm Hg) and hypercapnia ($PaCO_2$ ≥50 mm Hg) are independently associated with poor neurologic outcome.[282] Few randomized data are available, and large prospective randomized trials are in progress.[281] In the absence of evidence to support a specific $PaCO_2$ goal for patients, extrapolating from traumatic brain injury suggests it is best to ventilate with a goal of normocarbia ($PaCO_2$ 35–45 mm Hg).

Glucose Control

Elevated serum glucose is common after cardiac arrest and is associated with poor outcome,[139,283] but hyperglycemia may simply be a marker of greater illness severity. Both epinephrine and physiologic stress can elevate serum glucose, and mild hypothermia may reduce insulin sensitivity.[284] However, multivariate models that account for resuscitation time and medication usage show an effect of serum glucose on admission and the first 48 hours of intensive care on long-term outcome.[5,285] Monitoring of glucose and treatment of hyperglycemia are reasonable.

Intensive glycemic control with a low target range (72–108 mg/dL, 4–6 mmol/L) has not proven beneficial outside of the surgical population where it was first studied[286] and may be harmful in medical intensive care.[287,288] After cardiac arrest, there was no difference in outcome when a moderate glucose range was targeted (108–144 mg/dL; 6–8 mmol/L) versus a strict lower range (72–108 mg/dL; 4–6 mmol/L).[289] However, the incidence of hypoglycemic events was higher in the strict versus moderate control group (18% vs. 2% of patients). Given the available data, treatment of glucose levels above 180 mg/dL (10 mmol/L) is reasonable.

Hematologic Changes

Cardiac arrest is associated with activation of coagulation that is not balanced by fibrinolysis and is perhaps related to ischemic injury to the endothelium. This hematologic profile is reminiscent of disseminated intravascular coagulation and may contribute to subsequent end-organ dysfunction via the no-reflow phenomenon.[290] Markers of thrombogenesis that have been reported include increased thrombin–antithrombin complexes and fibrinopeptide A.[290,291] These increases are not balanced by fibrinolytic factors for at least 24 hours.

At present, use of anticoagulation is variable, and there are no prospective trials evaluating the effect of empiric anticoagulation after resuscitation. Anticoagulation and even fibrinolytic drugs are safe after CPR.[169,292–294] A retrospective series noted a univariate relationship between anticoagulation and 6-month survival that was not significant in a multivariate model.[285] Given the hematologic evidence of active thrombogenesis, anticoagulation should be considered whenever there is a possibility of a thrombotic etiology.

Infection

Both ischemia-triggered systemic inflammatory responses and infections are common after cardiac arrest.[263] Pneumonia, bloodstream infections, and catheter-related infections are the most common infectious complications.[263,295] Pneumonia, especially, is associated with the duration of mechanical ventilation and length of ICU stay but does not appear to have an impact on mortality or neurologic outcome.[263,295,296] Bacteremia occurs in 39% of patients during the first 12 hours after resuscitation.[224] The accurate diagnosis of post–cardiac arrest infections is hampered by an associated increase in inflammatory markers[297,298] and body temperature control.

Observational studies suggest that antibiotic prophylaxis is not associated with a reduction in the incidence of pneumonia or improved clinical outcomes. Subsequent randomized trials of antibiotic prophylaxis compared with placebo in mechanically ventilated adults resuscitated from cardiac arrest found a lower incidence of early ventilator-associated pneumonia (VAP), but no statistical change in other intermediate outcomes or clinical outcomes.[299] Institutional VAP prevention bundles are appropriate, but the clinical value of prophylactic antibiotics does not appear to outweigh the associated costs and adverse effects.[299] Otherwise, selective treatment of identified infections is reasonable and appropriate.

Predicting Neurologic Recovery

The goal of clinical practice is always to restore the patient to full consciousness and function.[300] Nearly all patients with circulatory arrest of more than 1 or 2 minutes will be comatose at initial presentation, but some of these patients can recover and awaken. Therefore signs of neurologic activity immediately after restoration of circulation are encouraging, but their absence does not preclude eventual recovery. Unfortunately, many cardiac arrest survivors fail to completely awaken and may meet criteria for a persistent vegetative state.[301,302] The status of patients who do not quite meet these criteria but are not awake has been described as a minimally conscious state.[303] Less than 10% of patients who are hospitalized after cardiac arrest progress to formal brain death.[23]

Determining the neurologic prognosis of patients resuscitated from cardiac arrest has been the subject of multiple reviews and guideline statements[304–307] before and after the setting of modern ICU care. Some of the traditional findings associated with poor outcome[308–310] are no longer valid in the setting of modern ICU care and targeted temperature management. In fact, good survival has been reported after some situations previously believed to have universally poor outcomes such as post–cardiac arrest status myoclonus and seizures[311,312] or the absence of cortical responses on evoked potentials.[313] Neurologic recovery continues over a longer period than the 3 days recommended in historical publications.[304,305] Therefore longer periods of support and observation are appropriate for many patients. Furthermore, a multimodal approach that includes physical examination, imaging, and neurophysiologic studies is essential to determine prognosis.[311] No examination finding or test should be used in isolation to finalize neurologic prognosis. In a practical approach, the clinician can make an initial estimate of the probability of recovery based on clinical examination. As more information becomes available from clinical progression, imaging studies, and neurophysiologic studies, this estimate is revised in order to advise families and proxy decision makers. Daily reevaluations are required to decide if ongoing therapy is consistent with the patient's goals in light of the best estimate of the probability of various outcomes.

Baseline Probability of Recovery

In cohorts of patients admitted to a hospital after in-hospital and out-of-hospital cardiac arrest, approximately 31%–33% of patients recovered to a favorable functional status.[22,23] Although clinicians could start with an estimate that all patients have about 30% chance of good recovery, it is obvious that some patients have much greater illness severity than others at admission. The initial expectation of survival should be revised based on this fact. Various prognostic tools or scores can refine the estimated odds of recovery based on initial physiologic status or case features.[314,315] One simple score is the Pittsburgh Cardiac Arrest Category (PCAC) (Box 45.1). This score divides patients into four categories based on initial coma examination and degree of cardiopulmonary failure.[316] Probability of survival, good functional recovery, and risk of multiple organ failure vary by category. This particular score offers the advantages of being fast, easy to communicate, and validated in prospective cohorts.[317]

BOX 45.1 Post–Cardiac Arrest Category

The category of a patient can be assessed quickly on arrival to better stratify the initial probability of survival and risk of different complications. Precise research definitions of the categories use scoring systems assessed within 6 hours of return of pulses,[316] but clinical examination can usually sort patients into categories. Neurologic examination cannot be assessed if drugs or paralytics are confounding.

Category 1—Awake (Follows Commands)
80% chance of survival; 60% chance of good functional recovery
<5% chance of multiple organ failure

Category 2—Coma With Preserved Brainstem Reflexes*
60% chance of survival; 40% chance of good functional recovery
20% chance of multiple organ failure

Category 3—Coma With Preserved Brainstem Reflexes and Severe Cardiopulmonary Failure**
40% chance of survival; 20% chance of good functional recovery
40% chance of multiple organ failure

Category 4—Coma With Loss of Brainstem Reflexes
10% chance of survival; 7% chance of good functional recovery
35% chance of multiple organ failure

* Coma with preserved brainstem reflexes = FOUR score Motor + Brainstem scale ≥4; typically present with pupillary light reflex, corneal reflex, and some movement of extremities (at least posturing)
** Severe cardiopulmonary failure = SOFA score cardiac + respiratory subscales ≥4; typically more than one pressor drug, norepinephrine, or equivalent at rates >0.1 μg/kg/min and/or ventilator settings with PaO_2/FiO_2 ratio <100.

Clinical Examination

Pupillary reflexes, corneal reflexes, and motor activity can change over the first 72 hours after resuscitation and should not be used to definitively prognosticate during these initial 3 days.[310] The false-positive rate ([FPR] percentage where tests predict a poor outcome but patients have a good outcome) for absent pupillary light reflexes is much lower after 72 hours or more (FPR 0%–10%) compared with less than 72 hours (FPR 8%–52%). Likewise, absent corneal reflexes after 72 hours or more (FPR 0%–11%) are more informative compared with less than 72 hours (FPR 11%–75%).[27] Motor response less than flexion at 3 days has an FPR of 8%–14%.[27] The presence of myoclonus is less precise for predicting poor outcome (FPR 3%–12%) and must be distinguished from status myoclonus (persistent, repetitive myoclonus). Status myoclonus within 72 hours is associated with death or vegetative state (FPR 0%–3%).[27] Regardless of the clinical examination

finding in question, subjects with lower body temperature require longer periods of observation to clear potentially confounding factors introduced by sedation.[318]

Physiologic response to targeted temperature management provides another avenue for insight into the potential for neurologic recovery. The presence of shivering,[319] the amount of patient heat generation (derived from the inverse average water temperature of cooling devices),[320] and the presence of bradycardia (<60 beats/min)[321] during the induction and maintenance of temperature management are each associated with favorable neurologic outcome.

Imaging Studies

Imaging of the brain is important to exclude injury incurred at the time of collapse and to exclude intracranial causes of collapse. A noncontrast cranial CT scan to exclude hemorrhage is prudent in comatose patients after cardiac arrest and before anticoagulation or fibrinolytic therapy.[322,323] In general, noncontrast CT scan is insufficiently sensitive to determine prognosis after cardiac arrest unless severe changes are present, such as generalized edema that is often associated with loss of brainstem reflexes and may progress to herniation and brain death (Fig. 45.7). The amount of brain edema can be quantified with a ratio of attenuation (Hounsfield units) in select regions of gray matter and white matter. This "gray-to-white ratio" (GWR) is directly associated with survival and functional outcome.[324,325] Very low GWR values averaged throughout the brain within 6 hours after restoration of circulation are associated with poor outcome (FPR 0%–15%). Whether treatment of cerebral edema is worthwhile or futile has not yet been studied.

Magnetic resonance imaging (MRI) can visualize subtler changes in the brain after cardiac arrest via increased cortical signals on diffusion-weighted images (DWI) or apparent diffusion coefficient (ADC) maps.[326–328] For patients who remain comatose for several days and in whom clinical or electrophysiologic testing is indeterminate, MRI provides additional information about the extent of brain injury. Expectations and enthusiasm for long-term support may be reduced if extensive cortical lesions are present, whereas persistence may be justified if the anatomic extent of injury appears limited. An important caveat with the interpretation of all brain imaging after global ischemia is the differing clinical impact of lesions in different brain regions. The anatomic complexity of the brain precludes any simple quantitative relationship between the number or size of lesions and outcome. Isolated DWI abnormalities or low ADC values in single anatomic locations are not specific for poor neurologic outcome.[329] Furthermore, the existing literature about MRI is limited by indication bias: only a select subgroup of patients who are not improving clinically have this test, potentially inflating the prognostic significance of any findings. Long-term cognitive deficits are associated with global brain volume loss after cardiac arrest.[330] MRI should be used as an adjunct for assessing post–cardiac arrest brain damage in centers with neurologic or neuroradiologic expertise for interpreting these tests.

Neurophysiology

Electroencephalogram (EEG) patterns after resuscitation change over time.[331,332] The primary utility of an EEG is to diagnose seizures and exclude nonconvulsive seizures as an etiology of unresponsiveness. Seizures are diagnosed clinically in 5%–20% of comatose patients after cardiac arrest,[312] and the true incidence of nonconvulsive electrographic seizures may be higher. Termination of seizures, if possible, is essential to allow untainted assessment of the neurologic examination (Fig. 45.8). EEG abnormalities occur over a spectrum of severity (nothing epileptiform, nonperiodic epileptiform discharges, periodic discharges, and polyspike-wave discharges) directly associated with subsequent likelihood of poor outcome.[333] Generalized suppression (<20 μV), burst-suppression pattern associated with generalized epileptic activity, or diffuse periodic complexes on a flat background during the first week after resuscitation are associated with poor neurologic outcome.[308] Likewise, refractoriness of epileptiform patterns to antiepileptic therapy, as estimated by the number of antiepileptic drugs administered, also portends worse outcomes.[333] The presence of malignant EEG patterns provides information that is additive with clinical evaluation.[334] Thus EEG should not be used by itself to determine prognosis, but the information provided by EEG can exclude confounders (seizures) and be integrated into the total clinical picture used to assess prognosis.

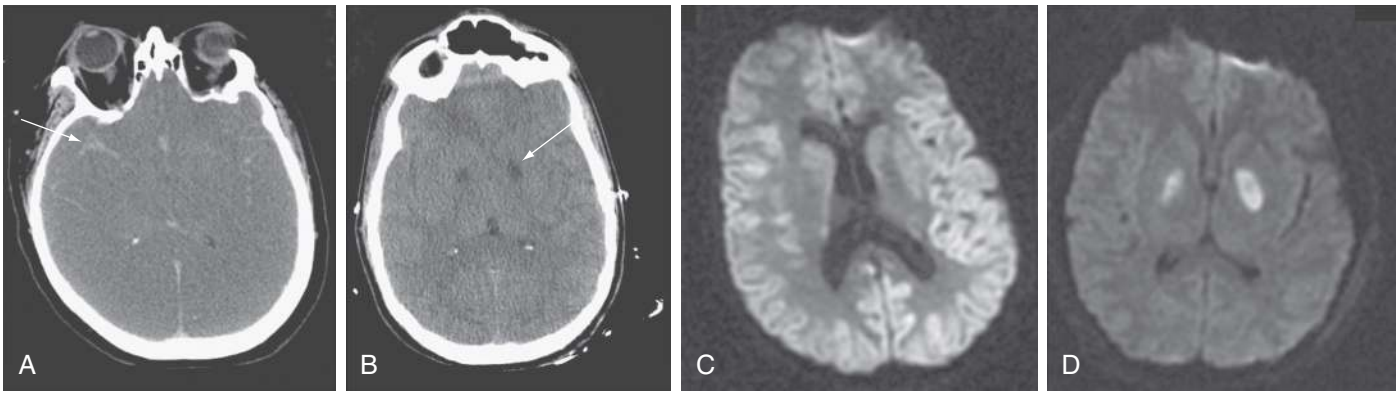

Fig. 45.7 Imaging of the brain after cardiac arrest. **A,** Severe cerebral ischemia appears as sulcal effacement, with loss of contrast between gray matter and white matter. Congestion of blood in meninges (pseudosubarachnoid hemorrhage *[arrow]*) sometimes is evident. This pattern on early computed tomography (CT) scan often progresses to herniation and brain death. **B,** Less severe early changes show edema (hypodensity) restricted to the basal ganglia *(arrow)*, with sparing of the cortex. **C,** Increased magnetic resonance imaging (MRI) signal from extensive areas of cortex on diffusion-weighted images (DWI) of this patient correspond to devastating brain injury with persistent coma. This patient showed no improvement in coma. **D,** DWI for same patient in **B** illustrates high-intensity signal from damaged subcortical areas. In this case, the cortex and other structures are normal. After 5 days of coma, this patient awoke, completed rehabilitation, and recovered completely.

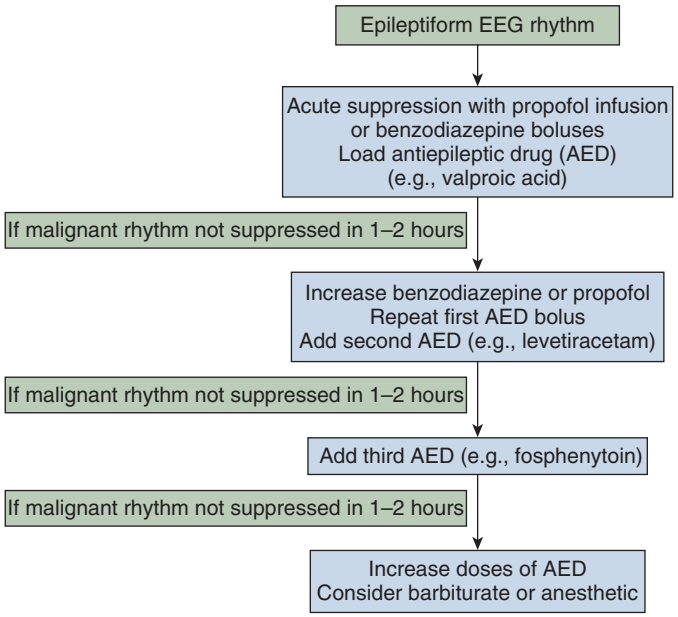

Fig. 45.8 Electroencephalogram (*EEG*) and antiepileptic drug (*AED*) management after resuscitation.

Electrophysiologic response to stimuli can also be used to assess whether cortical regions are intact. Recovery of longer latency event-related potentials are associated with awakening.[335–337] Conversely, absence of short latency (N20) cortical response to somatosensory evoked potentials (SSEPs) is very specific for poor neurologic outcome (FPR 0%; 95% confidence interval [CI], 0%–2%).[305–307] Like EEG, SSEP responses vary with the elapsed time since resuscitation.[331] Recent data suggest that the use of therapeutic hypothermia may increase the time-dependent changes in SSEP. One case series reported two patients treated with hypothermia who had absent N20 responses at 3 days after cardiac arrest but recovered cognition.[312] Therefore it may be reasonable to repeat SSEPs that show absent N20s several days apart in order to avoid false-negative tests.

Blood Markers

Several peptides appear in the blood after brain injury, including neuron-specific enolase (NSE) and the glia-derived protein S-100B. After cardiac arrest, NSE reaches a maximum level in serum at 72 hours. High NSE levels at 48–72 hours or NSE levels that continue to rise over the first 72 hours after resuscitation are associated with poor outcome.[337–339] In contrast to NSE, peak levels of S-100B in serum occur during the first 24 hours after resuscitation, and higher S-100B levels are associated with poor neurologic outcome.[338,340] Hypothermia treatment appears to alter serum NSE levels.[341] Use of NSE or S-100B to determine prognosis is limited by the absence of a clear cutoff value that is unsurvivable and the lack of a universal standard for laboratory assays. NSE can also be released by injury from nonbrain organs.[342] These neuronal markers may be considered a tool for following brain injury longitudinally, analogous to troponin levels for following myocardial injury. Additional biomarkers under investigation include glial fibrillary acidic protein, serum tau protein, and serum neurofilament light chain.

In summary, the determination of neurologic prognosis after cardiac arrest varies from patient to patient. Changes in clinical examination are the cornerstone of prognostication. While the patient is recovering, hypothermia and supportive care may increase the likelihood of recovery. However, electrophysiologic and imaging techniques add further useful information to help guide clinicians and families. The approximate timing for each of these studies is depicted in Fig. 45.9. Prognostication guidelines from the European Resuscitation Council and European Society of Intensive Care Medicine[343] emphasize the bilateral absence of pupillary and corneal reflexes or N20 wave of

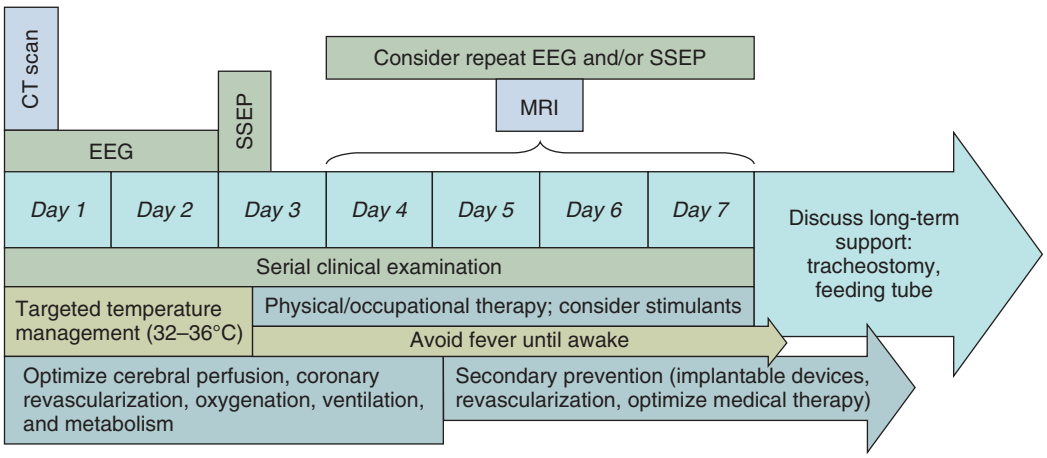

Fig. 45.9 Rational approach to neurologic treatment, monitoring, and testing after cardiac arrest. For patients remaining in a coma, hypothermia treatment followed by therapy and stimulation may improve recovery. Early electroencephalogram (*EEG*) monitoring is recommended to allow detection and treatment of seizures and to supplement estimations of prognosis. Absence of cortical response on somatosensory evoked potential (*SSEP*) or malignant EEG patterns after hypothermia treatment help identify subsets of patients unlikely to ever show improvement. When those tests are indeterminate and there is no sign of clinical improvement, magnetic resonance imaging (*MRI*) of the brain helps quantify the extent and location of injury, which in turn assists in decisions about continuing long-term support in light of patient and surrogate wishes. Most tests are not required when patients exhibit clear clinical improvement. Conversely, patients who progress to brain death should undergo formal brain death testing once sedative confounders, metabolic abnormalities, and shock have been corrected.

SSEPs as the most robust predictors of poor outcome irrespective of body temperature. Early myoclonus, elevated values of NSE at 48–72 hours from cardiac arrest, unreactive malignant EEG patterns after rewarming, and diffuse signs of anoxic injury on CT or MRI are useful but less robust predictors. Prolonged observation should be considered when the results of these initial assessments are inconclusive.

REHABILITATION

The role of rehabilitation or other therapy in recovery from neurologic impairment after cardiac arrest is an active area of investigation. It is clear that both patients and their caregivers have complex needs if neurologic injury is severe.[344] Rehabilitation after global brain ischemia can produce similar improvements to those after traumatic brain injury.[345,346] Early utilization of basic rehabilitative services, including physical therapy and occupational therapy, may help promote recovery, just as in acute stroke.[347] When arousal or level of consciousness is impaired after traumatic brain injury, stimulants such as methylphenidate or amantadine have been employed with reduction in total ICU stay or improved final status.[348,349] Although these data are few and indirect, addition of stimulants for post–cardiac arrest patients who linger in intermediate coma might be considered, if medically tolerated.[350] Functional and cognitive recovery in survivors who were initially comatose occurs over at least 6 months.[122] Global measures of outcome such as cerebral performance category (CPC) and modified Rankin scale (mRS) do not fully characterize the nuanced patterns of disability, which tend to center around memory, attention, executive function, mood, fatigue, and participation.[351,352]

WITHDRAWAL OF LIFE-SUSTAINING TREATMENT

For adults who are neurologically devastated after cardiac arrest in North America, it is more common to die in a hospital than to receive long-term care. An estimated 44% of patients who are initially resuscitated from cardiac arrest in a hospital have withdrawal of care later in their hospitalization.[14] For patients resuscitated from out-of-hospital cardiac arrest, 61% die after withdrawal of life-sustaining treatments because of predicted neurologic prognosis.[23] Because these decisions are often based on the neurologic prognosis of the patient, withdrawal of life-sustaining treatment limits the number of neurologically impaired individuals who are discharged from the hospital. Consequently, quality of life for those patients who do leave the hospital is generally high.[21,353,354] Popular reports of awakening after long coma may cause inappropriate optimism for families of patients or surrogate decision makers. Partial awakening of patients into a persistent vegetative state or minimally conscious state can further confuse their expectations. Decision makers should receive information about these syndromes, realistic expectations of recovery, and any specific considerations for the individual patient. Religious, cultural, and personal beliefs will contribute to decisions, and appropriate social service and pastoral support should be provided. Finally, for patients who survive cardiac arrest but who later progress to death or brain death, it is reasonable to evaluate their candidacy to become organ donors: outcomes for transplanted organs from this population are comparable to all other donors.[355]

SUMMARY

Improvement in outcome after cardiac arrest will require attention both to the reversal of cardiopulmonary arrest and to restoration of consciousness. Isolated attention to only the heart or only the brain is unlikely to improve outcomes for many patients. Appropriate prioritization of the various tools for cardiac resuscitation, along with emphasis on the basic mechanics of artificial circulation, may increase the number of individuals reaching the ICU. Induction of mild hypothermia, correction of hemodynamic and metabolic perturbations, along with proper treatment of the root cause of the cardiac arrest may increase the number of initially comatose patients who awaken. Constant reassessment of the likelihood of meaningful recovery, based on clinical examination and ancillary testing, can guarantee that continued care and interventions are appropriate.

KEY POINTS

- Improvement in outcome after cardiac arrest requires attention both to immediate reversal of cardiopulmonary arrest and promoting recovery of brain function through subsequent ICU interventions. Isolated attention to only the heart or only the brain is unlikely to improve outcomes for many patients (see Fig. 45.8).
- Increased emphasis on the basic mechanics of artificial circulation, specifically uninterrupted vigorous chest compressions, may increase the number of individuals reaching the ICU.
- It is necessary to prioritize the various adjunct tools for cardiac resuscitation. For example, time devoted to tracheal intubation may delay drug therapy and interrupt chest compressions without altering overall hemodynamics.
- The cornerstone of drug therapy during resuscitation attempts is the selective administration of vasoactive drugs that will increase CPP developed by chest compressions. Rote, repeated administration is unlikely to result in favorable neurologic outcome.
- Induction of targeted temperature management, correction of hemodynamic and metabolic perturbations, and proper treatment of the root cause of the cardiac arrest may increase the number of initially comatose patients who awaken.
- Neurologic prognosis is determined using serial clinical examinations supplemented by neurophysiologic or imaging tests. Clinical examination continues to change for many days after cardiac arrest, and even longer periods of observation are required for patients with lower body temperature. Constant reassessment of the likelihood of meaningful recovery can guarantee that continued care and interventions are appropriate.

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Granfeldt A, Avis SR, Nicholson TC, et al. Advanced airway management during adult cardiac arrest: a systematic review. *Resuscitation*. 2019;139:133–143.
This systematic article synthesizes the randomized and observational data on advanced airway management during adult cardiac arrest. Notably, three randomized trials conducted in different EMS systems with a range of intubation success have compared advanced airway strategies (tracheal intubation or supraglottic airway) with each other and to bag-mask ventilation. In settings with lower tracheal intubation success rates, supraglottic airway insertion improved short-term survival and neurologic outcomes. In settings with higher tracheal intubation success rates, advanced airway management did not improve survival or neurologic outcomes compared with bag-mask ventilation. The rationale for transitioning from a basic to advanced airway strategy is highly dependent on the clinical context, including patient anatomy, aspiration risk, and oxygenation and ventilation success. If an advanced airway strategy is used, clinicians should choose an advanced airway strategy based on their particular skill set.

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This trial randomized 552 patients without STEMI resuscitated after out-of-hospital cardiac arrest from a shockable rhythm to a strategy of immediate or delayed invasive coronary angiography. Patients with ongoing shock were excluded. Most patients had stable coronary artery disease and comparatively few had unstable lesions or acute thrombotic occlusion. Some patients randomized to delayed coronary angiography crossed over after subsequently manifesting cardiac deterioration. The trial was statistically neutral for survival or neurologic recovery at 90 days, suggesting that hemodynamically and electrically stable patients without STEMI may tolerate a delay in coronary angiography to optimize critical care and estimate neurologic recovery.

Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33°C versus 36°C after cardiac arrest. *N Engl J Med.* 2013;369:2197–2206.
This trial in patients with out-of-hospital cardiac arrest detected no difference in short- or long-term outcomes between two temperature management regimens: 33°C versus 36°C for 24 hours. The outcomes for both groups were similar to the intervention groups in prior trials and much better than the outcomes in prior control groups that had no temperature management, supporting the use of active temperature management, even at a higher temperature of 36°C.

Perkins GD, Ji C, Deakin CD, et al. A randomized trial of epinephrine in out-of-hospital cardiac arrest. *N Engl J Med.* 2018;379:711–721.
This trial randomized 8103 patients with out-of-hospital cardiac arrest to receive 1 mg epinephrine or placebo every 3–5 minutes. Epinephrine improved the rate of restoration of circulation, survival to hospital admission, survival to hospital discharge, and 3-month survival. The net increase in survivors constituted additional patients with both favorable and unfavorable neurologic outcomes without clear evidence of long-term benefit or harm.

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Management of Acute Ischemic Stroke

Ashutosh P. Jadhav and Lawrence R. Wechsler

Stroke is currently recognized as the fifth most common cause of death and the leading cause of permanent disability in the United States, affecting nearly 795,000 people annually.[1] Acute ischemic stroke is a true medical emergency and must be treated with a swift yet pragmatic approach. The rationale for acute ischemic stroke treatment is based on the concept of the *ischemic penumbra*. When arterial occlusion occurs, an area of irreversibly infarcted brain (i.e., core infarct) is surrounded by a region that has reduced blood flow that impairs function (i.e., ischemic penumbra), although not of sufficient severity to result in irreversible infarction. If adequate blood flow can be restored within a critical time frame, this area of at-risk tissue may be salvageable and return to normal function. The relationship between blood flow levels and duration for human stroke is still being elucidated, but based on laboratory studies, the more quickly restoration of blood flow occurs, the greater the probability that the salvageable tissue will be spared from permanent damage.[2,3]

In 1995 the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study Group showed for the first time an improvement in ischemic stroke outcome with acute treatment.[4] At present, intravenous tissue plasminogen activator (tPA) is the only treatment that has been approved by the Food and Drug Administration (FDA) for acute ischemic stroke patients presenting within 3 hours of symptom onset. Intraarterial therapy with stent retriever thrombectomy should be considered in patients presenting with acute ischemic stroke within 24 hours of symptom onset.[5,6] Other treatments for acute ischemic stroke, such as neuroprotective agents and cell replacement therapy, continue to be investigated.

EMERGENT STROKE EVALUATION

For patients in the field who develop symptoms concerning for acute ischemic stroke, once emergency medical services (EMS) are activated, a rapid neurologic assessment is performed using one of several prehospital stroke scales. These quick screening tools allow uniformity in assessing stroke deficits that clarify communication of the patient's status to the receiving emergency department. It is helpful if prehospital personnel are able to firmly establish with family or bystanders who witnessed the patient's symptom onset the precise time at which the patient last appeared normal. Upon arrival, or more ideally, before arrival at the emergency department, a "brain attack code" or "stroke code" is disseminated to members of the stroke team.

A stroke team typically consists of individuals from multiple disciplines with specialized knowledge and interest in acute stroke care and often includes a vascular neurologist, nursing coordinator, and where available, a neurointerventionalist. A neurologist performs a National Institutes of Health Stroke Scale (NIHSS) (Table 46.1) assessment as an additional rapid neurologic assessment tool to better localize and ascertain the degree of clinical deficit, as the score may affect which therapies are available to the patient. For patients developing focal neurologic symptoms while already hospitalized in an intensive care unit (ICU) or other hospital floor, the algorithm should be identical.

Ischemic strokes generally are classified as large artery atherosclerosis, small vessel occlusion, cardioembolism, stroke of other determined etiology, or stroke of undetermined etiology.[7] In the first few minutes to hours after ischemic stroke, identification of stroke mechanisms may be difficult or impossible. Emergent diagnosis is greatly enhanced by imaging modalities and should include both parenchymal and vessel imaging, such as computed tomography (CT) and magnetic resonance imaging (MRI)[8] with angiography.

IMAGING OF ACUTE STROKE

Differentiating ischemic from hemorrhagic stroke is necessary before deciding on thrombolytic administration, and imaging obviously plays a key role in this regard. However, imaging may provide much more information. At most stroke centers, time from symptom onset (i.e., time when patient was last confirmed to be seen at normal baseline) is a major determining factor in whether a patient is a candidate for intravenous thrombolysis (up to 3 hours) or intraarterial therapy (up to 24 hours). An emerging concept is that physiology rather than time should be used to decide on treatment eligibility.[9] For example, some patients within the 3-hour time window may already have established infarction that would not reverse with thrombolysis and may result in hemorrhage owing to reperfusion of infarcted brain. Conversely, some patients may have salvageable brain tissue despite presentation well after the 3-hour time window.[10,11] A physiologic estimate of tissue viability would be preferable to a fixed time interval if a study were found that reliably predicted viability of brain after stroke. CT and MRI have the potential to provide this measurement.[12]

Computed Tomography

A noncontrast head CT is the initial imaging modality of choice for patients with suspected stroke. The foremost reason is that CT scans can be readily and quickly obtained because of the widespread availability of CT scanners; the second reason is the ability of CT to exclude intracranial hemorrhage. In addition to differentiating ischemic stroke from hemorrhage, CT may demonstrate subtle parenchymal abnormalities indicative of early edema or infarction. Previously, it was believed that these changes did not occur on CT for at least 6 hours after ischemic stroke. More recent studies indicate, however, that early changes of ischemia frequently occur within a few hours of stroke onset and have been seen as soon as 1 hour after stroke.[13] These changes include reduced attenuation in the basal ganglia[2]; loss of gray-white differentiation, particularly in the insular region[14]; low density in the cortex and subcortical white matter; and loss of sulcal markings, suggesting early mass effect and edema (Fig. 46.1A and B).[15]

TABLE 46.1 National Institutes of Health Stroke Scale

1A. Level of Consciousness (LOC)	1B. LOC Questions	1C. LOC Commands
0 = Alert 1 = Not alert, but arousable 2 = Not alert, obtunded 3 = Coma	Ask the month and his or her age. 0 = Answers both correctly 1 = Answers one correctly 2 = Answers neither correctly	Open and close the eyes. Open and close the nonparetic hand. 0 = Performs both tasks correctly 1 = Performs one task correctly 2 = Performs neither task correctly
2. Best Gaze (Horizontal)	**3. Visual Fields**	**4. Facial Palsy**
0 = Normal 1 = Partial gaze palsy 2 = Forced deviation or total gaze paresis	0 = No visual loss 1 = Partial hemianopia 2 = Complete hemianopia 3 = Bilateral hemianopia	0 = Normal 1 = Minor paralysis 2 = Partial paralysis (total or near-total paralysis of lower face) 3 = Complete paralysis of upper and lower face
5. Motor Arm	**6. Motor Leg**	**7. Limb Ataxia**
Right Arm extended with palms down 90 degrees (if sitting) or 45 degrees (if supine) for 10 seconds 0 = No drift 1 = Drift; limb drifts down from position and does not hit bed or support in 10 seconds 2 = Some effort against gravity 3 = No effort against gravity 4 = No movement **Left**	**Right** Leg extended at 30 degrees, always tested supine for 5 seconds 0 = No drift 1 = Drift; limb drifts down from position and does not hit bed or support in 5 seconds 2 = Some effort against gravity 3 = No effort against gravity 4 = No movement **Left**	The finger-nose-finger and heel-shin tests 0 = Absent 1 = Present in one limb 2 = Present in two limbs
8. Sensory	**9. Best Language**	**10. Dysarthria**
To Pinprick or Noxious Stimuli 0 = Normal 1 = Mild to moderate sensory loss 2 = Severe to total sensory loss	0 = No aphasia, normal 1 = Mild to moderate aphasia 2 = Severe aphasia 3 = Mute, global aphasia, coma	0 = Normal 1 = Mild to moderate 2 = Severe (including mute/anarthric because of aphasia); do not score if intubated
11. Extinction and Inattention		**Total Score:**
0 = No abnormality 1 = Present 2 = Profound (two modalities)		

Fig. 46.1 A, Normal computed tomography (CT) scan of brain 2 hours after onset of aphasia and left hemiparesis. **B,** Repeat CT scan at 5 hours after stroke onset shows early CT changes, including basal ganglia hypodensity, loss of the insular ribbon, and slight effacement of the sulci on the left. **C,** CT angiogram at 5 hours after stroke onset shows complete occlusion of the left middle cerebral artery (MCA). **D,** Rapid reconstruction of the CT angiogram again shows occlusion of the left MCA.

A hyperdense middle cerebral artery (MCA) occurs in 20%–37% of cases,[16] indicating acute thrombus within the artery. This condition rarely occurs without at least one other early CT abnormality. Hyperdensity in the basilar artery associated with thrombosis also has been reported.[17] In 100 patients studied within 14 hours (mean 6.4 hours) of stroke onset, multiple early CT abnormalities correlated with the size of the subsequent infarct and poor outcome.[16] In the ECASS I trial of tPA for acute stroke, early CT changes correlated with larger subsequent infarct volume and a greater likelihood of hemorrhagic conversion after tPA.[18] Quantitative assessment of CT changes using the

Alberta Stroke Program Early CT Score (ASPECTS) scale in patients treated with intravenous tPA also showed a relationship between early CT hypodensity (ASPECTS <8) and hemorrhage.[19,20] Thus some experts recommend withholding thrombolytic therapy in patients with extensive early CT changes, particularly in those later in the thrombolytic time window,[21] although this practice is controversial. For example, subsequent analysis of the NINDS rt-PA trial data revealed that early ischemic changes did not predict symptomatic hemorrhage or response to treatment,[22] and more recent evidence reports no association between early ischemic CT changes and outcome.[23]

Computed Tomography Angiography

CT angiography (CTA) can be performed using spiral CT, allowing for imaging of the intracranial and extracranial circulation. Optimally, CTA of the neck should also include visualization of the aortic arch. The typical single bolus of iodine contrast material is about 70 cc. This injection limits the use of CTA in patients with renal failure or contrast hypersensitivity. In acute stroke, CTA of the head and neck is highly reliable for diagnosis of intracranial occlusions and correlates with other imaging modalities.[24,25] Three-dimensional reconstruction images can also be created, providing additional views and information about the carotid bifurcation and carotid lesions, revealing eccentric lesions and ulceration (see Fig. 46.1C and D).

Computed Tomography Perfusion

In addition to imaging the brain parenchyma with a noncontrast head CT and the cerebral vasculature with CTA, CT perfusion (CTP) adds assessment of cerebral blood volume (CBV) and cerebral blood flow (CBF) (Fig. 46.2). In patients with acute stroke, CTP has been correlated with final infarct size and outcome, particularly after recanalization.[26] CTP maps combining CBV and CBF identify brain tissue that progresses to infarction if not reperfused, consistent with ischemic penumbra.[27] Recent evidence suggests that the inclusion of CTP in a stroke imaging protocol increases diagnostic performance.[26,28,29]

Whereas CTP serves as a qualitative measure of CBF, there have been investigations into using xenon CT to measure CBF quantitatively.[30] Stable xenon is an inert gas inhaled as a mixture of 27% xenon and 73% oxygen. During inhalation over a few minutes, rapid scanning is performed, and pixel-by-pixel blood flow values are calculated at different brain levels (Fig. 46.3). In a series of patients with MCA occlusion studied with xenon CT, areas of penumbra were present in all patients, and the percentage of MCA territory in the penumbral range (CBF 8–20 mL/100 g/min) remained relatively constant across the group. In contrast, the percentage of MCA territory with CBF values representing infarcted tissue (CBF <8 mL/100 g/min) varied greatly. Outcome correlated highly with the area of infarcted MCA territory, not the amount of ischemic penumbra. Thus after the first few hours, the size of the core infarcted tissue, not the amount of penumbral tissue, may be the most important imaging parameter to determine suitability for acute stroke therapy.[31]

Magnetic Resonance Imaging

Compared with CT modalities, MRI is advantageous because it is more sensitive to cerebral infarction, especially in the brainstem and deep white matter. Typical sequences included in an MRI stroke protocol include diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) to evaluate for potential acute ischemia, multiplanar gradient-recalled (MPGR) or gradient-recalled echo (GRE) to evaluate for hemorrhage, and fluid-attenuated inversion recovery (FLAIR) to evaluate for important signs in both hyperacute and acute stages of stroke (i.e., assessment for absence of flow void in major cerebral arteries, suggesting occlusion or slow flow in that artery). Perfusion-weighted imaging (PWI) is often used to determine abnormal tissue perfusion based on transit times for contrast material through brain parenchyma (Fig. 46.4).

DWI shows parenchymal abnormalities earlier than conventional T2-weighted images in patients with acute stroke.[32] It detects the diffusion of water in the brain and shows hyperintensity in areas of reduced diffusion (see Fig. 46.4). As water moves from the extracellular to the intracellular space, there is less movement of water and loss of signal, resulting in hyperintensity.[33] Early detection of lesions by DWI helps differentiate cerebral ischemia from other conditions that mimic stroke, such as seizures or toxic-metabolic states. Additionally, combining DWI with PWI may identify reversibly ischemic tissue. If there is a large area of PWI abnormality indicating reduced CBF but limited established infarction, as evidenced by DWI abnormality, penumbral tissue is likely present, indicating areas at risk of undergoing infarction.

In stroke patients, the size of the DWI lesion and the growth of these abnormal DWI regions are strong predictors of outcome. In acute stroke, a marker of tissue viability is needed, and some investigators have suggested that the extent of mismatch between lesions on DWI and PWI could serve as this marker. The concept of DWI/PWI

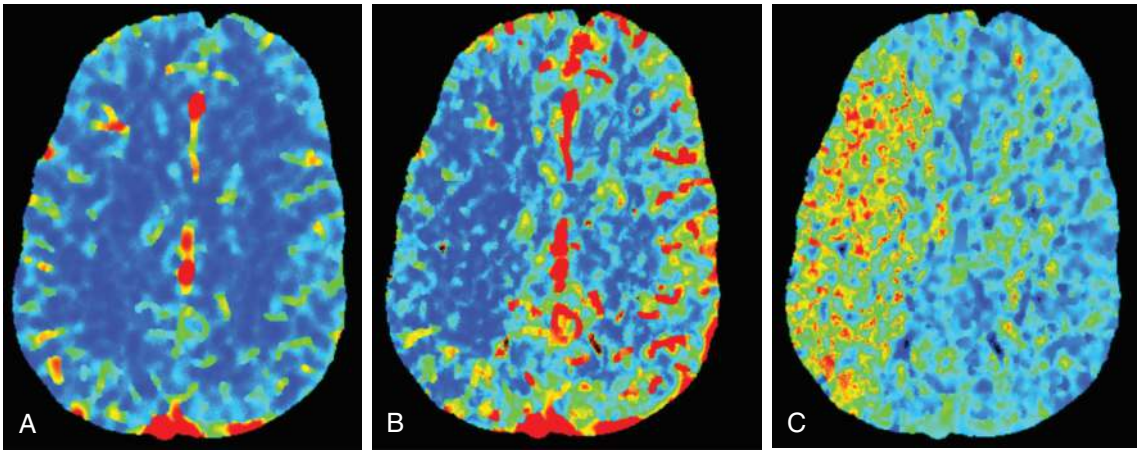

Fig. 46.2 Computed Tomography Brain Perfusion Scan with Sequencing Maps. **A,** Cerebral blood volume (CBV) showing no clear evidence of core infarct. **B,** Cerebral blood flow (CBF) showing a decrease in the right middle cerebral artery (MCA) territory. **C,** Mean transit time (MTT) showing delayed perfusion in the right MCA territory. These sequences together indicate a large ischemic penumbra in the right MCA territory.

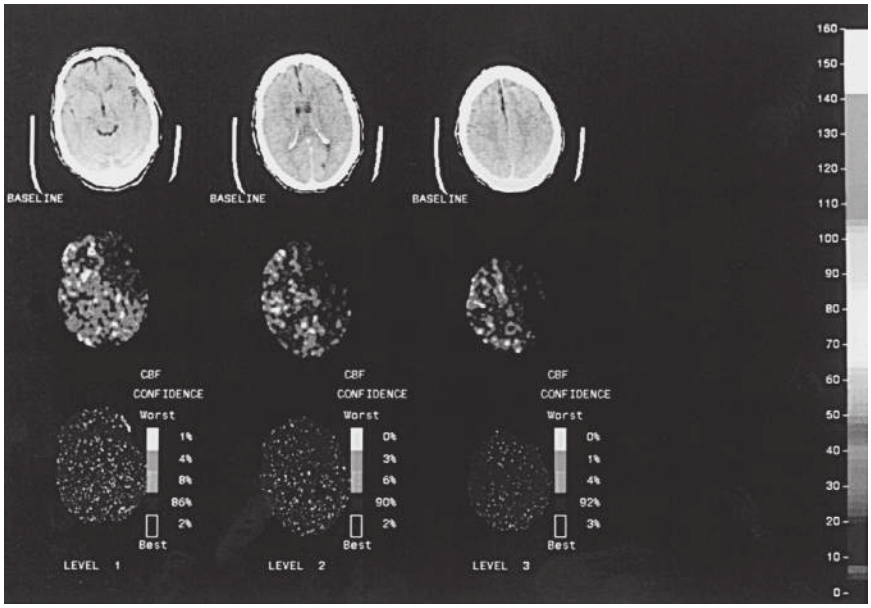

Fig. 46.3 Xenon Computed Tomography Blood flow Study from a Patient with a Large Left Hemisphere Stroke 3 Hours after Onset of Symptoms. Flow is nearly absent throughout the middle cerebral artery territory on the left.

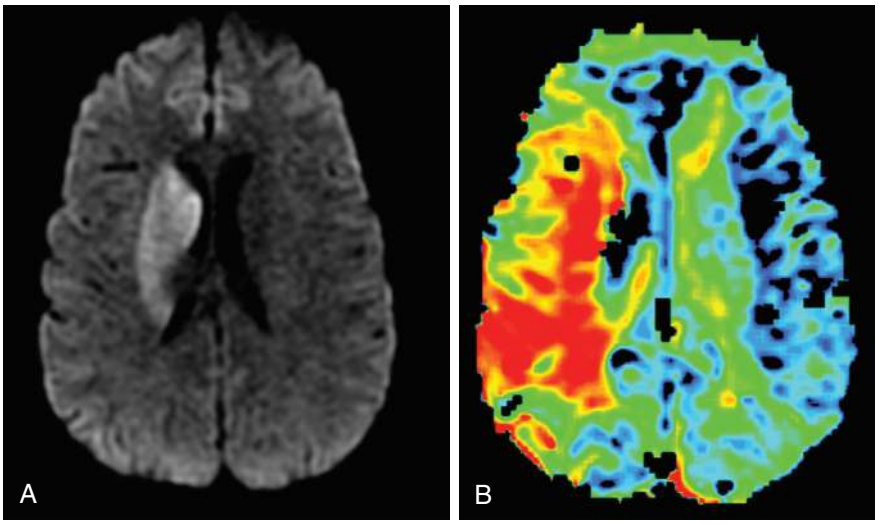

Fig. 46.4 Magnetic Resonance Imaging of the Same Patient in Fig. 46.2. **A,** Diffusion-weighted imaging (DWI) showing right basal ganglia stroke. **B,** Perfusion-weighted imaging (PWI) showing enhanced mean time to enhancement. These sequences together suggest a large ischemic penumbra in the right middle cerebral artery (MCA) territory.

mismatch has been used as an inclusion criterion in several studies (DIAS, DIAS-2, among others) assessing thrombolytic agents and is being employed more frequently to select patients who may benefit from reperfusion therapy.[34–41] Patients[11] with mismatch might be more likely to respond to reperfusion therapy.[42] Patients with large areas of DWI abnormality or large severe PWI abnormalities may be at greater risk for hemorrhage if reperfusion therapy is pursued.[10,43]

Magnetic Resonance Angiography

Magnetic resonance angiography (MRA) of the head and neck offers a noninvasive method of imaging the intracranial and extracranial vasculature. MRA typically uses gadolinium contrast in appropriate patients, but important information can be obtained based on time-of-flight techniques not using contrast.[44,45] Detection of dissection or occlusion in the circle of Willis and the extracranial vertebral and carotid arteries can be examined with MRA, but occlusions of small peripheral branch arteries may not be detected. Artifacts may also obscure proper identification of arterial pathology. Signal dropout may occur at the site of arterial stenosis owing to the effects of turbulent flow. If an artery is tortuous, it may extend out of the imaging section and appear occluded. MRI tends to overestimate the severity of stenosis, and evidence of severe stenosis should be confirmed with another modality. MRA is better for localizing the site of stenotic lesions than determining severity of stenosis. Similarly, differentiation between severe stenosis and occlusion is unreliable with MRI, and apparent occlusions by MRA should also be confirmed with angiography.

Digital Subtraction Angiography

Catheter-based digital subtraction angiography (DSA) remains the gold standard for determining the degree of vessel stenosis and understanding

the collateral circulation. The high quality of anatomic delineation allows for precise determination of carotid stenosis as with CTA, whereas MRA and carotid Dopplers can misclassify stenosis. Historically, the procedure has been associated with a high risk of complications, although more modern experience estimates a much lower risk of stroke (0.3%) at experienced centers.[46,47] The technique requires specialized personnel and equipment and may not be readily available at all centers.

TREATMENT OF ACUTE STROKE

Intravenous Thrombolysis

Acute stroke trials using intravenous thrombolytic agents date back to the early 1960s, with the use of streptokinase,[48] fibrinolysin,[49] and urokinase[50] showing either no benefit or a higher mortality in patients treated with thrombolysis. These studies preceded CT imaging, and thus patients with hemorrhage were not excluded. The discouraging results hindered the development of more acute stroke trials until the 1980s, when several case reports showed favorable outcomes with intraarterial thrombolytic therapy within a few hours of stroke onset.[51,52] These reports resulted in small randomized trials and feasibility studies of intravenous thrombolytics[53,54] that ultimately gave rise to the pivotal NINDS rt-PA trial that showed a beneficial effect of thrombolytic therapy for acute stroke treatment when administered within 3 hours of symptom onset.[4]

Tissue Plasminogen Activator Within 3 Hours

The NINDS trial included more than 600 patients with acute ischemic stroke. All patients were treated within 3 hours, and half of the patients were treated within 90 minutes. Patients were randomly assigned to receive either intravenous tPA at a dose of 0.9 mg/kg to a maximum of 90 mg or intravenous placebo. Primary outcome measures were favorable outcomes at 90 days measured by the NIHSS, Barthel Index, Glasgow Outcome Scale, and modified Rankin Scale (mRS). By all four measures, significantly more patients had a favorable outcome at 90 days in the tPA group compared with placebo. Treatment with tPA resulted in an 11%–13% absolute increase in good outcomes and a minor, nonsignificant decrease in mortality at 3 months. The benefit was sustained at 12 months.[55] Intracerebral hemorrhage with clinical deterioration occurred in 6.4% of patients treated with tPA versus only 0.6% of placebo patients. Despite the increased hemorrhage rate, there was no significant increase in mortality or severe disability in the tPA group versus placebo. All subtypes of strokes had more favorable outcomes with tPA. There were no clear factors that predicted response to tPA.[56] Patients with large strokes as measured by NIHSS score >20 and evidence of early low density or edema on CT had a higher rate of hemorrhage after tPA.[57]

Based on these results, the FDA approved intravenous tPA for treatment of stroke within 3 hours of onset in June 1996. This result was supported by the results of an analysis of patients treated within 3 hours of onset in the ATLANTIS trial.[58] A subsequent pooled analysis of NINDS rt-PA, ECASS, and ATLANTIS data showed that clinical benefit with tPA is greatest when given early, especially if started within 90 minutes (Table 46.2).[59] Not all patients recanalize with intravenous tPA. In a dose escalation trial of intravenous tPA, angiography was performed before thrombolysis in all patients documenting the site of arterial occlusion and was repeated 2 hours later. Proximal occlusions in the MCA opened less frequently than distal branch occlusions, and only 8% of carotid occlusions recanalized.[60]

Given the importance of early drug administration, much attention has been placed on improving systems of care to deliver the drug early and often. The use of telemedicine has played a great and expanding role in allowing patients presenting to stroke-ready hospitals without in-house vascular neurology expertise to receive remote clinical examination and imaging review via video streaming. Within our stroke network at the University of Pittsburgh, the implementation of telemedicine at 12 neighboring hospitals increased the use of intravenous thrombolysis from 2.8% to 6.8%, with a lower incidence of symptomatic hemorrhage.[61] Similar experiences have been reported across the country. Emphasis has also been placed on minimizing additional tests (i.e., coagulation profile or platelet count) in selected patients and prioritizing imaging and early stroke team activation. Campaigns to improve times have driven door-to-needle times down to 22 minutes at some centers.

TABLE 46.2 Odds Ratios for Modified Rankin Score 0–1 in the Combined tPA Analysis

Time	N	Odds Ratio	95% CI
0–90	311	2.83	1.77, 4.53
91–180	618	1.53	1.11, 2.11
181–270	801	1.40	1.06, 1.85
271–360	1046	1.16	0.91, 1.49

CI, Confidence interval; *tPA,* tissue plasminogen activator.
Data from The ATLANTIS, ECASS, and NINDS rt-PA Study Group Investigators. Association of outcome with early stroke treatment: Pooled analysis of ATLANTIS, ECASS and NINDS rt-PA stroke trials. *Lancet.* 2004;363(9411):768–774.

Tissue Plasminogen Activator Beyond 3 Hours

Several subsequent tPA trials attempted to extend the window for treatment beyond 3 hours. The ECASS I and II trials and the ATLANTIS trial treated patients with intravenous tPA up to 6 hours after stroke onset but failed to show benefit versus placebo.[62–64] Pooled analysis of NINDS rt-PA, ECASS, and ATLANTIS data suggested a potential benefit beyond 3 hours. The ECASS III trial recently revealed that intravenous alteplase administered between 3 and 4.5 hours after symptom onset significantly improved clinical outcomes in patients with acute ischemic stroke, thereby potentially extending the therapeutic window in which patients may receive intravenous tPA. In addition to standard intravenous tPA exclusion criteria (Table 46.3), ECASS III exclusion criteria include the combination of previous stroke and diabetes, an NIHSS score >25, oral anticoagulant treatment, or age >80 years.[65] Whether patients in this time window with these exclusions also benefit from intravenous tPA is unknown.

IST-3 is a clinical trial that randomized 3035 patients with ischemic stroke within 6 hours of symptom onset to intravenous alteplase (0.9 mg/kg; $n = 1515$) plus standard care or standard care alone (control; $n = 1520$). Although the primary endpoint of good outcome was no different between groups, the study did show improved outcomes in patients presenting within early time windows and enrolled a high percentage of elderly patients (age >80), thus establishing the efficacy of intravenous tissue plasminogen activator (IV tPA) in this population. Several ongoing trials are investigating a role for IV tPA in patients presenting at late time windows with favorable imaging profiles (i.e., small core and large penumbra or DWI/FLAIR mismatch).

Mild and Rapidly Improving Symptoms

Whereas the original NINDS study considered mild or rapidly improving symptoms as a relative contraindication for IV thrombolysis, subsequent retrospective analysis of this population has revealed poor

TABLE 46.3 ASPECTS Measurement Tool for Early Changes on Computed Tomography

TEN REGIONS OF INTEREST*	
At the Level of the Basal Ganglia and Thalamus	**At the Level Just Rostral to Deep Nuclei**
Anterior middle cerebral artery (MCA) cortex	Superior to anterior MCA cortex
MCA cortex lateral to insula	Superior to MCA cortex lateral to insula
Posterior MCA cortex	Superior to posterior MCA cortex
Caudate	
Lentiform nucleus Internal capsule Insular ribbon	

*One point is subtracted for each defined area of early ischemic change, such as focal swelling or parenchymal hypoattenuation. Score varies from 0 to 10.

Adapted from Pexman JH, Barber PA, Hill MD, et al. Use of the Alberta Stroke Program Early CT Score (ASPECTS) for assessing CT scans in patients with acute stroke. *AJNR Am J Neuroradiol*. 2001;22(8):1534–1542.

outcomes, with up to 30%–40% of patients requiring inpatient rehabilitation at discharge and a subset suffering further neurologic decline. Although the natural history in this population may not be as benign as previously perceived, the benefit of intravenous thrombolysis remains to be proven. A review of patients within the SPOTRIAS database revealed practice variation across centers with a range of 2.7%–18% of mild stroke patients receiving IV tPA. Furthermore, the proportion of patients with mild NIHSS increased from 4.8% in 2005 to 10.7% in 2009 ($P = .001$). The PRISMS trial did not demonstrate any additional of alteplase versus aspirin in patients with acute onset of nondisabling mild symptoms.

Tenecteplase

Tenecteplase is a modified form of human tPA designed to achieve more effective thrombolysis. The half-life of tenecteplase is longer, allowing administration as a single bolus. Tenecteplase has greater fibrin specificity and less fibrinogen depletion than tPA.[66] A phase IIb study randomly assigned 75 patients to receive alteplase (0.9 mg per kilogram of body weight) or tenecteplase (0.1 mg per kilogram or 0.25 mg per kilogram) less than 6 hours after the onset of ischemic stroke. The two tenecteplase groups had greater reperfusion ($P = .004$) and clinical improvement ($P < .001$) at 24 hours than the alteplase group, with no differences in intracranial bleeding or serious adverse events. The higher dose of tenecteplase (0.25 mg per kilogram) was superior to the lower dose and to alteplase for all efficacy outcomes, including absence of serious disability at 90 days. The NOR-TEST phase III trial compared intravenous tenecteplase to intravenous alteplase in patients presenting within 4.5 hours of symptom onset who met intravenous r-tPA criteria. The primary endpoint of mRS 0–1 was comparable in both groups with similar safety profiles. The EXTEND-TNK trial compared intravenous tenecteplase with intravenous alteplase in patients presenting within 4.5 hours of symptoms onset in the setting of a large vessel occlusion. The primary outcome of reperfusion of greater than 50% of the target lesion territory was met in 22% of the tenecteplase cohort compared with 10% of the alteplase cohort. Several trials are now underway to test the efficacy of tenecteplase versus alteplase in the early time window in addition to tenecteplase in the late time window.

Intravenous tPA Beyond 4.5 Hours

A pooled analysis of IV tPA trials indicated a declining benefit of treatment with increasing time from stroke onset reaching unity at approximately 4.5 hours. However, there is growing recognition that in some patients, particularly those with good collateral, reversibility might extend well beyond the perceived time limits. Imaging software now enables identification of patients with large territories at risk and small established infarcts likely to benefit from reperfusion therapy. In addition, those who awaken with deficits or with undetermined time of onset who have similar favorable physiology can now be identified with imaging tools. Two recent trials demonstrated benefit of IV tPA treatment beyond the 4.5-hour time window in patients selected using imaging.

In the WAKE-UP trial[10] 503 patients with unknown time of onset but greater than 4.5 hours underwent MRI. If a diffusion abnormality was present without a corresponding hyperintensity on FLAIR imaging, they were randomized to standard-dose IV tPA or placebo. The mismatch between DWI and FLAIR imaging suggests the true time from stroke onset was within 3 hours. Favorable outcomes at 90 days were 11.5% greater in the tPA group (53.3% vs. 41.8%, odds ratio [OR] 1.61 $P = .02$). The study did not reach planned completion because of lack of funding, and the difference in favorable outcome did not correspond to a difference in final infarct volume.

The EXTEND trial[11] tested the hypothesis that advanced imaging could identify patients beyond 4.5 hours likely to benefit from IV tPA. The study enrolled 225 patients but was terminated early because of publication of the WAKE-UP trial results. Patients were randomized to IV tPA or placebo if they were 4.5–9 hours since last seen well and if there was a mismatch between the ratio of perfusion abnormality and core infarct volume of at least 1.2 using CT or MR perfusion using RAPID automated software. Favorable outcome (mRS 0–1) occurred in 35.4% of the tPA group and 29.5% of the placebo group ($P = .05$) at 90 days. In both trials there was an increase in hemorrhages in the tPA group.

These studies suggest treatment with IV tPA is reasonable to consider in patients waking up with stroke deficits or with unknown time from onset and last-known well time between 4.5 and at least 9 hours using imaging to select those with favorable physiology.

Intraarterial Therapy

Intraarterial Thrombolysis

An alternative approach to intravenous thrombolysis is direct delivery of thrombolytic agents by a microcatheter embedded in the clot (Fig. 46.5). The advantage of the intraarterial approach is direct visualization of the occluded artery and knowledge of the recanalization status as thrombolysis proceeds. Theoretically, delivery of the thrombolytic agent to the site of the clot should be more effective than intravenous infusion. The disadvantage is the additional time needed to bring the patient to the angiography suite, prepare the groin, catheterize the femoral artery, and guide the catheter from the femoral artery to the intracranial circulation before the thrombolytic agent can be administered.

Urokinase was used in early studies of intraarterial thrombolysis but is no longer available.[67] Recombinant prourokinase was evaluated formally in clinical trials,[68–70] and the PROACT II study was the first acute stroke trial to show a significant improvement in outcome when administered within 6 hours of stroke symptom onset. The median time to treatment was 5.5 hours, and most patients were treated after

Fig. 46.5 **A,** Right carotid angiogram from a patient with embolic occlusion of the right middle cerebral artery (MCA) 4 hours after onset of symptoms. **B,** Angiogram from the same patient after placement of a microcatheter into the MCA clot and infusion of 120,000 U of urokinase. There is no recanalization. **C,** Angiogram after infusion of 1 million U of urokinase directly into the clot, showing complete recanalization of the MCA.

5 hours.[69] The clinical benefit was apparent despite this late time to treatment; a greater benefit may have been found had patients been treated earlier or mechanical manipulation also been allowed. Symptomatic hemorrhage occurred in 10% of patients treated with recombinant prourokinase and in 2% of controls. Although the hemorrhage rate was higher than previous intravenous thrombolytic studies, the median NIHSS score of 17 indicates that the patients in the PROACT II study had more severe strokes treated at a later time interval. A higher hemorrhage rate would be expected in these scenarios. There was also no differential effect of recombinant prourokinase across risk strata, indicating that all patients, regardless of risk, benefit equally from recombinant prourokinase.[70] Nevertheless, prourokinase has not been FDA approved to date, and tPA tends to be more often used in cases of intraarterial thrombolysis. The exact dose, efficacy, and safety profile of intraarterial tPA is limited, but recent studies have suggested doses up to 40 mg are reasonably safe for use.[71]

First-Generation Mechanical Devices

Although most thrombolytic studies concentrate on time to treatment, the most important factor for clinical outcome is probably time to recanalization of an occluded vessel. When infusion of thrombolytic agents often requires 1–2 hours for complete thrombus dissolution, time to recanalization can be quite long. Mechanical devices offer the possibility of considerably shortening time to recanalization. Devices may be able to clear thrombi from large arteries within a few minutes. The use of thrombolytic agents may not be necessary, possibly reducing the rate of intracranial hemorrhage.

The revolutionary Merci Retriever clot retrieval device (Concentric Medical, Inc., Mountain View, CA) received FDA approval for the removal of blood clots from the brain in patients experiencing ischemic stroke after it was shown to be effective in restoring vascular patency in patients within 8 hours of symptom onset and could serve as an alternative therapy for patients who are otherwise ineligible for thrombolytic drug administration.[72] The Merci device is a flexible nickel titanium (i.e., nitinol) wire that assumes a helical shape once it is passed through the tip of the guidance catheter. In practice, the catheter/wire is passed distal to the thrombus, the catheter is removed, and a helical configuration is assumed by the wire. The clot is then trapped in the helix and withdrawn from the vasculature. Second-generation Merci devices (e.g., L5 Retriever) have been developed and their use shown to be associated with higher rates of recanalization, although these differences did not achieve statistical significance. They also produced lower mortality and a higher proportion of good clinical outcomes.[73] Mechanical embolectomy using an aspiration platform was the basis for the creation of the Penumbra System (Penumbra, Inc., Alameda, CA), which uses a microcatheter and separator-based debulking approach that allows for continuous aspiration of thrombus. A recent trial found that the Penumbra System resulted in safe and effective revascularization in patients who present with large vessel occlusive disease within 8 hours of stroke onset, as 81.6% of patients achieved a Thrombolysis In Myocardial Infarction (TIMI) grade of 2 or 3.[74]

First-Generation Randomized Trials of Intraarterial Therapy

Three clinical trials investigated the role of intraarterial therapy as an alternative or adjunctive treatment to standard medical therapy. The SYNTHESIS trial compared intravenous thrombolysis alone with intraarterial therapy alone and showed comparable outcomes in both cohorts despite an hour delay in initiating intraarterial therapy.[75] Although the trial did not observe improved outcomes in the intraarterial therapy group, it did not require documentation of a large vessel occlusion before initiation of treatment; 92 patients were treated with intraarterial therapy outside the context of the trial, further diluting the study population of patients likely to benefit from intraarterial therapy. The MR RESCUE trial implemented a penumbral imaging-based paradigm in which patients were randomized to medical or intraarterial therapy.[76] There was no difference between groups. Finally, IMS 3 compared the additional benefit of mechanical thrombectomy in patients receiving IV tPA.[77] Once again, intraarterial therapy proved to be safe but no more efficacious than medical therapy. However, it is likely that a high percentage of patients had little or no chance of benefit.[78] Time to treatment was prolonged, as the mean IV tPA start to groin puncture time was 81 ± 27 minutes and the mean groin to IA start time was 41 ± 21 minutes, with a greater than 2-hour delay between CT head and groin puncture.[79]

Stent Retrievers and Recent Trials

These three first-generation trials highlighted an important concept in revascularization—namely, that treatment likely favors patients with a

large clinical deficit in the setting of a small core on presentation who undergo early and effective recanalization. In 2012 the FDA approved two new devices for the indication of thrombus removal in acute stroke: SOLITAIRE and TREVO. Both devices are in the stent retriever class of mechanism and consist of intracranial stents that can be delivered across the thrombus with the dual benefit of achieving a temporary endovascular bypass and trapping the clot within the struts of the stent. The stent retriever is subsequently recovered along with the thrombus. In comparison to the Merci device, stent retrievers yield higher rates of high-quality recanalization (86%–89% vs. 60%–66%).[80,81] Several randomized clinical trials have now tested the hypothesis that intraarterial therapy may be superior to medical management if revascularization is achieved implementing this new technology.[82–86] The first trial to be completed was MR CLEAN, which demonstrated an adjusted common OR of 1.67 in favor of intervention and an absolute difference of 13.5% in the rate of functional independence. These results prompted several ongoing trials to review their outcomes, and a similar benefit was seen across studies (Tables 46.4–46.6).

Most of these trials focused on patients presenting within early time windows and predominantly used CT imaging to determine patient selection. The role of intraarterial therapy beyond 6 hours was studied in the DAWN[87,88] and DEFUSE-3 trials. Both trials used advanced imaging to identify patients with large vessel occlusion (M1 or ICA location) in the setting of a small core that was disproportionate to the clinical deficit (clinical-core mismatch in the DAWN trial) or perfusion deficit (perfusion-core mismatch in the DEFUSE-3 trial). In both trials, endovascular therapy was associated with significantly higher rates of functional independence (see Tables 46.4–46.6).

Intraarterial therapy trials predominantly focused on patients with anterior circulation occlusions in the setting of small core and high NIHSS. The subject on future and ongoing trials includes patients with large core (TENSION, TESLA, and IN EXTREMIS-LASTE) and low NIHSS (ENDO-LOW, IN EXTREMIS-MOSTE). Many practitioners favor revascularization for patients with basilar artery occlusive disease, given the high rate of mortality in this stroke subtype.[89] The recently completed BEST trial randomized patients presenting with basilar artery occlusions within 8 hours of symptom onset to endovascular therapy versus medical therapy[90]. There was no difference in favorable outcomes between the two groups; however, there were high rates of crossovers because of lack of equipoise. Secondary prespecified analyses of the primary outcome showed higher rates of mRS 0–3 at 90 days in patients who actually received the intervention compared with those who received standard medical therapy alone. The ongoing BAOCHE

TABLE 46.4 Summary of Trial Design in Mechanical Thrombectomy Trials

	Age	Time	IV tPA	NIHSS	LVO	Imaging Criteria
MR CLEAN ($n = 500$)	≥18	6 hr	~90%	>2	ICA M1, M2, ACA A2	"Gray area principle"
EXTEND-IA ($n = 70$)	≥18	6 hr	100%	None	ICA M1, M2	Rapid imaging: Core <70 cc Penumbra >10 cc Mismatch ratio >1.2
SWIFT PRIME ($n = 196$)	18–80	6 hr	100%	>7	ICA M1	ASPECT >6 Rapid imaging encouraged (81%)
ESCAPE ($n = 314$)	≥18	12 hr	~75%	>5	ICA M1	ASPECT >5 Moderate or good collateral circulation
REVASCAT ($n = 206$)	18–85	8 hr	~70%	>5	ICA M1	ASPECT >6 DWI ASPECT 0.5

TABLE 46.5 Summary of Patient Population in Mechanical Thrombectomy Trials

	Age (yr)	Time (min)	NIHSS	LVO	Baseline Imaging
MR CLEAN ($n = 500$)	65.8 (55–76)	260* (210–313)	17 (14–21)	ICA 25% M1 66% M2 8%	ASPECTS: 9 (7–10)
EXTEND-IA ($n = 70$)	68.6 ± 12	248 (204–277)	17 (13–20)	ICA 31% M1 57% M2 11%	Core: 12.3 cc (4–32) Penumbra: 106 cc (76–137)
REVASCAT ($n = 206$)	65.7 ± 11	355 (269–430)	17 (14–20)	ICA 26% M1 64% M2 10%	ASPECTS: 7 (6–9)
ESCAPE ($n = 314$)	71 (60–81)	341 (176–359)	16 (13–20)	ICA 28% M1 68% M2 4%	ASPECTS: 9 (8–10) Collaterals: 94% moderate to good
SWIFT PRIME ($n = 196$)	66.3 ± 11	252 (190–300)	17 (13–19)	ICA 16% M1 77% M2 6%	ASPECTS: 9 (8–10)

TABLE 46.6 Summary of Outcomes in Mechanical Thrombectomy Trials

Trial	Pts	% Reperfusion IAT/Medical	mRS 0–2 IAT/Medical	sICH IAT/Medical	Mortality IAT/Medical
ESCAPE	238	72.4%TICI 2b/3	53%/29.3%	3.6%	10.4%
		32.2% mAOL 2–3	53%/29.3%	2.7%	19%
EXTEND-IA	70	89% mTICI 2b/3	71%/40%	0%	9%
		34% mAOL 2–3	71%/40%	6%	20%
MR CLEAN	500	58.7% mTICI 2b/3	32.6%/19.1%	7.7%	21%
		57.5 mAOL 2–3	32.6%/19.1%	6.4%	22%
REVASCAT	206	65.7% mTICI 2b/3	43.7%/28.2%	1.9%	18.4%
		NA	43.7%/28.2%	1.9%	115.5%
SWIFT-PRIME	196	82.8% mTICI 2b/3	60.2%/35.5%	1.0%	9.2%
		40.4% mAOL 2–3	60.2%/35.5%	3.1%	12.4%

trial is comparing the benefit of endovascular therapy versus medical therapy in patients presenting with basilar artery occlusion between 8 and 24 hours of symptoms.

Surgical Options

Cerebral edema and herniation are frequent causes of death from stroke in the first few days after massive infarction. Edema gradually increases and peaks 2–3 days after stroke onset. Steroids do not effectively reduce edema caused by stroke, and antiedema measures such as mannitol or hyperventilation are of limited benefit. Control of intracranial pressure (ICP) is associated with improved outcome, but whether ICP monitoring is helpful to guide therapy remains unclear. Surgical decompression of large hemispheric infarcts causing edema and increased ICP is logical because the edema is usually self-limited. If herniation can be avoided, recovery may occur similar to stroke without severe edema. Several different approaches to decompression have been proposed.

Hemicraniectomy is the first and most commonly performed procedure. It involves removal of a generous bone flap ipsilateral to the side of the infarction. Often, a durotomy is performed to allow outward herniation of the brain to decrease ICP and prevent downward herniation. For large MCA infarctions, timing of surgery, side of lesion, presence of signs of herniation before surgery, and involvement of other vascular territories do not significantly affect outcome.[91] This analysis was obtained from uncontrolled, retrospective data; thus no meta-analysis could be completed.

The optimal timing of hemicraniectomy in patients with malignant MCA infarction is unclear. If herniation is in progress, irreversible brainstem damage may occur, thereby limiting the benefit of the operation. More recent evidence suggests that surgical intervention should occur early regardless of whether signs of herniation are present. Three concurrent European trials (i.e., DECIMAL, DESTINY, HAMLET) including patients undergoing hemicraniectomy for malignant MCA infarction were combined in a pooled analysis.[92–94] In this analysis, thresholds were established for 45 hours to randomization and 48 hours to surgery from stroke onset. The combined results showed that decompressive surgery undertaken within 48 hours of stroke onset decreased mortality and increased the number of patients with a favorable functional outcome.[95]

Surgical decompression for hemispheric infarction should be considered for younger patients with a greater potential for recovery from massive stroke. The role of surgical decompression of extensive MCA stroke in patients greater than 60 years of age remains controversial. A comparison of medical management versus early decompression in patients greater than 60 years of age in the DESTINY 2 trial did show improved survival in the surgical group, although a majority of the survivors required assistance for most daily activities. Cerebellar infarction is a special case that requires urgent surgical intervention.[96] Compression of the brainstem and fourth ventricle leading to hydrocephalus or severe pontomedullary compromise can be reversed by rapid surgical decompression of the infarcted cerebellum.

Other Medical Therapies

Anticoagulation

The use of anticoagulants in acute stroke is controversial, although several randomized clinical trials provide information regarding its efficacy. Retrospective data previously suggested a significant incidence of early recurrences after ischemic stroke, with reported rates of 20%. These studies also suggested that anticoagulation with heparin reduced recurrences. Hemorrhagic complications were acceptably low, particularly when patients with large strokes and uncontrolled hypertension were excluded from treatment. The results of recent randomized clinical trials have challenged these findings and call into question the value of anticoagulation for treatment of acute stroke.[97] However, more recent studies indicate that for cardioembolic stroke, warfarin can be safely started shortly after stroke without bridging therapy with heparin or enoxaparin.[98]

The studies do not support a reduced recurrence rate or improved outcome with anticoagulation when given within 24–48 hours of stroke onset. Hemorrhage rates ranged from 1% to 2.5%. The results suggest that there is little value in anticoagulation for all patients with acute stroke, but it remains possible that some subgroups benefit. The TOAST study suggested that patients with large vessel disease may achieve better functional outcome with anticoagulation.[99] The relatively high hemorrhage rate in some studies also may have obscured some benefit. In the International Stroke Trial (IST), a significant reduction in recurrent strokes from 3.8% in the control group to 2.9% in patients treated with subcutaneous heparin ($P < .01$) was offset by an increase in hemorrhagic stroke from 0.4% in controls to 1.2% in patients receiving heparin ($P < .0001$).[100] Even in patients with atrial fibrillation, the value of early anticoagulation is uncertain, with some studies showing benefit and others showing lack of benefit in reducing recurrent stroke.[97] If anticoagulation is started, it should only be given more than 24 hours after intravenous thrombolysis and after imaging confirmation that no hemorrhagic transformation has occurred. The roles of newer anticoagulant drugs such as rivaroxaban, apixaban, and dabigatran in the acute stroke setting remain unclear, although similar to warfarin, acute administration of these medications is likely safe if

the stroke burden is small. These medications have the added benefit of not requiring bridging therapy, as therapeutic dosage is reached early after administration.

Antiplatelet Therapy

There is less uncertainty about the benefit of aspirin in acute stroke. Two large randomized controlled trials, CAST[101] and IST,[100] showed a small but significant improvement in outcome in patients treated with aspirin. In IST, patients received 300 mg of aspirin daily for 14 days. There was a significant reduction in stroke recurrence within 14 days in the aspirin group (2.8%) versus nonaspirin groups (3.9%) and a significant decrease in the risk of death or nonfatal recurrent stroke in the aspirin group (11.3%) versus nonaspirin group (12.4%). In CAST, 160 mg of aspirin was given per day for 4 weeks or until hospital discharge. In the aspirin group, there was a significant reduction in death within 4 weeks (3.3%) versus placebo (3.9%) and a significant reduction in death or nonfatal stroke during hospitalization. There also was a significant reduction in recurrent ischemic strokes in the aspirin group (1.6%) versus placebo (2.1%), which was offset only by a trend of excess hemorrhagic strokes (aspirin 1.1% versus placebo 0.9%).

CAST and IST were designed to be considered together and included more than 40,000 patients. Combining the results of both studies shows a significant reduction in recurrent stroke of 7 per 1000 ($P < .000001$) and reduction of death or dependency of 12 per 1000 ($P = .01$).[102] The risk of aspirin in the absence of thrombolytics is minimal, and the small but significant benefit argues in favor of routine treatment, but only after 24 hours if intravenous thrombolysis has been used and absence of hemorrhagic transformation is confirmed.

The initiation of dual antiplatelets (aspirin and clopidogrel) was shown to reduce recurrent ischemic events in patients with transient ischemic attack (TIA) or mild strokes in the CHANCE trial. The generalizability of this study across populations is unclear, as the trial was conducted in China, where there is a higher incidence of intracranial atherosclerotic disease compared with the US population, and so the treatment effect may reflect a particular benefit of dual antiplatelets in this stroke subtype. Furthermore, the metabolism of the prodrug clopidogrel into the active form is dependent on several P-450 enzymes, with highly variable degrees of active drug across individuals depending on particular genetic variants of the enzyme.

The POINT trial was conducted in North America, Europe, Australia, and New Zealand and randomized a TIA and mild stroke population in double-blind fashion to receive aspirin alone versus dual antiplatelets for 90 days. Dual therapy was associated with lower risk of major ischemic events, but there was a higher risk of hemorrhage at 90 days compared with the aspirin monotherapy group. A pooled individual patient-level data analysis of the POINT and CHANCE trials revealed that the clopidogrel-aspirin group had reduced risk of major ischemic events at 90 days when treatment was confined to the first 21 days.

Statin Therapy

Statins reduce the incidence of strokes among patients who are at increased risk for cardiovascular disease. However, whether statins reduce the risk of stroke after a recent stroke or TIA was established by the SPARCL trial. In SPARCL, patients who had a stroke or TIA within 1–6 months before randomization, had a low-density cholesterol (LDL) of 100–190, and had no known coronary artery disease were randomized to receive 80 mg of atorvastatin or placebo. The primary endpoint was a first nonfatal or fatal stroke. In the cohort receiving high-dose atorvastatin, the overall incidence of strokes and cardiovascular events was reduced. High-dose atorvastatin should thus be administered in the setting of acute ischemic stroke, although there may be a higher risk of hemorrhagic stroke.[103]

Special ICU Management Considerations

General Assessment

In patients with acute stroke, initial concerns include assessment of respiratory function, cardiovascular stability, and level of consciousness. An adequate airway must be established to ensure proper ventilation, particularly in obtunded or comatose patients. Aspiration is a serious concern that often results in pneumonia and serves as a major cause of morbidity and mortality during hospitalization. Supplemental oxygen is often administered, but the benefit is uncertain when oxygenation is already adequate. Hypoxemia should be corrected immediately, however, and its source aggressively investigated. Arrhythmias are common in acute stroke, as bradycardia may signal underlying increased ICP or cardiac ischemia. Atrial fibrillation associated with rapid ventricular response often impairs cardiac output requiring immediate treatment and may also be an embolic source of stroke. Ventricular tachycardia or fibrillation rarely occurs with stroke; when present, it usually is the result of coexistent myocardial infarction. Hypotension should be corrected with intravenous fluids. Seizures should be controlled with anticonvulsants. Fever should be treated aggressively with antipyretics.

Blood Pressure

Hypertension often accompanies ischemic stroke, and in most cases abrupt lowering of blood pressure is not advised because of the risk of further impairing perfusion in the ischemic region.[104] In the presence of a systemic or cardiac reason for reducing blood pressure, such as aortic dissection or acute myocardial infarction, the relative importance of the systemic and neurologic issues must be considered. Hypertensive encephalopathy is a syndrome of extreme hypertension, papilledema, altered mental status, microangiopathic hemolytic anemia, and renal insufficiency that responds to the lowering of blood pressure. In the absence of papilledema or systemic features, it is unlikely that acute neurologic deficits are caused by hypertensive encephalopathy, and acute lowering of blood pressure will more likely worsen than improve deficits.

When thrombolytic therapy is considered, reducing blood pressure within the prescribed limits is necessary. Before thrombolytic therapy is given, systolic blood pressure should be less than 185 mm Hg and diastolic less than 110 mm Hg.[21] Labetalol typically is administered in increasing doses every 5–10 minutes to control blood pressure. Enalapril is a reasonable alternative. Sublingual nifedipine should be avoided because of its potential to lower blood pressure precipitously. If these agents do not provide adequate control, a nicardipine drip could be considered, although such patients may not be good candidates for thrombolysis. After thrombolysis, blood pressure should be aggressively controlled, keeping systolic blood pressure below 185 mm Hg and diastolic pressure below 110 mm Hg for the first 24 hours.

Fluids

Most patients with acute stroke are volume-depleted, and intravenous fluids should be replete with either normal saline or lactated Ringer's solution. In patients with large strokes in danger of developing brain edema, fluid administration should be titrated carefully, and free water should be limited. Mild hyponatremia need not be treated acutely, but more severe hyponatremia should be corrected slowly and usually reverses with infusion of normal saline.

The role of hypertonic saline (3%–23%) in the treatment of acute ischemic stroke and its ability to minimize cerebral edema remains

controversial. Those who oppose its use cite that it can lead to rebound parenchymal swelling once it is weaned off. Proponents will usually use a goal serum sodium range of 145–150 mEq/L and a serum osmolality goal of 315–320 mOsm/L. Sodium and serum osmolality levels are usually checked every 6 hours.[105,106]

Glucose

Evidence from animal models of stroke suggests that hyperglycemia increases the severity of ischemic injury.[107] Increased glucose concentration in the area of ischemia causes higher lactate concentrations and local acidosis, which increases free radical formation and thus damages neurons. Hyperglycemia also may increase ischemic edema, release excitatory amino acid neurotransmitters, and weaken blood vessels in the ischemic area. Studies of stroke in humans show an inconsistent association between outcome and initial blood glucose; however, admission glucose concentration correlates with initial stroke severity. Initial hyperglycemia also has been associated with higher mortality rates after stroke.[108] Some suggest that hyperglycemia in acute stroke is a stress reaction, but the relationship between initial blood glucose concentration and outcome is independent of initial stroke severity, arguing against a stress phenomenon.

The GIST-UK trial investigated whether treatment with a glucose-potassium-insulin (GKI) infusion to maintain euglycemia immediately after the acute stroke event had an impact on mortality at 90 days. This trial was stopped because of slow enrollment but concluded that whereas GKI infusions reduced plasma glucose concentrations and blood pressure, treatment was not associated with clinical benefit. The study was underpowered, and alternative results should not be dismissed.[109] The GRASP pilot trial found that insulin infusion for patients with acute ischemic stroke is feasible and safe. Three treatment arms were used, employing controls that were tight (70–110 mg/dL), loose (70–200 mg/dL), and usual (70–300 mg/dL).[110] More recently, the SHINE trial randomized acute ischemic strokes to intensive (80–130 mg/dL) versus standard (80–179 mg/dL) glucose control for up to 72 hours after presentation. Intensive insulin treatment compared with standard treatment did not lead to better functional outcomes. An important limitation of the SHINE trial was that recanalization data were not captured.

SUMMARY

The availability of effective treatments to alter outcome within the first few hours after stroke onset is rapidly evolving. Patients with symptoms suggesting cerebral ischemia must be treated emergently, and imaging must be performed rapidly and in a high-quality manner. Therapy for acute stroke includes much more than thrombolysis, and understanding the benefits and hazards of thrombolysis continues to evolve with greater experience and additional clinical trials. Newer generations of mechanical devices are being developed, and neuroprotection and neurorestoration hold great promise as synergistic complements to stroke reperfusion therapies. Appropriate management of blood pressure, glucose, and intravenous fluids all contribute to the overall outcome from acute stroke. At present, only a small fraction of patients with stroke (less than 5%) arrive at an emergency department in time for acute stroke therapy. Development of new acute stroke therapies and expected improvements in outcome with lower hemorrhage rates should encourage the medical system to further support the framework for a seamless and integrated stroke system of care. Such efforts should ensure that all stroke patients receive the optimal available therapy in the shortest time possible.

KEY POINTS

- When an arterial occlusion occurs, an area of irreversibly infarcted brain (core infarct) is surrounded by a region of reduced blood flow impairing function (ischemic penumbra) that is not yet severe enough to result in irreversible infarction. If adequate blood flow can be restored within a critical time frame, this area of at-risk tissue may be salvageable and return to normal function.
- Acute ischemic stroke imaging ideally involves some combination of a noncontrast head CT, CA of the head and neck, CT brain perfusion, MRI brain, MRA of the head and neck, or MR brain perfusion.
- The only FDA-approved therapy for acute ischemic stroke presenting within 3 hours of symptom onset is IV tPA.
- Evidence from the ECASS III trial indicates that the therapeutic window for IV tPA may be extended to 4.5 hours in select patients.
- Several studies (MR CLEAN, EXTEND-IA, ESCAPE, SWIFT PRIME, and REVASCAT) have demonstrated improved outcomes in select patients undergoing intraarterial therapy with a stent retriever device within 6–12 hours of symptom onset.
- Intraarterial therapy for acute ischemic stroke presenting beyond 6 hours is superior to medical management in appropriately selected patients (DAWN and DEFUSE-3 trials).
- Surgical decompression for large infarctions is recommended to be completed within 48 hours from symptom onset in appropriately selected patients.
- In patients receiving intravenous thrombolysis, no anticoagulation or antiplatelet agents should be administered in the first 24 hours until hemorrhagic transformation can be excluded. After that time, anticoagulation can be started in appropriate patients. If anticoagulation is not used, antiplatelet agents should always be started.
- High-dose statin therapy can be administered acutely after ischemic stroke in patients with previous stroke or TIA and without history of coronary artery disease.
- Patients presenting with TIA or mild stroke may be at high risk for recurrent events. A short course of dual antiplatelets (21 days) reduces the likelihood of recurrent ischemic events in patients. Longer periods of dual antiplatelets may lead to higher risk of hemorrhage.
- Although hyperglycemia has been associated with higher mortality in acute ischemic stroke patients there are no current data to suggest improved outcomes with intensive glucose control.

References for this chapter can be found at expertconsult.com.

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The ATLANTIS, ECASS and NINDS rt-PA Study Group Investigators. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS and NINDS rt-PA stroke trials. *Lancet.* 2004;363:768–774. *This article represents a combined analysis of five clinical studies in 2775 patients randomly allocated to rt-PA or placebo. The study addresses the use of intravenous rt-PA and provides specific insight into its use beyond 3 hours of*

the onset of stroke. The authors concluded that the sooner that rt-PA is given to stroke patients, the greater the benefit, especially if started within 90 minutes. Their findings also suggested a potential benefit from this therapy applied beyond 3 hours, but this potential might come with some risks.

Broderick JP, Palesch YY, Demchuk AM, et al. Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. *N Engl J Med*. 2013;368(10):893–903.
This landmark study was the first randomized controlled trial to compare the efficacy of first-generation intraarterial therapy as an adjunctive therapy to intravenous thrombolysis compared with intravenous thrombolysis alone. Although the results were neutral in the two study groups, analysis of this trial identified a potential benefit with adjunctive intraarterial therapy in patients with small infarct on presentation with documented proximal large vessel occlusion undergoing fast and high-quality recanalization.

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Furlan A, Higashida R, Wechsler L, et al. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. *JAMA.* 1999;282:2003–2011.
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Campbell BC, Mitchell PJ, Kleinig TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med*. 2015;372(11):1009–1018.
These five seminal studies collectively demonstrate the benefit of stent retriever mechanical thrombectomy in patients presenting with early time windows with anterior circulation occlusions. A majority of the patients received intravenous rt-PA, were treated within 6 hours of symptom onset, and predominantly underwent intraarterial therapy with the Solitaire stent retriever device.

Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med*. 2008;359(13):1317–1329.
This is the first randomized controlled trial confirming the efficacy and safety of alteplase given between 3 and 4.5 hours after the onset of a stroke. There are some exclusion criteria in addition to the normal contraindications for administration of intravenous tPA for this extended therapeutic window. Intravenous alteplase administered between 3 and 4.5 hours significantly improved clinical outcomes in patients with acute ischemic stroke, but it was also more frequently associated with symptomatic intracranial hemorrhage versus placebo.

The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med.* 1995;333:1581–1587.
A key clinical report in the field of stroke that showed for the first time in a randomized controlled trial a reduction in stroke morbidity with acute treatment. In June 1996 the FDA approved intravenous tPA for the treatment of stroke within 3 hours of onset.

Smith WS, Sung G, Starkman S, et al. Safety and efficacy of mechanical embolectomy in acute ischemic stroke: results of the MERCI trial. *Stroke*. 2005;36(7):1432–1438.
This trial evaluated the alternative strategy of mechanical embolectomy for opening intracranial vessels during stroke. Patients who were ineligible for intravenous tPA and found to have occluded intracranial large vessels within 8 hours of stroke symptom onset received this therapy. The strategy was deemed both safe and efficacious and was the primary support for the FDA approval of the Merci retriever device.

Vahedi K, Hofmeijer J, Juettler E, et al. Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials. *Lancet Neurol*. 2007;6(3):215–222.
Pooled analysis of three concurrent European randomized controlled trials (i.e., DECIMAL, DESTINY, HAMLET) evaluating decompressive surgery for patients with large MCA hemispheric infarctions in terms of mortality and functional outcome. The analysis included 93 patients between the ages of 18 and 60 years who were either treated within 48 hours after stroke onset or randomized to a control group. Early decompressive surgery was found to reduce mortality and increase the likelihood of a favorable outcome.

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Nontraumatic Intracerebral and Subarachnoid Hemorrhage

Subhan Mohammed and Christopher P. Robinson

HEMORRHAGE

Epidemiology

Intracerebral hemorrhage (ICH) is the second most common type of stroke, following only ischemic stroke in frequency. Spontaneous, nontraumatic ICH accounts for approximately 9%–27% of all strokes globally.[1,2] The incidence doubles every decade after age 35.[3,4] Outcomes are typically poor, with a mortality of 50% at 30 days.[5] A systematic review in 2013 found that the burden of death and disability is greatest with ICH, although the incidence of ischemic stroke is far greater.[6]

Causes and Risk Factors

The major risk factor for ICH, accounting for over 50% of cases, is hypertension.[7] Old age, anticoagulant use, and cerebral amyloid angiopathy (CAA) are other important risk factors. The impact of smoking,[8] alcohol abuse,[9,10] and diabetes mellitus[11,12] on the risk of ICH is disputed.

Hypertension

The most common etiology of ICH is hypertension. Hypertension more than doubles the risk of ICH.[13–16] Hypertensive ICH predominantly occurs deep in the cerebral hemispheres, most often in the putamen,[17] thalamus, lobar white matter, cerebellum, and pons (Fig. 47.1). The link between these sites is the supply of small penetrating arteries[18]—that is, perpendicular branches directly off major arteries that are subject to high shear stress and have no collaterals.

Intracranial Aneurysms and Vascular Malformations

Although aneurysmal rupture is most commonly associated with hemorrhage in the subarachnoid space, blood may also be directed into the parenchyma of the brain. Aneurysms located at the middle cerebral artery bifurcation can produce hemorrhages into the basal ganglia similar to hypertensive hemorrhage, and anterior communicating artery aneurysms can produce flame-shaped hemorrhages at the base of the frontal lobes. About half of adults with intracranial arteriovenous malformations (AVMs) present with ICH.[19] In 60% of cases, the hemorrhage is parenchymal, involving virtually any location of the brain.[20] Hemorrhage resulting from AVM occurs more frequently in a younger population than that resulting from aneurysms or hypertension.

Cerebral Amyloid Angiopathy

CAA is an important cause of primarily lobar, often recurrent, ICH in the elderly. The prevalence of amyloid deposition in cerebral vessels increases dramatically with age[21,22] and may contribute to the exponential rise in the risk of ICH with age. Although CAA is asymptomatic, it is an important cause of ICH. Apolipoprotein E ϵ2 and ϵ4 genotypes are associated with an earlier age at onset of first hemorrhage and a higher risk of early recurrence.[23,24] The presence of multiple or recurrent lobar ICH in individuals 55 years or older without other known causes of hemorrhage strongly suggests this etiology.[25]

Antithrombotic Therapy

Antithrombotics include anticoagulants, antiplatelets, and thrombolytic agents, which increase the risk of spontaneous ICH. The incidence of oral anticoagulant–associated ICH has been increasing in parallel with the rising use of the anticoagulants. Warfarin increases the risk of ICH by twofold. Although the risk of ICH is greater with a supratherapeutic international normalized ratio (INR), a significant number of hemorrhages occur when the INR is therapeutic.[26] Hematoma expansion among warfarin users may be more common and occur over a longer time frame, contributing to a higher mortality rate versus spontaneous ICH.[27] The novel anticoagulants (NOACs), which act by inhibition of thrombin or factor Xa, may have a lower risk of ICH than warfarin.[28–31]

Most studies suggest that antiplatelet use at ICH onset is not associated with larger hematoma size, hematoma growth, or poor clinical outcome.[32] Platelet dysfunction is associated with hematoma expansion and worse outcome,[33] but to date, platelet transfusion has not provided a mortality benefit or improved functional outcome.[34]

Alteplase administered intravenously for the treatment of acute ischemic stroke (presenting within the time window) increases the risk of spontaneous ICH 5%–7%.[35,36]

Other Causes

Hemorrhage from an underlying neoplasm is rare but occasionally occurs with malignant primary central nervous system (CNS) tumors such as glioblastoma multiforme and lymphoma and with metastatic tumors.[37]

ICH may also occur in association with infection,[38,39] vasculitis,[40] venous sinus occlusion,[41] after head trauma,[42] after reperfusion,[43] and with the use of various drugs, particularly sympathomimetics.[44] Some degree of hemorrhagic transformation of acute cerebral infarcts is common,[45] although symptomatic ICH in this setting is rare in the absence of anticoagulation or thrombolytic therapy.

Systemic diseases (e.g., thrombocytopenia, leukemia, and hepatic and renal failure) and congenital or acquired clotting factor deficiencies also increase the risk for spontaneous ICH.

Pathophysiology

Several mechanisms account for brain injury in ICH. Primary brain injury occurs secondary to local tissue destruction from initial vessel

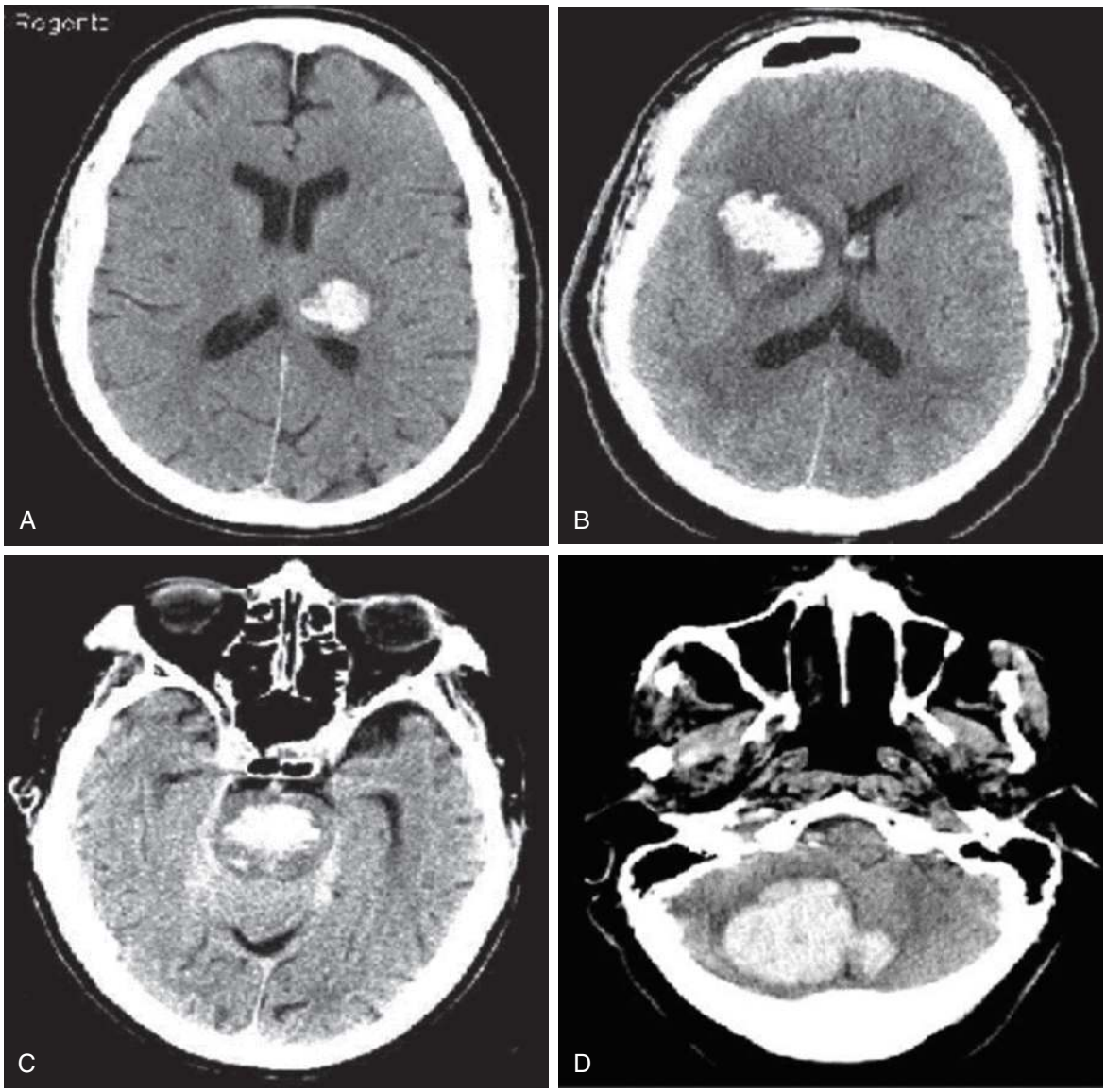

Fig. 47.1. CT Scans Showing Common Locations of Spontaneous Hypertensive Intracranial Hemorrhage. **A,** Thalamus, **B,** caudate/putamen, **C,** pons, and **D,** cerebellum.

rupture. Further bleeding into the hematoma cavity results in hematoma enlargement,[46] producing further tissue distortion and mass effect.

Secondary brain injury is believed to occur after the bleeding stops. Proposed mechanisms include ischemia, perilesional edema, and toxic effects of parenchymal blood. Although each of these can be detected in animal models, their clinical importance remains unsettled. Contrast enhancement seen in the peri-hematomal area on computed tomography (CT) or magnetic resonance imaging (MRI) represents blood–brain barrier disruption.[47,48]

Despite experimental models of ICH[49,50] and studies in human patients[51–53] consistently demonstrating reduced blood flow around the hematoma, this does not appear to represent ischemia.[54,55] Positron emission tomography (PET) and MRI studies in humans indicate that the peri-hematomal cerebral metabolism is reduced to a greater degree than local cerebral blood flow (CBF).[56] These findings suggest that hypoperfusion reflects reduced metabolic demand of the tissue surrounding the hematoma rather than ischemia.[55,57]

Cerebral edema occurs within hours of ICH and may result from the toxic effects of blood-derived enzymes, increased osmotic pressure exerted by clot-derived serum proteins, or ischemia.[58] The cause, time course, and importance of edema formation in humans are debated, and the best predictor of edema volume is the size of the hematoma. Early edema does not appear to contribute to increases in mass effect,[59] worsened functional outcome, or increased mortality.[60]

Clinical Features

The clinical presentation of ICH is often indistinguishable from that of ischemic stroke; however, ICH more commonly presents with an altered level of consciousness, headache, and vomiting.[17] Signs and symptoms usually correspond to the location of ICH. Blood pressure is elevated in the majority of patients. Seizures may occur at onset or in the first few days in approximately 15% of patients,[61–63] particularly in those with lobar hemorrhages or underlying vascular or neoplastic lesions.[64] Symptoms may be maximal at onset or evolve over minutes

to hours. Neurologic deterioration within 48 hours after hospital admission has been reported to occur in 20% of patients.[65] A majority are related to hematoma expansion, but, for some, the cause is not always evident. Some patients may be obtunded or comatose on presentation.

Diagnostic Studies

Noncontrast CT scan is the gold standard for the diagnosis of acute ICH. The typical CT appearance of an acute hematoma consists of a well-defined, hyperdense area surrounded by a rim of hypodensity. Over time, the borders of both the high- and low-attenuation regions become increasingly indistinct such that the hematoma is isodense with adjacent brain parenchyma by 2–6 weeks.[66] Termed the *swirl sign,* these hypodense or isodense foci represent fresh, unclotted blood of lower attenuation signifying acute extravasation of blood into a hyperdense hematoma.[67,68] Although MRI also has high sensitivity and specificity for the diagnosis of acute ICH,[69–71] it is less accessible and more time consuming.[72] The benefits of MRI over CT are accuracy in determining the approximate age of a hematoma[73] and its ability to detect evidence of previous asymptomatic hemorrhages.[74]

CT angiography (CTA) is a noninvasive imaging modality useful in evaluating the cause of ICH if an underlying aneurysm or vascular malformation is suspected. It has a sensitivity of 96% and a specificity of 99%–100%.[75,76] The yield is higher in younger patients, those without hypertension or impaired coagulation, and those with lobar or infratentorial ICH.[75] CTA can identify active contrast extravasation into the hematoma, an indicator of active hemorrhage. The *spot sign* is a foci of intralesional contrast enhancement seen in up to one-third of patients with acute ICH.[77] *Swirl sign* on a CT is analogous to *spot sign* on a CTA. They are independent predictors of hematoma expansion, in-hospital mortality, and poor outcome in survivors.[67,78–80]

Diagnostic cerebral angiography is an invasive diagnostic study useful in evaluating the cause of ICH if the suspicion for underlying aneurysm or vascular malformation remains high despite a negative CTA. Conventional angiography is able to identify aneurysms smaller than 3 mm in size that can be missed on CTA.[81] The yield is extremely low when patients have hypertension and the ICH is in a typical site associated with hypertensive hemorrhage.[82]

Treatment

Initial Stabilization

Acute ICH is a medical emergency requiring careful attention to airway, blood pressure, and correction of underlying coagulopathy. Multidisciplinary teams with expertise in emergency medicine, neurology, and neurosurgery should evaluate and manage ICH patients in a dedicated neurocritical care unit. Acute-phase care may require mechanical ventilation, blood pressure control, reversal of coagulopathy, ventriculostomy, treatment of intracranial hypertension and seizures, and surgical evacuation. Blood pressure is often elevated at presentation, sometimes markedly so, and early control is an important component of initial stabilization.

Airway and Respiratory Management

As many as half of all patients with ICH require mechanical ventilation.[83] With decreased level of consciousness, the pharyngeal and tongue musculature relax and cough and gag reflexes are inhibited, leading to airway compromise. Additionally, if the hemorrhage is in the brainstem or cerebellum, there may be complete loss of pharyngeal tone and early airway obstruction.

Initial airway management includes proper positioning,[84] frequent suctioning, and placement of an oral or nasal airway to maintain patency. If snoring respiration, inability to clear oral secretions, or decreased oxygen saturation does not improve, intubation is warranted. A rapid-sequence intubation is necessary for patients showing signs of herniation, apneic breathing, Glasgow Coma Scale (GCS) score <8, or soiled airway. In the absence of these findings, a semi-elective protective intubation is recommended to avoid the harmful consequences of hypotension, exaggerated sympathetic reflex from stimulation during laryngoscopy, and worsening of intracranial hypertension.[85] Perform a complete neurologic examination if time permits.

Premedication should be administered to produce adequate sedation and jaw relaxation and to prevent elevation of intracranial pressure (ICP). Short-acting intravenous (IV) anesthetic agents (e.g., etomidate or thiopental) block this response[86] and additionally suppress brain metabolic rate.[87] Etomidate is generally preferred over thiopental because it is less likely to lower blood pressure. IV lidocaine (1–1.5 mg/kg) has been recommended to block this response,[88] although data supporting its use are lacking.[89] Paralytic agents are usually unnecessary, but if needed, short-acting agents should be used.

Hemodynamics

Arterial blood pressure is often elevated on admission in the majority of patients with ICH, even in the absence of a history of hypertension.[17,90] Although this acute increase in blood pressure is often implicated as the cause of the hemorrhage, it more likely reflects the brain's attempt to maintain cerebral perfusion pressure (CPP) in response to the sudden increase in ICP, pain, anxiety, and sympathetic activation. Even without treatment, blood pressure tends to decline to premorbid levels within a week of ICH.[91]

There has been substantial controversy over if and when to lower elevated blood pressure after acute ICH.[92] Proponents of rapid treatment of acute hypertension argue that high blood pressure may make the hematoma prone to enlargement and exacerbate vasogenic edema. Another compelling reason to lower blood pressure in ICH patients with moderate to severe hypertension is the potential for end-organ damage, including myocardial ischemia, congestive heart failure, and acute renal failure.

The major argument against the treatment of elevated blood pressure is reduction of CBF and exacerbation of ischemia surrounding the hematoma.[93] Because chronic hypertension shifts the cerebral autoregulatory curve to the right, a higher CPP may be required to maintain adequate CBF.[94,95] Lowering the blood pressure to "normal" levels might thus lead to ischemic damage. Similarly, lowering blood pressure may critically reduce CPP in patients in whom ICP is elevated.

Several studies have addressed this issue in patients with mean arterial pressure (MAP) more than 130–140 mm Hg.[96–98] These studies demonstrate that regional and global CBF are preserved when MAP is lowered to 110 mm Hg or 80% of the admission MAP.

These observations set the stage for the INTERACT trial,[99] a prospective trial of blood pressure management beginning within 6 hours of symptom onset. Patients were randomized to either an early, intensive blood pressure–lowering group (systolic blood pressure [SBP] <140 mm Hg) or a control group (SBP <180 mm Hg). After adjusting for initial hematoma volume and time from onset to CT, median hematoma growth at 24 hours differed by 1.7 mL. Intensive blood pressure lowering did not increase the risk of adverse events or improve 90-day clinical outcome. This was followed by the much larger INTERACT2, which used the identical protocol and enrolled almost 3000 patients.[100] Again there was a very small, if any, impact on hematoma expansion, although the hematoma sizes of those enrolled were fairly small. Although the study did not reach its primary endpoint, an ordinal analysis of modified Rankin scores (mRS) indicated improved functional outcomes with intensive lowering of blood pressure. Based on this study, many clinicians are now more aggressive in treating early hypertension in these patients. For patients presenting with SBP

between 150 and 220 mm Hg, lowering of SBP to 140 mm Hg is generally safe. In patients presenting with SBP >220 mm Hg, the optimal target is unknown, and targeting SBP between 140 and 160 mm Hg is reasonable.[61] In the ATTACH-2 trial, the group with intense lowering of SBP to <140 mm Hg (110–139 mm Hg) was found to have more adverse renal events compared with less intense SBP lowering from 140 to 179 mm Hg.[101]

In the setting of ICH, the ideal antihypertensive agent would be easily titrated, have minimal cerebral hemodynamic effects, and not be prone to sudden, large reductions in blood pressure. Vasodilators, especially venodilators, can raise ICP by increasing cerebral blood volume and should be avoided. Sodium nitroprusside[102] and nitroglycerin[103] increase ICP and lower CBF in patients with reduced intracranial compliance and should not be used. Calcium channel blockers, beta-blockers, and angiotensin-converting enzyme inhibitors have minimal effect on CBF within the autoregulatory range of MAP and do not alter ICP. Therefore popular treatment options in the setting of acute ICH include intermittent boluses of labetalol,[84,104] enalapril,[84] and/or hydralazine[84] or continuous infusion of nicardipine[104] or clevidipine.

Prevention of Hemorrhage Extension and Reversal of Anticoagulation

Abrupt discontinuation of all antithrombotic therapy is imperative. Hemorrhage expansion occurs within the first few hours after symptom onset in about one-third of patients; therefore it is reasonable to correct any existing coagulopathy as rapidly as possible. Patients taking warfarin should receive IV vitamin K and replacement clotting factors. Until recently, fresh frozen plasma (FFP) was used for this purpose, but it can precipitate congestive heart failure, transfusion-related acute lung injury, and transfusion-associated circulatory overload. Four-factor prothrombin complex concentrate (PCC) is an effective alternative that can be administered much more quickly without these risks and is now primarily recommended for reversal.[105]

Management of hemorrhage in patients taking thrombin and factor Xa inhibitors is more difficult. Recently, the Food and Drug Administration (FDA) has approved the antidotes idarucizumab[106] and andexanet alfa[107] for agent-specific reversal.

Symptomatic ICH occurs after thrombolytic treatment of acute ischemic stroke in about 6% of patients.[108] No reliable data are available to guide correction of the thrombolytic effect of tissue plasminogen activator (tPA). Current practice is highly variable and may include administration of FFP, PCC, cryoprecipitate, platelets, and antifibrinolytic agents.

Even in those patients without coagulopathy, promoting early hemostasis might limit ongoing bleeding and decrease hematoma volume. Factor VIIa is a coagulation factor that interacts with tissue factor to initiate platelet aggregation and accelerate formation of a fibrin clot. Although earlier studies suggested a decrease in the hematoma expansion with its use, there was no significant difference in clinical outcomes.[109] Therefore routine use of factor VIIa is not recommended.[110]

Intraventricular Hemorrhage and Hydrocephalus

Intraventricular hemorrhage (IVH) (Fig. 47.2) complicates about 40%–60% cases of ICH.[111,112] It is independently associated with death and poor outcome, especially when it occurs late in the course.[113–115] IVH may present with an abrupt headache, nausea, vomiting, and worsening of neurologic status that may partly be attributed to a sudden rise in ICP. Hydrocephalus may develop because of obstruction of the cerebrospinal fluid (CSF) flow in the ventricles in association with IVH or because of direct mass effect on a ventricle. CT scan is the imaging modality of choice to diagnose IVH. External ventricular drainage (EVD) is often used to treat hydrocephalus and IVH. Ventriculostomy in the setting of IVH is difficult to manage because of catheter obstruction from thrombus, interrupting drainage and raising ICP. Flushing the system helps remove thrombus but increases the risk of ventriculitis. A multicenter randomized study of Clot Lysis Evaluation of Accelerated Resolution (CLEAR-III) of IVH compared the use of ventriculostomy with intraventricular alteplase to ventriculostomy with saline. At 180 days, the treatment group had lower case fatality versus placebo but functional outcomes were no different. Ventriculitis was less in the treatment group, whereas the rate of symptomatic bleeding was similar in both groups.[116]

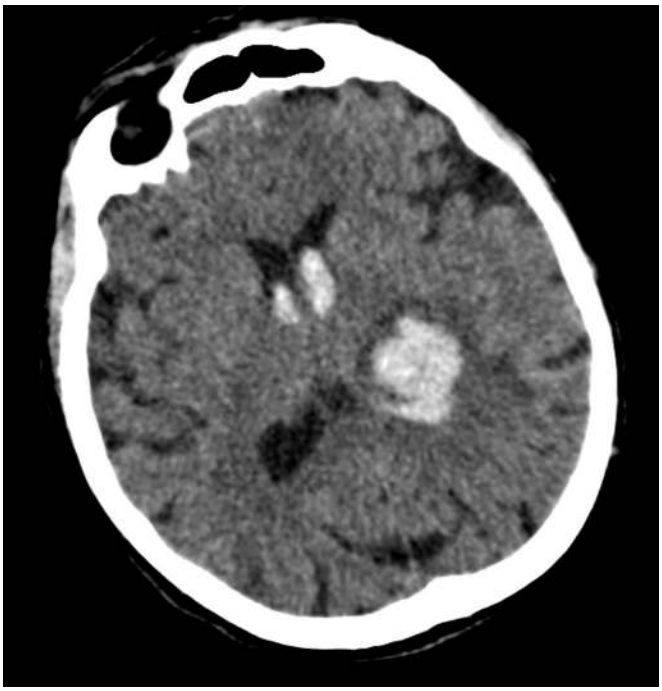

Fig. 47.2. CT Scan Showing Associated Intraventricular Hemorrhage in the Setting of Acute Thalamic Intracranial Hemorrhage.

Intracranial Hypertension

Factors contributing to intracranial hypertension in ICH include hematoma size, minimal degree of underlying cerebral atrophy, hydrocephalus, and cytotoxic edema. The true incidence of intracranial hypertension is unclear, as routine ICP monitoring is not performed. Because the hematoma is localized, increases in volume can be compensated for to some degree by reduction in the size of the ventricles and subarachnoid space—a global increase in ICP may not be seen unless the hemorrhage is large or associated with marked hydrocephalus. However, mass effect from the hematoma and local tissue shifts can compress the brainstem and result in herniation in the absence of a global increase in ICP.[117,118] Thus the utility of ICP monitoring is not clear. In some cases, EVD placement is considered to manage hydrocephalus or IVH.

Acutely elevated ICP, edema, and tissue shifts are often treated with osmotic agents. There are only a few small clinical trials of osmotic agents in ICH, which do not provide sufficient data to support their routine use.[119] Furthermore, corticosteroids in ICH or IVH do not provide benefit. Their use is not routinely recommended, as they increase comorbidities.[120]

Management of Seizures

Risk of seizures in patients with acute spontaneous ICH is approximately 15%.[61–63] They are more common in patients with lobar hemorrhage

compared with cerebellar or deep ICH. Seizures may be convulsive or nonconvulsive; thus the true frequency depends at least partly on the extent of monitoring. Although seizures may theoretically exacerbate ICH, they have not been shown to alter outcome. The 2015 American Heart Association/American Society of Anesthesiologists (AHA/ASA) guidelines recommended against antiseizure prophylaxis.[61] A 2019 systematic review and meta-analysis evaluating antiseizure prophylaxis found no reduction in incident seizures, disability, or mortality in patients with spontaneous ICH.[121] Any seizure should be treated to prevent recurrent seizures. Treatment of clinical seizures typically begins with an IV benzodiazepine followed by an IV antiepileptic depending on individual circumstances and contraindications. The use of phenytoin is discouraged based on the poor outcomes associated in observational studies.[61]

Surgical Evacuation

The role of surgery in hematoma evacuation is controversial and lacks well-defined indications. The rationale for surgical evacuation is reducing mass effect and removing neurotoxic clot constituents to minimize injury to adjacent brain tissue, decrease the risk for herniation, improve ICP, and hence improve outcome. Early randomized controlled trials of surgery for supratentorial ICH, however, failed to show a benefit.[122–125] A meta-analysis of three of these trials reported that patients undergoing surgical evacuation via open craniotomy had a higher rate of death or dependency at 6 months compared with those managed medically.[126] Criticisms of these trials are that outdated surgical techniques were used, patient selection was inadequate, and surgery was delayed. Because open craniotomy is complicated by tissue damage sustained during the approach to the hematoma, a variety of new techniques for clot removal have been proposed, including an ultrasonic aspiration and endoscopic approach. However, the recurrence of bleeding because of the loss of tamponade effect on adjacent tissue remains a concern. In addition, because the newer techniques involve limited surgical exposure, concern exists that rebleeding will be more difficult to control than with open craniotomy.

A lack of benefit of surgery in ICH was also shown in the STICH trial, a multicenter study in which 1033 patients were randomized within 72 hours of ICH onset to surgical hematoma evacuation or initial conservative management. Outcome did not differ between groups. Subgroup analysis, however, suggested a possible benefit of surgery in patients with superficial hematomas.[127] Subsequently, the STICH II trial enrolled conscious patients with superficial lobar ICH of 10–100 mL and no intraventricular hemorrhage within 48 hours of ictus. There was a trend toward better survival in the surgical group.[128] In the Minimally Invasive Surgery with Thrombolysis in Intracerebral hemorrhage Evacuation (MISTIE) phase III trial, 516 patients with supratentorial ICH ≥30 mL were randomized to stereotaxic placement of a catheter in the hematoma and instillation of tPA for up to 72 hours or medical management. The number of patients with a good functional outcome, defined by a mRS of 0–3, was similar for both groups at 365 days, although mortality was lower in the surgical group.[129]

Because of the high risk of brainstem compression and hydrocephalus, cerebellar hemorrhages were excluded from the randomized trials of surgery. Case series report good outcomes for surgically treated patients with cerebellar hemorrhages that are large, associated with brainstem compression, or obstruct the fourth ventricle. Recommended criteria for evacuation of a cerebellar hematoma have thus included diminished level of consciousness, large size of the hematoma (>3 cm in diameter), midline location, compression of basal cisterns and/or brainstem, and presence of hydrocephalus.[130–132] Patient selection is important, as many patients with smaller hemorrhages do well with medical management.[133] A recent 2019 individual participant data meta-analysis of four observational ICH studies concluded that surgical hematoma evacuation in cerebellar hemorrhages compared with conservative medical management did not improve functional outcome.[134]

Supportive Care

Patients with ICH are prone to the same medical complications seen in patients with ischemic stroke, including fever, deep venous thrombosis (DVT), pulmonary embolism, myocardial infarction, dysphagia, gastrointestinal bleeding, and pneumonia.[135,136] Given the association between fever and worsened outcome in experimental models of brain injury, it is reasonable for antipyretic medications to be administered in febrile patients with ICH. A meta-analysis found that fever was significantly associated with higher rates of mortality, disability, dependency, worse functional outcome, higher severity, and longer intensive care unit (ICU) stays.[137] The randomized trials Clots in Legs Or sTockings after Stroke (CLOTS) 1, 2, and 3 assessed different treatment modalities for the prevention of DVT.[138–141] In the CLOTS 1 trial, the use of thigh-high compression stockings did not reduce DVT, pulmonary embolism (PE), or death.[139] In the CLOTS 2 trial, the incidence of DVT was higher in patients who had below-knee graduated compression stockings compared with thigh-high graduated compression stockings.[138] In the CLOTS 3 trial, intermittent pneumatic compression reduced the occurrence of proximal DVT, with the effect being particularly prominent in patients with hemorrhagic stroke.[140] Subcutaneous heparin at a dose of 5000 units three times daily when initiated on day 2 after hemorrhage has been shown to significantly reduce the frequency of DVT relative to treatment begun on day 4 or 10, with no concomitant increase in hematoma expansion.[142] In another study, subcutaneous enoxaparin (40 mg daily) initiated at 48 hours after ICH was also safe.[143] A meta-analysis of thromboprophylaxis assessing the early use of subcutaneous enoxaparin or heparin (from 1 to 6 days after admission) observed a significant reduction in PE, a nonsignificant mortality reduction, and no difference in DVT or hematoma enlargement.[144]

Similar to patients with ischemic stroke, ICH patients should not be fed orally until swallowing is evaluated. Dysphagia is a common complication after ICH and a cause for aspiration pneumonia.[145] Patients should consistently be monitored for signs of aspiration pneumonia. Early mobilization and rehabilitation are generally recommended for clinically stable patients with ICH.

Prognostic Factors and Causes of Mortality

Thirty-day mortality after ICH is high (35%–52%),[146–152] with over half of the deaths occurring in the first 48 hours.[149,153,154] Overall mortality from ICH has been decreasing because of advances in treatment, whereas a majority of ICH survivors have significant residual disability.[5,155–157] Predictors of poor outcome are impaired level of consciousness, hematoma size, hematoma expansion, associated IVH, age, antecedent antithrombotic use, uncontrolled hypertension, history of diabetes, male gender, and elevated troponin level. Predictive radiographic features of poor prognosis include deep or infratentorial hematoma location, IVH, midline shift, hydrocephalus, hematoma growth, and the presence of the spot or swirl sign on CTA.[77–80,113–115] A number of prognostic models have been developed to allow risk stratification upon presentation with ICH. The ICH score (Table 47.1), which is based on point assignments for GCS, ICH volume, presence of IVH, infratentorial location, and patient age, has been validated to accurately predict 30-day mortality.[158]

Concern has been raised, however, that withdrawal of life-sustaining interventions, including early use of do not resuscitate (DNR) orders in ICH patients, is likely to have a poor outcome bias on predictive models and invalidates the predictive value of other variables.[159–164] Thus the most frequent cause of death after ICH is withdrawal of care,

TABLE 47.1 ICH Score

Component		Score
GCS	13–15	0
	5–12	1
	3–4	2
Age	<80 years	0
	≥80 years	1
ICH volume	<30 mL	0
	≥30 mL	1
ICH location	Supratentorial	0
	Infratentorial	1
IVH	No	0
	Yes	1
TOTAL ICH SCORE		0–6

GCS, Glasgow Coma Scale; *ICH,* intracerebral hemorrhage; *IVH,* intraventricular hemorrhage.

followed by early (within 48 hours) transtentorial herniation with progression to brain death. Medical complications of immobility account for most of the subsequent deaths.[156]

SUBARACHNOID HEMORRHAGE

Epidemiology

Subarachnoid hemorrhage (SAH) is a sudden, dramatic event that has multisystem consequences. Hemorrhagic strokes account for approximately 20% of strokes, of which SAH accounts for 10%. In the United States, SAH accounts for approximately 3% of all strokes.[165] Approximately 80% of nontraumatic SAHs are caused by ruptured intracranial aneurysms. In 2019, a systematic review and meta-analysis concluded that the overall global incidence of aneurysmal was 7.9 per 100,000 person-years.[166] The incidence of aneurysmal SAH varies by geographic location.[166] In 2010, the incidence in North America was 6.9 per 100,000 person-years, whereas it was 28 in Japan and 5.1 for Central and South America regions.[166] Approximately 15%–20% of patients with SAH do not have a vascular lesion on initial cerebral angiography, referred to as *nonaneurysmal SAH.*[167] One-quarter of patients presenting with SAH die before reaching medical attention,[168] and because of secondary insults (rebleeding, hydrocephalus, and delayed ischemia), more than half of those who reach medical attention either die or are left with significant neurologic deficits.

Causes and Risk Factors

Rupture of saccular aneurysms is the most common cause of spontaneous SAH. Cigarette smoking and hypertension are the most common modifiable risk factors associated with aneurysmal formation.[169,170] Genetic conditions susceptible to developing aneurysms include polycystic kidney disease and connective tissue disorders. In some patient populations, genetic factors play a role in aneurysm formation without other associated conditions.[171] Some environmental factors have been implicated in increasing the susceptibility in the familial form.[172,173] Other types of aneurysms that less commonly cause SAH include atherosclerotic, mycotic, and traumatic aneurysms. Trauma is the most common cause of nonaneurysmal SAH. AVMs, stimulant abuse, neoplasia, and vasculitis account for the bulk of the remainder of cases. SAH may accompany ICH, particularly in the setting of CAA. In 10%–15% of cases of SAH, no source of bleeding is identified.

Pathophysiology

In SAH, the primary site of bleeding is the subarachnoid space, but it may also involve hemorrhage into the brain parenchyma, ventricular system, or subdural space.[174,175] Aneurysm rupture causes local tissue damage because of the jet of blood under arterial pressure, in addition to a transient increase in ICP to match arterial pressure. Saccular, or berry, aneurysms are small, rounded protrusions of the arterial wall occurring predominantly at bifurcations of the large arteries of the circle of Willis at the base of the brain. About 20% of patients have multiple aneurysms.

Most aneurysms rupture at the dome, where the wall may be as thin as 0.3 mm. Tension on the aneurysm wall is determined by the radius of the aneurysm and the pressure gradient across the wall. The probability of rupture is related to location and size. The most common sites of ruptured aneurysms are the distal internal carotid artery and its posterior communicating artery junction (41%), anterior communicating artery/anterior cerebral artery (34%), middle cerebral artery (20%), and vertebrobasilar arteries (4%).[176] Aneurysms less than 5 millimeters in diameter have a very low rate of rupture, and the aneurysm–to–vessel size ratio may help predict the risk of rupture.[177]

Clinical Features

Presentation

The most common initial symptom of SAH, occurring in over 90% of patients, is a sudden and severe thunderclap headache.[178] Less severe warning or sentinel headaches may precede the presenting event in as many as half of patients and are thought to represent minor aneurysmal leaks.[179] In about half of patients, loss of consciousness accompanies the headache because of either the sudden surge in ICP at the moment of hemorrhage or cardiac arrhythmias.[180,181] Vomiting can be a prominent symptom. Seizures may be reported,[182] but it is unclear whether this represents true epileptic seizures or reflex posturing. Focal deficits at the onset of hemorrhage occur in less than 10% of cases. Meningismus, characterized by a stiff neck, can develop after a few hours, reflecting meningeal inflammation induced by the presence of blood in the subarachnoid space.[183]

Complications

Neurologic and medical complications are common after SAH and contribute significantly to morbidity and mortality.[184] A worsening of neurologic status often indicates one of the four major complications of SAH: rebleeding, hydrocephalus, vasospasm, or delayed cerebral ischemia (DCI). An understanding of the timing and nature of the deterioration facilitates rapid diagnosis and treatment. It must be emphasized that systemic perturbations such as infection, hyponatremia, fever, hypoxia, and hypotension may produce similar symptoms and should be sought out and corrected as part of the evaluation process.

Rebleeding. Rebleeding is heralded by a sudden worsening of headache, vomiting, blood pressure elevation, development of a new neurologic deficit, or arrhythmia. It occurs in up to one-third of patients and has a mortality rate of up to 70%. The risk of rebleeding is greatest during the first 24 hours (4%–14%),[185] declining rapidly over the next 2 weeks. Rates of rebleeding are highest in patients with seizure or loss of consciousness at onset, previous sentinel headaches, large aneurysm size, those who are a poor clinical grade, those who have hypertension, and longer time to aneurysm treatment.[185,186] Rerupture is associated with a significantly high mortality.[187]

Hydrocephalus. Hydrocephalus occurs in approximately 20%–30% individuals after SAH because of disturbances of CSF flow or reabsorption. Acute hydrocephalus can develop within the first few minutes to hours of SAH,[188] often in the absence of intraventricular blood. It usually manifests as a gradual decline in the level of consciousness

and can easily be treated by placement of an EVD. In many, but not all, patients, ocular signs of elevated ICP (miosis, downward-eye deviation, or restricted upgaze) occur. Delayed hydrocephalus may also develop gradually days to weeks later. If acute hydrocephalus is untreated, about one-third of patients progress, one-third spontaneously improve, and one-third remain static.[189]

Vasospasm and delayed cerebral ischemia. The term *vasospasm* refers to complex changes in intracerebral vessels, with segmental or diffuse narrowing of the lumen secondary to spasmogenic substances generated from lysed blood clots. If the reduction in flow is severe enough, ischemia and infarction typically follow. The term *DCI* describes the clinical scenario where vasospasm, impaired autoregulation, hypovolemia, spreading cortical depression, and microthrombosis combine to produce ischemia.[190] Arterial narrowing can be detected angiographically in up to 70% of patients,[191] of whom almost half will have symptoms. The onset of vasospasm is delayed, most commonly developing 5–10 days after initial hemorrhage, and may persist for up to 3 weeks. The strongest predictors of vasospasm are clinical condition on presentation and the amount of subarachnoid blood on the initial CT scan.[192–194] The highest risk is in those who have thick subarachnoid clots and intraventricular blood (graded using a modified Fisher Scale; Table 47.2).[192,193] Focal neurologic deficits resulting from vasospasm may appear abruptly or gradually and may fluctuate, exacerbated by hypovolemia, hypotension, or fever. If untreated, cerebral infarction may occur.

Hypertension. Blood pressure is often elevated after SAH and is associated with a greater risk of rebleeding, vasospasm, and mortality. Multiple factors may underlie the rise in blood pressure, including increased sympathetic outflow, agitation, and pain. Early on, blood pressure management focuses on treating hypertension to help prevent re-rupture of the aneurysm. After repair of the aneurysm, the risk of rebleeding is decreased, and spontaneous elevations in blood pressure should be allowed to occur without intervention, because the risk of vasospasm becomes the primary concern in management.

Hyponatremia and hypernatremia. Disturbances in sodium and water balance occur in about one-third of patients, and hyponatremia and volume depletion after SAH are correlated with an increased risk of symptomatic vasospasm and poor outcome.[195–197] Although hyponatremia was previously attributed to syndrome of inappropriate antidiuretic hormone (SIADH), later evidence suggests that both sodium and water are lost because of cerebral salt wasting (CSW).[198] SIADH is a state of euvolemia or hypervolemia, whereas CSW is a hypovolemic state.[198] In fact, when administered normal, maintenance volumes of fluid (2–3 L/day), as many as half of patients develop intravascular volume contraction.[199]

TABLE 47.2 Fisher Grade of Subarachnoid Hemorrhage on Initial CT Scan

1. No blood detected
2. Diffuse or vertical layers <1 mm thick
3. Localized subarachnoid clot and/or vertical layers ≥1 mm thick
4. Intraparenchymal or intraventricular clot with diffuse or no SAH

Modified Fisher CT Rating Scale

1. Minimal or diffuse thin SAH without IVH
2. Minimal or thin SAH with IVH
3. Thick cisternal clot without IVH
4. Thick cisternal clot with IVH

CT, Computed tomography; *IVH,* intraventricular hemorrhage; *SAH,* subarachnoid hemorrhage.

Cardiopulmonary. Cardiac abnormalities are common in the first 48 hours after SAH. Electrocardiographic (ECG) changes, including peaked T waves (cerebral T waves), diffuse T-wave inversion, ST-segment depression, and prolonged QT segments,[200,201] occur frequently and are linked to elevated levels of circulating catecholamines. These changes usually do not represent myocardial ischemia, as the myocardial lesions reported are pathologically distinct from ischemia. Cardiac enzymes may be mildly elevated.[202] Cardiac rhythm disturbances occur in about 30%–40% of patients, especially on the day of hemorrhage or in the postoperative period.[203,204] In rare cases, a stunned myocardium, referred to as *Takotsubo cardiomyopathy,* may occur, with impairment of myocardial contractility leading to a fall in cardiac output, hypotension, and pulmonary edema.[205] Apical ballooning is a common echocardiographic finding. This can be dramatic but is transient, usually lasting 2–3 days, after which cardiac function recovers.[206] Management is the same as with other causes of cardiogenic shock.[207] During hemodynamic treatment for vasospasm, pulmonary edema may occur in up to one-quarter of patients,[208] although its incidence is now lower with careful monitoring.[209]

Diagnostic Studies

CT is the imaging modality of choice in screening for SAH.[210] Blood appears as high attenuation within the basal cisterns, Sylvian fissure, and sulci (Fig. 47.3). CT may fail to demonstrate SAH if the volume of blood is very small, if the hemorrhage occurred several days before the CT scan, or if the hematocrit is extremely low.[211] Lumbar puncture for CSF analysis is indicated if the CT is negative and clinical suspicion is high. Red blood cells in the CSF are indicative of SAH but can also be seen with traumatic puncture. The common technique of comparing cell counts in the first and last tubes collected is not reliable; however, the presence of yellow pigment (xanthochromia), resulting from red cell breakdown, can help distinguish between the two.[212] Xanthochromia develops 6 hours after hemorrhage and persists for 1–4 weeks.[213]

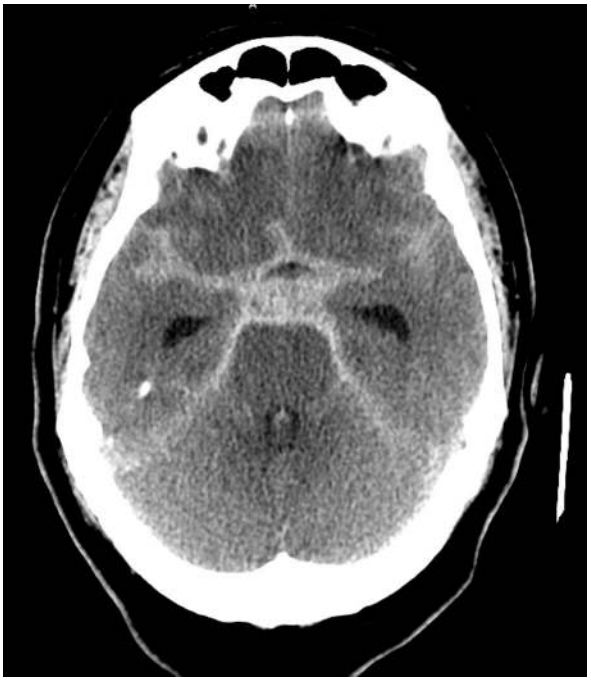

Fig. 47.3. Characteristic CT Scan Showing Acute Aneurysmal Subarachnoid Hemorrhage with Blood in the Perimesencephalic Cisterns and Sylvian Fissures.

Once the diagnosis of SAH is established, the etiology must be determined. With its wide availability, ease of use, and safety profile, CTA is increasingly being used as the initial diagnostic tool. Overall sensitivity is more than 90% compared with conventional angiography but is notably lower for aneurysms smaller than 5 mm[214]; thus a negative CTA should be followed by conventional catheter angiography.[215] Magnetic resonance angiography (MRA) has good sensitivity for detecting medium and large aneurysms, but sensitivity falls to less than 40% for small aneurysms. MRA and CTA may also be of assistance in planning surgical or endovascular approaches to treatment.

Angiography fails to identify a source of bleeding in 10%–15% of patients with nontraumatic SAH. Repeat angiography in about 1 week is thus recommended.[216] There are a subset of patients in whom the blood on CT is localized to the perimesencephalic cisterns. In these cases, angiography is usually negative, and the bleeding is thought to be venous in origin; the prognosis is typically excellent, and repeat angiography is almost always negative.[215]

Treatment

In 2011, the Neurocritical Care Society (NCS) held an international consensus conference on the critical care management of patients with SAH, and evidence-based recommendations were developed.[217]

Initial Stabilization

The initial steps in the evaluation of a patient with suspected SAH should include assessment of airway, hemodynamic status, and the level of neurologic function. The Hunt and Hess Scale[218] and the World Federation of Neurological Surgeons Scale[219] provide standardized measures of the patient's clinical condition (Tables 47.3 and 47.4). These scales should be scored after the patient is stabilized, including treatment of seizures and hydrocephalus if indicated. If the patient is lethargic or agitated, elective intubation should be considered before angiography, as sedation is often necessary. Indications for endotracheal intubation include a GCS ≤8, elevated ICP, poor oxygenation or hypoventilation, hemodynamic instability, and requirement of heavy sedation or paralysis.

TABLE 47.3 Hunt and Hess Clinical Classification of Subarachnoid Hemorrhage

Grade	Neurologic Status
I	Asymptomatic or mild headache and neck stiffness
II	Moderate to severe headache and neck stiffness ± cranial nerve palsy
III	Mild focal deficit, lethargy, or confusion
IV	Stupor, moderate to severe hemiparesis
V	Deep coma, extensor posturing

TABLE 47.4 World Federation of Neurological Surgeons Clinical Classification of Subarachnoid Hemorrhage

Grade	Glasgow Coma Scale	Motor Deficits
I	15	Absent
II	13–14	Absent
III	13–14	Present
IV	7–12	Present or absent
V	3–6	Present or absent

Admit or Transfer to an Expert Center

Early, aggressive, and expert care can dramatically affect outcomes in SAH. Dedicated neurocritical care units and expert staff, including neurocritical care intensivists, neurosurgeons, and neurovascular surgeons, play a critical role in providing appropriate care of SAH patients.[220–224]

Routine Care and Monitoring

The routine monitoring of all patients with acute SAH should include serial neurologic examinations; continuous ECG monitoring; and frequent determinations of blood pressure, electrolytes, body weight, and fluid balance.

Antithrombotic Reversal

Initial management should include discontinuation of all antithrombotic therapy. The 2015 NCS and Society of Critical Care Medicine (SCCM) guidelines recommend reversal of antithrombotics until the aneurysm is secured. For patients on antiplatelet therapy deemed to be candidates for neurosurgical procedures, a single IV dose of desmopressin and platelet transfusion are reasonable after platelet function testing demonstrates decreased function.[225]

Seizure Prophylaxis

Use of prophylactic anticonvulsants is controversial but may be reasonable in the immediate posthemorrhagic period in patients with unsecured aneurysm, poor neurologic grade, and associated ICH; however, the duration of administration should be limited to several days.[185,226] Recent retrospective studies have suggested that routine use of anticonvulsants for a longer duration is associated with worse neurologic outcome.[227,228]

Fluid Management

A stable intravascular volume should be maintained by hydration with crystalloids or colloids.[185] The goal of IV fluids is to achieve and maintain euvolemia, a counterbalance to vasospasm.[229] Combining multiple clinical indicators of volume status such as daily monitoring of fluid balance, body weight, hematocrit, central venous pressure, and replacing urine output is needed.[185,230]

Sodium Homeostasis

Hyponatremia in SAH can be either from SIADH or CSW.[198] SIADH is often managed with restriction of free water, which is not desirable in SAH patients. Thus hypertonic fluids should be used to treat hyponatremia associated with SIADH. There may be a role for antidiuretic hormone (ADH) antagonists such as conivaptan, but because they increase urine volume, extreme caution must be exercised to avoid hypovolemia.[231] In CSW, excessive secretion of natriuretic peptides leads to hypovolemia and hyponatremia. Aggressive fluid resuscitation with isotonic or hypertonic fluids is required to prevent intravascular volume contraction.[232,233] Fludrocortisone may be helpful in treating salt wasting and hypovolemia[198,199,234,235]

Hypertension

Optimal management of blood pressure is not well defined in SAH patients. SBP <140 mm Hg or MAP <100 mm Hg is a reasonable goal in patients with unsecured aneurysm.[185,217] Initial attempts to treat hypertension should include analgesics and nimodipine; other antihypertensive agents should follow if needed. Useful medications include intermittent doses of beta-blockers and vasodilators. If a continuous infusion is needed, nicardipine or clevidipine are effective.[185] When

significant hydrocephalus is present, hypertension should not be treated until after the hydrocephalus is addressed, as the hypertension may be acting to maintain adequate cerebral perfusion in the face of elevated ICP.

DVT Prophylaxis

Intermittent pneumatic compression devices should be started on admission even before the definitive treatment of aneurysm,[176] with subcutaneous heparin started after securing the aneurysm.

Magnesium Sulfate

Magnesium antagonizes calcium and thus can potentially reduce vasospasm, but recent meta-analysis and systematic review found no support for its use.[236,237]

Statins

Statins are not routinely recommended in the treatment of SAH patients.[238] A multicenter phase III trial of simvastatin 40 mg or placebo found no short- or long-term benefit of the drug.[239]

Aneurysm Treatment

Surgical and endovascular methods are available to secure the ruptured aneurysm. Surgical management involves placing a clip across the neck of the aneurysm. Advancement of microsurgical techniques has made clipping a safe and effective method. Endovascular techniques such as electrolytically detachable platinum coils, stent-assisted coiling, and balloon-assisted coiling are routinely used to repair ruptured aneurysms.[185]

Management of Secondary Complications

Rebleeding.

Multiple clinical trials have demonstrated that antifibrinolytic agents such as aminocaproic acid and tranexamic acid (TXA) reduce the risk of rebleeding, but this benefit is offset by an increased incidence of vasospasm and hydrocephalus.[240,241] With the advent of early intervention, the use of these agents has declined dramatically. More recently, there has been interest in a shorter course of antifibrinolytic therapy while awaiting surgery or endovascular treatment in the absence of medical contraindications.[185] TXA begun immediately upon SAH diagnosis and continued until the aneurysm was secured (within 72 hours) reduced the risk of rebleeding from 10.8% to 2.4% and did not increase the risk of DCI.[242]

Other measures directed at prevention of rebleeding include avoiding situations that produce sudden changes in the transmural pressure across the wall of the aneurysm. Patients are placed on bed rest and stimulation minimized. Agitated patients should be carefully sedated and long-acting agents avoided. Measures should be taken to minimize cough and Valsalva maneuvers. Stool softeners are administered to avoid straining. The definitive way to prevent rebleeding is to repair the aneurysm[243] by surgical or endovascular means as early as possible, preferably within 24 hours.

Hydrocephalus

The decision to treat hydrocephalus is usually based on the CT appearance of enlarging ventricles in a patient whose level of consciousness is deteriorating. During placement of an EVD, the CSF pressure must be reduced slowly to lessen the risk of aneurysmal re-rupture. CSF drainage may be needed for many days to clear intraventricular blood before it can be determined if a permanent shunt is required. Approximately 14%–40% of patients with acute hydrocephalus develop shunt-dependent chronic hydrocephalus. The need for a shunt is evaluated in the subacute period with weaning of the EVD and subsequent clamping trial.[228,244–246]

Delayed Cerebral Ischemia

Approximately 30% of cases of SAH are complicated by DCI, which typically occurs between 3 and 14 days after symptom onset.[247,248] It contributes significantly to morbidity and mortality.[185] Vasospasm is presumed to be the most common cause of DCI.[249] Monitoring for DCI involves serial neurologic examinations, serial transcranial Doppler (TCD),[250,251] and catheter angiography. Neurologic signs may be vague, such as a global decline in responsiveness, or may include focal deficits. Symptoms may wax and wane, being exacerbated by hypovolemia or hypotension. Daily TCD recordings provide a window of opportunity for vasospasm treatment before neurologic decline. Vasospasm can be identified on TCD by an increase in linear blood flow velocity, defined as mild (>120 cm/sec), moderate (>160 cm/sec), or severe (>200 cm/sec).[252] Alternatively, the rate of rise in the Lindegaard Ratio, calculated as mean velocity in the middle cerebral artery (MCA) / mean velocity in ipsilateral extracranial internal carotid artery, is used to define the onset of vasospasm. The sensitivity of TCD in detecting vasospasm is about 80% when compared with angiography, at least partly because TCD samples only a small segment of the vasculature.[253] Noninvasive techniques such as CTA and CT perfusion (CTP) can be used to confirm DCI on TCD.[185] Digital subtraction angiography (DSA) is recommended in patients with symptomatic vasospasm who might benefit from intervention.

When making a clinical diagnosis of DCI, alternative causes of neurologic changes such as sedatives, rebleeding, hydrocephalus, cerebral edema, seizures, metabolic derangements, and infections should be promptly excluded. Detection of clinical signs of DCI is particularly difficult in poor-grade patients because of the limited examination that is possible.

Prevention. Routine measures taken to reduce the risk of DCI include mechanical removal of subarachnoid blood at the time of aneurysm surgery or by CSF drainage, administration of the centrally acting calcium channel antagonist nimodipine, and avoidance of intravascular volume contraction or hypotension. Nimodipine for 3 weeks after SAH is the standard of care and improves functional outcomes.[254–256] Its beneficial effect may be the result of action on the cerebral vessels or by preventing calcium influx into ischemic neurons. Any hypotension developing with nimodipine can usually be managed with fluids or by adjusting the dosage schedule. If the impact of nimodipine on blood pressure cannot be overcome in patients with DCI, it may have to be discontinued and reevaluated when hemodynamically stable.

Although there is general agreement that hypovolemia must be avoided, the use of prophylactic hypervolemia is more controversial.[185,257–259] In a prospective controlled study, prophylactic volume expansion with albumin failed to reduce the incidence of clinical or TCD-defined vasospasm and had no effect on outcome.[260] Costs and complications may be higher with the use of prophylactic hypervolemia.

Prophylactic use of transluminal balloon angioplasty was evaluated in a prospective, randomized controlled trial.[261] Although it reduced the need for therapeutic angioplasty and reduced ischemic deficits, these benefits were offset by procedure-related vessel complications.

Treatment of DCI

The trigger for instituting more aggressive interventions varies widely. Some centers actively intervene in the setting of rising TCD velocities[262] or angiographic vasospasm in asymptomatic patients,[263] whereas others institute aggressive measures in the setting of clinical deterioration. Aggressive measures include both hemodynamic and endovascular manipulations.[264–266] The goal is to improve CBF in ischemic regions. Hemodilution, hypervolemia, and induced hypertension *(triple H therapy)* was previously employed to achieve an increase in CBF, but accumulating evidence has shown that maintaining euvolemia and only inducing hypertension during vasospasm are beneficial.[229,267,268]

Induced Hypertension

Blood pressure augmentation is considered the first-line therapy for DCI in euvolemic patients and can be achieved with vasopressor agents, although the optimal target is not well defined.[229] Goals for blood pressure should be defined as a percent change from baseline (beginning with an approximately 15% change) rather than prespecified levels.

The presence of other small, untreated aneurysms does not exclude use of this therapy. The degree of blood pressure augmentation should be titrated continuously to the patient's neurologic status; thus if a goal is reached but there is no neurologic improvement, the goal should be modified. Once the optimal goals have been reached, they are usually maintained for 2–3 days and then gradually weaned. Risks associated with this therapy include volume overload, pulmonary edema, heart failure, and cerebral edema.

Anemia is common after SAH and may contribute to DCI by compromising brain oxygen delivery.[185,269] Although transfusion can have beneficial effects on brain physiology, it may be associated with medical complications, infection, vasospasm, and poor outcome after SAH. Still, given the high risk of ongoing cerebral ischemia, the results of the Transfusion Requirements in Critical Care Trial and subsequent observational studies on red blood cell transfusion in general critical care should not be applied to SAH patients.[270,271] Practice surveys indicate that transfusion thresholds of 8–10 g/dL are commonly used, with the higher range reserved for patients with DCI. Current recommendations are to maintain hemoglobin closer to 10 g/dL in patients at risk of ischemia rather than use the standard transfusion threshold of 7 g/dL.[272]

Endovascular Treatments

The endovascular approach to vasospasm involves treatment of constricted vessels with either balloon angioplasty or intraarterial infusion of vasodilating agents.[230,273] Angioplasty on the proximal segments of vasospastic cerebral vessels yields impressive sustained angiographic changes.[274,275] Vasoconstriction in more distal vessels usually cannot be reached by angioplasty catheters and can be treated with intraarterial infusion of vasodilators. Intraarterial papaverine rapidly dilates the entire cerebral vasculature, but reversal of clinical deficits is inconsistent.[276–278] Its use has largely been abandoned because of its short-lived effect and complications, including increased ICP, apnea, worsening of vasospasm, neurologic deterioration, and seizures.[279] It has been replaced by nicardipine, verapamil, nimodipine, and milrinone.[280–282]

The timing of when to initiate endovascular therapy is debated. It is generally used if, after a few hours, the response to hemodynamic augmentation is inadequate, but it may be the initial therapy in patients with poor cardiac function who are at high risk of complications of hemodynamic manipulation.[283]

Endothelin-1 Antagonists

Endothelin-1 (ET-1) is a 21–amino acid peptide that mediates vasoconstriction. In early studies, an endothelin antagonist, clazosentan, reduced angiographic vasospasm[284,285] and tended to reduce vasospasm-related morbidity/mortality. Subsequently, two very large randomized controlled trials confirmed the reduction in angiographic vasospasm, but clazosentan did not change clinical outcome.[286]

Fever

After SAH, fever develops in well over half of patients and is associated with increased length of stay, worse outcome, and higher mortality.[287–290] Early in the disease course, most fevers are central in origin. Antipyretics are effective in a minority of patients, although IV forms may be more effective. Surface and intravascular cooling devices are much more effective, but benefits from cooling may be offset by negative consequences from shivering.[291]

Prognostic Factors and Causes of Mortality

Untreated aneurysmal SAH carries a poor prognosis, with an estimated mortality rate of about 50%.[292,293] Of those who make it to medical attention, mortality is 20%–40%. Causes of death are about equally distributed among direct effects of the initial hemorrhage, rebleeding, vasospasm, and medical complications. Overall, less than one-third of patients achieve good neurologic recovery. Predictors of poor prognosis include loss of consciousness or poor neurologic condition on admission, older age, hypertension, preexisting medical illness, ≥1 mm thickness of subarachnoid blood on CT, seizures, cerebral edema, aneurysm location in the basilar artery, and symptomatic vasospasm.[294–298] Scales quantifying the degree of physiologic illness are also predictive of outcome in patients with SAH.[299] Long-term survivors of the initial hemorrhage continue to suffer a 3% annual risk of re-hemorrhage unless the aneurysm is repaired. Advancements in diagnostic and therapeutic options in neurocritical care are plausible explanations for improved prognosis in patients with SAH.[300]

KEY POINTS

- Major risk factors for primary ICH include hypertension and CAA, which account for nearly 80% of all cases.
- Initial management and stabilization of ICH should include aggressive blood pressure reduction with IV medications to a target blood pressure less than 160 mm Hg and, with caution, to less than 140 mm Hg.
- Prognostic factors in ICH associated with poor outcomes include low CGS on admission, IVH, advanced age, large hematoma size, and infratentorial location of the hemorrhage.
- Abrupt discontinuation and reversal of anticoagulation with ICH are imperative to decrease the risk of hematoma expansion and rebleeding.
- Patients presenting to a tertiary care center with either intracerebral or subarachnoid hemorrhage should be urgently triaged to a neurocritical care intensive care unit based upon evidence of improved outcomes.
- SAH is classified as either nonaneurysmal or aneurysmal, with the latter accounting for 80% of all hemorrhages.
- Early complications such as rebleeding and late complications such as vasospasm and DCI occur in aneurysmal SAH.
- The use of nimodipine in SAH has been shown to improve neurologic outcomes, but not reduce the prevalence of vasospasm.

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Seizures in the Critically Ill

Sebastian Pollandt, Adriana C. Bermeo-Ovalle, and Thomas P. Bleck

INTRODUCTION

The routine use of continuous electroencephalographic (cEEG) recordings in intensive care demonstrates that clinical seizures in critically ill patients, both with neurologic and nonneurologic conditions, are the tip of the iceberg regarding seizure frequency in this vulnerable population. Nonconvulsive seizures are detected in 10%–30% of critically ill patients with altered mental status and in up to 60% of critically ill patients who have been witnessed to have prolonged clinical seizures earlier during their hospital stay.[1] The presence of seizures in this population is associated with worse functional outcome at discharge,[2] multiple markers of disease severity,[3] and long-term neurologic injury.[4] The routine use of cEEG monitoring and quantitative EEG (qEEG) analysis leads to the diagnosis of electrographic seizures and timely modification of treatment,[5] which may affect early and long-term disability and mortality. The use of cEEG has become standard care in the intensive care unit (ICU). Its use is strongly recommended in cases of recent status epilepticus, unexplained coma, altered mental status, and behavioral changes and also in most patients with intracranial hemorrhage, as these cases are more likely to be associated with subclinical seizures.[1]

Among patients without primarily neurologic conditions, the presence of a seizure may be the first indication of a central nervous system (CNS) complication; delay in recognition and treatment of seizures is associated with an increased risk of mortality.[6] Thus rapid diagnosis, treatment, and follow-up of epileptic activity and seizures are crucial. In addition, because epilepsy affects around 2% of the population, patients with a predisposition to seizures may enter the ICU for treatment of other systemic problems. These patients are at high risk for developing seizures and status epilepticus in the context of acute or severe illness.[7] Patients developing status epilepticus often require critical care management as treatment escalates to include multiple antiseizure medications and sedatives that require airway protection, hemodynamic support, and close monitoring.

Status epilepticus refers to prolonged seizure activity beyond the usual duration of a self-limited, isolated seizure; it may be the primary indication for admission to the ICU, or it may occur in ICU patients. Seizures that persist longer than 5 minutes or recurrent seizures without recovery to the patient's neurologic baseline between seizures should be considered and treated as status epilepticus.[8] Status epilepticus can also be subclinical, with little or no overt signs of seizures. Of patients monitored with EEG as part of a coma evaluation, 8%–10% were reported to be in nonconvulsive status epilepticus (NCSE).[9] Recognizing the risk factors, clinical presentation, diagnosis, and management of clinical and subclinical seizures in the ICU is a frequent task for the intensivist. Recent technologic advances enormously facilitate the diagnosis and follow-up of these patients in real time. Communication between the ICU team and the neurology/neurophysiology team is crucial to offer the patient timely therapy that significantly affects outcome.[6]

EPIDEMIOLOGY

Limited data are available on the epidemiology of seizures in the ICU. A 10-year retrospective study of all ICU patients with seizures revealed that 7 patients had seizures per 1000 ICU admissions.[10] A 2-year prospective study of medical ICU patients identified 35 with seizures per 1000 admissions.[11] In a retrospective analysis of 570 patients undergoing cEEG monitoring, seizures were detected in 110 patients (19%). Of those patients with seizures, the majority were in ICUs at the time of the EEG ($n = 101$; 89%). In this series, 92% of the recorded seizures were nonconvulsive, requiring EEG for the diagnosis.[12] Up to 34% of hospital inpatients experiencing a seizure die during their hospitalization.[11] In a study of medical ICU patients, having even one seizure while in the ICU for a nonneurologic reason doubled in-hospital mortality.[11] Incidence estimates for status epilepticus in the United States and Europe vary from 10.3 to 41/100,000.[3,13–15] The incidence has a bimodal distribution, peaking in young children and in the elderly.[13,16]

Mortality estimates vary widely, but data suggest that prolonged seizure duration is a negative prognostic factor. For patients whose generalized convulsive status epilepticus (GCSE) resolves within 30–59 minutes, the reported mortality is 2.7%, whereas patients seizing for more than 60 minutes have a mortality of 32%.[17] If GCSE develops de novo in hospitalized patients, the mortality is 61%.[18] For patients in NCSE, the mortality has been reported as high as 57%[6] and correlates with the underlying cause, severe impairment of mental status, and development of complications, especially respiratory failure and infection.[19] Determining the contribution of status epilepticus to mortality is challenging because of the large impact of the underlying etiology on outcomes.

Table 48.1 summarizes the most common causes of status epilepticus in adults in the community. Almost 50% of the cases were attributed to cerebral vascular disease.[20] Antiseizure medication nonadherence is the main cause of status epilepticus in patients with a previous history of epilepsy; CNS infection, stroke, and metabolic disturbances predominate in patients without previous seizures.[7]

Limited data are available concerning the functional abilities of GCSE survivors, and no data reliably permit distinction between the effects of status epilepticus and the effects of its causes. GCSE has the worst prognosis for neurologic recovery. Causes associated with increased mortality include anoxia, intracranial hemorrhages, tumors, infections, and trauma. In addition, intellectual ability declines as a consequence of status epilepticus.[21] Survivors of status epilepticus often have memory and behavioral disorders out of proportion to the structural damage produced by the cause of their seizures. Case reports

TABLE 48.1 Causes of Status Epilepticus in Adults Presenting From the Community

Previous Seizures	No Previous Seizures
Common	
Subtherapeutic antiseizure medication	Ethanol-related
Ethanol-related	Drug toxicity
Intractable epilepsy	CNS infection
	Head trauma
	CNS tumor
Less Common	
CNS infection	Metabolic aberration
Metabolic aberration	Stroke
Drug toxicity	
Stroke	
CNS tumor	
Head trauma	

CNS, Central nervous system.

of severe memory deficits after prolonged focal status epilepticus with impairment of consciousness have been published.[22] Conversely, one prospective study of 180 children with febrile status epilepticus reported no deaths or new cognitive or motor disability.[23] Experimental animal[24] and human[25] epidemiologic studies suggest that status epilepticus may be a risk factor in the development of future seizures. Whether treatment of prolonged seizures reduces the risk of subsequently developing epilepsy remains uncertain.

CLASSIFICATION

Seizures are the clinical manifestation of the underlying predisposition for abnormal excessive and synchronous brain activity that defines epilepsy. Seizures can affect all measurable brain functions and follow a predictable clinical presentation largely related to the site of origin of the epileptic activity and the pattern of propagation.

The most recent revision of the terminology and classification of seizures and epilepsy from the International League Against Epilepsy (ILAE) was published in 2017 (Table 48.2).[26–29] Seizures are initially divided into focal- versus generalized-onset or unknown-onset seizures. Focal seizures are then further subdivided into focal-aware or focal-impaired awareness seizures. Additional classifiers for motor onset and nonmotor onset may be added. The motor classifiers include automatisms, atonic, clonic, epileptic spasms, hyperkinetic, myoclonic, and tonic, whereas nonmotor classifiers are autonomic, behavior arrest, cognitive, emotional, and sensory. Similarly, generalized-onset seizures are classified based on motor (e.g., tonic-clonic, myoclonic, atonic, and others) or nonmotor (i.e., typical absence, atypical absence, myoclonic) features.[26,27,29]

The ILAE terminology classifies epilepsy types based on varying levels of diagnosis: seizure type, epilepsy type, and epilepsy syndrome. Based on the three seizure types (focal, generalized, or unknown), the epilepsy type is determined as either focal, generalized, combined generalized and focal, or unknown. Potential etiologies should be considered, which include structural, genetic, infectious, metabolic, immune, or unknown etiologies. Epilepsy syndromes such as juvenile myoclonic epilepsy or childhood absence epilepsy refer to a cluster of features (seizure type, EEG, and imaging findings) that typically occur together.[28] Determining the epilepsy type may aid in the selection of treatment options and prognosis. Careful

TABLE 48.2 2017 ILAE Classification of Seizure Types – Expanded Version[26,27,29]

Focal-Onset Seizures
Aware versus Impaired Awareness
Motor onset:
Automatisms
Atonic
Clonic
Epileptic spasms
Hyperkinetic
Myoclonic
Tonic
Nonmotor onset:
Autonomic
Behavioral arrest
Cognitive
Emotional
Sensory

Generalized-Onset Seizures
Motor:
Tonic-clonic
Clonic
Tonic
Myoclonic
Myoclonic-tonic-clonic
Myoclonic-atonic
Atonic
Epileptic spasms
Nonmotor (absence):
Typical
Atypical
Myoclonic
Eyelid myoclonia

Unknown Onset
Motor
Tonic-clonic
Epileptic spasms
Nonmotor
Behavior arrest

Unclassified
Insufficient information or not fitting into any of the other categories

ILEA, International League Against Epilepsy.

description of the phenomenology of seizures, etiology, and localization continues to be an important part of the patient's care. The identification of clinical features of seizures can be challenging in the ICU, except for observation of motor manifestations. ICU patients often have altered awareness caused by medications, hypotension, sepsis, or intracranial lesions; thus the presentation of focal seizures may be difficult to establish by observation alone, and EEG monitoring is often the only way to determine if a patient is seizing.

An ICU patient who has continuous, regular repetitive contractions in a stable muscle group in the right arm while awake and responsive can be classified as having focal right arm clonic status epilepticus without impairment of consciousness or awareness. *Epilepsia partialis continua,* a special form of focal status epilepticus in which repetitive movements of epileptic origin affect a small area of the body, can sometimes continue relentlessly for months or years and is notoriously refractory to treatment. The ILAE continues to work toward revising

and updating the current classification system. For the most recent information, refer to www.ilae.org.[30]

PATHOGENESIS AND PATHOPHYSIOLOGY

The causes and effects of status epilepticus at the cellular, brain, and systemic levels are interrelated, but their individual analysis is useful for understanding them and their therapeutic implications. The ionic events of a seizure follow the opening of ion channels coupled to excitatory amino acid receptors. From the standpoint of the intensivist, three channels are important, as their activation may raise intracellular free calcium to toxic levels: alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPAR), *N*-methyl-D-aspartate receptor (NMDAR), and metabotropic channels. These excitatory amino acid systems are crucial for learning and memory. Counterregulatory ionic events are triggered by the epileptiform discharge as well, such as the activation of inhibitory interneurons suppressing excitatory neurons via ionotropic gamma-aminobutyric acid ($GABA_A$) synapses.

The cellular effects of excessive excitatory amino acid channel activity include the following: (1) generation of toxic levels of intracellular free calcium; (2) activation of autolytic enzyme systems; (3) production of oxygen free radicals; (4) generation of nitric oxide, which both enhances subsequent excitation and serves as a toxin; (5) phosphorylation of enzyme and receptor systems, making seizures more likely; and (6) an increase in intracellular osmolality, producing neuronal swelling. If adenosine triphosphate production fails, membrane ion exchange ceases, and neurons swell further. These events produce the neuronal damage associated with status epilepticus. Longer status epilepticus duration produces profound alterations and an increasing likelihood of becoming refractory to treatment.[31] Many other biophysical and biochemical alterations occur during and after status epilepticus. The mechanisms by which status epilepticus damages the nervous system have been reviewed.[32,33] Absence status epilepticus is an exception; it consists of rhythmically increased inhibition and does not appear to produce clinical or pathologic abnormalities.[34]

The electrical phenomena of status epilepticus seen in the scalp EEG reflects the seizure type (e.g., absence status epilepticus begins with a 3-Hz spike-and-wave pattern). The sustained depolarizations that characterize status epilepticus alter the extracellular milieu, raising extracellular potassium, which subsequently exceeds the buffering ability of astrocytes.

The increased cellular activity of status epilepticus increases oxygen and glucose demands, and cerebral blood flow initially increases. After about 20 minutes, however, energy supplies are exhausted, causing local catabolism to support ion pumps, which is thought to be a major cause of epileptic brain damage. GCSE also produces life-threatening systemic effects.[35] Excess secretion of epinephrine and cortisol causes systemic and pulmonary arterial pressures to rise dramatically at seizure onset and produce hyperglycemia. Muscular work accelerates heat production, increases core body temperature, and raises blood lactate levels. Airway obstruction and abnormal diaphragmatic contractions impair respiration. Carbon dioxide production increases markedly while excretion falls. The combined respiratory and metabolic acidosis frequently reduces the arterial blood pH to 6.9 or lower. The associated hyperkalemia has deleterious effects on cardiac electrophysiology and may propagate seizure activity. Coupled with hypoxemia and the elevation of circulating catecholamine levels, these conditions can produce cardiac arrest. Neurogenic pulmonary edema is the likely cause of death in many cases. Rapid termination of seizure activity is the most appropriate treatment; the restitution of ventilation and the metabolism of lactate quickly restore a normal pH.

After about 30 minutes of continuous convulsions, motor activity may diminish while electrographic seizures persist. Hypotension and hyperthermia ensue, and gluconeogenesis can fail, resulting in hypoglycemia. GCSE patients often aspirate oral or gastric contents, producing chemical pneumonitis or bacterial pneumonia. Rhabdomyolysis is common and may lead to renal failure. Compression fractures, joint dislocations, and tendon avulsions are other serious sequelae.

The mechanisms that terminate seizure activity are poorly understood. Leading candidates are inhibitory mechanisms, primarily GABAergic interneurons and inhibitory thalamic neurons.

CLINICAL MANIFESTATIONS

The ICU environment poses a challenge to early seizure recognition because of multiple factors: (1) the occurrence of nonconvulsive seizures in patients with impaired awareness, (2) the occurrence of seizures in patients receiving neuromuscular blockade and/or sedation, and (3) misinterpretation of nonepileptic abnormal movements and behaviors as seizures. The most common symptom of nonconvulsive status epilepticus is altered mental status. Although other symptoms such as speech disturbances, myoclonias, bizarre behaviors, and others do occur, they are far less frequent.[36] ICU patients often have depressed consciousness in the absence of seizures owing to their disease, its complications (such as hepatic[37] or septic[38] encephalopathy), or drug administration. A further decline in alertness may reflect a seizure, but unless actions are taken to make this diagnosis, seizures and even status epilepticus may go unrecognized.

Patients receiving neuromuscular blocking agents do not manifest motor signs of seizures. Patients with increased intracranial pressure (ICP) from primary brain injury, hepatic encephalopathy, or other critical illnesses may be both paralyzed and sedated, making identification of seizures challenging in the absence of EEG monitoring. Tachycardia, tachypnea, and hypertension are signs of seizures that can be misinterpreted as evidence of inadequate sedation or primary cardiorespiratory conditions.

Seizures are the second most frequent neurologic complication after encephalopathy in critically ill patients with primarily nonneurologic conditions,[11] making it imperative for ICU providers to be able to identify and suspect the presence of seizures in all patients with altered awareness in the ICU setting.

Generalized motor seizures and convulsive status epilepticus are more common in patients with a prior history of epilepsy in relation to acute illness or medication nonadherence. However, even among patients without a history of epilepsy, subtle clinical seizures and NCSE are increasingly recognized in the context of systemic illness or acute brain injury. Nonconvulsive seizures and NCSE occur in 10%–30% of patients with altered mental status in the ICU. Risk factors include the presence of CNS infection (meningitis or encephalitis) and focal lesions such as a brain tumor or an area of encephalomalacia. Seizures in the ICU are often subtle and may be related to the anatomic location of the brain lesion. Minor twitching of the face or extremities, fluctuating levels of awareness or level of interaction, nystagmus or eye deviation, abnormal orofacial movements, and repetitive blinking are more commonly seen than generalized tonic-clonic events. cEEG monitoring is warranted in this population if seizures are suspected, because a delay in the diagnosis and treatment of NCSE likely leads to worse functional prognosis at discharge and increased mortality.[39]

Patients with metabolic disturbances, anoxia, and other types of CNS injuries may demonstrate abnormal movements that can be mistaken for a seizure. Asterixis is a brief asynchronous loss of tone at the wrist or hip joints that can appear in the setting of metabolic encephalopathy. Stimulus-sensitive massive myoclonus after anoxia can be

dramatic but usually self-abates in a few days. Controversy exists as to the epileptic origin of this disorder, and post–anoxic myoclonus has been reported in the presence of almost total cortical suppression.[40] Brain-injured patients may manifest paroxysmal sympathetic hyperactivity and associated rigidity or extensor posturing.[41] Patients with tetanus are awake during their spasms and flex rather than extend their arms as seizure patients do. Psychiatric disturbances in the ICU occasionally manifest as psychogenic nonepileptic events. As these events tend to cluster and manifest as dramatic convulsive episodes, they are often treated in the emergency department as refractory status epilepticus, which may prompt ICU admission. The clinical manifestations of seizures and status epilepticus depend on the type and the cortical area of abnormality. Table 48.2 presents the classification of epileptic seizures recognized by the ILAE; all of these may be seen in the ICU.

Convulsive seizures or status epilepticus are described when the main characteristics of the seizures are generalized tonic-clonic movements. During the tonic phase, there is a sustained muscle contraction of a group of muscles in a regional or generalized distribution. During the clonic phase, there are regular, predictable, rhythmic, and repetitive contractions of a muscle group. Myoclonic seizures are brief, involuntary muscle contractions; they are unpredictable and irregular. Motor seizures can manifest in any combination of the described motor phenomena and in any order; they can involve the axial muscles and extremities from the beginning of the seizure without warning, or they can start regionally in one body part and progress into a generalized motor seizure.

When a patient with GCSE is treated with antiseizure medications in inadequate doses, visible convulsive activity can stop, but the electrographic seizure may continue. A prospective evaluation of 164 patients showed that nearly half manifested persistent electrographic seizures in the 24 hours after clinical control of convulsive status epilepticus.[42] Thus EEG monitoring after control of convulsive status epilepticus is essential in directing therapy.[43]

Patients typically begin to awaken within 15–20 minutes after the successful termination of status epilepticus; many regain consciousness much faster. Patients who do not start to awaken after 20 minutes should be assumed to have entered NCSE. Careful observation may disclose slight motor activity as described earlier. However, patients may present in NCSE without an inciting episode of GCSE. Failure to recognize NCSE is common in patients presenting with nonspecific neurobehavioral abnormalities such as delirium, lethargy, bizarre behaviors, cataplexy, or mutism.[44] A high suspicion of this disorder should be maintained in ICU patients with unexplained alteration of consciousness or cognition.

DIAGNOSTIC APPROACH

Observation is very important when a patient has a single clinical seizure, as this is the time to collect evidence of a focal onset suggestive of a structural brain lesion. The postictal examination is similarly valuable; language, motor, sensory, or reflex abnormalities after an apparently generalized seizure may uncover evidence of focal pathology.

Seizures in ICU patients have several potential causes that must be investigated. Drugs are a major cause of ICU seizures, especially in the setting of diminished renal or hepatic function or when the blood-brain barrier is breached. Imipenem-cilastatin[45] and fluoroquinolones[46] can lower the seizure threshold, especially in patients with renal dysfunction. However, they should be avoided in patients at risk for seizures. Other antibiotics, especially beta-lactams, are also implicated.[47] Sevoflurane, a volatile anesthetic agent, is dose-dependently epileptogenic in patients with no predisposition to seizures.[48]

Recreational drugs are overlooked offenders in patients presenting to the ICU. Acute cocaine or methamphetamine intoxication is characterized by a state of hypersympathetic activity followed by seizures.[49] Although ethanol withdrawal is a common cause of seizures, discontinuing any hypnosedative agent may prompt convulsions 1–3 days later. Narcotic withdrawal may produce seizures in the critically ill.[11] In the absence of a structural etiology for the seizure, complete toxicologic, infectious, and metabolic screening should be performed.

Serum glucose, electrolyte concentrations, and serum osmolality should be measured. Nonketotic hyperglycemia[50,51] and hyponatremia can precipitate both focal and generalized seizures. Seizure activity may infrequently be the first presenting sign of diabetes mellitus. Hypocalcemia rarely causes seizures beyond the neonatal period, and its identification on analysis must not signal the end of the diagnostic work-up. Hypomagnesemia has an equally unwarranted reputation as the cause of seizures in malnourished alcoholic patients.

The physical examination should emphasize assessment for both global and focal abnormalities of the CNS. Evidence of cardiovascular disease or systemic infection should be sought, and the skin and fundi examined closely. The need for imaging studies should be addressed as soon as the clinical seizure is controlled. The management of epileptic seizures and convulsive status epilepticus should not be delayed by the need to obtain images or neurophysiologic data. If possible, treatment and diagnostic strategies should be instituted simultaneously. A prospective study in medical ICU patients determined that 38 of 61 patients (62%) had a vascular, infectious, or neoplastic explanation for their seizures.[11] Magnetic resonance imaging (MRI) should be performed on all ICU patients with new-onset seizures. Many ICP monitors are compatible with MRI. Patients who need cerebrospinal fluid analysis always require imaging of the brain first. When CNS infection is suspected, empiric antibiotic treatment should be started while these studies are being performed.

EEG is a vital diagnostic tool for evaluating patients with diagnosed or suspected seizures. Focal seizures usually show EEG abnormalities that begin in the region of cortex that produces seizures. Primary generalized seizures show bilateral hemispheric involvement from the onset. Postictal slowing or an asymmetric EEG amplitude provides clues as to the focal cause of the seizures, and epileptiform activity helps classify the type and origin of epileptic activity and may guide treatment. An emergency EEG is necessary to exclude NCSE soon after clinical seizures have apparently been controlled (Fig. 48.1).

cEEG can help establish the diagnosis, frequency, localization, and duration of seizures. It also aids in the evaluation of the response to treatment and degree of encephalopathy. It offers continuous and often long-term data and real-time feedback that can be lifesaving in the ICU, with few added risks or costs to the patient.[52] Given the high prevalence of NCSE in this patient population and the low relative risks associated with cEEG, a low level of suspicion should trigger such evaluation. The advent of modern techniques of EEG analysis and trend analysis, as in qEEG, are invaluable in the ICU, as they allow the reviewer to identify trends of electrographic activity over longer periods, identify subtle asymmetries, and aid in the identification and quantification of EEG seizures. The use of this technology has gained recent attention and interest from the EEG and the ICU community. Indications for cEEG include patients with altered mental status and history of epilepsy, fluctuating level of consciousness, acute brain injury, after convulsive status epilepticus, and abnormal stereotypical movements or behaviors. Other indications include assessing the level of sedation, vasospasm monitoring, and monitoring the response to antiseizure medications or sedative weaning.[53,54] In the context of hypothermia after cardiac arrest, cEEG may provide prognostic information[55] and should

(Text continued on page 331)

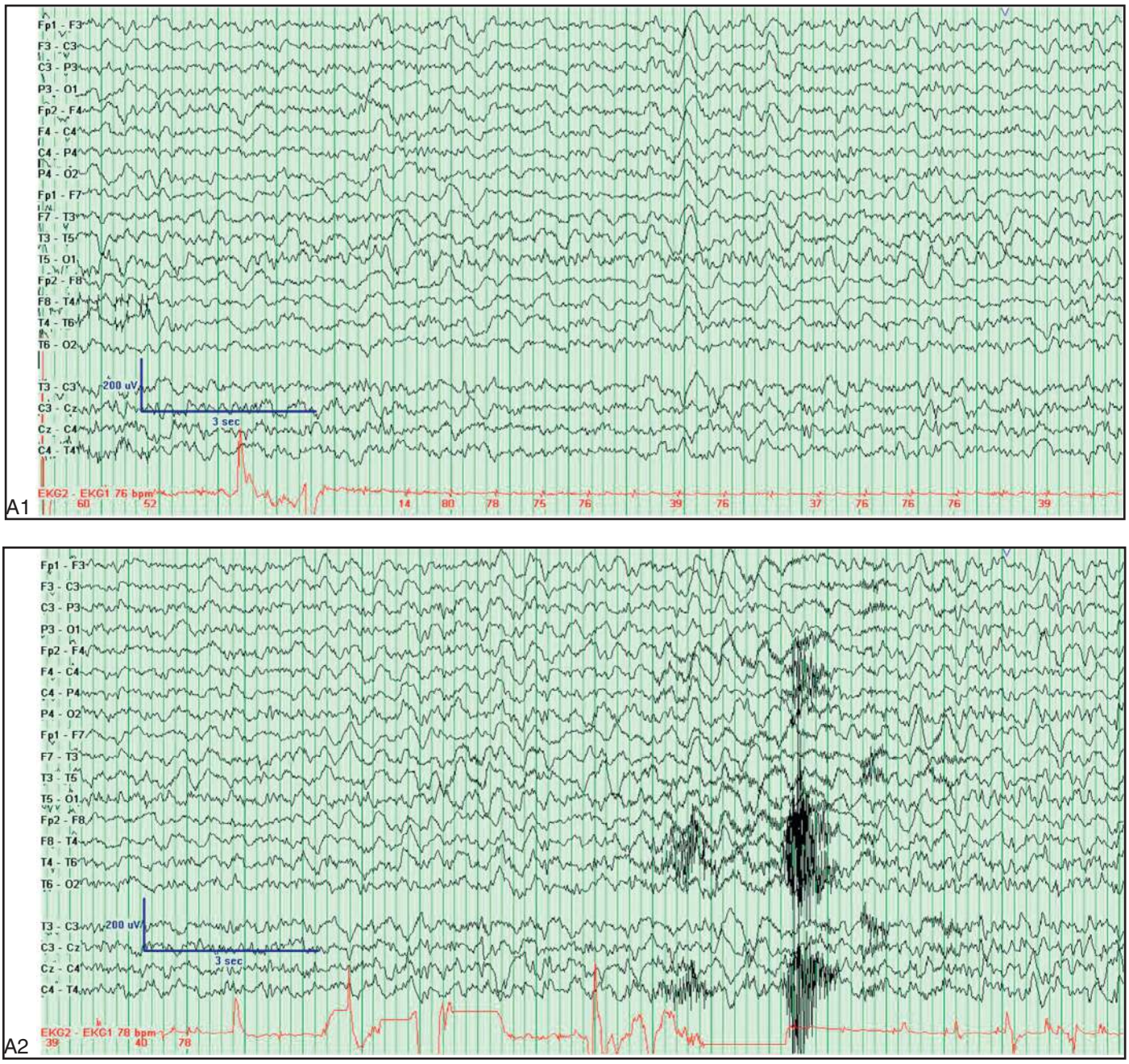
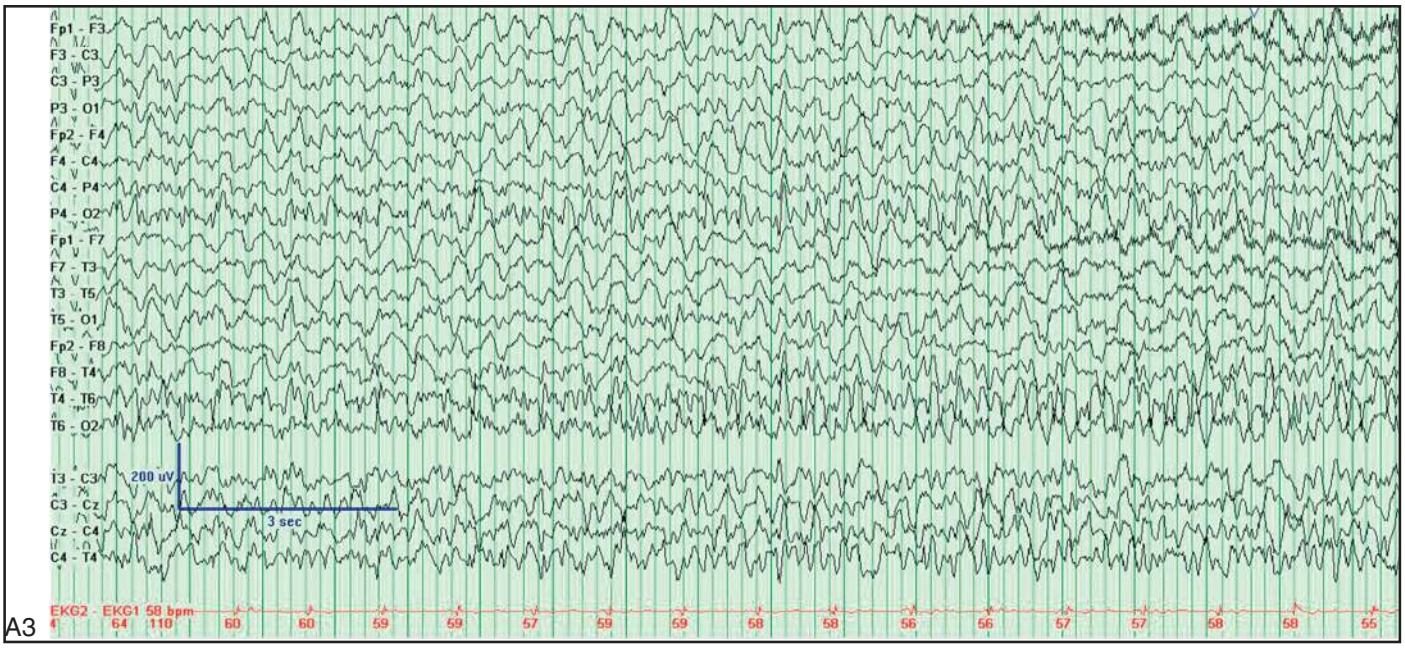
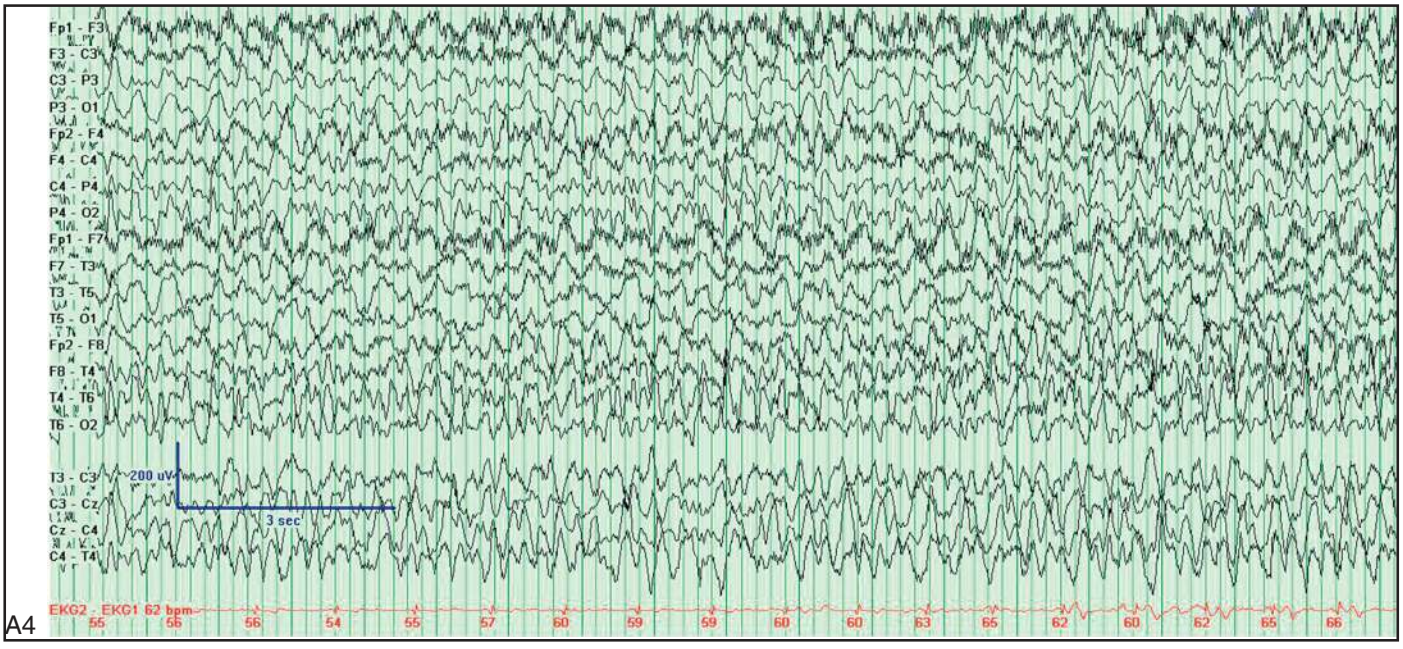


Fig. 48.1 **A,** Electroencephalographic (EEG) recordings during status epilepticus in an 18-year-old comatose patient with autoimmune encephalitis. Panels illustrate onset **(A1),** evolution **(A2–A6),** and subsequent offset **(A7)** of a seizure. **B,** Quantitative EEG display demonstrating recurrent nonconvulsive seizures in the same patient.

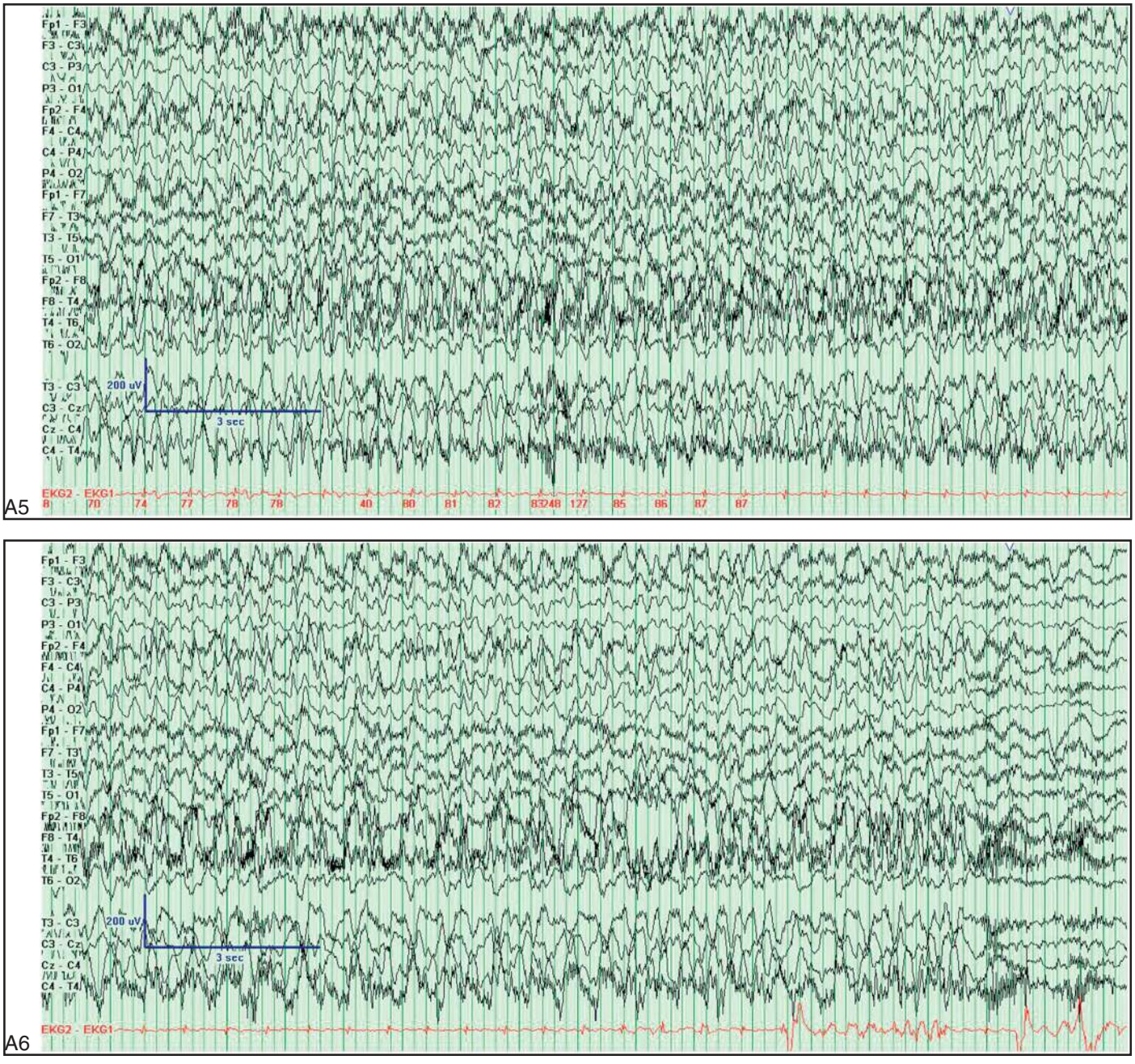


A3



A4

Fig. 48.1, cont'd



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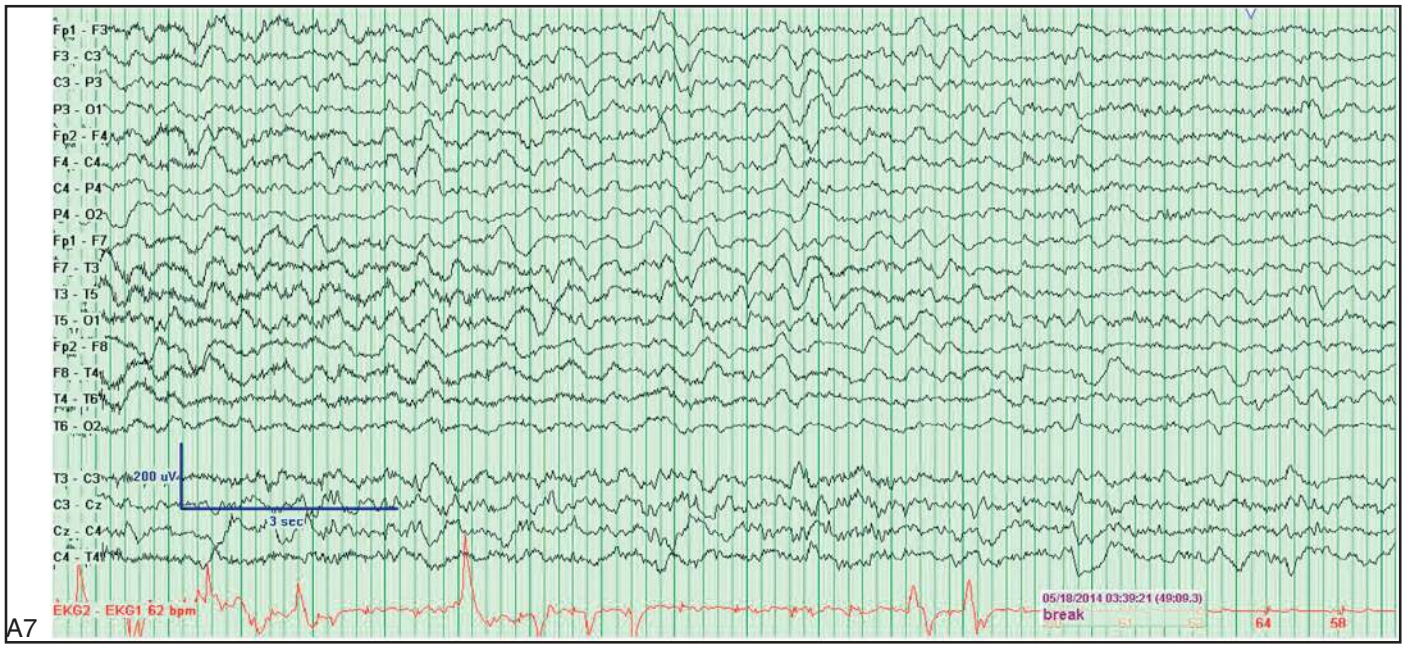
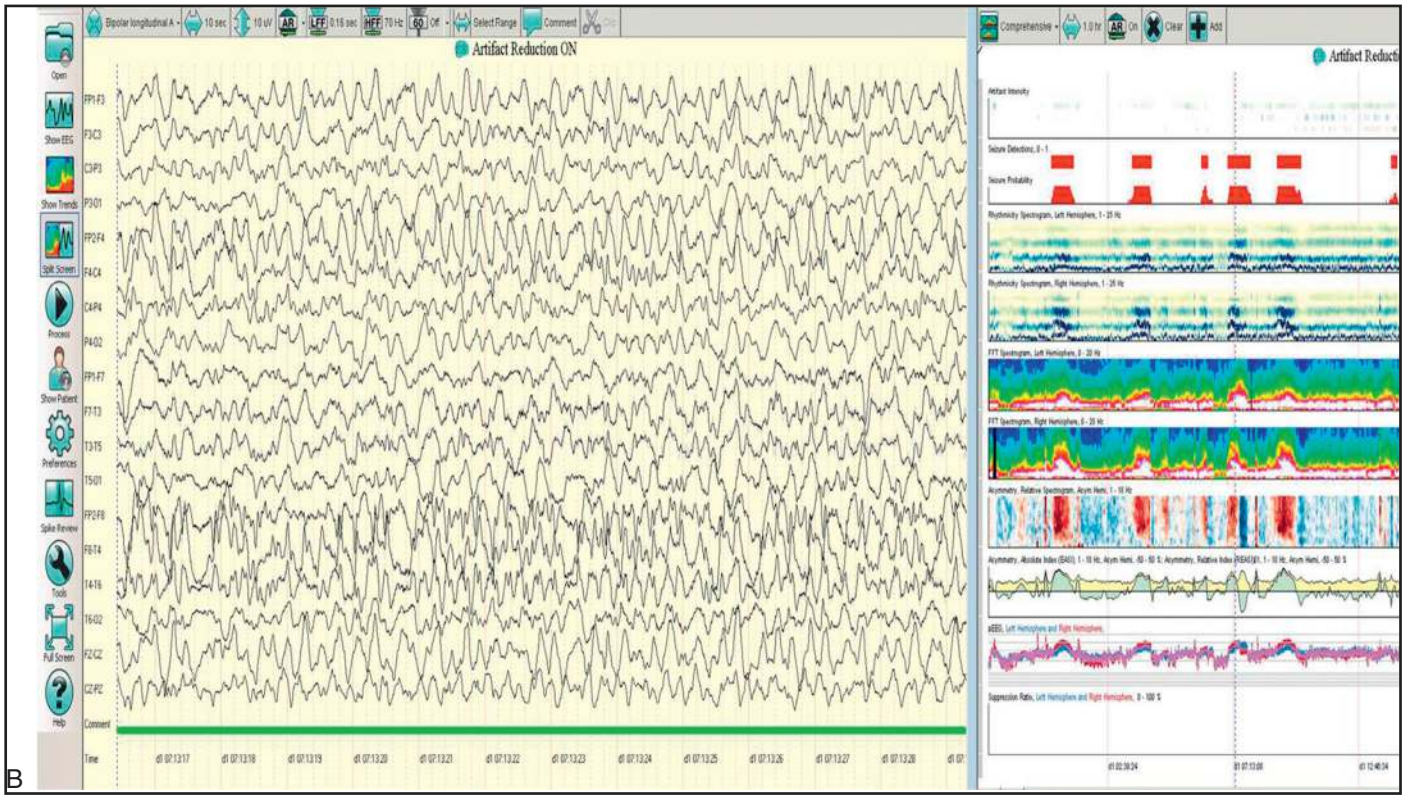


A7



B

Fig. 48.1, cont'd

be used throughout the cooling protocol and until rewarming has been completed. The value of cEEG in the long-term evaluation of severe anoxic encephalopathy with or without myoclonus remains to be determined.

The interpretation of EEG findings seen in the ICU is challenging for neurophysiologists and clinicians alike. Many EEG patterns, in particular rhythmic and periodic patterns, are of uncertain clinical significance. In an effort to standardize terminology and to aid in future research of EEG patterns encountered in critically ill patients, a subcommittee of the American Clinical Neurophysiology Society (ACNS) proposed a classification system in 2005.[56] The classification system has been revised several times, most recently in 2021.[57] All terms consist of two main terms with numerous modifiers that can be added to the descriptions. The use of this system has been validated with good interrater reliability. Details of the terminology for these rhythmic and periodic patterns are outlined in Table 48.3.

A routine EEG may miss the chance to diagnose seizures in critically ill patients, and cEEG recording is generally recommended in this setting. The presence of NCSE, lateralized periodic discharges, generalized periodic discharges, and an abnormal EEG background are associated with worse outcomes.[2] More than half of the seizures diagnosed in ICU patients with EEG monitoring are detected within the first 30 minutes of recording; a third of these patients are found to have interictal epileptiform discharges within the same period. The risk of seizures diminishes if no epileptiform abnormalities are seen within 2 hours.[58] A quick but accurate seizure risk assessment tool is the 2HELPS2B score, which assigns points to six clinical and EEG variables: 2 points for brief (ictal) rhythmic discharges; 1 point for the presence of lateralized periodic discharges, lateralized rhythmic delta activity, or bilateral independent periodic discharges; 1 point for a prior seizure; 1 point for sporadic epileptiform discharges; 1 point for periodic/rhythmic patterns at >2.0 Hz; and 1 point for the presence of "plus" features according to ACNS terminology. A score of 0 portends a seizure risk of only 5%, whereas a score of 6 or 7 indicates a seizure risk >95%.[59]

The diagnosis of NCSE can be challenging. A unified terminology and classification system for NCSE was proposed at the Fourth London-Innsbruck Colloquium on status epilepticus in Salzburg, which has become known as the *Salzburg criteria.* Clinical signs and symptoms have to be present for at least 10 minutes, and concordant clinical data are essential in establishing the diagnosis of NCSE. EEG findings compatible with NCSE include epileptiform discharges at 2.5 Hz or faster, or at less than 2.5 Hz, if secondary criteria are fulfilled. These include typical spatiotemporal evolution, subtle clinical phenomena associated with the discharges, or EEG and clinical improvement with the administration of an antiseizure drug. Similarly, continuous rhythmic or quasi-rhythmic delta-theta activity faster than 0.5 Hz may also indicate NCSE, if secondary criteria are fulfilled. These criteria have been validated with high diagnostic accuracy and excellent interrater agreement and are deemed suitable for clinical practice.[60–62]

MANAGEMENT APPROACH

Treating Isolated Seizures

Administering antiseizure medications to an ICU patient experiencing one or a few seizures in the absence of structural CNS lesions requires consideration of a provisional cause, estimation of the likelihood of recurrence, and recognition of the utility and limitations of antiseizure medications. For example, the occurrence of seizures during ethanol withdrawal does not necessarily indicate the need for chronic treatment. The patient may need prophylaxis against delirium tremens, but the few seizures themselves seldom require treatment. Patients with convulsions during barbiturate or benzodiazepine withdrawal, in contrast, should receive short-term treatment with a benzodiazepine to prevent status epilepticus. Prolonged or frequent seizures caused by metabolic disturbances can be treated temporarily with benzodiazepines while the abnormality is being corrected. For example, treatment of patients with focal seizures related to nonketotic hyperglycemia should be directed at correction of the hyperglycemia and hypovolemia rather than antiseizure medications.[51] On the other hand, ICU patients with CNS disease who have even one seizure should be given chronic antiseizure medication. Initiating this treatment after the first *unprovoked* seizure may help prevent subsequent epilepsy,[63] although there is considerable difference of opinion regarding this concept.[64] If a critically ill patient's clinical condition would be seriously complicated by a convulsion, antiseizure medication even after the first seizure may be vitally important.

In general, intravenous (IV) formulations are preferred for critically ill patients to avoid variability in drug absorption and metabolism. In the United States, IV formulations of levetiracetam, brivaracetam, lacosamide, phenytoin/fosphenytoin, valproate, and phenobarbital are available.

Levetiracetam is a newer antiseizure medication that is being used increasingly in ICUs for seizure treatment and prophylaxis.[65] The

TABLE 48.3 ACNS Terminology for Rhythmic or Periodic EEG Patterns[57]

Main Term #1 Localization	Main Term #2 Type of Activity	Main Modifiers	Minor Modifiers
Generalized	Periodic discharges	Prevalence	Sudden onset versus gradual onset
Lateralized	Rhythmic delta activity	Duration	
Bilateral Independent	Spike-and-wave or sharp-and-wave	Frequency	Triphasic morphology
Unilateral Independent		Number of phases	Anterior-posterior or posterior-anterior lag
Multifocal		Sharpness	
		Voltage	Polarity
		Stimulus-induced or stimulus-terminated	
		Evolution	
		Plus modifiers:	
		+F – fast activity	
		+R – rhythmic delta	
		+S – sharp waves, spikes, or sharply contoured morphology	

ACNS, American Clinical Neurophysiology Society.
Adapted from Hirsch et al. American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2021 Version (*J Clin Neurophysiol* 2021;38:1–29).

recommended initial dose is 500–1000 mg per day every 12 hours. Monitoring of serum concentrations is not indicated. Levetiracetam is efficacious against a wide variety of seizure types, is generally well tolerated, has minimal drug-drug interactions, and is not metabolized by the liver. Renal failure requires dose adjustments, and supplementary doses should be given after hemodialysis.

Lacosamide was approved as adjunctive therapy for focal-onset seizures in adults in 2008 and is commonly used in ICUs given its efficacy and favorable side-effect profile. It has a novel mechanism of action and has been studied for use in status epilepticus. The initial dose is 100 mg twice a day, to be increased based on response and tolerability to a recommended dose of 150–200 mg twice a day. No target serum concentration has been established. It has no known drug-drug interactions, but dose adjustments for renal and hepatic impairment are recommended. It has not been studied in severe hepatic failure. The most common side effects include PR prolongation and hypotension.

Despite growing evidence of deleterious adverse effects on cognition, fever, and increased risk of poor outcome,[66,67] phenytoin is still frequently selected for prophylaxis or treatment of seizures. It is indicated for all seizure types at a dose of 100 mg two to four times per day, with target serum levels of 10–20 μg/mL. Hypotension and arrhythmias may complicate IV administration. Because of the rare occurrence of third-degree atrioventricular block, an external cardiac pacemaker should be available when patients with known conduction abnormalities receive IV phenytoin. Phenytoin requires propylene glycol as a solvent, is highly protein bound, and free serum levels can vary widely depending on nutritional status. The phenytoin prodrug fosphenytoin is water soluble; local adverse effects are less common with fosphenytoin than with IV administration of phenytoin, although cardiovascular complications are just as frequent.[68,69] Fosphenytoin is dosed by phenytoin-equivalent units, and no dosage adjustments are needed when converting patients from phenytoin to fosphenytoin. It is rapidly converted to phenytoin in vivo, and free phenytoin levels after fosphenytoin administration do not differ markedly from those of phenytoin. If seizures recur despite a serum phenytoin level of 10–20 μg/mL (corresponding to an unbound concentration of about 1–2 μ/mL if the albumin is normal), a second agent is typically required. Both renal and hepatic dysfunction interfere with metabolism and excretion of phenytoin; serum levels should be monitored closely. Adverse reactions to phenytoin and other antiseizure medications have been reviewed elsewhere.[70] Because of its efficacy for generalized seizures, valproate may be the agent of choice for patients with a history of primary generalized epilepsy presenting with seizures. Caution is advised in patients with traumatic brain injury, as a trend toward higher mortality rates was seen in a trial of valproate versus phenytoin for the prevention of posttraumatic seizures.[71] The recommended starting dose is 10–15 mg/kg/day, targeting total serum concentrations of 50–100 μg/mL. Valproate is 80%–90% protein bound and does not require dose adjustment in renal impairment. Lower doses should be used in hepatic impairment, and it is contraindicated in severe hepatic impairment. Side effects of chronic valproate therapy are numerous, including hyperammonemia, thrombocytopenia, hepatotoxicity, and pancreatitis, in addition to many drug-drug interactions.

Phenobarbital remains a useful antiseizure medication for patients who continue to have seizures or are intolerant of other antiseizure medications. Initial dose recommendations are 1–3 mg/kg/day in one to two doses, with a target serum concentration of 20–40 μg/mL. Hepatic and renal dysfunction alter phenobarbital metabolism and require close monitoring of serum levels. Sedation is the major adverse effect; allergy to the drug occurs rarely.

TREATING STATUS EPILEPTICUS

The definition of status epilepticus has evolved over time. Historically, seizures lasting less than 5 minutes are considered brief, seizures lasting 5–30 minutes are prolonged, and seizures lasting more than 30 minutes are considered status epilepticus. However, there is evidence that permanent neuronal injury may occur before this cutoff, and seizures lasting more than 5 minutes often do not stop spontaneously. Therefore treatment algorithms typically start earlier in the course of status epilepticus, with the aim to prevent seizures from reaching 30 minutes.[72] The Neurocritical Care Society Guidelines from 2012 defined status epilepticus as continuous electroclinical or electrographic seizures lasting for 5 minutes or more, or recurrent seizures without recovery to the patient's neurologic baseline between seizures.[1] The 2021 version of the ACNS's Standardized Critical Care EEG Terminology defines electroclinical status epilepticus as an electroclinical seizure lasting continuously for 10 minutes or more, or for a total duration of 20% or more of any 60-minute period of recording. Of note, ongoing seizures with bilateral tonic-clonic motor activity only require 5 minutes of continuous seizure activity to qualify as status epilepticus. The definition of electrographic status epilepticus includes the same time cutoffs of an electrographic seizure lasting 10 minutes or more, or 20% or more of any 60-minute period.[57]

Both GCSE and NCSE have been associated with increased morbidity and mortality and should be approached as neurologic emergencies. Fig. 48.2 shows a management algorithm for status epilepticus, and Table 48.4 summarizes the management approach, including details on drug administration.[1] The treatment approach is generally subdivided into stages. Traditionally, these have been termed first-, second-, third-, and fourth-line treatments, but this may not necessarily reflect the emergent need for control of status epilepticus. The NCS guidelines use the terms *emergent initial therapy, urgent control therapy,* and *treatment of refractory status epilepticus.*[1] The American Epilepsy Society's guidelines for convulsive status epilepticus refer to these stages as *stabilization phase, initial therapy phase, second,* and *third therapy phase.*[72] Immediate considerations to stabilize the patient include airway protection, rapid correction of metabolic abnormalities (in particular, hypoglycemia), obtaining IV access, and ensuring hemodynamic stability. Antiseizure medications should be initiated as soon as the diagnosis of status epilepticus has been established. The goal is termination of clinical and electrographic seizure activity as soon as possible.

Emergent initial therapy or initial therapy phase refers to the administration of first-line agents for termination of seizure activity. There is consensus that benzodiazepines are the agents of choice for initial therapy. A large multicenter clinical trial compared multiple first-line regimens and found that the highest success rate was achieved with lorazepam.[74] Preferred administration routes include IV and intramuscular (IM) injection, but buccal, nasal, or rectal routes are possible. Lorazepam is the agent of choice if IV access is available; midazolam is preferred for the IM route.[75] Diazepam is commonly used for rectal administration. A randomized controlled trial showed that patients treated with lorazepam had lower rates of respiratory or circulatory complications compared with placebo, alleviating concerns of potential respiratory depression with benzodiazepines.[76] The initial dosing for lorazepam is 0.1 mg/kg IV, up to 4 mg per dose, which may be repeated after 5 to 10 minutes. Midazolam is given at a dose of 0.2 mg/kg IM up to a maximum of 10 mg. Some advocate even higher doses for either of these benzodiazepines. In Europe, an IV formulation of clonazepam is available and has been used as emergent initial therapy. From a pharmacokinetic perspective, benzodiazepines are rapidly redistributed, resulting in a short duration of action. Hence,

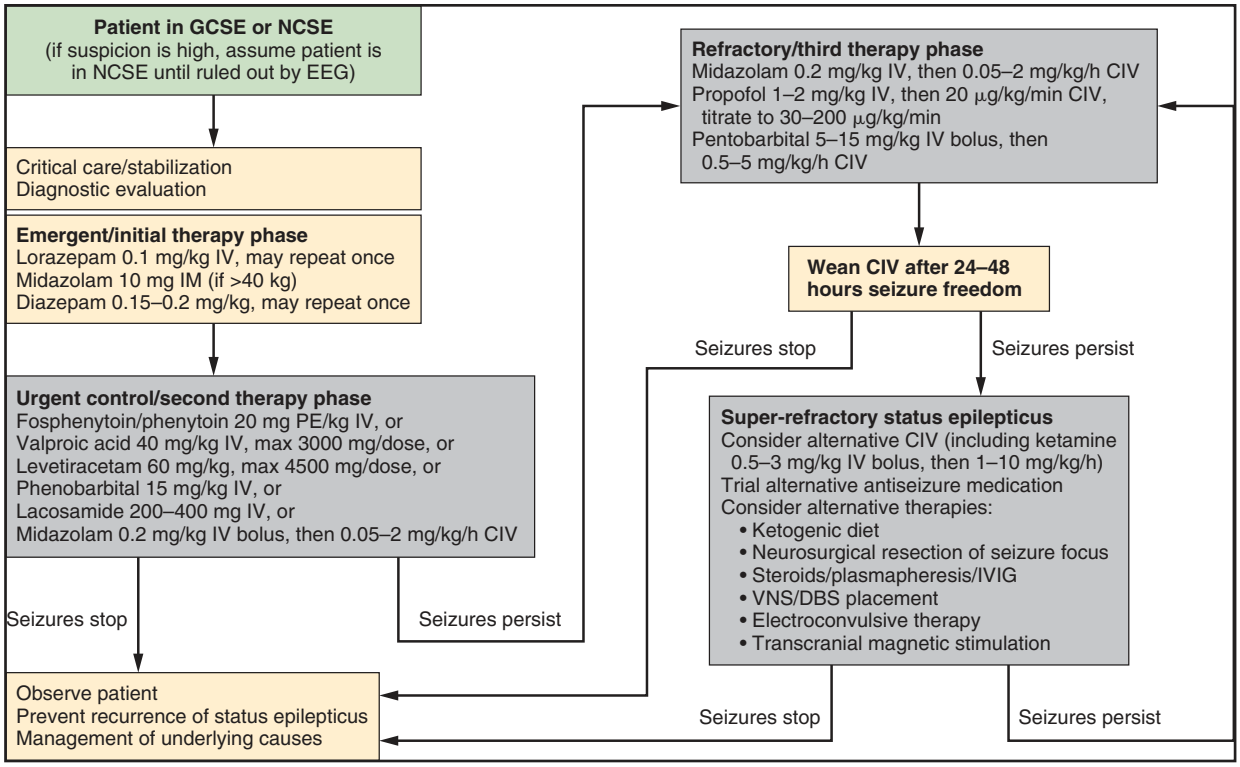


Fig. 48.2 **Suggested management algorithm for status epilepticus.** *CIV,* Continuous intravenous infusion; *DBS,* deep brain stimulation; *EEG,* electroencephalogram; *GCSE,* generalized convulsive status epilepticus, *IM,* intramuscular; *IV,* intravenous; *IVIG,* intravenous immune globulin; *NCSE,* nonconvulsive status epilepticus; *VNS,* vagus nerve stimulation.[1,72,73]

TABLE 48.4 Treatment Approach to Status Epilepticus[1,72]

Appropriate critical care treatment should be provided as soon as possible and simultaneously with emergent initial therapy for seizures. Treatment should be escalated quickly until seizures are controlled.

1a. Critical care treatment (dictated by clinical circumstances):
- a. Intubation for airway protection and mechanical ventilation
- b. Vital sign monitoring
- c. Peripheral IV access
- d. Treatment of hypotension with vasopressors
- e. Finger stick blood glucose
- f. Nutrient resuscitation (thiamine before dextrose)
- g. Hypertension may be related to ongoing seizure activity, and termination of status epilepticus often substantially corrects it. Additionally, many agents used to terminate status epilepticus can produce hypotension.

1b. Emergent initial therapy with benzodiazepines:
- a. Lorazepam 0.1 mg/kg IV, up to 4 mg per dose, may repeat once after 5–10 min
- b. Midazolam 10 mg IM if body weight >40 kg, 5 mg if body weight 13–40 kg
- c. Diazepam 0.15–0.2 mg/kg, up to 10 mg per dose, may repeat once after 5 min

2. Urgent control therapy—antiseizure medications available in IV formulations
- a. Fosphenytoin/phenytoin 20 mg PE/kg IV, up to 1500 mg PE/dose
- b. Valproic acid 40 mg/kg IV, up to 3000 mg/dose
- c. Levetiracetam 60 mg/kg, up to 4500 mg/dose
- d. Phenobarbital 15 mg/kg IV
- e. Lacosamide 200–400 mg IV
- f. Midazolam 0.2 mg/kg IV bolus, followed by 0.05–2 mg/kg/h continuous infusion

3. Refractory therapy—continuous infusion of antiseizure medications, titrated to either seizure cessation, suppression-burst, or complete suppression on cEEG
- a. Midazolam 0.2 mg/kg IV bolus, followed by 0.05–2 mg/kg/h continuous infusion
- b. Propofol 1–2 mg/kg IV bolus, followed by 20 μg/kg/min continuous infusion, titrate up to 30–200 μg/kg/min
- c. Pentobarbital 5–15 mg/kg IV bolus, may repeat 5–10 mg/kg IV bolus, followed by 0.5–5 mg/kg/h continuous infusion

4. Treat complications

Complications of status epilepticus are numerous and can involve multiple organ systems. In particular, convulsive status epilepticus is associated with cardiac complications such as hypertension and tachycardia, as well as rhabdomyolysis and hyperthermia. Respiratory complications, including respiratory failure, hypoxia, and neurogenic pulmonary edema, may be seen. Status epilepticus is associated with neuronal damage and cerebral edema with increased intracranial pressure, which may require intracranial pressure monitoring and aggressive treatment with hypertonic agents.

cEEG, Continuous electroencephalogram; *IM,* intramuscular; *IV,* intravenous; *PE,* phenytoin-equivalent units.

emergent initial therapy should be seamlessly followed by urgent control therapy (or second therapy phase) that targets rapid attainment of therapeutic levels of conventional antiseizure medications. If benzodiazepines fail to control seizures, the goal of urgent control therapy is seizure termination. If seizures are controlled by benzodiazepines, urgent control therapy targets prevention of seizure recurrence.

As with the treatment of isolated seizures in the ICU, the IV formulation is preferred, especially because therapeutic drug levels can be achieved significantly faster. Phenytoin/fosphenytoin, valproate, levetiracetam, phenobarbital, and continuous infusion of midazolam have all been studied for urgent treatment, and there is no evidence-based preferred agent of choice. A pivotal trial of three antiseizure medications for benzodiazepine-refractory convulsive status epilepticus found that levetiracetam, fosphenytoin, and valproate were each effective and led to seizure cessation and improved alertness in about half of patients with a similar rate of adverse events.[77] Additionally, lacosamide has emerged as an option to treat status epilepticus but has mostly been investigated in refractory status epilepticus.[78,79] Dosing of these drugs in status epilepticus is outlined in Table 48.4.

Refractory status epilepticus refers to status epilepticus that does not respond to a standard treatment regimen. There is controversy regarding this definition, but most experts agree that treatment has failed if seizures persist or recur after adequate doses of an initial benzodiazepine followed by one conventional antiseizure medication.[1] cEEG monitoring is typically required to exclude ongoing electrographic seizure activity. It may be reasonable to attempt management of recurrent seizures with additional intermittent boluses of an alternative antiseizure medication, provided the patient is clinically stable and has not required intubation for airway protection. Once it has been determined that intermittent bolus therapy has failed, treatment should be quickly escalated to a continuous infusion to induce a therapeutic coma. Patients who require any of these treatments will typically require intubation, mechanical ventilation, and close cardiovascular monitoring. The most commonly used drugs for this purpose are midazolam, propofol, pentobarbital, and thiopental. Dosing recommendations are listed in Table 48.4. There is insufficient evidence to recommend any agents over another. Midazolam is the preferred agent at our institution because of its high efficacy in adults and children,[80,81] its water solubility, and the lower incidence of cardiovascular adverse effects compared with pentobarbital or propofol. However, terminal half-lives of three to eight times normal have been reported with extended administration.[82] Propofol is reported to be effective in refractory status epilepticus, but comparisons with other agents have shown mixed results.[83,84] Especially in younger patients, the risk of propofol-related infusion syndrome needs to be considered, particularly if high doses are required for a prolonged period to control seizures. Severe hypotension is the most frequent side effect of pentobarbital therapy and is associated with increased mortality.[85] Increases in nosocomial respiratory tract infection have been reported in patients treated with pentobarbital infusion.[86]

The optimal duration of therapeutic coma remains to be determined. Customarily, 24–48 hours of seizure control has been used,[1] but shorter durations with a deeper therapeutic coma have been suggested.[87] Once clinical or nonconvulsive seizures have been controlled for a certain period, a gradual withdrawal of the continuous infusion should be initiated. If seizures recur upon withdrawal, a diagnosis of super-refractory status epilepticus is made and the continuous infusion should be resumed until seizures are controlled. The addition of other antiseizure medications or other therapies such as hypothermia, immunomodulation, or neurosurgical resection of the seizure focus may be considered at that point. Ketamine can be efficacious for super-refractory status epilepticus and is associated with lower vasopressor requirement. There is literature noting a concern that ketamine increases ICP, leading many practitioners to avoid this drug in patients with intracranial lesions at risk for elevated ICP. However, there is evidence that ketamine does not affect ICP in patients with super-refractory status epilepticus,[88] and it may be considered in patients who fail to respond to other refractory status epilepticus treatment options.[1]

KEY POINTS

- Seizures and status epilepticus are common in ICU patients and are associated with high morbidity and mortality.
- Observation is crucial when a patient has a single seizure. Postictal language, motor, sensory, or reflex abnormalities after a generalized seizure indicate focal pathology.
- Seizures persisting longer than 5 minutes or two or more discrete seizures without neurologic recovery in between should be treated as status epilepticus. Patients who do not regain consciousness within 20 minutes after clinical seizure cessation should be considered to have entered NCSE, and cEEG monitoring is essential in directing the course of treatment.
- The ICU patient with CNS disease who has even one seizure should be given chronic antiseizure medication. This therapy should be reviewed before discharge.
- Emergent initial therapy for treatment of status epilepticus is benzodiazepines (lorazepam, midazolam, diazepam) followed by urgent control therapy with IV formulations of levetiracetam, valproate, phenytoin/fosphenytoin, phenobarbital, or lacosamide. Status epilepticus refractory to an initial benzodiazepine and an appropriately chosen and dosed conventional antiseizure medication should be treated with continuous infusion of midazolam, barbiturates, or propofol.

References for this chapter can be found at expertconsult.com.

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Neuromuscular Disorders in the Critically Ill

Thomas P. Bleck

Abnormal neuromuscular function may precipitate a patient's admission to an intensive care unit (ICU) or it may develop because of another critical illness and its treatment. This chapter focuses primarily on respiratory failure caused by neuromuscular disease but also addresses autonomic dysfunction that occurs in this setting. A brief review of the motor unit and its physiology is provided to facilitate understanding of the concepts involved, along with consideration of the specific muscles critical to ventilation.

THE MOTOR UNIT AND ITS PHYSIOLOGY

Central nervous system (CNS) activity for motor output is ultimately conducted by the lower motor neurons, also known as *alpha motor neurons*. A motor unit is composed of a lower motor neuron and its distal ramifications, its neuromuscular junctions, and the muscle fibers it innervates. The cell bodies of the lower motor neurons are located in the brainstem for cranial musculature and the anterior horn of the spinal cord for somatic muscles. Motor axons project through the subarachnoid space and penetrate the dura mater as nerve roots. They may join with other motor axons and with sensory and autonomic fibers in a plexus and then travel via the peripheral nerves to the muscles they innervate. Alpha motor neurons are myelinated, a feature that accelerates nerve impulse propagation. The multiple terminal ramifications of the motor neuron synapse on individual muscle fibers.

The motor axon communicates with muscle via a specialized area termed the *neuromuscular junction*. On the presynaptic side of the neuromuscular junction, the neurotransmitter acetylcholine is synthesized, packaged in vesicles, and stored for release. Depolarization of the axon opens the presynaptic voltage-gated calcium channels, which activate the molecular machinery responsible for drawing the vesicles to the presynaptic membrane. The vesicles then fuse with the membrane and release acetylcholine into the synaptic cleft. Acetylcholine molecules bind to receptors on the postsynaptic membrane and cause an influx of sodium, which in turn increases the muscle endplate potential. When the endplate potential exceeds the threshold level, the muscle membrane becomes depolarized. This depolarization releases calcium ions from the sarcoplasmic reticulum, and muscle contraction occurs through a process known as excitation-contraction coupling. After activating the acetylcholine receptor complex, the acetylcholine molecule is degraded by cholinesterase, and the presynaptic neuron then recycles the choline released by this reaction.

MUSCLES OF RESPIRATION

Three muscle groups may be defined based on their importance for respiration (Fig. 49.1)[1]:

1. *Upper airway muscles:* palatal, pharyngeal, laryngeal, and lingual
2. *Inspiratory muscles:* sternomastoid, diaphragm, scalenes, and parasternal intercostals
3. *Expiratory muscles:* internal intercostal muscles (except for parasternals) and abdominal muscles

The upper airway muscles receive their innervation from the lower cranial nerves. Sternomastoid innervation arrives predominantly from cranial nerve XI, with a small contribution from C2. The phrenic nerve originates from cell bodies located between C3 and C5, with a maximum contribution from C4, and innervates the diaphragm. Innervation to the scalenes arises from C4 to C8, whereas that of the parasternal intercostals is from T1 to T7. The other intercostal muscles receive innervation from T1 to T12, and the abdominal musculature receives it from T7 to L1.

Clinical Presentation of Neuromuscular Respiratory Failure

Patients experiencing respiratory dysfunction as a result of neuromuscular disease typically present with a combination of upper airway dysfunction and diminished tidal volume (V_T). Upper airway muscle weakness typically presents with difficulty swallowing liquids, including respiratory secretions, along with a hoarse or nasal voice. In addition to the risk of aspiration, these patients have difficulty with negative-pressure ventilation because the weakened muscles cannot keep the airway open as the pressure falls.

Loss of V_T occurs secondary to weakness of the inspiratory muscles. In addition to diaphragmatic weakness, which may present with paradoxical abdominal movement, parasternal intercostal muscle weakness also causes diminished V_T by preventing the chest wall from expanding against negative intrapleural pressure. Thus lower cervical spinal cord injuries may induce respiratory failure despite preserved phrenic nerve function. The patient often attempts to maintain V_T by contraction of accessory muscles such as the sternomastoids. As parasternal intercostal muscles develop spasticity over weeks, respiratory function of this type typically improves and may permit weaning from mechanical ventilatory support, at least during the daytime.

Patients with progressive generalized weakness (e.g., Guillain-Barré syndrome) commonly begin to lose V_T before developing upper airway weakness. To maintain minute ventilation and carbon dioxide excretion, a patient's respiratory rate increases. Respiratory rate is thus one of the most important clinical parameters to monitor. As the vital capacity falls from the norm of about 65 mL/kg to 30 mL/kg, a patient's cough weakens, and clearing secretions becomes difficult. A further decrease in the vital capacity to 20 mL/kg to 25 mL/kg results in an impaired ability to sigh, resulting in progressive atelectasis. At this point, hypoxemia may be present because of ventilation-perfusion mismatching, and an increasing percentage of V_T is used to ventilate dead space. Respiratory failure is imminent, and ICU admission is recommended for all patients with a vital capacity $<$20 mL/kg. The precise point at which mechanical ventilation is necessary varies with the patient, the underlying condition, and especially the likelihood of a rapid response to treatment.

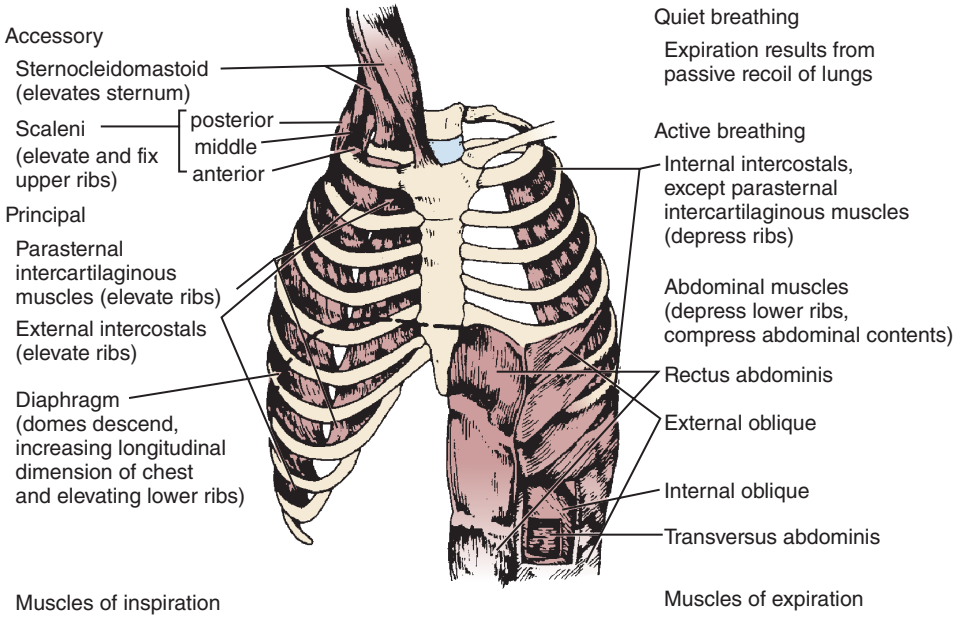

Fig. 49.1 Major respiratory muscles. Inspiratory muscles are indicated on the left, and expiratory muscles are indicated on the right. (From Garrity ER. Respiratory failure due to disorders of the chest wall and respiratory muscles. In: KF McDonnell, PJ Fahey, MS Segal, eds. *Respiratory Intensive Care.* Boston, MA: Little, Brown; 1987:313.)

Regardless of the vital capacity, indications for intubation and mechanical ventilation include evidence of fatigue, hypoxemia despite supplemental oxygen administration, difficulty with secretions, and a rising arterial partial pressure of carbon dioxide ($PaCO_2$). In the absence of hypercapnia, occasional patients (e.g., those with myasthenia gravis) can be managed with very close observation in an ICU with less invasive techniques (e.g., bilevel positive airway pressure [BiPAP]).[2]

In addition to vital capacity, trended measurements of the maximum inspiratory pressure (PImax, also called *negative inspiratory force* [NIF]), are useful indicators of ventilatory capacity. The inability to maintain a PImax greater than 20–25 cm H_2O usually indicates a need for mechanical ventilation. Although the maximum expiratory pressure (PEmax) is a more sensitive indicator of weakness, it has not proven to be as useful as an indicator of the need for mechanical ventilation.

Because a patient with neuromuscular respiratory failure has an intact ventilatory drive,[3] the fall in V_T is initially matched by an increase in respiratory rate, keeping the $PaCO_2$ normal or low until the vital capacity becomes dangerously reduced. Many patients initially maintain their $PaCO_2$ in the range of 35 mm Hg because of either (1) a subjective sense of dyspnea at low V_T or (2) hypoxia from atelectasis and increasing dead space. When the $PaCO_2$ begins to rise in these circumstances, abrupt respiratory failure may be imminent, as CO_2 displaces more oxygen from the alveolar gas. The modest degree of hypoxia in most of these patients therefore worsens when the $PaCO_2$ begins to rise. Moreover, aspiration pneumonia and pulmonary embolism are also frequent causes of hypoxemia in these patients. To determine the relative contributions of these conditions to a patient's hypoxemia, one can use a simplified version of the alveolar gas equation:

$$P_AO_2 = PiO_2 - (PaCO_2/R)$$

where P_AO_2 is the alveolar partial pressure of oxygen, PiO_2 is the partial pressure of the inspired oxygen (in room air, 150 mm Hg), and R is the respiratory quotient (on most diets, about 0.8). This allows for the estimation of the alveolar-arterial oxygen difference ($P_AO_2 - PaO_2$). Under ideal circumstances in young people breathing room air, this value is about 10 mm Hg, but it rises to about 100 mm Hg when the fraction of inspired oxygen (FiO_2) is 1.0. The alveolar air equation allows one to assess the contribution of hypercarbia to the decrease in arterial partial pressure of oxygen (PaO_2); it determines whether there is a cause of significant hypoxemia in addition to the displacement of oxygen by carbon dioxide.

Physicians must observe patients for rapid, shallow breathing[9]; recruitment of accessory muscles; and paradoxical movement of the abdomen during the respiratory cycle. Direct observation is particularly important, as patients may have orbicularis oris weakness, causing an artificially low vital capacity and NIF measurements because they cannot form a tight seal around the spirometer mouthpiece. In addition to physical examination findings, fluoroscopy of the diaphragm is occasionally valuable for the diagnosis of diaphragmatic dysfunction.

Autonomic dysfunction commonly accompanies some of the neuromuscular disorders requiring critical care, such as Guillain-Barré syndrome, botulism, and porphyria (Table 49.1). In Guillain-Barré syndrome (vide infra), dysautonomia is common and may arise in parallel with weakness or may follow the onset of the motor disorder after one or more weeks.

NEUROMUSCULAR DISORDERS

Many chronic neuromuscular disorders and other CNS conditions affecting the suprasegmental innervation and control of respiratory muscles eventually compromise ventilation. In this chapter, we emphasize the more common acute and subacute neuromuscular disorders that precipitate or prolong critical illness caused by ventilatory failure and autonomic dysfunction. A complete listing of neuromuscular diseases appears in Table 49.1; reviews of this subject[6] and Table 49.1 detail the rarer disorders. Some of the diseases listed (e.g., Lambert-Eaton myasthenic syndrome) rarely cause respiratory failure in isolation but may be contributing causes in the presence of other conditions,[7] such as a neuromuscular junction blockade intended only for the duration of a surgical procedure.

TABLE 49.1 Neuromuscular Causes of Acute Respiratory Failure

Location	Disorder	Associated Autonomic Dysfunction?
Spinal cord	Tetanus[4]	Frequent
Anterior horn cell	Amyotrophic lateral sclerosis	No
	Poliomyelitis	No
	Rabies	Frequent
	West Nile virus flaccid paralysis	No
Peripheral nerve	Guillain-Barré syndrome	Frequent
	Critical illness polyneuropathy	No
	Diphtheria	No, but cardiomyopathy and arrhythmias may occur
	Porphyria	Occasional
	Ciguatoxin (ciguatera poisoning)	Occasional
	Saxitoxin (paralytic shellfish poisoning)	No
	Tetrodotoxin (pufferfish poisoning)	No
	Thallium intoxication	No
	Arsenic intoxication	No
	Lead intoxication	No
	Buckthorn neuropathy	No
Neuromuscular junction	Myasthenia gravis	No
	Botulism[5]	Frequent
	Lambert-Eaton myasthenic syndrome	Yes, frequent dry mouth and postural hypotension
	Hypermagnesemia	No
	Organophosphate poisoning	No
	Tick paralysis	No
	Snake bite	No
Muscle	Polymyositis/dermatomyositis	No
	Acute quadriplegic myopathy	No
	Eosinophilia-myalgia syndrome	No
	Muscular dystrophies	No, but cardiac rhythm disturbances may occur
	Carnitine palmitoyl transferase deficiency	No
	Nemaline myopathy	No
	Acid maltase deficiency	No
	Mitochondrial myopathy	No
	Acute hypokalemic paralysis	No
	Stonefish myotoxin poisoning	No
	Rhabdomyolysis	No
	Hypophosphatemia	No

Neuromuscular Diseases Precipitating Critical Illness

Guillain-Barré Syndrome

Guillain-Barré syndrome, or acute inflammatory demyelinating polyradiculoneuropathy, is typically a motor greater than peripheral sensory neuropathy with subacute onset, monophasic course, and nadir within 4 weeks. Although the precise etiology is unknown, it is immune mediated and related to antibodies directed against peripheral nerve components. About 1.7 cases occur per 100,000 population annually. Most patients suffer from a demyelinating neuropathy, but in about 5% of cases, the condition is a primary axonopathy. Numerous antecedents have been implicated, the most common of which are listed in Box 49.1. The association with antecedent infections suggests that certain agents may provoke the production of antibodies that cross-react with peripheral nerve gangliosides. Ganglioside antibodies have been found in Guillain-Barré syndrome after *Campylobacter jejuni* infections, such as GM_1 antibodies in axonal forms and GQ_{1b} antibodies in the Miller-Fisher variant.[8] Immune checkpoint inhibitors have rarely been associated with the development of Guillain-Barré syndrome, although no autoantibody association has been established to date.[9] The association of vaccine administration with the syndrome remains uncertain, with the possible exception of the 1976 influenza vaccine. Patients who have recovered from Guillain-Barré syndrome should not be denied the protective effect of vaccines.[10]

The initial findings of patients with Guillain-Barré syndrome are a subacute and progressive weakness, usually most marked in the legs, associated with sensory complaints but without objective signs of sensory dysfunction. Deep tendon reflexes are often reduced or absent at presentation, though this finding may take several days to develop. The

Box 49.1 Major Antecedents of Guillain-Barré Syndrome

Frequent
Upper respiratory tract infections
Campylobacter jejuni enteritis
Cytomegalovirus (CMV) infection
Epstein-Barr virus (EBV) infection
Hepatitis A infection
Hepatitis B infection
Hepatitis C infection
Human immunodeficiency virus (HIV) infection

Infrequent
Mycoplasma pneumoniae infection
Haemophilus influenzae infection
Leptospira icterohaemorrhagiae infection
Salmonellosis
Rabies vaccine
Tetanus toxoid
Bacille Calmette-Guérin immunization
Sarcoidosis
Systemic lupus erythematosus
Lymphoma
Trauma
Surgery

Questionable
Hepatitis B vaccine
Influenza vaccine
Hyperthermia
Epidural anesthesia

cerebrospinal fluid (CSF) typically reveals an albumin-cytologic dissociation (elevated protein concentration without pleocytosis); however, this may not develop until the second week of illness. The major reason to examine the CSF is to preclude other diagnoses. Although mild CSF lymphocytic pleocytosis (10–20 cells/mm^3) may suggest the possibility of associated human immunodeficiency virus (HIV) infection, in most patients, the nucleated cell count is <10 cells/mm^3.[11] Although they may be normal initially, results of electrodiagnostic studies (motor and sensory nerve conduction studies and needle electromyography) often reflect segmental nerve demyelination with multifocal conduction blocks, temporally dispersed compound muscle action potentials, slowed conduction velocity, and prolonged or absent F waves. Diagnostic considerations for patients with suspected Guillain-Barré syndrome are primarily those listed in the Peripheral Nerve section of Table 49.1.

The components of treatment for patients with Guillain-Barré syndrome are as follows:

- Management of ventilatory failure
- Management of autonomic dysfunction
- Meticulous nursing care
- Psychological support
- Physical and occupational therapy
- Prevention of deep venous thrombosis
- Nutritional support
- Early planning for rehabilitation
- Immunotherapy for the underlying autoimmune condition

Patients with Guillain-Barré syndrome with evolving respiratory failure should be intubated when the vital capacity falls to about 15 mL/kg or when difficulty with secretions begins because the response to treatment is slow. If a patient has been immobile for several days before intubation and a neuromuscular junction blockade is needed, a nondepolarizing agent should be used to avoid transient hyperkalemia. Oral intubation is preferable to the nasal route because the tracheal tube is frequently required for a week or longer, raising the risk of sinusitis.

Many patients are too weak to trigger the ventilator, and in such cases, the assist/control or intermittent mandatory ventilation mode is initiated. Weaning patients with Guillain-Barré syndrome from mechanical ventilation must wait for an adequate improvement in strength reflected by a vital capacity of greater than 15 mL/kg and NIF greater than 25 cm H_2O. However, a formula using a combination of ventilatory and gas exchange variables may allow for a more accurate determination of a patient's ability to be weaned. Although pressure support ventilation is often used for weaning, evidence of its superiority over intermittent mandatory ventilation or synchronized intermittent mandatory ventilation modes is anecdotal. Most patients require mechanical ventilation for more than 4 weeks; however, as many as one-fifth need at least 2 months of support before they can breathe without assistance. Autonomic dysfunction typically presents as a hypersympathetic state and is often heralded by unexplained sinus tachycardia. The blood pressure may fluctuate wildly. Patients can also experience bradycardic episodes, which may require temporary pacing. Autonomic surges during tracheal suctioning or because of a distended viscus may be very dramatic and should be minimized. Autonomic failure and pulmonary embolism are now the major causes of mortality in Guillain-Barré syndrome.

Nursing care for patients with Guillain-Barré syndrome is similar to that for other paralyzed and mechanically ventilated patients, but special care must be taken to remember that patients are completely lucid. In addition to explaining any procedures carefully, arranging for distractions during the daytime (e.g., television, movies, conversation, or visitors) and adequate sleep at night are very important. For the most severely affected patients, sedation should be considered. In concert with physical and occupational therapists, passive exercise should frequently be performed throughout the day.

Deep venous thrombosis is a significant danger. An episodic arterial desaturation is a common event, presumably owing to transient mucus plugging; therefore submassive pulmonary emboli may be overlooked. Adjusted-dose heparin (to slightly prolong the partial thromboplastin time) should be given, and sequential compression devices should be used on the legs. Moreover, therapeutic anticoagulation may be considered. The risk of fatal pulmonary embolism extends through the initial period of improvement until the patients are ambulatory.

Nutritional support should begin as soon as a patient is admitted, with appropriate concern for the risk of aspiration. Most mechanically ventilated patients with Guillain-Barré syndrome can be fed via soft, small-caliber feeding tubes; autonomic dysfunction affecting the gut occasionally requires total parenteral nutrition.

Immunotherapy for Guillain-Barré syndrome includes the removal of autoantibodies with plasma exchange or immune modulation with a high dose of intravenous immunoglobulin (IVIg). The efficacy of the plasma exchange has been evaluated in a Cochrane systematic review of six class II trials comparing plasma exchange alone with supportive care.[12] Most of the trials employed up to five plasma exchanges of 50 mL/kg over 2 weeks. In a large North American trial, the time needed to improve one clinical grade (i.e., being weaned from the ventilator or being able to walk) was reduced by 50% in the plasma exchange group compared with the control group. There was no significant benefit when the plasma exchange commenced later than 2 weeks after the onset of symptoms. A meta-analysis revealed more rapid recovery in

ventilated patients treated with a plasma exchange within 4 weeks of onset. The optimal number of plasma exchanges has been assessed in patients with mild (unable to run), moderate (unable to stand without assistance), and severe (requiring mechanical ventilation) Guillain-Barré syndrome by the French Cooperative Group.[13] On the basis of this trial, two exchanges are better than none in mild Guillain-Barré syndrome, four are better than two in moderate Guillain-Barré syndrome, and six are no better than four in severe Guillain-Barré syndrome. Albumin is the preferred replacement solution.[14] Treatment with IVIg for Guillain-Barré syndrome has also been examined in a Cochrane systematic review. Five randomized controlled trials in adults showed that IVIg (0.4–0.5 g/kg over 4–5 days) is as effective as plasma exchange in Guillain-Barré syndrome patients with impaired walking.[15] IVIg is also more likely to be completed than plasma exchange, although the adverse events were not different. A large international multicenter randomized trial compared plasma exchange (50 mL/kg × 5 exchanges over 8–13 days), IVIg (0.4 g/kg × 5 days), and plasma exchange followed by IVIg.[16] No significant outcome differences between these therapies were found with respect to functional improvement at 4 or 48 weeks. The lack of benefit of a second course of IVIg in a group of patients expected to have a poor prognosis was recently demonstrated in a double-blind, randomized trial.[17] In this trial, serious adverse events were significantly more common in the group receiving the second course.

Evidence-based guidelines for Guillain-Barré syndrome immunotherapy have been published by the Quality Standards Subcommittee of the American Academy of Neurology.[18] Plasma exchange is recommended for adult patients who cannot walk within 4 weeks of symptom onset. IVIg is recommended in these patients within 2 or possibly 4 weeks of symptom onset. Both treatments are deemed equivalent in efficacy, and combining treatment with plasma exchange and IVIg confers no additional benefit. In light of their therapeutic equivalence, the decision whether to employ plasma exchange or IVIg in treating acute Guillain-Barré syndrome may be determined by resource availability and by avoiding potential side effects related to a patient's medical comorbidities. Patients with heart disease, renal insufficiency or failure, hyperviscosity, or IgA deficiency may be more susceptible to complications of treatment with IVIg, whereas plasma exchange may be complicated in patients with labile blood pressure, septicemia, and significant venous access problems.

Despite the autoimmune pathophysiology of Guillain-Barré syndrome and the efficacy of corticosteroids in more chronic forms of inflammatory neuropathy, corticosteroids have not shown effectiveness in Guillain-Barré syndrome and are therefore not recommended.[18] A large multicenter trial failed to demonstrate efficacy of high-dose intravenous methylprednisolone, and another large multicenter trial reported no added clinical benefit with the combined treatment of IVIg and methylprednisolone.[19]

West Nile Virus Acute Flaccid Paralysis Syndrome

The large outbreak of West Nile virus encephalitis in the summer of 1999 in New York City marked the emergence of a relatively new cause of neuromuscular weakness with the potential for neuromuscular respiratory compromise. West Nile virus is a flavivirus transmitted by birds and mosquitoes. Humans may acquire West Nile virus from the bite of an infected *Culex* species mosquito, and a corresponding peak in human disease occurs in the late summer and fall. West Nile virus may also be transmitted to humans by organ transplantation,[20] blood and blood product transfusion,[21] transplacental exposure,[22] breastfeeding,[23] and percutaneous laboratory injuries.[24] About 20% of humans experience a mild flulike illness lasting 3–6 days, and about 1 in 150 develops CNS disease, which usually presents as meningoencephalitis.[25]

In the initial North American outbreak of West Nile virus, about 10% of infected patients experienced flaccid weakness with clinical features resembling Guillain-Barré syndrome.[26] Although patients with West Nile virus infection exhibit a spectrum of clinical weakness,[27,28] the most prominent and distinctive syndrome documented in several subsequent reports is an acute "poliomyelitis-like" or acute flaccid paralysis syndrome with pathology localized to the ventral horns of the spinal cord and/or ventral roots.[29–35] These relatively younger patients developed acute, asymmetric, flaccid weakness in the absence of sensory abnormalities, diffuse areflexia, or bowel/bladder dysfunction.[36] Some of the patients experienced concurrent meningoencephalitis, and a few required mechanical ventilation.[28,30]

Electrodiagnostic studies in patients with West Nile virus acute flaccid paralysis syndrome exhibit normal sensory potentials, and the absence of findings suggests segmental demyelination (e.g., motor conduction block, reduced conduction velocities, prolonged distal, and F-wave latencies), low-amplitude compound muscle action potentials in the affected regions, and marked denervation changes in the affected limbs and in corresponding paraspinal muscles on needle electromyography. Corresponding magnetic resonance imaging (MRI) findings are sometimes observed and include an abnormal signal in the spinal cord on T2-weighted images[34,35] and abnormal enhancement of the nerve roots and cauda equina.[32,33] CSF analysis usually reveals mild pleocytosis with lymphocytic predominance and a mild to moderate protein elevation and normal glucose.[37] Prognosis for the recovery of strength in these patients appears to be poor.[38]

West Nile virus infection may be diagnosed by demonstrating West Nile virus RNA in the serum, CSF, or other tissues by reverse-transcriptase polymerase chain reaction, although this test is not highly sensitive.[39] More commonly, a diagnosis is made by the demonstration of West Nile virus immunoglobulin M (IgM) in CSF or serum by antibody-capture enzyme-linked immunosorbent assay (ELISA). When serum West Nile virus IgM is present, diagnosis is confirmed by a fourfold increase in West Nile virus immunoglobulin G (IgG) titers between acute and convalescent sera obtained 4 weeks apart. Positive IgM and IgG antibody titers should be confirmed by a plaque-reduction viral neutralization assay to exclude false-positive results related to other flaviviral infections, such as St. Louis encephalitis. Serology may not become positive until 8 days after symptom onset.[25]

Particularly in the absence of a more typical encephalitic presentation of West Nile virus infection, a high index of clinical suspicion is needed to make a diagnosis and to distinguish such cases from Guillain-Barré syndrome in patients presenting with acute weakness in the late summer or fall. Electrodiagnostic studies may help localize the pathology to the ventral horns of the spinal cord or ventral roots in West Nile virus cases and to exclude findings of segmental demyelination suggesting Guillain-Barré syndrome. CSF evaluation can help discriminate between the albumin-cytologic dissociation of Guillain-Barré syndrome and the lymphocytic pleocytosis in a West Nile virus infection.

There is no specific treatment for West Nile virus. A multicenter study to evaluate the efficacy of Israeli IVIg (containing high levels of West Nile virus antibodies) in patients with West Nile virus meningoencephalitis or weakness was terminated early because of lower-than-expected enrollment, expiration of the study product, and insufficient quantities of control IVIg.[40] Two candidate vaccines against West Nile virus are currently being evaluated.[41,42]

Myasthenia Gravis

Myasthenia gravis is a consequence of the autoimmune attack on the acetylcholine receptor complex at the postsynaptic membrane of the neuromuscular junction. This process results in clinical weakness with

a fluctuating pattern that is most marked after prolonged muscle exertion. Myasthenia gravis occurs at a higher rate in early adulthood in women, but in later life, the incidence rates for men and women become nearly equal. The reported prevalence is 14.2 cases per 100,000 population. Myasthenia gravis typically involves ocular muscle weakness producing ptosis and diplopia, in addition to bulbar muscle weakness resulting in dysphagia and dysarthria. A clinical diagnosis of myasthenia gravis may be supported by electrophysiologic studies, including repetitive nerve stimulation studies and single-fiber electromyography, and by acetylcholine receptor and muscle-specific receptor tyrosine kinase (MuSK) antibody testing.[43]

Approximately 20% of patients with myasthenia gravis develop myasthenic crisis with respiratory failure requiring mechanical ventilation. The most common precipitating factors include bronchopulmonary infections (29%) and aspiration (10%).[44] Other precipitating factors include sepsis, surgical procedures, rapid tapering of immune modulation, beginning treatment with corticosteroids, pregnancy, and exposure to drugs that may increase myasthenic weakness (Box 49.2).[44] Patients with myasthenia gravis are exceptionally sensitive to nondepolarizing neuromuscular blocking agents but are resistant to depolarizing agents. Thymomas are associated with more fulminant disease and identified in about one-third of patients in a myasthenic crisis.

Upper airway muscle weakness is a common mechanism leading to the myasthenic crisis.[45] Oropharyngeal and laryngeal muscle weakness may result in upper airway collapse with obstruction. Dysphagia further contributes to the obstruction and aspiration of secretions. Because a direct assessment of oropharyngeal muscle strength is impractical, a focused history and examination to assess surrogate muscles in the head and neck region are important. Findings of bulbar myasthenia associated with upper airway compromise include flaccid dysarthria with hypernasal, staccato, or hoarse speech; dysphagia (sometimes associated with nasal regurgitation); and chewing fatigue. Patients may exhibit facial weakness with difficulty holding air within the cheeks. Jaw closure is often weak and cannot be maintained against resistance. Patients with myasthenic tongue weakness may be unable to protrude the tongue into either cheek. Although neck flexors are often weaker, a dropped head syndrome because of neck extensor weakness may occur. Vocal cord abductor paralysis may produce laryngeal obstruction with associated stridor.[46]

Patients with features of impending myasthenic crisis, including severe bulbar weakness, marginal vital capacity (less than 20–25 mL/kg), weak cough with difficulty clearing secretions from the airway, or paradoxical breathing while supine should be admitted to an ICU and made nothing by mouth (NPO) to prevent aspiration. Serial vital capacity and NIF measurements may be used to monitor ventilatory function in an impending myasthenic crisis. However, with significant bulbar weakness, these measurements are often inaccurate if the patient has difficulty sealing the lips around the spirometer mouthpiece or is unable to seal the nasopharynx. Vital capacity measurements may not reliably predict respiratory failure in myasthenia gravis, owing to the fluctuating nature of the myasthenic weakness.[47] The criteria for intubation and mechanical ventilation are similar to those for Guillain-Barré syndrome. If the upper airway is competent and there is no difficulty handling secretions or gross hypercapnia ($PaCO_2$ >50 mm Hg), intermittent nasal BiPAP may be a useful temporizing measure.[2] Most patients who develop hypercapnia in myasthenic crisis require intubation, as do those who are becoming fatigued.

Plasma exchange is an effective short-term immunomodulating treatment for myasthenic crisis and surgical preparation in symptomatic myasthenic patients. Significant strength improvement in myasthenic crisis is well documented in several series, although there have been no controlled trials. We perform a series of five to six exchanges of 2–3 L every other day. The onset of improved strength is variable but occurs after two to three exchanges.

IVIg may represent an alternative short-term treatment for myasthenic exacerbations or crises in patients who are poor candidates for plasma exchange because of difficult vascular access or septicemia. Comparable efficacy for plasma exchange and IVIg was demonstrated in myasthenic exacerbations and crises in a relatively small randomized controlled trial of IVIg at 1.2 and 2 g/kg over 2–5 days.[48] However, in a retrospective multicenter study of myasthenic crisis, plasma exchange proved more effective than IVIg in the ability to extubate at 2 weeks and in the 1-month functional outcome. Treatment failures to IVIg subsequently responding to plasma exchange have also been reported.[49] Experience with preoperative IVIg for thymectomy in myasthenia gravis suggests that the time course of the maximal response may be considerably delayed in some patients.

Corticosteroids (e.g., prednisone 1 mg/kg/day) are occasionally used in prolonged myasthenic crises that fail to respond to plasma exchange or IVIg. If begun early in the course of the myasthenic crisis, the transient increase in myasthenic weakness associated with initiating corticosteroids may prolong mechanical ventilation. When preceded by an unequivocal improvement in strength after plasma exchange or IVIg treatment, long-term treatment with corticosteroids may begin, with a reduced risk for corticosteroid-related exacerbations. Treatments with monoclonal antibodies appear promising in clinical trials.

In the context of myasthenic crisis, excessive dosing of cholinesterase inhibitors may superimpose a cholinergic crisis caused by depolarization blockade and result in increased weakness. Other symptoms of cholinergic crisis include muscle fasciculations and prominent muscarinic symptoms, including miosis, excessive lacrimation and salivation, abdominal cramping, nausea, vomiting, diarrhea, thick bronchial secretions, diaphoresis, and bradycardia. Cholinergic crisis is rare in contemporary series of myasthenic crisis, and it is now common practice to avoid repeated dose escalations of cholinesterase inhibitors in an impending myasthenic crisis and to discontinue the use of cholinesterase inhibitors after intubation to reduce muscarinic complications. When there is a question of cholinergic excess contributing to respiratory insufficiency, it is prudent to discontinue all cholinesterase inhibitors, protect the airway, and support respiration as necessary.

Thymectomy may result in the long-term improvement of patients with a suspected thymoma or with a life expectancy of more than 10 years.

Box 49.2 Drugs That May Increase Weakness in Myasthenia Gravis

- Neuromuscular blocking agents
- Selected antibiotics
  - Aminoglycosides, particularly gentamicin
  - Macrolides, particularly erythromycin and azithromycin
- Selected cardiovascular agents
  - Beta-blockers
  - Calcium channel blockers
  - Procainamide
- Quinidine
- Quinine
- Corticosteroids
- Magnesium salts
  - Antacids, laxatives, intravenous tocolytics
- Iodinated contrast agents
- d-Penicillamine

However, a patient in acute respiratory failure is considered a poor operative risk, and thymectomy is delayed until the patient's condition has improved.[50] Post-thymectomy pain control and ventilatory function may be improved by the postoperative administration of epidural morphine.

Neuromuscular Diseases Secondary to Critical Illness and Its Treatment

Critical Illness Polyneuropathy and Myopathy

Critical illness polyneuropathy is a widespread axonal peripheral neuropathy that develops in the context of multiple organ failure and sepsis. In a prospective series of 43 patients with sepsis and multiorgan failure, 70% developed electrophysiologic evidence of a sensorimotor axonal neuropathy, and 15 patients developed difficulty weaning from mechanical ventilation as a consequence of the neuropathy.[51] Critical illness polyneuropathy is possibly the most common neuromuscular cause of prolonged ventilator dependency in patients without prior known neuromuscular disease. Given the limitations to the detailed clinical motor and sensory examinations in the setting of critical illness, the clinical features of critical illness polyneuropathy (extremity muscle weakness and wasting, distal sensory loss, and paresthesias) may not be recognized. Deep tendon reflexes are reduced or absent in the setting of superimposed CNS insult with pyramidal tract dysfunction; however, deep tendon reflexes may be normal or increased.

Electrodiagnostic studies are important in establishing a diagnosis of critical illness polyneuropathy because the clinical findings may be unobtainable or indeterminate in this setting. Nerve conduction findings include normal or near-normal conduction velocity and latency values and significantly reduced compound muscle action potential and sensory nerve action potential amplitudes. Needle electrode examination reveals denervation changes that are the most marked in the distal muscles, including fibrillation potentials, positive sharp waves, and reduced recruitment of motor unit potentials. With recovery over time, the denervation potentials abate, and the motor unit potentials become polyphasic and enlarged. Peripheral nerve histopathology has revealed widespread primary axonal degeneration in distal motor and sensory fibers, and skeletal muscle has exhibited fiber-type grouping.

Although the clinical history is usually adequate to distinguish between critical illness polyneuropathy and Guillain-Barré syndrome, the latter can develop in the context of recent surgery complicated by infection. However, Guillain-Barré syndrome is commonly associated with facial and oropharyngeal weakness, which is rarely seen in critical illness polyneuropathy. Furthermore, dysautonomia and occasionally external ophthalmoplegia is also observed in Guillain-Barré syndrome but has virtually never been attributed to critical illness polyneuropathy.

Electrophysiologic findings are also helpful in distinguishing between these two disorders. Features of segmental demyelination may be observed in Guillain-Barré syndrome on nerve conduction studies (e.g., reduced conduction velocity, prolonged distal and F-wave latencies, conduction block, and temporal dispersion of compound muscle action potentials); these findings are not observed in critical illness polyneuropathy. Needle electromyographic findings may differ in that relatively less spontaneous activity is observed in clinically weak muscles within the first few days in patients with Guillain-Barré syndrome. Although electrophysiologic studies are quite helpful in demonstrating the classic demyelinating form of Guillain-Barré syndrome, an electrophysiologic distinction between the axonal forms of Guillain-Barré syndrome and critical illness polyneuropathy may not be reliable. The mean CSF protein level in Guillain-Barré syndrome is significantly higher than in critical illness polyneuropathy, although there is overlap between these populations. Peripheral nerve histopathology may also distinguish between these two groups because segmental demyelination and inflammatory changes may be observed in Guillain-Barré syndrome and are not observed in critical illness polyneuropathy.

Although the overall prognosis in critical illness polyneuropathy is dependent on recovery from the underlying critical illness, most patients who survive experience a functional recovery from the neuropathy within several months. Critical illness polyneuropathy may prolong ventilator dependence, but it does not worsen the long-term prognosis. Proper positioning and padding are important to prevent compression neuropathies because the prognosis from superimposed compression neuropathies in the context of critical illness polyneuropathy is less favorable.

The pathophysiology of critical illness polyneuropathy is unknown. No clear metabolic, drug, nutritional, or toxic factors have been identified, although the severity of critical illness polyneuropathy has been correlated with the amount of time in the ICU, the number of invasive procedures, increased glucose concentrations, a reduced albumin concentration, and the severity of multiple organ failure. Given the common antecedents of multiple organ failure and sepsis in which release of cytokines occurs, increased microvascular permeability has been postulated to produce axonal hypoxia and degeneration as a consequence of endoneurial edema.[52]

Critical illness neuromyopathy, with evidence of myonecrosis, is the co-occurrence of neuropathy and myopathy; the latter is discussed later under Acute Quadriplegic Myopathy. The diagnosis requires electrophysiologic studies and may be confirmed with muscle biopsy, although the latter is rarely performed.[53]

Prolonged Effects of Neuromuscular Blocking Agents

A prolonged neuromuscular blockade may occur with most depolarizing and nondepolarizing agents, particularly when the hepatic or renal function is impaired.[54] In one study, the administration of vecuronium for 2 or more consecutive days resulted in prolonged neuromuscular blockade and paralysis lasting from 6 hours to 7 days.[55] Although vecuronium is hepatically metabolized, patients with renal failure were susceptible to prolonged effects because of delayed excretion of the active 3-desacetyl metabolite. Acidosis and elevated serum magnesium levels were also associated with prolonged paralytic effects of vecuronium. A peripheral nerve stimulator may be used to monitor muscle twitch responses to a train-of-four stimulus during the use of neuromuscular blocking agents. Drug dosage should be titrated to preserve one or two twitches to avoid overdosing. Two- to three-Hz repetitive nerve stimulation studies may also be used to confirm neuromuscular blockade when it is suspected. Because atracurium and cisatracurium do not require organ metabolism for clearance, they are rarely associated with this problem.

Acute Quadriplegic Myopathy

The syndrome, known as *acute quadriplegic myopathy* or *acute myopathy of intensive care*, was originally described in 1977 by a young woman who developed severe myopathy after treatment of status asthmaticus with high doses of corticosteroids and pancuronium.[56] Subsequently, there have been many citations of an acute myopathy developing in critically ill patients without preexisting neuromuscular disease. Acute quadriplegic myopathy has developed most frequently in the setting of severe pulmonary disorders in which neuromuscular blockade is used to facilitate mechanical ventilation, and high doses of corticosteroids are concurrently administered. In most reported cases, myopathy developed when nondepolarizing neuromuscular blocking agents were used for more than 2 days.[56] The development of acute necrotizing myopathy with myosin loss also occurs in patients receiving high doses of corticosteroids and hypnotic doses of propofol and benzodiazepines to induce paralysis.[57] This observation highlights the

significance of high-dose corticosteroid exposure in the development of this syndrome and suggests that the paralyzed muscles may be susceptible to the toxic effects of corticosteroids. The mechanism of this myosin abnormality appears to lie at the level of transcriptional regulation of protein synthesis. The occurrence of acute quadriplegic myopathy after organ transplantation may be caused by the use of high doses of corticosteroids to prevent graft rejection, along with perioperative exposure to neuromuscular blocking agents.[58] Although most cases of acute quadriplegic myopathy have been associated with critical illness and high doses of corticosteroids and paralytic agents, acute quadriplegic myopathy has developed after isolated corticosteroid exposure,[59] isolated nondepolarizing neuromuscular blocking agent use, or neither. Factors that may impair neuromuscular transmission (e.g., hypermagnesemia and aminoglycoside exposure), factors that may slow the elimination of nondepolarizing neuromuscular blocking agents (e.g., hepatic or renal failure), and factors associated with critical illness (e.g., sepsis and acidosis) are also associated with acute quadriplegic myopathy.

In typical cases, a diffuse flaccid quadriparesis with the involvement of respiratory muscles and muscle wasting evolves after several days of induced paralysis. External ophthalmoparesis has rarely been noted. Sensation remains intact, but deep tendon reflexes are reduced or absent. The creatine kinase level is commonly elevated, but this may not be observed if creatine kinase is measured well after the myopathy has developed. Although the paralysis may be quite severe and necessitate or prolong mechanical ventilation, the prognosis for the myopathy is good, with functional recovery over several weeks to months. Electromyographic findings include reduced amplitude of compound motor action potentials with normal sensory nerve action potentials and normal nerve conduction velocities. M-wave amplitude improvement accompanies clinical recovery. Repetitive nerve stimulation studies may yield decremental responses, while the residual effects of nondepolarizing neuromuscular blocking agents or their active metabolites persist. Needle electromyography often reveals small, low-amplitude, polyphasic motor unit potentials exhibiting early recruitment, along with positive sharp waves and fibrillation potentials. A spectrum of muscle histologic changes may be observed, ranging from type II fiber atrophy and the loss of adenosine triphosphatase (ATPase) reactivity in atrophic fibers to fiber necrosis in severe cases. However, the distinctive findings in most cases is an extensive loss of thick filaments corresponding to myosin loss.[59] This finding may be demonstrated by immunohistochemical staining or electron microscopy. The increased expression of steroid receptors in denervated and immobilized muscle may render these muscles susceptible to toxic catabolic effects of steroids. Given the growing recognition of acute quadriplegic myopathy, the use of high doses of corticosteroids should be avoided if possible when neuromuscular blockade or induced paralysis is required. One should exclude nutritional causes of muscle breakdown, along with drug toxicity (e.g., because of statins).

However, in a Cochrane review of interventions for preventing critical illness polyneuropathy and critical illness myopathy,[60] a randomized controlled trial of 180 patients with acute respiratory distress syndrome comparing corticosteroids with placebo that found no effect of treatment on critical illness polyneuropathy/myopathy[61] was cited as moderate-quality evidence. Additional results from the review found moderate-quality evidence for intensive insulin therapy in reducing polyneuropathy/myopathy at the expense of increased hypoglycemia[62,63] and for a potential benefit for early rehabilitation.[64] Larger randomized controlled trials of early rehabilitation and electrical muscle stimulation are needed to explore the value of these therapies.

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KEY POINTS

- Respiratory dysfunction resulting from neuromuscular disease typically presents with a combination of upper airway dysfunction and diminished tidal volume (V_T).
- Along with vital capacity, trended measurement of the maximum inspiratory pressure (PImax or NIF) is a useful index of ventilatory capacity. Inability to maintain a PImax greater than 20–25 cm H_2O usually indicates a need for mechanical ventilatory assistance.
- Autonomic failure and pulmonary embolism are now the major causes of mortality in Guillain-Barré syndrome.
- Evidence-based guidelines for Guillain-Barré syndrome immunotherapy have been published by the Quality Standards Subcommittee of the American Academy of Neurology. Plasma exchange is recommended for adult patients who cannot walk within 4 weeks of symptom onset. IVIg is recommended in these patients within 2 or possibly 4 weeks of symptom onset. Plasma exchange and IVIg are considered equivalent in efficacy, and no additional benefit is conferred by combining these treatments. In light of the therapeutic equivalence, the decision whether to employ plasma exchange or IVIg in treating acute Guillain-Barré syndrome may be determined by resource availability and by avoiding potential side effects related to a patient's medical comorbidities.
- In the initial North American outbreak of West Nile virus, about 10% of infected patients experienced flaccid weakness with clinical features resembling Guillain-Barré syndrome.
- Approximately 20% of patients with myasthenia gravis develop myasthenic crisis with respiratory failure requiring mechanical ventilation.
- Critical illness polyneuropathy is a widespread, axonal peripheral neuropathy that develops in the context of multiple-organ failure and sepsis. Critical illness polyneuropathy is possibly the most common neuromuscular cause of prolonged ventilator dependency in patients without prior known neuromuscular disease.
- Acute quadriplegic myopathy has developed most frequently in the setting of severe pulmonary disorders in which neuromuscular blockade is used to facilitate mechanical ventilation, and high-dose corticosteroids are concurrently administered.

References for this chapter can be found at expertconsult.com.

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Traumatic Brain Injury

Thaddeus J. Puzio and Sasha D. Adams

INTRODUCTION

Traumatic brain injury (TBI) is a medical and social problem worldwide, with an estimated 10 million cases leading to hospitalization or death each year.[1] Most TBIs are mild, and the incidence of TBI varies widely by ages and between countries.[2] In the United States, trauma is the leading cause of death in individuals aged 1–45 years old, and TBI accounts for the majority of these, with over 50,000 deaths per year.[3]

Traditionally, TBI has been classified based on mechanism (closed vs. penetrating), clinical severity (by Glasgow Coma Scale), and assessment of structural damage (by neuroimaging). TBI is a constellation of cellular responses that result from a primary and secondary injury. Primary brain injury results from external forces to the brain via various mechanisms. This can occur as a consequence of direct impact, rapid acceleration or deceleration, penetrating objects (e.g., gunshot), or blast waves from an explosion.[4] Secondary brain injury occurs from physiologic derangements that occur after the initial insult.[5]

PREHOSPITAL CARE

Care of the patient with TBI begins immediately in the prehospital setting. Proper field triage is critical, as the acutely injured brain is immediately vulnerable to secondary injury from physiologic derangements such as hypotension, hypercarbia, and hypoxemia. Care of the TBI victim always should begin with evaluating and securing a patent airway and restoring normal breathing and circulation, as such treatment has been shown to reduce mortality after severe TBI.[6] The airway can be quickly and safely secured by orotracheal intubation, but in patients with concomitant maxillofacial trauma, a surgical airway (cricothyroidotomy) should be performed if other attempts to secure an airway have failed. Rapid-sequence intubation is recommended to prevent transient hypertension, tachycardia, increased intracranial pressure (ICP), and agitation that can interfere with the procedure. Avoid inadvertent hyperventilation. Ventilatory rates of 10–12 breaths per minute for adults, 20 breaths per minute for children, and 25 breaths per minute for infants should supply adequate oxygenation. Therapeutic hyperventilation is inadvisable unless neurologic deterioration is clearly evident during evaluation and transport. Aggressive hyperventilation can cause cerebral vasoconstriction, reducing already low cerebral blood flow (CBF) and potentially causing or exacerbating cerebral ischemia.[7]

Another critical component of prehospital care for TBI patients is avoidance of hypotension. Rapid resuscitation and restoration of a normal blood pressure are critical, as hypotension has been associated with doubling of the mortality rate after severe TBI. In multisystem trauma, the most likely cause of hypotension is hemorrhage, usually in the abdomen or chest. Hypovolemia should be assumed to be hemorrhagic, and therefore these patients are ideally treated with blood transfusion. If blood products are unavailable, isotonic crystalloid should be infused, targeting normotension.

In all cases of suspected TBI, patients should be treated as if they have a spinal fracture until an adequate examination of the spine proves otherwise. Among those who survive long enough to reach the emergency department, the likelihood of a cervical spine fracture is 2%–7%. More troubling, however, is that an estimated 10%–25% of all posttraumatic cervical spinal cord injuries are iatrogenic because of improper cervical spine manipulation occurring during transport to the hospital in the setting of cervical spine fracture.[8] Spinal immobilization should occur immediately by placing the patient in a neutral position on a flat, hard surface. A rigid cervical spine collar should be placed, followed by immobilization on a long spine board.

It is important for prehospital providers to monitor patients for the "Cushing reflex." This phenomenon often signals impending brainstem herniation and is identified by hypertension, bradycardia, and abnormal breathing rhythm.[9] These patients need immediate neurosurgical evaluation with neuroimaging and may benefit from temporary hyperventilation.

PATHOPHYSIOLOGY

Under normal conditions, the total volume within the skull remains constant and is determined by the sum of the cerebrospinal fluid (CSF), blood, and brain tissue compartments.[4] This relationship is known as the *Monro–Kellie hypothesis.* CBF remains constant under normal conditions over a range of blood pressures via cerebral autoregulation. When one compartment is increased, such as in the setting of hematoma, there must be a compensatory decrease in another compartment in order to prevent intracranial hypertension.[3] A large proportion of TBI management is spent attempting to maintain homeostasis by controlling ICP, mean arterial pressure (MAP), and cerebral perfusion, and preventing cerebral edema.

FORMS OF PRIMARY BRAIN INJURY

Epidural Hematoma

Epidural hematomas (EDHs) develop between the inner table of the skull and the dura and are seen on computed tomography (CT) as a lens-shaped hyperdensity (Fig. 50.1). They are most commonly caused by disruption of the middle meningeal artery or one of its branches by a skull fracture. Classically, patients have a brief loss of consciousness followed by a "lucid interval" of normal mentation and then suffer an abrupt loss of consciousness. EDHs occur in 8%–10% of those rendered comatose by TBI.[10]

The majority of epidural hematomas are located in the temporal or parietal regions, but they can also occur over the frontal or occipital lobes and (rarely) in the posterior fossa. Their spread is limited by the

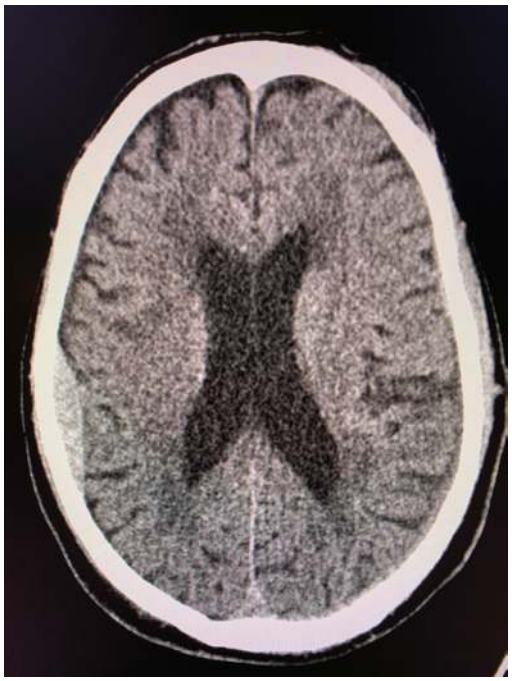

Fig. 50.1 Epidural hematomas have a lens shape and smooth inner border because they strip the dura from the inner table of the skull as they enlarge (axial computed tomography scan).

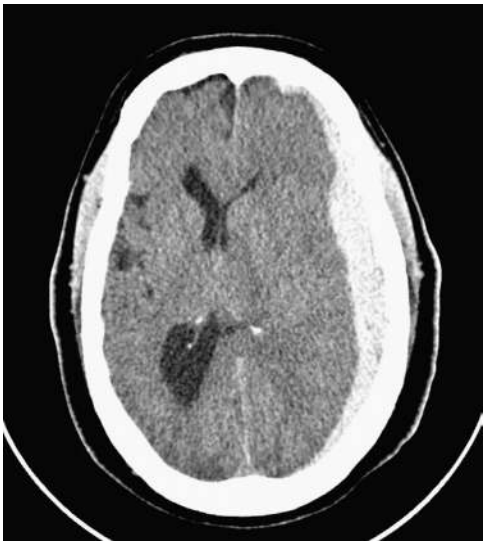

Fig. 50.2 Acute subdural hematomas (SDHs) typically spread over the entire surface of the hemisphere. Occasionally, mixed-density SDH is seen, indicative of injuries occurring at different times.

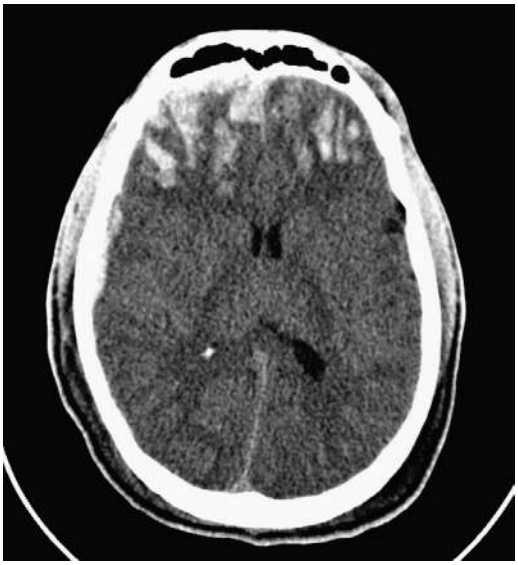

Fig. 50.3 Subarachnoid hemorrhage (SAH) is bleeding in the subarachnoid space, which lies between the arachnoid and pia mater.

suture lines of the skull, where the dura is very adherent. EDHs are uncommon in infants and toddlers, presumably because their skulls are more deformable and less likely to fracture, and in TBI victims older than 60 years of age, because the dura is extremely adherent to the skull.

Subdural Hematoma

Subdural hematomas (SDHs) develop between the surface of the brain and the inner surface of the dura and are seen on CT as a crescent-shaped hyperdensity (Fig. 50.2). They are believed to result from the tearing of bridging veins over the cortical surface or from disruption of major venous sinuses or their tributaries. The hematoma is limited to a single hemisphere by the falx cerebri and therefore does not cross hemispheres. SDHs are seen in 20%–25% of all comatose victims of TBI.[10]

SDHs are classified as acute, subacute, or chronic, each having a characteristic appearance on noncontrasted CT. Acute hematomas are bright white, subacute lesions; they are isodense with brain tissue and are therefore often overlooked. Chronic hematomas are hypodense relative to the brain.[11] Patients with SDH have a worse prognosis than patients with EDH because of the concomitant damage to neural tissue more commonly seen with traumatic SDH. Underlying cerebral contusions were found in 67% of patients with SDHs in one series.[12]

Subarachnoid Hemorrhage

Subarachnoid hemorrhage (SAH) is bleeding in the subarachnoid space, which lies between the arachnoid and pia mater (Fig. 50.3). This injury results from disruption of the parenchyma and subarachnoid vasculature. Trauma is the most common cause of SAH, but 80% of nontraumatic SAHs are the result of aneurysmal rupture.[13]

Traumatic SAH can sometimes be differentiated from nontraumatic SAH with noncontrasted CT, as traumatic SAH are typically located in a peripheral distribution and nontraumatic SAH are more likely to be central. CT angiogram (CTA) is the most sensitive and can identify nontraumatic SAH from a ruptured aneurysm. Traumatic SAH seen in the setting of moderate and severe TBI is a poor prognostic indicator and is associated with increased morbidity and up to twofold increase in mortality.[10,14] These patients may present with headache, meningeal signs, and photophobia.[13]

Diffuse Axonal Injury

Diffuse axonal injury (DAI) refers to lacerations or punctate contusions at the interface between the gray and white matter. Such punctate contusions are thought to result from the disparate densities of the gray and white matter and the consequent difference in centripetal force associated with a rotational vector of injury.[15] DAI was once thought to result solely from mechanical disruption at the time of

impact; however, more recent research has identified cases in which the histologic footprints of DAI, such as fragmentation of axons and axonal swelling, do not appear until 24–48 hours after the incident, suggesting that some cases are a secondary manifestation of trauma.[15] The gold standard for radiographic diagnosis of DAI is magnetic resonance imaging (MRI) of the brain. DAI is present in almost half of all patients with severe TBI and in a third of those who die, and it is a common cause of persistent vegetative or minimally conscious state.[16]

Cerebral Contusion

Contusions are heterogeneous lesions comprising punctate hemorrhage, edema, and necrosis and are often associated with other intracranial lesions (Fig. 50.4). One or more contusions occur in 20%–25% of patients with severe TBI. Because they evolve over time, contusions may not be evident on the initial CT scan or may appear as small areas of punctate hyperdensities (hemorrhages) with surrounding hypodensity (edema). Local neuronal damage and hemorrhage lead to edema that may expand over the next 24–48 hours. With time, contusions may coalesce and look more like intracerebral hematomas. Depending on their size and location, they may cause significant mass effect, resulting in midline shift, subfalcine herniation, or transtentorial herniation. Contusions are most common in the inferior frontal cortex and the anterior temporal lobes,[17] where the surface of the inner table of the skull is very irregular. Direct blunt-force trauma to the head can produce a contusion in the tissue underlying the point of impact (coup contusion). If the head was in motion upon collision with a rigid surface, a contusion may occur in the brain contralateral to the point of impact (contrecoup contusion).

Skull Fracture

Skull fracture results from a contact force to the head that is usually severe enough to cause at least a brief loss of consciousness. Linear fractures are the most common type of skull fracture and typically occur over the lateral convexities of the skull. A depressed skull fracture, in which skull fragments are pushed into the cranial vault, usually results from blunt force by an object with a relatively small surface area, such as a hammer. Basilar skull fractures are most common in the anterior skull base and often involve the cribriform plate, disrupting the olfactory nerves and resulting in olfactory deficits (Fig. 50.5). Posterior basilar skull fractures may extend through the petrous bone and internal auditory canal, thereby damaging the acoustic and facial nerves.

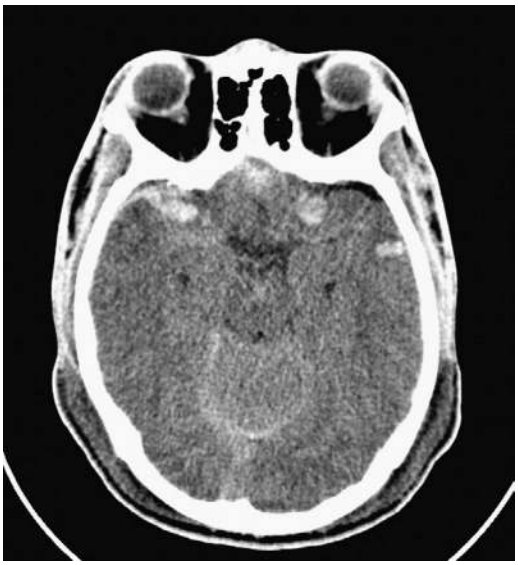

Fig. 50.4 Contusions are most common in the inferior temporal and frontal lobes. In the first few hours after injury, they appear only as areas of hemorrhage mixed with edematous brain. Within 24–48 hours after injury, further hemorrhage may occur, causing significant enlargement of the contusion and hematoma (axial computed tomography scan).

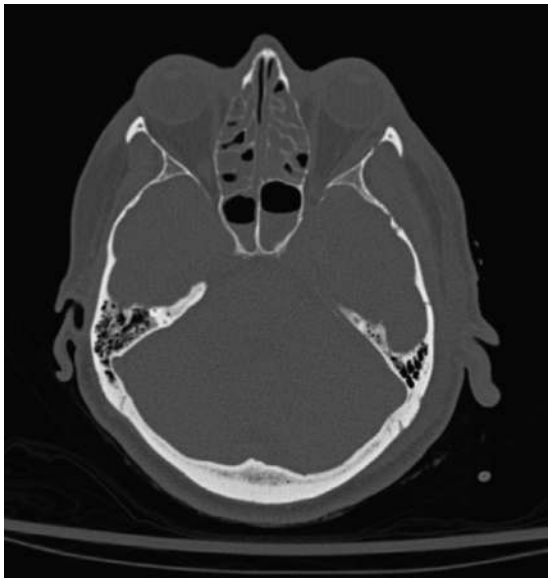

Fig. 50.5 Basilar skull fractures through the anterior skull base typically cause rhinorrhea and tears in adjacent dura. Computed tomography (CT) scans through the base of the skull may not show the fracture itself, but often show fluid in the sphenoid sinus or other paranasal sinuses (axial CT scan, bone window).

Skull fractures are markers of significant force to the head and are normally associated with underlying injuries. Skull fractures that involve the squamous portion of the temporal bone are frequently accompanied by a tear of the middle meningeal artery, causing an epidural hematoma. They can also cause facial nerve injury, exhibited as facial asymmetry that can present immediately or in a delayed fashion. Depressed skull fractures are often associated with contusions of the underlying brain tissue, and a scalp laceration overlying a depressed skull fragment can contaminate the fragment with bacteria from the scalp and hair. With a basilar skull fracture, the dura underlying the fracture is often disrupted, resulting in a CSF fistula and leakage of CSF from the nose or ear. Such fistulas may allow bacteria to enter the intracranial space from the normally colonized nose, paranasal sinuses, or external auditory canal.

CHARACTERIZATION AND MANAGEMENT

Glasgow Coma Scale

Patients with TBI are assessed with the Glasgow Coma Scale (GCS). This scoring system was originally developed in the United Kingdom in 1974 for patients with altered levels of consciousness.[18] It is now the cornerstone for assessing and comparing patients with TBI (Table 50.1). The GCS provides a common language to describe these patients, which then drives treatment decisions, allows for classification, and improves the quality of research on these patients.[19] Patients with TBI should be assessed for GCS in a prehospital setting, reassessed at hospital arrival, and continually reassessed throughout the course of their stay to monitor for changes.

TABLE 50.1 Glasgow Coma Scale

Response	Points
Speech	
Alert, oriented, and conversant	5
Confused, disoriented, but conversant	4
Intelligible words, not conversant	3
Unintelligible sounds	2
No verbalization, even with painful stimulus	1
Eye Opening	
Spontaneous	4
To verbal stimuli	3
To painful stimuli	2
None, even with painful stimuli	1
Motor	
Follows commands	6
Localizes painful stimulus	5
Withdraws from painful stimulus	4
Flexor posturing with central pain	3
Extensor posturing with central pain	2
No response to painful stimulus	1

Data from Teasdale G, Jennett B. Assessment of coma and impaired consciousness: a practical scale. *Lancet.* 1974;2:81–84.

The GCS is a sum of three component scores assigned for eye, verbal, and motor response. The score ranges from 3 to 15, and it is important to report the individual scores in addition to the total score. Up to 4 points are scored for the best eye-opening response, up to 5 points for the best verbal response, and up to 6 points for the best motor response.[18] The motor score provides the most points and has the most relevance to long-term prognosis. It is important to point out that in addition to brain injury, scores can be influenced by multiple other factors such as alcohol, drugs, and shock.[19]

Finally, the GCS score allows us to define severity for head injuries, which provides useful prognostic information. A GCS score 13–15 reflects a mild TBI, GCS 9–12 a moderate TBI, and GCS less than 9 a severe TBI.[20]

Goal-Directed TBI Management

In the acute phase after injury, a patient with TBI is best treated with goal-directed therapy in an attempt to minimize the physiologic derangements that create secondary brain injury (Table 50.2). These parameters encompass multiple body systems with potential for multiple interactions.

Neurologic Goal-Directed Therapy

The guiding principle for maintaining homeostasis is the desire to maintain cerebral perfusion pressure (CPP). Goal CPP is ≥60 mm Hg. This is thesd within the brain and is not directly measured, but calculated by the following equation:

$$\text{Cerebral perfusion pressure} = (\text{Mean arterial pressure}) - (\text{Intracranial pressure})$$

CPP is worsened (lowered) by systemic hypotension and/or by increasing ICP. Intracranial hypertension is defined as sustained ICP

TABLE 50.2 Goal-Directed Parameters for Head Injury

Pulse oximetry ≥95%	ICP 20–25 mm Hg	Serum sodium 135–145 mEq/L
PaO_2 ≥100 mm Hg	$PbtO_2$ ≥15 mm Hg	INR ≤1.4
$PaCO_2$ 35–45 mm Hg	CPP ≥60 mm Hg*	Platelets ≥75 × 10^3/mm^3
SBP ≥100 mm Hg	Temperature 36°–38°C	Hemoglobin ≥7 g/dL
pH 7.35–7.45	Glucose 80–180 mg/dL	

CPP, Cerebral perfusion pressure; *ICP,* intracranial pressure; *INR,* international normalized ratio; *$PaCO_2$,* partial pressure of carbon dioxide; *PaO_2,* partial pressure of oxygen; *$PbtO_2$,* brain tissue oxygen tension; *SBP,* systolic blood pressure.
*Depending on status of cerebral autoregulation.

greater than 20 mm Hg. Several clinical studies have found that morbidity and mortality increase significantly when the ICP persistently remains above this threshold.[21] Based on this association and the widely accepted premise that elevated ICP can compromise cerebral perfusion and cause ischemia, the aggressive treatment of intracranial hypertension is almost uniformly endorsed. Seizures, fever, jugular venous outflow obstruction (e.g., poorly fitting cervical collars), and agitation can cause or exacerbate intracranial hypertension.

Seizures have been shown to be detrimental to the injured brain. For this reason, patients with moderate and severe TBI should be maintained on an antiepileptic medication for 7 days postinjury. Additionally, fevers can lower the seizure threshold and should be prevented with scheduled antipyretics and aggressive treatment of infections.

Paroxysmal sympathetic hyperactivity, also known as *sympathetic storming,* may become evident when sedation weaning begins in up to 30% of patients. Hallmarks of storming include periodic episodes of seemingly unprovoked hypertension, tachycardia, tachypnea, diaphoresis, and hyperthermia.[22] Spontaneous posturing or dystonia may also be present during these episodes. Recognition of these symptom complexes as being neurologic in origin is key to avoiding treatment delays and unnecessary diagnostic testing. Treatment protocols are individualized, with most patients requiring various combinations of pain management, sedation, and reduced stimulation.

Respiratory Goal-Directed Therapy

Patients with GCS less than 8 should undergo intubation. This is in part because of a desire to avoid hypercapnia and hypoxia, which worsen long-term outcomes. These patients should be maintained at normocapnia (partial pressure of carbon dioxide [$PaCO_2$] 35–45 mm Hg). Hyperventilation is to be avoided, as it can cause cerebral vasoconstriction and should only briefly be performed in the setting of pending herniation (Cushing triad). Additionally, these patients should be monitored with pulse oximetry, and hypoxia is to be avoided, as it can lead to a worse prognosis. Goal PaO_2 should be greater than 100 mm Hg and pulse oximetry ≥95%.

Patients suffering severe TBI will require mechanical ventilation in an intensive care unit (ICU). If their level of consciousness remains persistently depressed, these patients should undergo tracheostomy, which should be performed within 8 days of injury.[20] Benefits of performing tracheostomy for patients undergoing prolonged mechanical ventilation include improved patient comfort because of reduced oropharyngeal irritation and improved pulmonary toilet. Early tracheostomy (fewer than 8 days) is associated with shorter mechanical ventilation duration and shorter ICU and hospital stays. Additionally, it is associated with lower risks of pneumonia, deep venous thrombosis, and decubitus ulcers.[23]

Hemodynamic Goal-Directed Therapy

Hypotension has been associated with a dramatic increase in mortality rate after severe TBI.[24] Thus it is critically important to avoid hypotension with a goal systolic blood pressure (SBP) ≥100 mm Hg. Trauma patients should be transfused blood in the setting of hypotension, but vasopressors can be used once resuscitated to euvolemia. These patients should be monitored closely with arterial line pressure monitoring and consideration given to trending central venous pressure. Additionally, vasopressors should be used to increase MAP in an attempt to target goal CPP ≥60 mm Hg.

Electrolyte Goal-Directed Therapy

Sodium regulation disturbances are common in TBI, and goal serum sodium is 135–145 mEq/L.[20] Hypertonic saline is used as a therapy for elevated ICP, as discussed in the next section, and in these patients target serum sodium levels are higher. Hyponatremia, defined as serum sodium ≤135 mEq/L, is the most common electrolyte abnormality encountered in patients with TBI and is an independent predictor of poor neurologic outcome.[25] In the setting of TBI, hyponatremia is believed to worsen brain edema, increase ICP, and result in secondary brain injury. The most common causes for hyponatremia include cerebral salt wasting (CSW), syndrome of inappropriate antidiuretic hormone (SIADH), hypopituitarism, and inadequate salt intake.[26]

Another disorder of sodium disturbance seen in TBI is diabetes insipidus (DI). This disorder arises from damage to the hypothalamic antidiuretic (ADH)-producing neurons in the posterior pituitary, which leads to a lack of ADH production.[6] This form of DI is termed "central," which delineates a neurologic etiology, in contrast to "peripheral" DI, which is a renal disorder. Central DI results in high-volume, dilute urine. This disorder is common and can be seen in up to ≈26% of patients with TBI. It is most commonly transient, but permanent DI can develop.[27] Patients with TBI should be closely monitored for polyuria and urine evaluated for low osmolarity, and they are treated with DDAVP or vasopressin.[28]

ELEVATED INTRACRANIAL PRESSURE MONITORING

ICP monitoring is indicated in patients with GCS ≤8 and should be considered in patients with a GCS >8 who have structural brain damage with high risk for progression.[20] The preferred method for ICP monitoring is an external ventricular drain (EVD) because it can diagnostically measure ICP and therapeutically drain off CSF, but it can be difficult to place, particularly if there is already edema and/or distortion of the brain parenchyma, and has risks of causing bleeding during placement. Intraparenchymal ICP monitoring is also a reliable method but does not allow for therapeutic CSF drainage. Finally, newer devices are available to measure brain tissue oxygenation (PbO_2), but their effect on outcomes remains unclear.[29]

ELEVATED INTRACRANIAL PRESSURE MANAGEMENT

A stepwise tiered approach for ICP treatment is usually followed, with the least toxic therapies used first and more toxic therapies added only if the initial tier of treatment is unsuccessful.

First-Tier Treatment for Elevated ICP: Positioning and Sedation/Analgesia Medications

A simple noninvasive method to decrease ICP is to elevate the head of the bed (or reverse Trendelenburg if on spinal precautions) to improve cerebral venous outflow. Next, sedation and neuromuscular blockade are often an effective treatment, particularly if the patient is agitated or posturing.[30] Narcotics (e.g., morphine, fentanyl), short-acting benzodiazepines (e.g., midazolam), or hypnotic agents such as propofol can be used for sedation. Narcotic-induced hypotension can be averted by using relatively low doses and ensuring the patient is normovolemic before treatment. If an EVD is present, an additional method to decrease ICP is to intermittently drain CSF via an EVD. If ICP remains >20 mm Hg despite these measures, one should move to second-tier strategies.

Second-Tier Treatment for Elevated ICP: Osmotic Agents and Brief Hyperventilation

Hyperosmolar therapy should be administered via intermittent boluses. A bolus administration of mannitol (0.25-2g/kg every 3–4 hours as needed) or hypertonic saline is recommended.[8,31] Mannitol exerts its effect through osmotic diuresis, lowering the ICP and increasing the CPP by expanding the blood volume, reducing the blood viscosity, and increasing CBF and oxygen delivery to the tissues within a few minutes of infusion. Its duration of effect averages 3–5 hours, but it should be avoided in the setting of hypotension or hemorrhagic shock and is therefore often avoided in multitrauma patients with concomitant injuries. Hypertonic saline appears to create osmotic mobilization of water across the blood-brain barrier without significant diuresis and is more appropriate in the setting of hypotension. Concentrations ranging from 3% to 23.4% have been used to decrease ICP.[32] The serum osmolarity and sodium level should be monitored frequently during the use of osmotherapy. The drugs should be discontinued if the serum sodium level exceeds 160 mg/dL or the serum osmolarity exceeds 320 mOsm in order to minimize the risk of acute kidney injury.[33]

An additional measure to lower ICP includes adjusting the ventilatory rate to reduce the arterial PCO_2 to 30 mm Hg.[7] Hyperventilation should be used cautiously during the first 24–48 hours after injury, because it will cause cerebral vasoconstriction at a time when CBF is already critically reduced. Evidence also suggests that even brief periods of hyperventilation can lead to secondary brain injury by causing an increase in extracellular lactate and glutamate levels. Its clinical use is therefore limited to pending herniation or as a bridge to third-tier treatment. Finally, if the previous measures still fail to reduce ICP, third-tier measures should be employed.

Third-Tier Treatment for Elevated ICP: Barbiturates, Cooling, and Surgical Intervention

If intracranial hypertension persists despite all these treatments, particularly if the ICP rises rapidly or if the patient's initial CT scan showed a small contusion or hematoma, another CT scan should be obtained immediately to determine whether a new mass lesion is present or a preexisting lesion has enlarged. Even if the lesion has enlarged only slightly, an emergent craniotomy and evacuation of the contusion or hematoma may be the best way to reduce the ICP quickly and effectively.

In the absence of new or expanding mass lesions, deepening sedation with high-dose barbiturates can be considered in patients with salvageable neurologic examinations. Pentobarbital is the most commonly used drug for this purpose and is administered as an intravenous (IV) loading dose of 10–15 mg/kg over 1–2 hours, followed by a maintenance infusion of 1–2 mg/kg per hour. Continuous electroencephalographic monitoring is recommended while increasing the dose until a burst suppression pattern is observed. Hypotension is the most common adverse effect of barbiturates and can usually be averted by ensuring a normal intravascular volume before administering the drug. In addition to deepening sedation, a paralytic agent should be considered.

Therapeutic moderate hypothermia has been used in several clinical trials over the past decade. Although some clinical trials have not found that this treatment improves neurologic outcome compared with normothermia, they have consistently shown that hypothermia significantly reduces ICP.[34] The body temperature is lowered to 32°C–33°C as soon as possible after injury and kept at that temperature for 24–48 hours using surface cooling techniques.

The use of decompressive craniectomies, such as large lateral or bifrontal bone flaps, with or without a generous temporal or frontal lobectomy, can be considered for a small subset of patients. Two studies report good outcomes in 56%–58% of patients whose refractory intracranial hypertension was treated with decompressive craniectomy as a last resort,[35] and another study suggested that decompressive temporal lobectomy, when performed soon after injury, improves the outcome for young patients.[36] However, others found that decompressive craniectomy does not improve ICP, CPP, or mortality rates.[37] Because age has such a profound impact on the likelihood of a meaningful recovery, these third-tier therapies are recommended only for patients who are younger than 40 years old.

SPECIAL CONSIDERATIONS

Penetrating Injuries

The most common cause of penetrating TBI is gunshot wounds to the head, which usually cause massive destruction of brain tissue, severe brain swelling, and, if the trajectory is transcranial, death. The wounding potential of a bullet depends primarily on its velocity at impact and its mass, although the shape of the bullet and its lateral movements also play a role. The impact velocity is by far the most important determinant of a bullet's wounding potential. Consequently, high-velocity rifle wounds to the head are invariably fatal, whereas low-velocity open-chambered handgun wounds often are not. When a bullet enters the skull, it creates a variety of pressure waves within the brain, some of which can cause tissue pressures of nearly 100 atmospheres, resulting in further tissue injury. Bullets often fragment after they strike the skull, fracturing the bone into multiple fragments. Both the bullet and the bone fragments then become numerous secondary missiles that can cause additional tissue damage.

Low-velocity missile wounds, such as those from knives, ice picks, or arrows, do not cause the massive brain injuries seen with bullets. Usually only the tissue in the immediate path of the missile is damaged, and patients often have a complete neurologic recovery after the missile is surgically extracted. Nonetheless, vascular injuries are always possible with high- or low-velocity missile injuries to the head, especially those in or near the skull base or the sylvian fissures.

The initial assessment and resuscitation of patients with penetrating head injuries are the same as for those with closed head injuries. Knives or other missiles protruding from the head should never be removed in the field or emergency department, as they may be creating a tamponade effect and removal could lead to massive intracranial hemorrhage. When a patient has a gunshot wound to the head, the rest of the body should be inspected carefully for other gunshot wounds, because wounds to the heart or great vessels in the chest or abdomen may be even more life threatening. A CT scan of the head defines the intracranial path of the missile and related skull and tissue damage. More importantly, it identifies any large intracranial hematomas or contusions that may significantly affect outcome. If the missile trajectory is in or near the skull base or sylvian fissures and the patient is deemed salvageable, cerebral angiography should be performed because this injury pattern is often associated with the development of pseudoaneurysms.[21]

Most patients who are expected to survive a penetrating head injury require limited operative treatment. Large intracranial hematomas should be evacuated promptly, and a craniotomy is required for low-velocity missile wounds in which the object is still protruding from the head. After removing a segment of skull containing the missile and a large enough area to allow for intracerebral exploration, the surgeon can seek and immediately repair or occlude any vascular injuries caused by the missile. For gunshot wounds to the head, the surgeon should perform a limited debridement of the scalp and skull wound, removing scalp, bone, and bullet fragments penetrating the brain only if they lie near the surface. Easily accessible necrotic brain should be debrided and meticulous hemostasis achieved. Subsequent medical management of penetrating injuries is as described previously for closed head injuries. Because a penetrating TBI by definition disrupts and contuses brain tissue, all patients with these injuries should also receive anticonvulsants for at least 7 days.[32]

Management Considerations for TBI in the Elderly

Elderly patients represent a special population that is at a higher risk of TBI than the general population and has a worse prognosis than younger injury-matched controls. Factors that contribute to this higher risk include anticoagulation for comorbidities, baseline neurocognitive disorders, and higher risk of falls seen in this group.[38] Neurologic evaluation of the elderly patient with TBI can often be complicated by preexisting dementia, cognitive decline, or hearing/vision deficits. Family and caregivers can be invaluable sources of information when trying to determine a neurologic "baseline." Elderly patients with mild TBI are at higher risk for intracerebral bleeding than younger patients, and therefore any patient age ≥65 years who presents with a mild head injury should undergo CT scanning.[39] Additionally, a multicenter study established that older patients after isolated TBI have poorer functional status at discharge and make less improvement at 1 year compared with all other patients despite a higher initial GCS.[40]

Prognosis After TBI

Predicting outcome soon after a TBI can help guide acute and chronic care and help prepare family members for the typically protracted recovery process. Equally important is that further treatment may be deemed futile, and expensive critical care or surgery can be reserved for those who are likely to benefit. Of course, early prognostication must be reliable, especially when withdrawal of life support is a consideration.

Several clinical and radiographic characteristics have proven useful for outcome prediction, but they must be used in concert.[41] Moreover, these criteria are more reliable for predicting death or vegetative survival than for accurately predicting mild or no dysfunction and a complete return to normalcy. The most powerful outcome predictors are age, initial GCS score (particularly the motor component), pupil size and reaction to light, ICP, and the nature and extent of intracranial injuries.

Marshall and colleagues devised a CT-based classification scheme that proved prognostically useful when applied to the patients in the Traumatic Coma Data Bank study (Tables 50.3 and 50.4).[42] The classification emphasizes the mass effect of posttraumatic intracranial lesions. Not surprisingly, these investigators found the worst outcomes among patients with large intracranial mass lesions and uncal herniation.

The patient's salvageability and prognosis after a penetrating injury are far clearer than for those with closed head injuries. Most victims of high-velocity gunshot wounds to the head die before or shortly after hospital arrival. A meta-analysis of recent clinical studies examining civilian gunshot wounds to the head and initial GCS of 3–5 found that

TABLE 50.3 Computed Tomographic Classification of Traumatic Brain Injury

Category	Definition
Diffuse injury I	No visible intracranial pathology
Diffuse injury II	Cisterns present, with midline shift 0–5 mm; no high-density lesion >25 mL
Diffuse injury III (swelling)	Cisterns compressed or absent, with midline shift 0–5 mm; no high-density lesion >25 mL
Diffuse injury IV (shift)	Midline shift >5 mm; no high-density lesion >25 mL
Evacuated mass lesion	Any lesion surgically evacuated
Non-evacuated mass lesion	High-density lesion >25 mL; not surgically evacuated

Data from Marshall LF, Marshall SB, Klauber MR, et al. A new classification of head injury based on computerized tomography. *J Neurosurg.* 1991;75 (Suppl.):S14–S20.

TABLE 50.4 Relationship of Computed Tomographic Classification to Outcome at Discharge

Category	No. of Patients	Unfavorable Outcome* (%)	Favorable Outcome† (%)
Diffuse injury I	52	38	62
Diffuse injury II	177	65	35
Diffuse injury III	153	84	16
Diffuse injury IV	32	94	6
Evacuated mass	276	77	23
Non-evacuated mass	36	89	11

Data from Marshall LF, Marshall SB, Klauber MR, et al. A new classification of head injury based on computerized tomography. *J Neurosurg.* 1991;75(Suppl.):S14–S20.
*Death, persistent vegetative state, or severe disability.
†Moderate disability or good recovery.

favorable outcomes occurred in only 5 of 490 patients.[43] Mortality rates ranged from 51% to 87% for patients with scores of 8 or less. In contrast, those whose initial GCS scores were 13–15 all survived and had favorable outcomes. Other clinical signs associated with death or a poor outcome are fixed and dilated pupils, intracranial hypertension, and hypotension.

The CT-defined extent of intracranial injury caused by the missile also has prognostic significance. Hyperdense lesions with a volume greater than 15 mL, midline shift of more than 3 mm, compressed or absent basal cisterns, SAH, and intraventricular hemorrhage are all associated with mortality rates of 80%–90%, as is a bullet trajectory that traverses both hemispheres, the basal ganglia, or the posterior fossa.[44]

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KEY POINTS

- Severe TBIs are the leading cause of morbidity and mortality for Americans between the ages of 1 and 45 years.
- Outcome after TBI is determined not only by the primary injury, such as skull fracture and subdural hematoma, but also by secondary injuries caused by physiologic derangements.
- Under normal conditions, the total volume within the skull remains constant and is determined by the sum of the CSF, blood, and brain tissue compartments.
- Proper field triage is critical for patients with suspected TBI, as the acutely injured brain is immediately vulnerable to secondary injury from physiologic derangements such as hypotension, hypercarbia, and hypoxemia.
- In the acute phase after injury, a patient with TBI is best treated with goal-directed therapy in an attempt to minimize the physiologic derangements that create secondary brain injury.
- A stepwise tiered approach for ICP treatment is usually followed, with the least toxic therapies used first and more toxic therapies added only if the initial tier of treatment is unsuccessful.

References for this chapter can be found at expertconsult.com.

ANNOTATED REFERENCES

Aiolfi A, Khor D, Cho J, et al. Intracranial pressure monitoring in severe blunt head trauma: does the type of monitoring device matter? *J Neurosurg.* 2018;128:828–833.
This is a retrospective observational study based on the American College of Surgeons Trauma Quality Improvement Program database, which was searched for all patients with isolated severe blunt head injury who had an ICP monitor placed in the 2-year period from 2013 to 2014. Extracted variables included demographics, comorbidities, mechanisms of injury, head injury specifics (epidural, subdural, subarachnoid, intracranial hemorrhage, and diffuse axonal injury), Abbreviated Injury Scale (AIS) score for each body area, Injury Severity Score (ISS), vital signs in the emergency department, and craniectomy. Outcomes included 30-day mortality, complications, number of ventilation days, intensive care unit and hospital lengths of stay, and functional independence.

Livingston DH, Lavery RF, Mosenthal AC, et al. Recovery at one year following isolated traumatic brain injury: a Western Trauma Association prospective multicenter trial. *J Trauma.* 2005;59:1298–1304.
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Spaite DW, Hu C, Bobrow BJ, et al. Mortality and prehospital blood pressure in major traumatic brain injury: the absence of a hypotension threshold. *JAMA Surg.* 2017;152(4):360–368.
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Spinal Cord Injury

Christian Cain and Jose J. Diaz, Jr.

INTRODUCTION

Despite many advances made in its diagnosis and treatment, spinal cord injury (SCI) continues to present challenging critical care issues to be treated, both acutely and chronically. The injury undoubtedly results in substantial psychological and financial impact not only on patients and their families but also to the general society. To date, the basis of care for patients with SCI has primarily focused on providing supportive care and preventing secondary injury. However, current investigations will certainly expand treatment options and improve the quality of care provided.

EPIDEMIOLOGY

The latest tabulations and projections provided by the National Spinal Cord Injury Statistical Center report an estimated incidence of 54 cases of patients with SCI per 1 million people living in the United States. More than 17,000 new patients will experience a SCI this year (this number does not include those with multiple traumatic injuries who die at the scene). The prevalence of injury is roughly 291,000, related mostly to improvements in critical care, and this number has increased steadily. The average patient is 43 years old, likely male, and may come from various socioeconomic and racial backgrounds.

The estimated lifetime cost of caring for one patient injured at the age of 25 with a cervical SCI is estimated to be more than $5 million. Acute care of patients with SCI only represents one phase of the rest of their lives. Seventeen percent of patients are employed 1 year postinjury, and this increases over time to around 30%. The combination of costly medical expenses, increasing overall survival, and high unemployment rates position SCI as a significant public health burden estimated to cost the United States at least $9.7 billion annually.[1]

ETIOLOGY

The causes of SCI vary widely. As of 2019, the leading cause of injury is still vehicular crashes, followed by falls, violence, and sports-related causes. Although these are among the most represented, it is essential to consider other nontraumatic etiologies, found in Table 51.1, as well. Early assessment starts with determining whether the injury is complete versus incomplete. This assessment is most important for predicting neurologic prognosis. The American Spinal Injury Association (ASIA) provides a classification system that characterizes the severity of cord injury. An initial incomplete injury (ASIA B–D) predicts a "potentially greater improvement in functional status" compared with a complete injury (ASIA A).[2]

PATHOPHYSIOLOGY

Acute SCI is the result of blunt or penetrating injury (traumatic etiologies) or numerous nontraumatic etiologies that result in the disruption of normal motor, sensory, or autonomic function. Two distinct phases characterize SCI. The primary phase consists of the physical compression of the spinal cord because of acute fractures or dislocation, leading to microhemorrhage, axonal damage, and cellular membrane damage.[3] The secondary injury is the result of cell membrane permeability changes, leading to loss of membrane stability, apoptosis, and tissue loss.[3] The degree and extent of the primary and secondary injuries determine the neurologic deficit.

INITIAL MANAGEMENT

If the patient might have a SCI, it is crucial to maintain a high index of suspicion and use spinal immobilization. These maneuvers include the use of in-line immobilization, maintenance of neutral position, cervical immobilization with a rigid collar, and use of backboards. From the field, a rigid collar immobilizes the cervical spine, and spinal precautions are taken to transport the patient. Upon arrival at the emergency department, precautions continue until physical examination and imaging confirm or refute a diagnosis. Rigid backboards are removed to avoid pressure ulceration. A thorough history and physical examination will determine whether the injury is complete or incomplete (i.e., is there any function below the level of injury?). Note any risk factors the patient may have for SCI. The level of injury is determined and baseline sensory, motor, and reflex abilities are described. For suspected high cervical injuries, baseline respiratory mechanic data, such as negative inspiratory force (NIF), force vital capacity (FVC), and tidal volume (TV), are useful for clinical assessment. The use of these data points as trends may highlight impending respiratory failure.

Resuscitation of the hypotensive patient with an SCI proceeds as with all trauma patients. Although upper spinal cord injuries can be associated with neurogenic shock, hypotension in the traumatically injured patient should be presumed hemorrhage until proven otherwise and may require isotonic fluid replacement or blood transfusion. An additional consideration is due in the case of the concomitant head injury, where the goal of hemodynamic support coexists with avoiding cerebral edema.

Once the ABCs of advanced trauma life support (ATLS) are addressed, the diagnostic algorithm proceeds to obtain imaging, as indicated. The National Emergency X-Radiography Utilization Study (NEXUS)[4] and the Canadian C-Spine Rule (CCR)[5] offer clinical guidance to help decide which patients do not require cross-sectional imaging to rule out cervical spine injury. Table 51.2 summarizes the guidelines. When considering imaging, it is essential to remember the

TABLE 51.1 Common Etiologies of Spinal Cord Injury

Category	Definition
Trauma	Blunt trauma
	Penetrating trauma
	Central cord syndrome
Nontraumatic	Ankylosing spondylitis
	Spina bifida
	Polio
	Osteoporosis
	Multiple sclerosis
	Spinal stenosis
	Metastatic fractures
	Acute blood loss/cord ischemia
	Anterior cord syndrome

TABLE 51.2 Decision Rules Guiding the Radiologic Assessment of Cervical Spine Injury

National Emergency X-Radiography Utilization Study (NEXUS)[4]	Imaging not necessary if age <60 + all five of the following: • Absence of posterior midline cervical tenderness • Normal level of consciousness • No evidence of intoxication • No abnormal neurologic findings • No painful distracting injuries
Canadian C-Spine Rule (CCR)[5]	Condition one (perform imaging): • Age >65 • Dangerous mechanism • Extremity paresthesia Condition two (low-risk factor allowing for range-of-motion assessment): • Simple rear-end motor vehicle collision • Arriving to emergency department in sitting position • Ambulatory at any time • Delayed onset of neck pain • Absence of midline cervical spine tenderness Condition three (active rotation of the neck 45 degrees to the left and right): • Imaging not necessary in patients able to rotate their neck, regardless of pain

Note: These rules are not applicable to patients with direct blows to the neck, penetrating trauma, or adults >60 years (NEXUS).

limitations of each of the modalities and choose the type that is best suited to answer the clinical question. Computed tomography (CT) is the most often used modality of imaging for several reasons. First, imaging can be obtained rapidly and can provide swift clinical answers. Second, it is available in most centers. Lastly, it can provide a complete assessment of other body zones that may be traumatized. Conversely, magnetic resonance imaging (MRI) is the preferred modality for ruling out ligamentous injury, hematoma, or disc herniation. Also, it provides the ability to assess the degree of cord compression.

In the case of the obtunded patient, practice guidelines from the Eastern Association for the Surgery of Trauma Practice Management Guidelines Committee describe three options for management. These are leaving the cervical collar in place until a clinical examination can be performed, removing the collar based on a negative CT alone, or obtaining an MRI of the cervical spine.[6] The literature lacks support for one method versus another. There is no guideline recommendation and should be at the discretion of each institution.

Finally, disposition of the patient is at the discretion of the clinician, but an intensive care unit admission, especially in the case of cervical injuries, for respiratory monitoring is recommended.

PROGNOSTIC FACTORS FOR RECOVERY

To properly advise the patient and family on the expected outcome and projected clinical course, a thorough history and physical examination, in addition to imaging, is necessary. In general, the patient's age, the involved level of injury, and the neurologic grade of injury (i.e., incomplete vs. complete) predict overall survival.[4] Patients with SCI often suffer multiple traumatic injuries in addition to any medical comorbidities they may have. Thus these factors will augment projected morbidity and mortality.[7] Initially, the ASIA score, mentioned earlier, aids not only in characterizing each injury type but also provides outcome data for each subtype.[8] A complete injury is the lack of motor or sensory function below the level of injury. Patients with a complete cervical SCI who remain neurologically deficient in the first 24 hours of admission are unlikely to regain significant ambulatory function.[9,10] Most patients who have an incomplete injury, however, will attain some degree of neurologic recovery within the first year postinjury. Cervical injury, when compared with thoracic or thoracolumbar injuries, have a higher potential for recovery.

Although much in this chapter corresponds to the acute management of a patient with SCI, it is worth noting that some patients may require the assistance of palliative care and hospice. It is of particular importance in the care of a patient with a remote history of SCI who is no longer responding to medical management of chronic complications of SCI; with progressive worsening of symptoms; those who have increased emergency department, inpatient, or outpatient visits related to complications; or those with a life-threatening complication. Further resources to aid in discussions of prognosis and functional outcome are located at https://pva.org/research-resources/publications/clinical-practice-guidelines/.

PEDIATRIC SPINAL CORD INJURY

Pediatric spine trauma is relatively uncommon, representing approximately 5% of all SCIs.[11] For a specific discussion of pediatric SCI, see published guidelines on this topic.[4]

THERAPEUTIC HYPOTHERMIA

With prevention being the key to decreasing the incidence of primary injury, there are few options to decrease secondary injury mechanisms. Because the treatment of SCI has consisted mainly of high-quality critical care and avoidance of secondary injury, other treatment options have been sought to add to the clinical armamentarium. One such intervention is therapeutic hypothermia. The use of therapeutic hypothermia began in the 1950s with cardiac surgery, and its use expanded to neurosurgery and SCI in the 1970s and 1980s with regional hypothermia.[12,13] The degree of cooling is divided by target temperature as "profound" (below 30°C), "moderate" (30°–32°C), and "modest" (32°–34°C).[14] The use of modest cooling is neuroprotective and reduces many of the known unwanted effects of cooling: acidosis, myocardial contractility abnormalities, coagulopathy, decreased renal

and hepatic function, electrolyte disturbances, prolonged drug clearance, and impaired insulin resistance.[13] Several animal models using modest cooling support the concept that hypothermia mitigates many of the secondary injury mechanisms.[12] The use of therapeutic hypothermia was introduced in 2007 to the United States publicly after the high-profile SCI of a National Football League player who sustained a C3–C4 injury with complete motor and sensory deficits. As part of his treatment, he received doses of methylprednisolone per the treating institution's protocol, prompt surgical decompression and fusion, and was cooled to 33.5°C 16 hours postoperatively. Within 2 hours, he experienced remarkable neurologic improvement that continued weeks into his recovery. The cause of the dramatic clinical improvement is likely the resolution of spinal shock and prompt repair of an incomplete SCI.[12] This outcome has prompted further questions regarding the potential use of hypothermia with SCI.

The American Association of Neurological Surgeons/Congress of Neurological Surgeons (AANS/CNS) position regarding therapeutic hypothermia recognizes the lack of data and evidence for or against its use and finds that "modest hypothermia might be applied safely to the population," but data from a multicenter, randomized controlled trial is needed.[15,16] The Miami Project for Paralysis and the University of Miami are among the leading centers investigating this question with their Acute Rapid Cooling Therapy for Injuries of the Spinal Cord (ARTIC) trial that has completed phase I and is undergoing phase II/III to evaluate the safety of different durations of hypothermia initiated 6 hours postinjury.[13] Without question, the findings of this study are necessary and highly anticipated.

MANAGEMENT IN THE INTENSIVE CARE UNIT

When admitted to the intensive care unit, patients with SCI are best approached with consideration of particular system issues. Knowledge of these critical concerns is imperative for caring for the patient and potentially avoiding complications that have a significant impact on morbidity and mortality. What follows is a systematic review of these critical topics.

Respiratory System

Respiratory complications are the most common cause of morbidity and mortality of patients with SCI. An estimated 80% of deaths in hospitalized patients with SCI are attributable to pulmonary causes, with pneumonia responsible for half of these cases.[17] Multiple hypotheses exist regarding the vulnerability of patients with SCI to infections. These include prolonged exposure to hospital pathogens, prolonged intubation, reduced ciliary clearance, nutritional deficiencies, and elemental exposure secondary to surgical procedures.[18] Additionally, the term *acute SCI immunodeficiency* has been coined to describe the impaired immunity that may occur secondary to the impaired gut microbiome.[18]

Besides the alteration of the patient's immunity, neurologic deficits affect the risk of pulmonary complications and lead to respiratory failure. In general, functional impairment worsens as the level of injury is more cephalad. A complete SCI, defined as the absence of motor or sensory function below the injury (ASIA score A), yields greater impairment than incomplete injuries (ASIA scores B–D).[18,19]

In neurologically intact patients, the diaphragm is the essential inspiratory muscle. It derives its innervation from the phrenic nerve supplied by cervical nerves three through five. Contraction of the diaphragm, along with the intercostal and scalene muscles, increases negative intrathoracic pressure and improves the efficiency of inspiration by caudally displacing the abdominal contents.[19] Most cervical spine injuries below C4 maintain diaphragm innervation. Diaphragm dysfunction occurs in patients with more cranially located lesions. Expiration, which is generally considered a passive process, requires the use of abdominal musculature to aid in thoracic emptying. Because the abdominal musculature receives innervation from thoracic and lumbar nerves, abdominal muscle function is absent in patients with complete injuries or injuries arising from upper thoracic levels. As a result, the combined clinical effect is a reduction in TV (most notably in the upright position versus supine), FVC, inspiratory capacity, and forced expiratory volume in 1 second (FEV_1).[19] In general, patients tend to exhibit respiratory decline between 24 and 72 hours postinjury. Thus early recognition of dysfunction requires a high index of suspicion.

The most common respiratory complications are atelectasis, pneumonia, and acute respiratory distress syndrome (usually related to multitrauma etiology). Although the incidence is low, pulmonary embolism is also of concern. The pathophysiology of most of the respiratory complications is related directly to the neurologic deficit and the inability for deep breathing, coughing, and clearing tracheobronchial secretions. Accumulation of secretions and mucous plugs may result in respiratory failure. Plugging can be prevented with regular pulmonary toilet chest physiotherapy, the use of intrapulmonary ventilation machines, bronchodilators, and mechanical ventilation.

Pulmonary infections are relatively common in patients with SCI for many of the reasons highlighted previously. The cause of pneumonia, when recognized, should be assumed normal respiratory flora if present on admission. Nosocomial organisms are likely causative agents the longer the patient resides in the hospital.

When patients with SCI are mechanically ventilated, their weaning should follow medical stabilization and take into consideration the location of the neurologic insult and any contribution the injury may have for further respiratory failure (i.e., higher cervical spine injuries). Weaning follows the typical course as with other critically ill patients. Special consideration for early tracheostomy should be made for patients with injury patterns that portend a poor respiratory outcome, preexisting pulmonary disease, and advanced age. Studies support the use of early tracheostomy in patients with these risk factors and may help shorten the time for liberation from mechanical ventilation.[20,21] Additionally, there is support from the literature that early tracheostomy, even after anterior spinal fusion, is safe and does not increase infectious risk.[21]

An estimated 40%–85% of patients with SCI will have a need for long-term ventilation. This need increases the higher the level of injury because of the loss of neural input to the diaphragm. Diaphragmatic pacing systems (DPSs) are used to stimulate diaphragm contraction and aid in ventilator liberation. Published retrospective data from one institution's experience with DPS resulted in fewer days to ventilator liberation and shorter hospital length of stay in patients with DPS compared with those without.[22] More investigation is needed to elucidate the complete benefits DPS may offer patients with SCI, but should be considered among the strategies for ventilator liberation.

Cardiovascular System

Spinal cord injuries above T6 disrupting sympathetic input may lead to neurogenic shock. Heralded by the presence of bradycardia and hypotension, neurogenic shock is the manifestation of unopposed vagal tone secondary to the disruption of sympathetic input, slowing the heart rate, decreasing systemic vascular resistance, and ultimately requiring vasopressor support. Although this clinical entity exists in patients with SCI, hypotension in any acutely traumatized patient should be considered the result of hypovolemic/hemorrhagic shock until proven otherwise—a condition corrected only with blood replacement and/or surgical hemostasis.

This clinical entity differs from the commonly confused misnomer of "spinal shock," which refers to temporary disruption of sensory and motor abilities below the level of SCI secondary to contusion with the gradual recovery of reflexes. Spinal shock occurs mainly with complete injury and is seen clinically as a period of areflexia and flaccidity replaced with hypertonia and spasticity.

The hemodynamic goal for the patient with SCI is the restoration of normal hemodynamics. Correction of hypotension should proceed with periodic intravenous (IV) fluid boluses to restore intravascular volume and may ultimately require the use of vasopressors. In cases of decreased systemic vascular resistance, a peripherally acting vasoconstrictor, such as norepinephrine, will counter the tendency for venous pooling and increase cardiac venous return.

Hypotension should be avoided, as decreased perfusion may accentuate the blossoming secondary injury of the spinal cord. Early aggressive volume resuscitation and increasing a patient's mean arterial pressure ("MAP push") is associated with enhanced neurologic outcome in SCI, should be considered an additional management tool,[23] and has become an essential component of our clinical practice in patients with SCI. Catapano and colleagues found a positive correlation between MAP ≥85 mm Hg and neurologic recovery in ASIA A, B, and C subtypes and concluded that those with initially complete injuries might benefit the most from "MAP push."[24] Current management guidelines call for early surgical decompression and maintenance of MAP ≥85 mm Hg for 5 consecutive days.[25]

Gastrointestinal System

Most of the gastrointestinal complications in patients with SCI are a result of unopposed vagal stimulation. The goals for patients are to tolerate oral intake and have regular elimination of waste without diarrhea or constipation. Some well-recognized bowel symptoms with SCI are constipation and fecal incontinence. Additional symptoms of concern are generalized abdominal pain and distension. Gastric distention may predominate upon initial management, and nasogastric tube placement is indicated.[26]

Patients with SCI are at particular risk for developing stress gastric or duodenal ulcers and require acid suppression prophylaxis. This risk increases in the case of patients receiving corticosteroids, as the risk of gastrointestinal bleeding in patients receiving corticosteroids (methylprednisolone) in the NASCIS II trial was 1.5 times that of the control group.[27,28]

Gastric emptying may also be impaired and complicate the full resumption of oral intake. Feeding access may then be required to provide adequate caloric intake. Professional swallow evaluation may be deemed necessary, particularly in patients with complete SCI, as impaired abdominal muscular innervation is associated with this injury type and may lead to gastrointestinal motility abnormalities.

Urinary System

Several patterns of SCI result in genitourinary system complications. In traumatic suprasacral injury, there is a period of spinal shock, as described earlier in the "Cardiovascular System" section, with resultant detrusor atony and areflexia.[29] The bladder experiences no contractions during this time, and the return of function follows the recovery of skeletal muscle reflexes (typically 6–8 weeks postinjury). The bladder atony manifests clinically as urinary incontinence and may lead to autonomic dysreflexia (also discussed in the "Cardiovascular System" section). Patients may experience "detrusor-external sphincter dyssynergia," where the bladder contracts but the external sphincter may not completely relax, leading to inefficient voiding. The result is high voiding pressures required for bladder emptying, hydronephrosis, and renal dysfunction if not recognized in routine outpatient care of the patient. In SCI with sacral lesions, areflexic bladder predominates, where the bladder does not contract, causing an overdistended bladder.[29]

A Foley catheter is placed initially for bladder decompression and may be switched to intermittent catheterizations, every 4–6 hours, 4 days postinjury to maintain bladder volumes less than 500 mL. The combination of bladder dysfunction, stasis, and instrumentation increases the risk of urinary tract infection, and diagnosis follows the routine algorithm. More comprehensive urinary system management recommendations can be found at https://pva.org/research-resources/publications/clinical-practice-guidelines/.

Hematologic System

Patients with SCI are at risk for venous thromboembolism (VTE) despite an overall decreasing incidence of occurrence in recent years. These thrombi in the deep veins of the upper or lower extremity may propagate, leading to pulmonary emboli. The majority of these events occur early in the clinical course of treatment. A high index of suspicion should be maintained, especially in patients of advanced age, those who are obese, those with complete injuries, and those with a history of previous thromboembolic events.[30,31] Current recommendations for prevention are the combined use of mechanical, pneumatic compression stockings and chemical prophylaxis with low-molecular-weight heparins (LMWHs), as the duration of its half-life is longer. Additionally, a lower risk of hemorrhagic complications is associated with the use of LMWH versus other heparins, and they have a more predictable dose-related effect.[32]

Evaluation for suspected venous thromboemboli requires the use of Doppler ultrasound. Cross-sectional imaging with IV contrast is used for high-resolution imaging if pulmonary embolism is suspected. Heparin is used to treat identified thromboemboli, and an inferior vena cava (IVC) filter should be considered in cases where a contraindication to anticoagulation exists. Prophylactic placement of vena cava filters in patients with SCI is not recommended.[32–34] This recommendation rests on two important findings. First, the trend of using IVC filters in trauma has decreased despite level three recommendation from the Eastern Association for the Surgery of Trauma in 2002 suggesting IVC filters be placed prophylactically in "very high-risk trauma patients" who either cannot be anticoagulated or have an anticipated prolonged immobilization course. This decrease correlates with the findings that in some trauma patients, the use of IVC filters correlates with increased deep venous thrombosis (DVT) risk.[34] Second, despite the decrease in IVC filter use, the incidence of pulmonary embolism has remained roughly the same. The conclusion suggests that there is limited utility in the use of IVC filters in trauma patients.[33]

Integumentary System

Pressure ulcers are the most common skin complication affecting patients with SCI. Ulcers result from contact of the skin with support surfaces and result in ischemic insult to microvasculature, pain, necrosis, and skin sloughing.[35] A thorough history and physical examination identifies patients with skin at risk for pressure ulcers. Strategies for prevention include pressure offloading, daily integumentary checks, frequent repositioning, and proper wound care.[35] Treatment of the wound may be nonsurgical, surgical, or a combination of both. More extensive information is at https://pva.org/researchresources/publications/clinical-practice-guidelines/.

PHARMACOTHERAPY

The role of corticosteroids and gangliosides in the treatment of acute SCI is highly debated. The proposed benefit of the use of methylprednisolone

sodium succinate is attributed to its antiinflammatory properties. The properties prevent "the loss of spinal cord neurofilament proteins, facilitate neuronal excitability and impulse conduction, improve blood flow, enhance N^+/K^+-ATPase activity, and preserve the cord structure by decreasing lipid peroxidation and preventing ischemia-induced tissue damage."[3] To date, three trials have evaluated the outcomes of the use of corticosteroids in patients with SCI. Summarized in Table 51.3, the NASCIS trials (I–III)[27,36,37] explore questions regarding the role of glucocorticoids in the treatment of SCI. The lack of level one, evidence-based evidence makes the routine use of steroids highly controversial.

The use of GM-1 gangliosides has been proposed as a potential treatment for SCI. These compounds are found within the cell membrane of mammalian central nervous tissue and work to promote anti-excitotoxic activity and neuritic sprouting, potentiate the effect of nerve growth factor, and prevent apoptosis.[28] There are two studies published by Geisler and colleagues describing the use of the GM-1 ganglioside Sygen in acute SCI patients.[38,39] These outcome data did not demonstrate a significant difference in neurologic recovery between those receiving the drug versus placebo. Because of the limited supporting data, the most recent AANS/CNS guideline contains level one recommendations against the use of corticosteroids and GM-1 ganglioside for the treatment of acute SCI.[28]

CHRONIC COMPLICATIONS

Because neurologic deficits experienced by patients with SCI span multiple organ systems, chronic complications are frequent. A listing of these complications is included in Table 51.4.

TABLE 51.4 Common System-Based Problems in Patients With Spinal Cord Injury (Acute and Chronic)

	Acute	Chronic
Respiratory system	Atelectasis Pneumonia Diaphragmatic paralysis Need for tracheostomy	Atelectasis Pneumonia
Cardiovascular system	Neurogenic shock Symptomatic bradycardia Coronary artery disease (chronic)	Autonomic dysreflexia Orthostatic hypotension
Gastrointestinal system	Stress ulceration Delayed gastric emptying	Chronic diarrhea or constipation SMA syndrome Neurogenic bowel
Genitourinary system	Urinary tract infection Sexual dysfunction	Urinary calculi
Hematologic system	Venous thromboembolism	Venous thromboembolism
Integumentary/ musculoskeletal systems	Decubitus ulcers	Contractures Spasticity and pain syndromes Osteoporosis and bone fractures

SMA, Superior mesenteric artery.

FUTURE INTERVENTIONS

The current treatment of SCI focuses on spinal cord stabilization and prevention of secondary injury. However, more potential targets for therapy will be identified as more is understood regarding the pathogenesis of injury. As of this writing, there are no Food and Drug Administration (FDA)–approved treatments available for SCI and a limited number of evidence-based support therapies for symptom and complication management.[40] The combined effort of the National Institutes of Health (NIH), societies such as the AANS/CNS, and major academic institutions have led to the development of new clinical trials that may address the dearth of information and data. A few privately funded institutions are also dedicated to the development of therapeutics and expanding the available knowledge.

In general, the treatment arms of research can be divided broadly into two main categories: those that limit secondary injury and those that promote regeneration. Future areas of investigation will include pharmacologic treatments for SCI, cell-based therapies to aid in the modulation of the inflammatory response in secondary injury, biomaterials to aid in structural repair of the spinal cord, and interventions aimed to improve functional and rehabilitative outcomes.[41]

CONCLUSION

Although there have been several advancements in the acute identification and treatment of SCIs in recent years, many questions remain unanswered that could guide clinical decision making acutely and aid in the management of chronic complications. Many of those questions are currently under investigation with high-quality randomized controlled trials. For the time being, the most prudent strategy would be the provision of evidence-based strategies for high-quality critical care delivery and maintaining an open mind to the strategies that may be proposed.

TABLE 51.3 Summary of Key Studies of Methylprednisolone Use in Spinal Cord Injury

Study Name	Study Summary	Conclusions
NASCIS I[36]	Low- vs. high-dose methylprednisolone (MP) for 10 days' duration with acute spinal cord injury (SCI)	Patients receiving high-dose steroids had more incidence of infections.
NASCIS II[27]	MP vs. naloxone vs. placebo in thoracic SCI patients	No difference in resulting neurologic function; post ad hoc findings showed a moderate motor improvement in patients receiving MP versus placebo. Wound infections more commonly noted in MP group.
NASCIS III[37]	MP ×48 hours vs. MP ×24 hours vs. tirilazad mesylate ×48 hours	No difference in outcomes in patients receiving medications within 3 hours of injury; MP given between 3 and 8 hours of injury associated with greater motor but not functional recovery. Increased incidence of sepsis and pneumonia in MP group.

KEY POINTS

- SCI continues to be a relevant healthcare issue.
- Most SCIs result from high-speed motor vehicle collisions.
- Outcomes of SCI are influenced by primary (occurring at the time of impact) and secondary (causing the progressive changes associated with SCI) injury.
- The sequelae of SCI span various organ systems.
- There are not many novel interventions for treatment; current treatment depends on the delivery of high-quality critical care.

References for this chapter can be found at expertconsult.com.

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Retrospective review of 112 patients with acute SCI; 47% had prophylactically placed IVC filters and 20.7% of the cohort with DVT versus 5.2% in those with no filter.

Hoffman JR, Mower WR, Wolfson AB, et al. Validity of a set of clinical criteria to rule out injury to the cervical spine in patients with blunt trauma. *N Engl J Med.* 2000; 343:694–699.
NEXUS criteria recommendations providing a clinical framework for deciding which patients require advanced imaging to rule out cervical spine injury.

Lozano C, Chen K, Marks J, et al. Safety of early tracheostomy in trauma patients after anterior cervical fusion. *J Trauma Acute Care Surg.* 2018;85(4):741–746.
Retrospective review of 39 patients who received tracheostomy within 4 days of anterior cervical fusion compared with 59 patients who received tracheostomy between postoperative days 5 and 21; no increase in infections was noted in the early tracheostomy group.

Stiell IG, Wells GA, Vandemheen KL, et al. The Canadian C-Spine Rule for radiography in alert and stable trauma patients. *JAMA,* 2001;286(15):1841–1848.
CANADIAN C-Spine Rule recommendations providing a clinical framework for deciding which patients require advanced imaging to rule out cervical spine injury.

Vale FL, Burns J, Jackson AB, et al. Combined medical and surgical treatment after acute spinal cord injury: results of a prospective pilot study to assess the merits of aggressive medical resuscitation and blood pressure management. *J Neurosurg.* 1997;87(2):239–246.
Seventy-seven patients with acute SCI treated with aggressive volume re-expansion and "MAP push"; treatment associated with favorable outcomes.

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Neuroimaging

Orrin L. Dayton IV

This chapter reviews available neuroimaging methods and their application in the evaluation and management of the critically ill and injured.

IMAGING MODALITIES

Radiography

Plain radiography plays a minor role in evaluating the neurologically ill or injured patient. Radiography is not sensitive for the detection of intracranial pathology and is not part of the standard imaging approach for the evaluation of patients with such pathology.[1] Conventional radiography plays a role in the evaluation of suspected spinal pathology, particularly in the setting of traumatic spine injury and assessment of spinal stability and postoperative complications.[2] Plain radiography is also used as a screening tool to assess for metallic foreign bodies, particularly in the orbits and intracranial compartment, in patients requiring magnetic resonance imaging (MRI), as the presence of such foreign bodies may result in injury to adjacent structures secondary to heating and motion from the strong magnetic field.[3]

Computed Tomography

Computed tomography (CT) uses ionizing radiation to create anatomic images on the basis of differential attenuation of photons between various tissue types. This results in an image composed of grayscale pixels on a spectrum ranging from dark, or hypodense, from tissues with low photon attenuation (air, water, fat) to bright, or hyperdense, from tissues with high photon attenuation (bone, metal). Soft tissues, such as brain parenchyma and muscle, are intermediate attenuators of photons and therefore exhibit grayscale values between low and high attenuators.[4]

CT is widely available, and there are no absolute contraindications to CT imaging in the acute setting. Its use of ionizing radiation does confer minimal risk to the patient related to radiation exposure. However, in the acute setting, the risk–benefit ratio almost always points towards imaging to aid in timely diagnosis. Advances in CT technology, particularly multidetector row CT (MDCT) and volumetric acquisition, allow for rapid imaging with high temporal and spatial resolution.[5] MDCT also allows for thin-slice image acquisition with the ability to manipulate CT data in multiple planes and perform postprocessing, such as volume rendering.

Iodinated contrast may be administered intravenously to increase sensitivity for detection of blood–brain barrier disruption and mass lesions and to evaluate the cerebral vasculature with CT angiography (CTA) techniques. CT perfusion imaging of the brain allows for assessment and quantification of brain perfusion parameters, including cerebral blood flow, cerebral blood volume, mean transit time, and time to peak enhancement. CT perfusion imaging is primarily used in the setting of cerebral ischemia.

Magnetic Resonance Imaging

MRI uses a strong external magnetic field and a series of radiofrequency pulses (nonionizing radiation) to confer energy to protons in tissues. Images are constructed based on the differential responses of these energized protons in different tissues (protons in water versus protons in fat). Imaging parameters are adjusted to allow for variable tissue weighting, thus highlighting specific tissues and pathologic processes.[6]

MRI is more sensitive than CT for detection of brain and spine pathology in almost all circumstances. However, longer imaging time precludes particularly unstable patients, given the required time away from the intensive care unit. Patients with certain medical devices and known or suspected retained ferromagnetic foreign bodies may not be eligible for MRI.

MRI uses nonionizing radiation. Therefore no radiation risk is conferred to patients. Gadolinium-based contrast media can be administered intravenously to detect blood–brain barrier disruption, masses, and vascular lesions. Contrasted imaging may also be used to assess the cerebral vasculature and brain perfusion parameters, similar to that described with CTA and CT perfusion. Noncontrast MR angiography (MRA) and perfusion techniques are also available for patients who cannot receive gadolinium-based contrast. Gadolinium is now known to be retained in the brain and in other organ systems. There are no known clinical sequelae to date; however, many investigators are studying the potential long-term effects of gadolinium retention.[7]

Several advanced MRI techniques are used in the evaluation of critically ill patients. Diffusion-weighted imaging (DWI) is based on the principle of water molecules being freely mobile and able to diffuse freely in all directions. Some pathologic processes, such as ischemia, cytotoxic edema, and abscess, restrict this free diffusion of water, which can be represented visually with DWI techniques. Diffusion restriction is also seen in pathologic processes associated with high cellularity, such as high-grade neoplasms. Diffusion-tensor imaging (DTI) is based on the same principles as DWI and allows for anatomic mapping of white matter tracts in the brain. This can be used to assess for alterations in brain connectivity in the setting of traumatic brain injury and to assess the anatomic relationship of white matter tracts to focal brain lesions.[8]

Nuclear Medicine

Several nuclear medicine studies are encountered in the neurocritical care setting. Planar brain scans using Tc-99m–labeled radiotracers

assess brain perfusion and are used in the determination of brain death.[9] Nuclear medicine cisternography is used to confirm and localize the site of a suspected cerebrospinal fluid (CSF) leak. Positron emission tomography (PET) and single-photon emission tomography (SPECT) play a role in the evaluation of epilepsy and seizure focus localization. Nuclear medicine scans using gallium-68 and radiolabeled white blood cells are used to localize occult infection and are useful in monitoring response to therapy, particularly in the skull base and spine.

BRAIN

Patterns of Disease

Cerebral Edema

Cerebral edema is a common response to brain pathology and is classified as either cytotoxic, vasogenic, or interstitial. Cytotoxic edema results from failure of adenosine triphosphate (ATP)–dependent transmembrane ion channels, leading to intracellular accumulation of fluid. The major causes of cytotoxic edema are ischemia and excitotoxicity. Vasogenic edema is the result of blood–brain barrier disruption, resulting in extravascular extravasation of serum proteins and fluid into the extracellular space. Common pathologic processes that cause vasogenic edema include neoplasms, infection, hemorrhage, and acute hypertensive syndromes. Interstitial edema occurs in the setting of increased ventricular pressure, which results in CSF flow through the minor CSF drainage pathways in the periventricular white matter. Interstitial edema is seen in the setting of acute hydrocephalus.[10] Regardless of subtype, edema appears as areas of hypodensity on CT and increased intensity on T2-weighted and fluid-attenuated inversion recovery (FLAIR) MRI sequences.

Cytotoxic edema presents on CT as areas of hypodensity involving the cerebral cortex to a greater extent than the underlying white matter, resulting in loss of normal gray matter–white matter differentiation. Gyri become swollen, and sulci are effaced (Fig. 52.1A). MRI will show increased signal, or hyperintensity, on T2-weighted and FLAIR sequences, which are sensitive to water. T1-weighted sequences will show corresponding regions of decreased signal, or hypointensity. DWI sequences will show hyperintensity, implying the presence of restricted diffusivity of water molecules within swollen neurons and glial cells. In contrast to cytotoxic edema, vasogenic edema preferentially involves white matter with relative sparing of gray matter. CT and fluid-sensitive MRI sequences show hypodensity and hyperintensity, respectively, throughout the involved white matter extending up to adjacent cortex and deep gray structures (see Fig. 52.1B). Interstitial edema presents in the setting of acute hydrocephalus and will show hypoattenuation on CT and increased signal on T2/FLAIR MRI sequences in the periventricular white matter, especially near the frontal and occipital horns of the lateral ventricles (Fig. 52.2).[11]

Intracranial Hemorrhage

The CT appearance of intracranial hemorrhage varies with chronicity. Immediate hyperacute hemorrhage may appear isodense to brain parenchyma or heterogeneous with admixed areas of isodensity and hyperdensity. Acute hematoma (0–3 days) develops when blood begins to form clots and retract, resulting in increased density over the ensuing hours and days. Focal areas of low density within an acute hematoma, particularly in a swirling pattern, may represent active bleeding. Acute hemorrhage reaches peak density at 3 days.

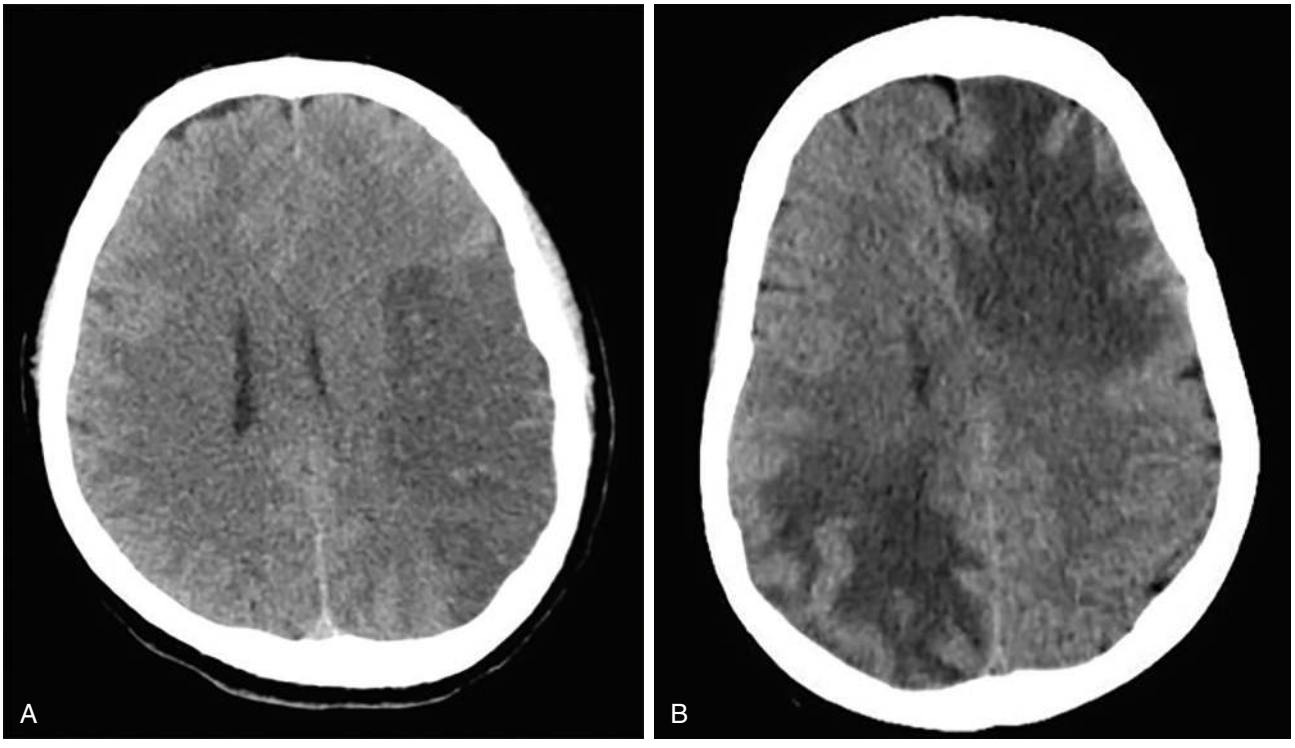

Fig. 52.1 Cytotoxic versus vasogenic edema. A, Noncontrast CT in this patient with left middle cerebral artery territory infarction shows cytotoxic edema as a region of hypoattenuation involving the cortex and adjacent white matter with effacement of the sulci. **B,** Vasogenic edema in a patient with metastatic disease presents as white matter–predominant hypoattenuation with relative sparing of the overlying cortex.

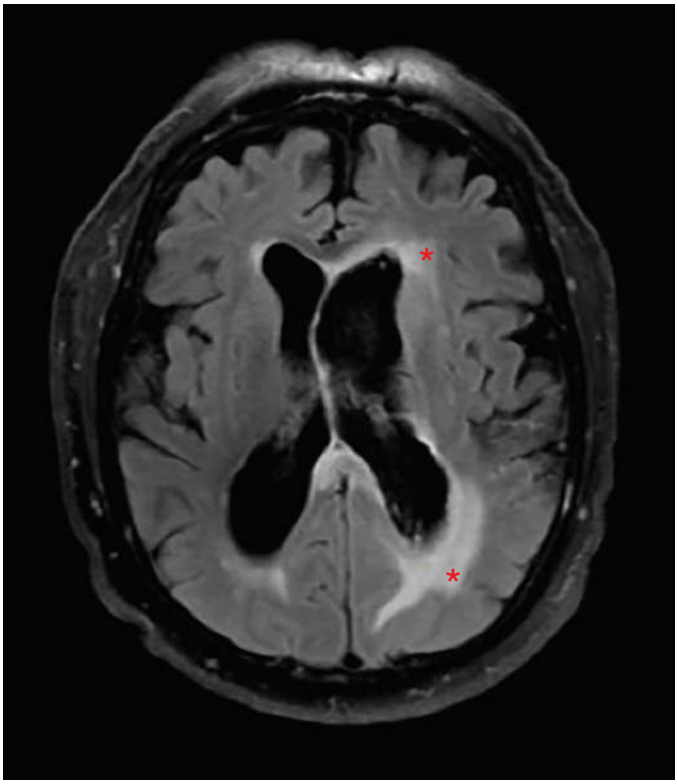

Fig. 52.2 Interstitial edema. FLAIR MRI shows hyperintense fluid signal in the periventricular white matter adjacent to the frontal and occipital horns of the left lateral ventricle *(red asterisks)* in this patient with intraventricular hemorrhage and acute obstructive hydrocephalus.

Progressive attenuation loss occurs after day 3 during the subacute phase of intracranial hemorrhage, with blood products usually becoming isodense to brain parenchyma 1–4 weeks after the initial hemorrhage. Chronic hemorrhage appears hypodense to parenchyma and similar to that of CSF, sometimes causing a diagnostic dilemma when trying to differentiate chronic subdural hematoma from subdural hygroma (Fig. 52.3).

Evolution of intracranial blood products on MRI is more complicated than on CT and is dependent on the stage of hemoglobin metabolism. Acute hemorrhage is composed predominantly of red blood cells (RBCs) containing deoxyhemoglobin, which presents as isointensity on T1-weighted images and hypointensity on T2-weighted images. Deoxyhemoglobin is oxidized to methemoglobin within RBCs during the early subacute stage, resulting in T1 hyperintensity and T2 hypointensity (Fig. 52.4A and B). The late subacute stage is characterized by RBC lysis, resulting in the release of methemoglobin into the extracellular space, which exhibits T1 hyperintensity and T2 hyperintensity (see Fig. 52.4C and D). Methemoglobin is consumed by macrophages and converted to ferritin and hemosiderin, resulting in areas of T1 and T2 hypointensity at the site of prior hemorrhage, representing chronic blood products (Fig. 52.5).

Mass Effect and Herniation

The dural partitions within the skull—the falx cerebri and the tentorium cerebelli—create compartments across which the brain may herniate.[12] The cranial vault is rigid, and therefore increased intracranial volume, in the form of blood, edema, or mass lesion, causes mechanical displacement of the brain parenchyma across dural reflections.[13]

Subfalcine herniation describes the herniation of the inferior portion of the medial frontal and parietal lobes—the cingulate gyrus—under the inferior margin of the falx cerebri. The ipsilateral ventricle

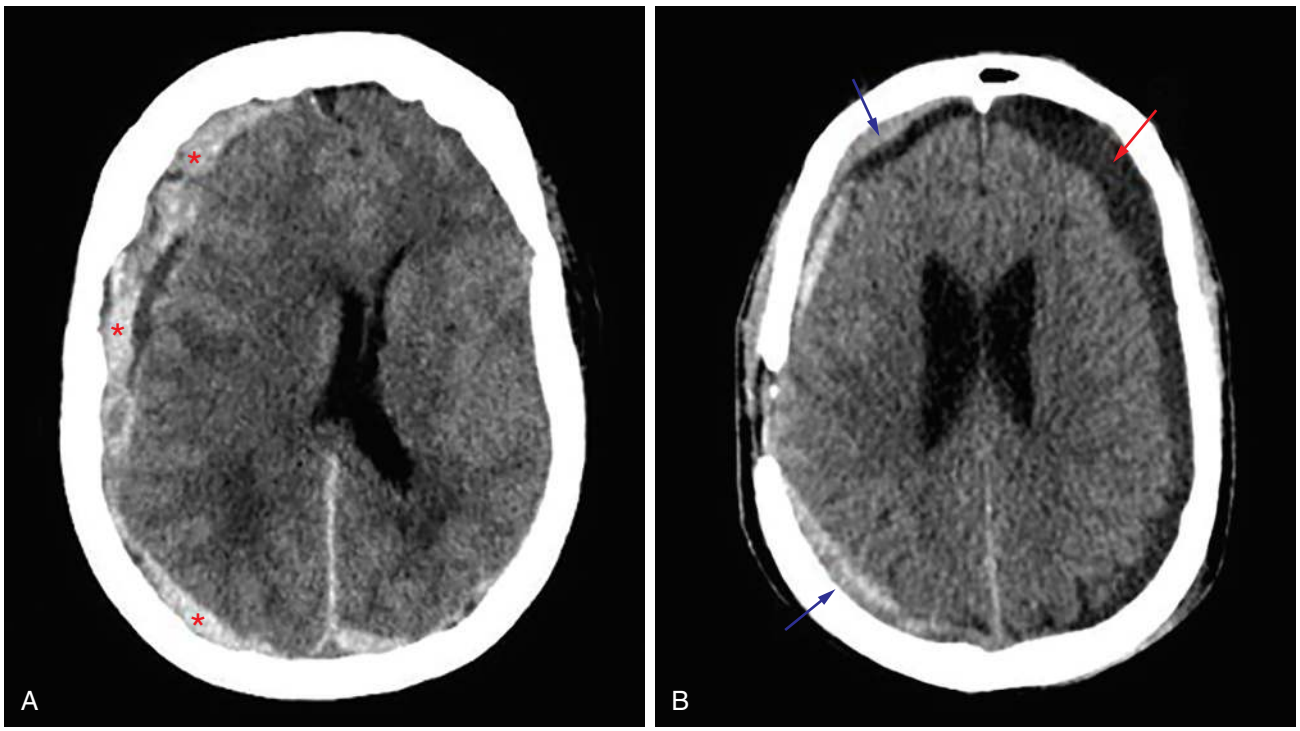

Fig. 52.3 Evolution of intracranial hemorrhage on CT. A, Acute subdural hematoma appears as a crescentic extraaxial collection hyperdense to adjacent brain parenchyma *(red asterisks)*. **B,** Subacute blood appears isodense to brain *(blue arrows)* and chronic blood appears hypodense to brain *(red arrow)* in this patient with mixed-age subdural hematomas.

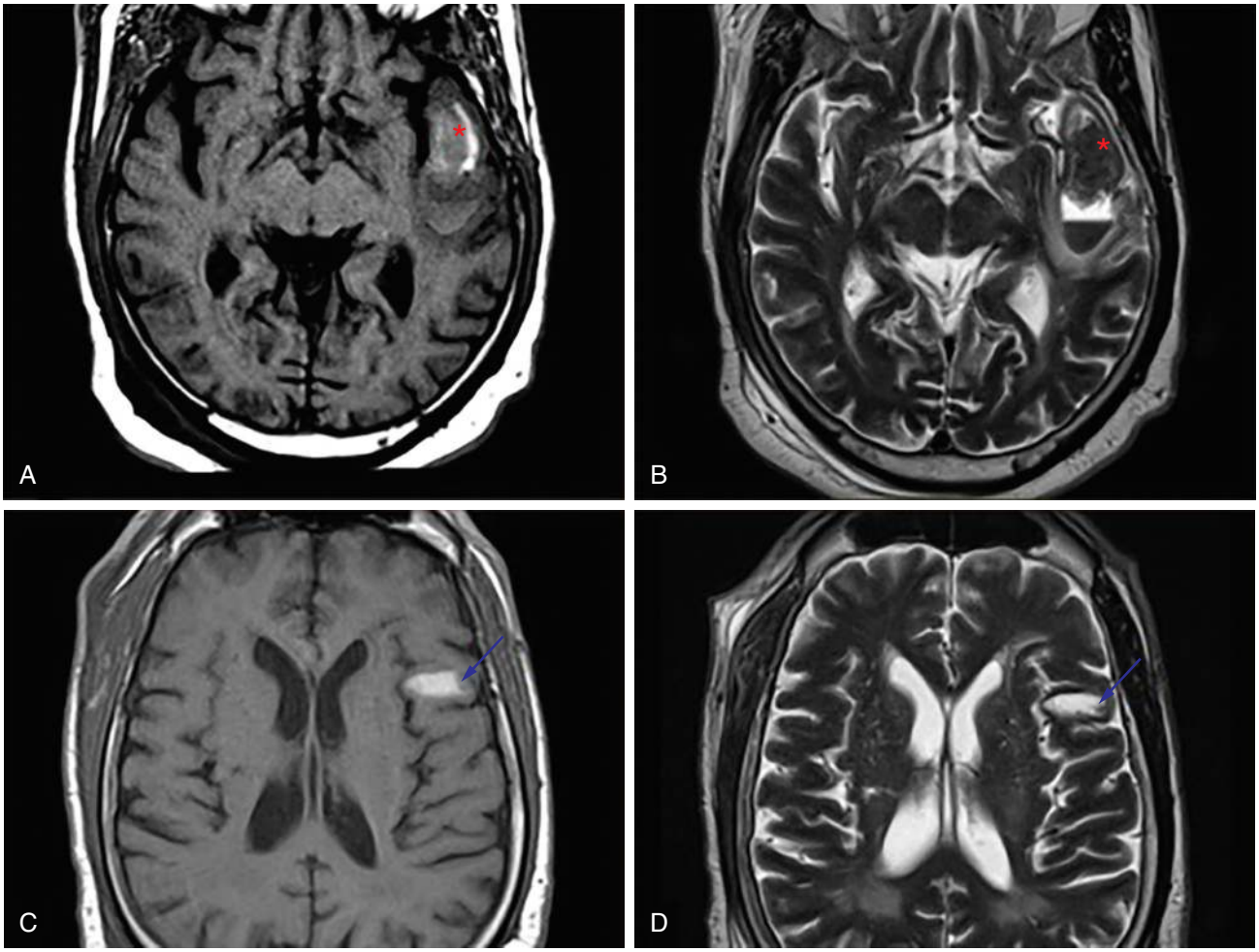

Fig. 52.4 Evolution of intracranial hemorrhage on MRI. **A and B,** Early subacute blood appears hyperintense on T1-weighted images **(A)** and hypointense on T2-weighted images **(B)** *(red asterisks).* **C and D,** Late subacute blood appears hyperintense on both T1- and T2-weighted images *(blue arrows).*

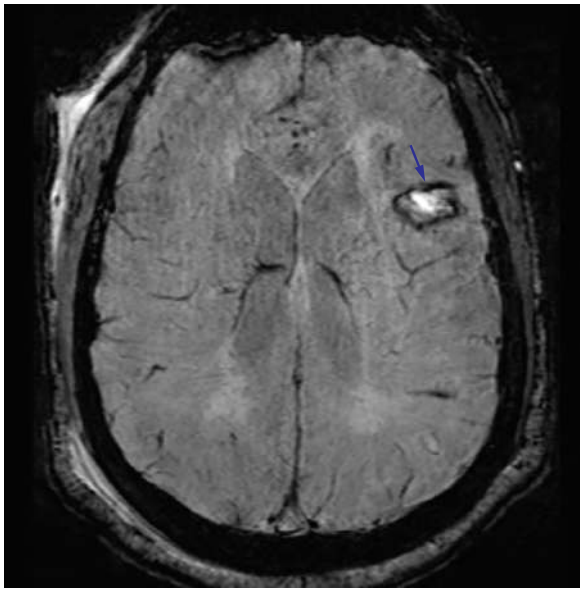

Fig. 52.5 Chronic blood products on susceptibility-weighted imaging (SWI). SWI sequence shows peripheral hypointensity surrounding an evolving intraparenchymal hemorrhage, representing deposition of chronic blood products in the form of hemosiderin *(blue arrow).*

will appear distorted and displaced across the midline, and the midline structures, including the third ventricle, will be shifted to the contralateral side. Severe subfalcine herniation may compress the contralateral foramen of Monro, resulting in entrapment of the contralateral lateral ventricle. The anterior cerebral arteries (ACAs) may become compressed under the falx cerebri, resulting in ACA territory ischemia and infarction (Fig. 52.6A).[14]

Descending transtentorial herniation occurs when the medial temporal lobe is displaced medially and inferiorly over the free edge of the tentorium cerebelli. The herniating brain effaces the suprasellar cistern and compresses the midbrain. The contralateral cerebral peduncle may be compressed against the contralateral tentorium, a phenomenon eponymously termed *Kernohan notch.* The ipsilateral posterior cerebral artery (PCA) may become compressed along the tentorial edge, resulting in occipital lobe ischemia and infarction (see Fig. 52.6B).[15] Ascending transtentorial herniation occurs in the setting of cerebellar pathology and is seen when the superior cerebellum herniates up through the tentorial incisura. The quadrigeminal cistern is effaced and the tectal plate of the midbrain is compressed, resulting in obstruction of the cerebral aqueduct and obstructive hydrocephalus.[16]

Tonsillar herniation describes the inferior displacement of the cerebellar tonsils through the foramen magnum into the upper cervical canal and occurs in the setting of posterior fossa pathology. The

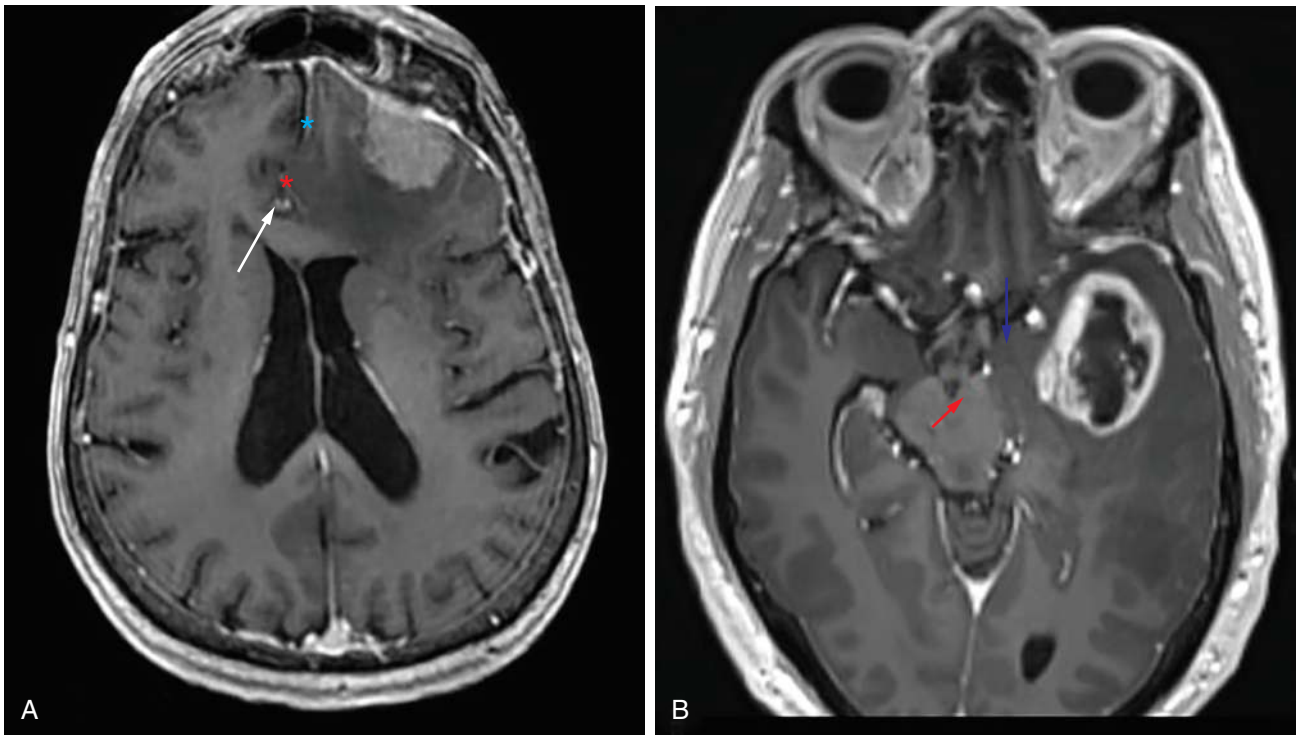

Fig. 52.6 Subfalcine and downward transtentorial herniation. **A,** T1-weighted image with contrast shows herniation of the left cingulate gyrus *(red asterisk)* under the inferior margin of the falx cerebri *(blue asterisk)* in this patient with a left frontal meningioma. Note deviation of the anterior cerebral arteries to the right *(white arrow)*, placing them at risk for injury. **B,** T1-weighted image with contrast shows downward herniation of the left uncus over the tentorium *(blue arrow)* in this patient with high-grade glioma, causing compression of the ipsilateral cerebral peduncle *(red arrow)*.

cerebellar tonsils may compress the medulla and upper cervical spinal cord, resulting in severe neurologic dysfunction and cardiorespiratory arrest.[17]

Transalar herniation describes the herniation of the brain and middle cerebral artery (MCA) vessels across the greater wing of the sphenoid and may be ascending (temporal lobe and MCA vessels) or descending (inferior frontal lobe). The major complication is MCA territory ischemia and infarction.

Pathologic Conditions

Traumatic Brain Injury

Traumatic brain injury (TBI) can be divided into primary injury and secondary injury. Primary injuries occur at the time of initial trauma and include skull fractures, contusion, intracranial hemorrhage, and axonal shear injury. Secondary injuries occur in a delayed manner and include cerebral edema and the herniation syndromes. Secondary injuries exacerbate the damage done at the time of primary injury.[18] The role of neuroimaging in TBI is to identify treatable primary injuries and to monitor for the development of secondary injuries. CT is the primary modality used for initial evaluation of TBI because of its wide availability, short image acquisition time, high sensitivity for intracranial hemorrhage, and lack of absolute contraindications. MRI is used to answer specific clinical questions and to provide more detailed information about the extent of injury.[19]

Cerebral contusions involve direct injury to the cortex and subjacent white matter as a result of direct impact of the brain against the calvarium or skull base. Typical locations include the inferior frontal and temporal lobes because of their close proximity to the undulating cortex of the anterior and middle cranial fossae, respectively. Contusions present as areas of hypodensity involving the cortex and white matter representing edema, which causes local mass effect and sulcal effacement. Areas of admixed hyperdensity represent petechial hemorrhage. Edema and hemorrhage often progress, or "bloom," in the first 24–48 hours resulting in increased mass effect and risk for secondary injury from brain compression and herniation (Fig. 52.7).[20]

Intracranial hemorrhage is a common sequela of TBI and may involve all intracranial compartments. Epidural hematoma appears as a lentiform extraaxial hematoma that does not cross calvarial suture lines. The outer layer of dura is adherent to the suture and is not stripped away by the expanding hematoma. Injury to a meningeal artery from a skull fracture is the most common etiology, and, as such, rapid hematoma expansion is possible (Fig. 52.8).[21] Subdural hematomas are caused by torn bridging veins, which traverse the subdural space as they drain the cerebral cortex to the overlying dura. They appear as a crescent-shaped extraaxial hematoma that crosses calvarial suture lines but not dural reflections (see Fig. 52.3).[22] Subarachnoid hemorrhage (SAH) and intraventricular hemorrhage (IVH) arise from injured cortical vessels and subependymal vessels, respectively. Traumatic SAH will present as curvilinear areas of high density within cerebral sulci commonly layering dependently in the posterior aspect of the sylvian fissure and the interpeduncular fossa of the midbrain. Traumatic IVH will present as high-density layering dependently in the occipital horns of the lateral ventricles.

Diffuse axonal injury (DAI) represents a pattern of injury involving axonal stretching and, in severe cases, shearing. It results from differential acceleration/deceleration forces on gray and white matter

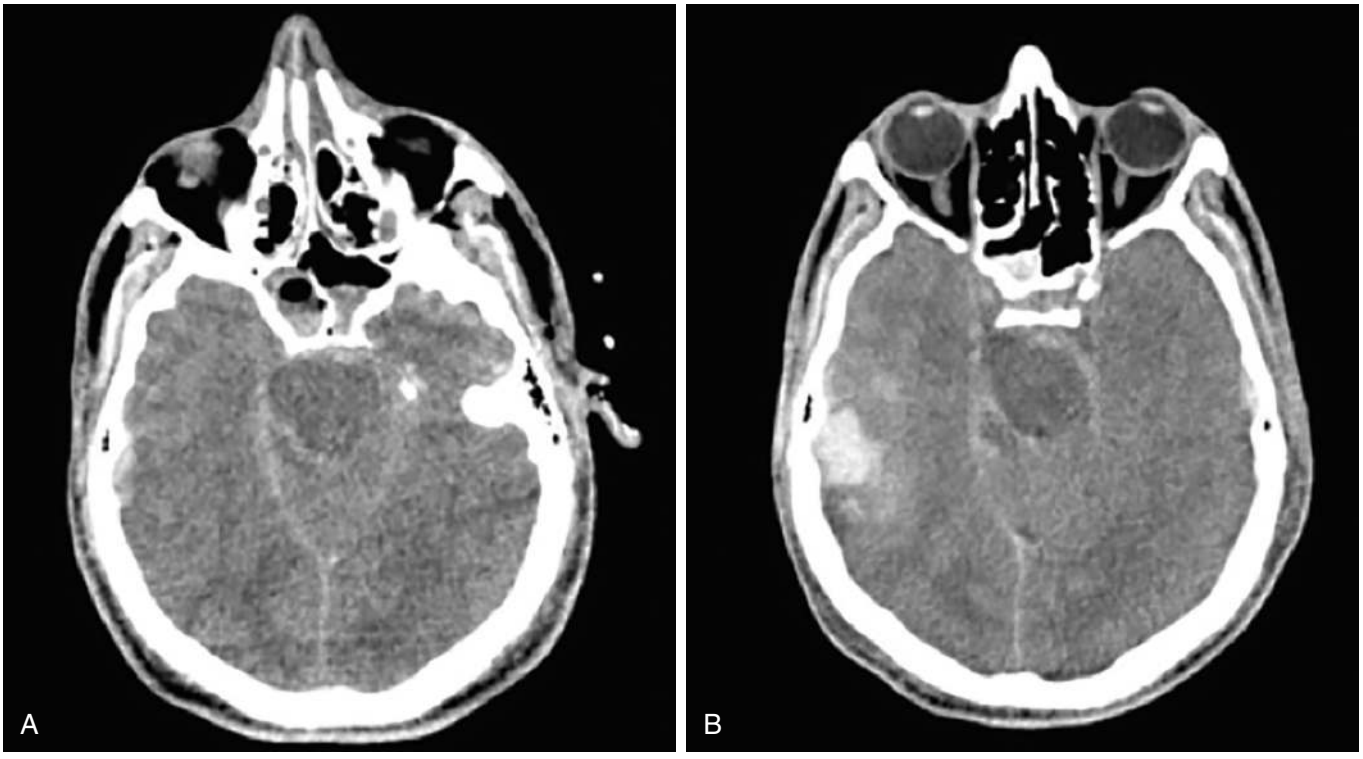

Fig. 52.7 Cerebral contusion. A, Noncontrast CT shows a subtle area of cortical hypodensity and interspersed hyperdensity along the inferolateral right temporal lobe in this patient with closed head injury representing a cerebral contusion. **B,** CT performed 24 hours later shows marked progression of the hemorrhagic right temporal lobe contusion.

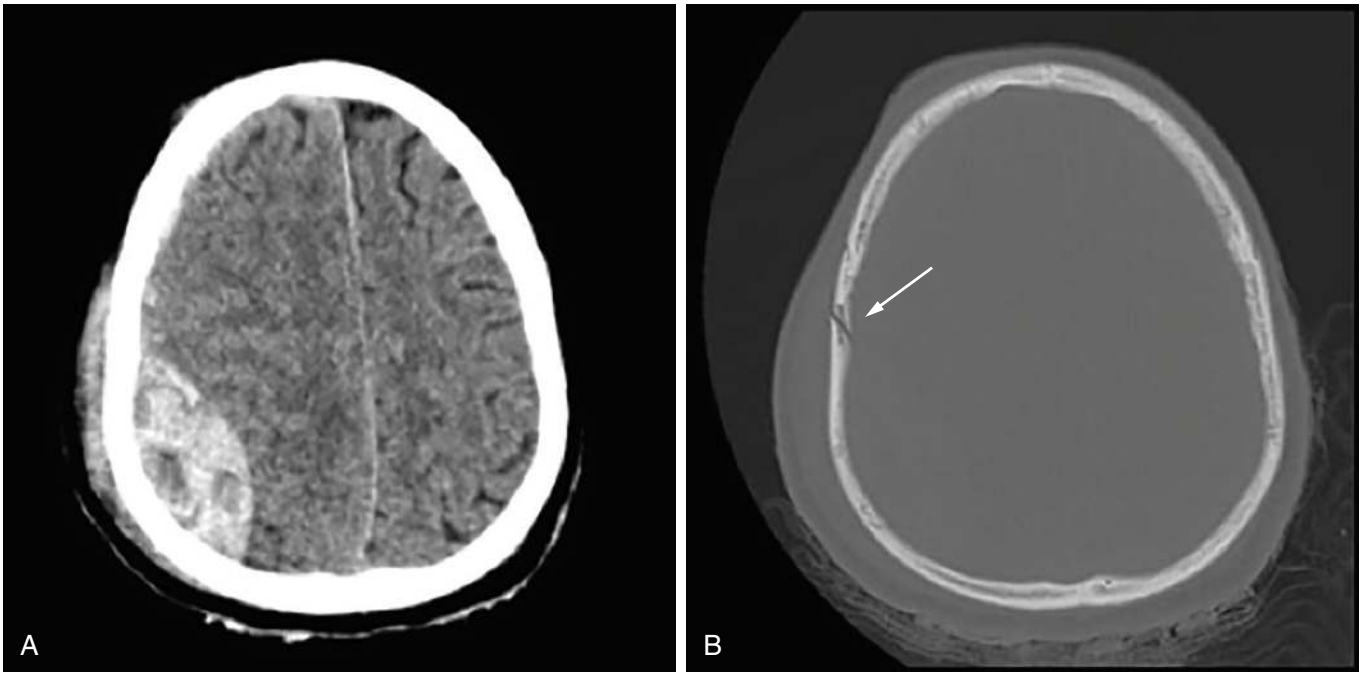

Fig. 52.8, Epidural hematoma. A, Noncontrast CT shows a hyperdense, lens-shaped extraaxial collection representing an acute epidural hematoma in this patient with closed head injury. **B,** Same CT viewed in bone windows shows a nondisplaced calvarial fracture *(white arrow)* associated with the epidural hematoma.

structures and occurs at predictable locations, including the gray matter–white matter junction (particularly in the frontal and temporal lobes), splenium of the corpus callosum, and dorsolateral brainstem. CT is normal in more than half of cases but may show small, round areas of hypodensity in nonhemorrhagic DAI and small, round foci of hyperdensity in hemorrhagic DAI. MRI is more sensitive for detection of DAI and is the modality of choice to delineate the extent of injury. Susceptibility-weighted imaging (SWI) sequences will show foci of hypointensity corresponding to small foci of hemorrhage, and DWI will show round or ovoid areas of restricted diffusion (Fig. 52.9). Several advanced MRI techniques, including DWI and DTI, are used to quantitatively assess the integrity of white matter tracts and provide a more detailed assessment of axonal damage. These techniques are also routinely being used to monitor changes in brain connectivity in the months and years after TBI.[23]

Vascular Pathology

Ischemia and infarction. Ischemic stroke accounts for approximately 85% of strokes and can be classified chronologically as acute, subacute, and chronic. CT is the initial imaging modality used to evaluate a patient with an acute neurologic deficit and primarily serves to identify an alternative cause for the patient's symptoms, such as intracranial hemorrhage or tumor. Acute stroke (0–48 hours) may present on CT as subtle loss of gray–white differentiation and parenchymal hypodensity representing cytotoxic edema. Thrombus within the affected vessels may appear hyperdense. Gyral swelling and sulcal effacement develops in 24–48 hours, representing progressive cytotoxic edema (see Fig. 52.1A). Subacute stroke (2–14 days) will show a wedge-shaped region of hypodensity with edema and mass effect peaking at 7–10 days. Contrast-enhanced CT will reveal a gyriform pattern of cortical enhancement beginning at 2 days, peaking at 2 weeks, and resolving at 2 months. Chronic infarct will appear as an area of hypodense, fluid-attenuation encephalomalacia and retracted parenchyma with volume loss resulting in ex vacuo enlargement of adjacent ventricles and sulci (Fig. 52.10).[24]

MRI is more sensitive than CT for detecting acute ischemia, especially in the first 24 hours. Acute infarct will present on DWI as an area of hyperintensity with a matching region of hypointensity on the apparent diffusion coefficient (ADC) map. It is important to interpret the DWI images in context with the ADC map to exclude T2 shine-through as the etiology for increased DWI signal (Fig. 52.11B and C). FLAIR shows increased signal in the affected cortex within 6 hours of ictus, representing developing cytotoxic edema (see Fig 52.11A). Slow or absent flow in leptomeningeal arteries may show increased signal on FLAIR images. SWI may show foci of hypointensity on the cortical surface corresponding to a clot within the vessel and correlating to the hyperdense vessel seen on CT (see Fig 52.11D). Subacute stroke is seen as parenchymal hyperintensity on T2 and FLAIR images involving the cortex and white matter, with mass effect and cytotoxic edema peaking at 7–10 days. Hemorrhagic transformation is best assessed on SWI, which is sensitive to even small regions of petechial hemorrhage. DWI will remain hyperintense, and ADC will normalize with the adjacent brain parenchyma and ultimately become hyperintense as gliosis and encephalomalacia predominate. Chronic infarct appears as areas of fluid-intensity encephalomalacia and hyperintense gliotic, contracted brain tissue. SWI may show foci of hypointensity corresponding to areas of hemosiderin deposition from chronic blood products.[25]

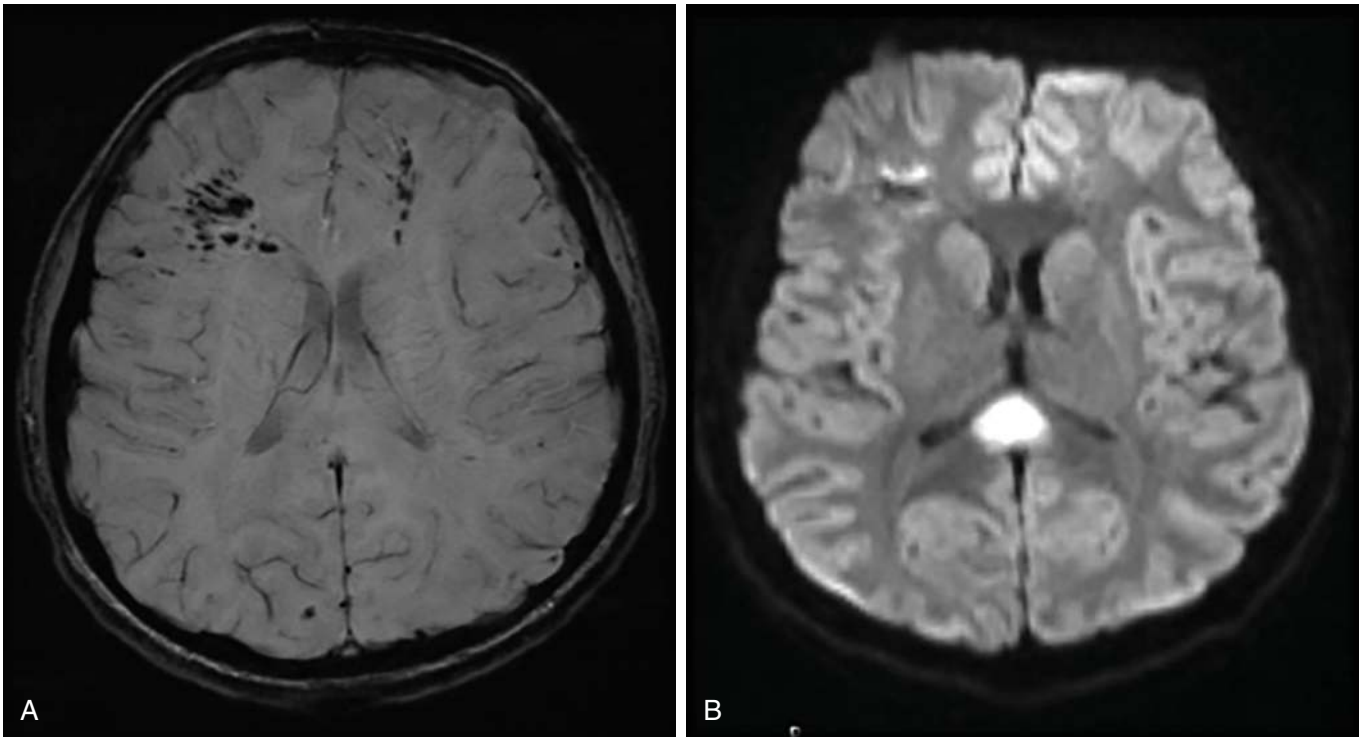

Fig. 52.9 Diffuse axonal injury. A, Susceptibility-weighted imaging demonstrates multiple foci of hypointensity centered at the gray matter–white matter junctions of both frontal lobes, representing hemorrhagic foci of diffuse axonal injury in a teenager with a closed head injury. **B,** Diffusion-weighted imaging in the same patient shows a large focus of restricted diffusion, representing nonhemorrhagic diffuse axonal injury centered in the splenium of the corpus callosum.

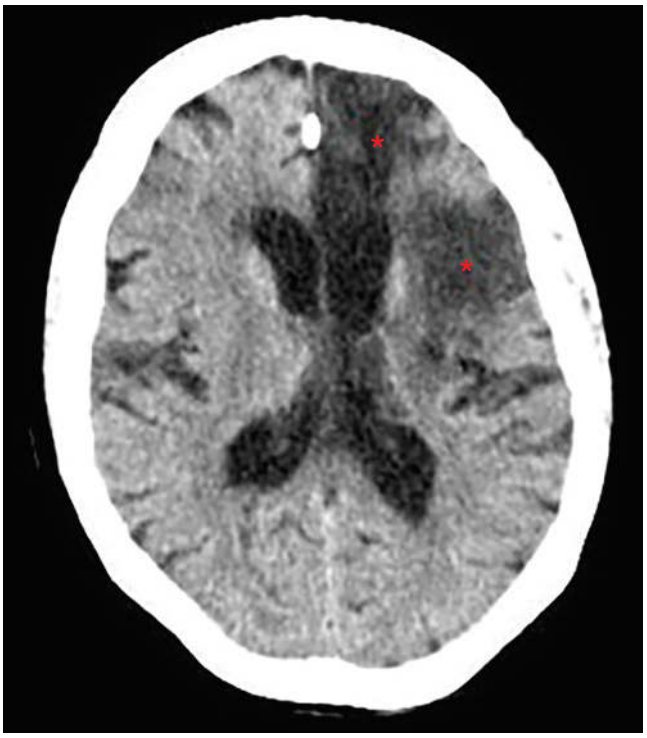

Fig. 52.10 Chronic infarction. Noncontrast CT shows fluid-density encephalomalacia and volume loss in the left anterior and middle cerebral artery territories *(asterisks)* in this patient with chronic left hemisphere infarctions.

CT and MR perfusion imaging techniques allow for qualitative and quantitative assessment of cerebral perfusion parameters. These techniques allow for early detection of reversible and potentially treatable areas of ischemic penumbra and differentiation of these lesions from areas of irreversible ischemia (Fig. 52.12).[25]

Aneurysmal subarachnoid hemorrhage. Cerebral aneurysms account for 85% of spontaneous SAH. CT is the initial imaging modality used to assess for the presence of SAH. Lumbar puncture is often pursued in patients with a compelling clinical presentation and negative CT to assess CSF for hemoglobin breakdown products. If CT for lumbar puncture is positive for SAH, then imaging with CTA or MRA is performed to identify the culprit aneurysm. CTA and MRA have reported sensitivities of 90%–95% for the detection of cerebral aneurysms (Fig. 52.13).[26]

Cerebral vasospasm is a complication of SAH and contributes to the high morbidity and mortality associated with aneurysmal hemorrhage. Vasospasm presents clinically 3–21 days after the ictus and can be detected with CTA. CT perfusion adds information regarding the physiologic significance of the vasospasm and guides management decisions. Symptomatic cerebral vasospasm can be treated endovascularly with pharmacologic agents and balloon angioplasty.[27]

Vascular malformations. Arteriovenous malformations (AVM) are the most common cerebral vascular malformations and are composed of a compact tangle of malformed vessels (the nidus) with feeding arteries and a single or multiple drainage veins. AVMs commonly present with intracerebral hemorrhage or seizures. An unruptured AVM may be apparent on CT as tubular structures that enhance with contrast. Conventional MRI may show the abnormal vessels as tubular hypointensities related to flow void from rapid blood flow. CTA and MRA are used to delineate important features of the AVM, including location, size, origin of feeding arteries, course of draining veins, and presence or absence of associated aneurysms (Fig. 52.14). AVMs may be treated endovascularly either completely or partially as a prelude to open surgical resection.[28]

Developmental venous anomalies (DVAs) are composed of a large draining vein surrounded by small feeding veins. The veins are typically inapparent on noncontrast-enhanced CT but enhance with contrast and can be seen on conventional MRI as flow voids. DVAs are rarely symptomatic other than when associated with a cavernous malformation, and dedicated cerebrovascular imaging is recommended

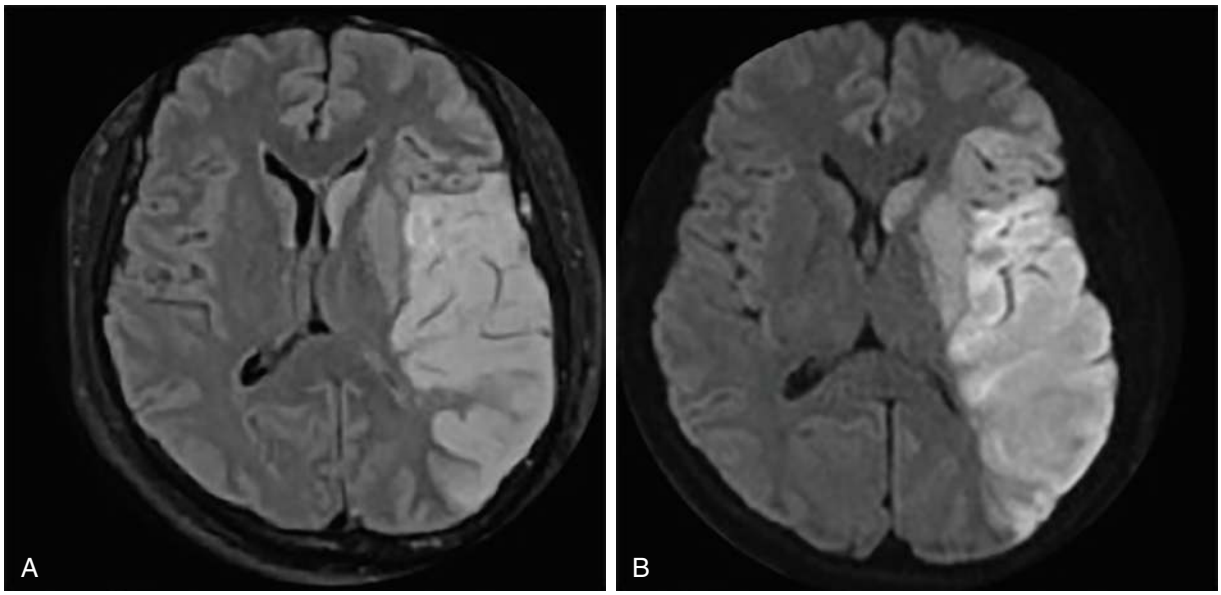

Fig. 52.11 MRI appearance of acute left middle cerebral artery territory infarct. A, FLAIR shows hyperintense cytotoxic edema involving the cortex and subjacent white matter in the left MCA territory with sparing of the left anterior and posterior cerebral artery territories. **B,** DWI shows increased signal intensity corresponding to the area of cytotoxic edema seen on FLAIR.

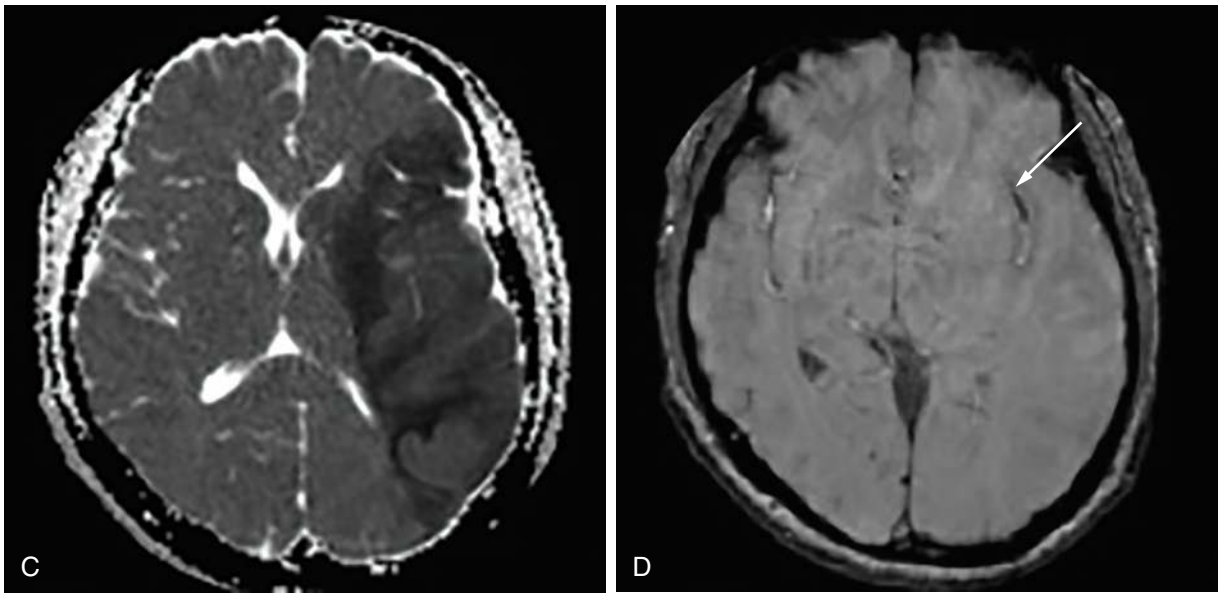

Fig. 52.11, cont'd **C,** ADC map shows correlative hypointensity in the same region, confirming the presence of true restricted diffusion, and thus confirming acute ischemia. **D,** SWI shows a linear focus of hypointensity in the left sylvian fissure *(white arrow),* representing thrombus in the left middle cerebral artery.

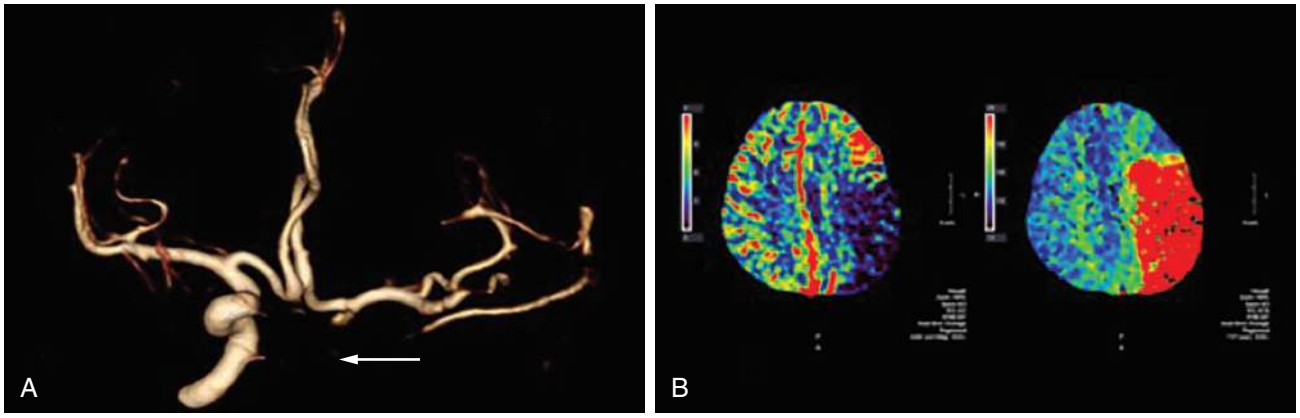

Fig. 52.12 **CT angiography and perfusion imaging in acute infarction. A,** Volume-rendered reconstruction of a CT angiogram shows absence of the cavernous and supraclinoid segments of the left internal carotid artery *(white arrow)* secondary to thrombotic occlusion. The left ACA and MCA partially fill via collateral flow through the anterior communicating artery. **B,** CT perfusion maps show increased time-to-peak enhancement *(right)* and decreased cerebral blood volume *(left)* in the left MCA territory consistent with core infarction and irreversible ischemia.

only when an apparently simple DVA is associated with unexplained hemorrhage or edema.

Neoplasia

The imaging appearance of brain tumors is variable and depends on tumor location (extraaxial versus intraaxial), histologic subtype, and grade. Vasogenic edema is a common finding in brain tumors, particularly high-grade gliomas and metastatic tumors, and results from disruption of the blood–brain barrier and neoangiogenesis. CT and MRI demonstrate vasogenic edema surrounding the lesion, which, if severe, results in mass effect and herniation. High-grade gliomas and metastases classically demonstrate peripheral ringlike enhancement after administration of intravenous contrast, with the central nonenhancing component representing areas of necrosis or cystic degeneration (Fig. 52.15). DWI may show restricted diffusion corresponding to the solid, enhancing component of the tumor, indicating high cellularity.[29]

Magnetic resonance spectroscopy (MRS) is a technique used to detect the presence and concentration of various metabolites in a region of interest and is helpful in differentiating neoplasia from other pathologies, such as demyelinating disease and infection. DTI and functional MRI allow for mapping of important white matter tracts and eloquent brain regions, respectively, with the aim of reducing the risk of neurologic impairment at the time of surgical resection (Fig. 52.16).[30]

Infection and Inflammation

Infectious and inflammatory processes can involve the meninges and brain parenchyma. Meningitis is diagnosed based on clinical and

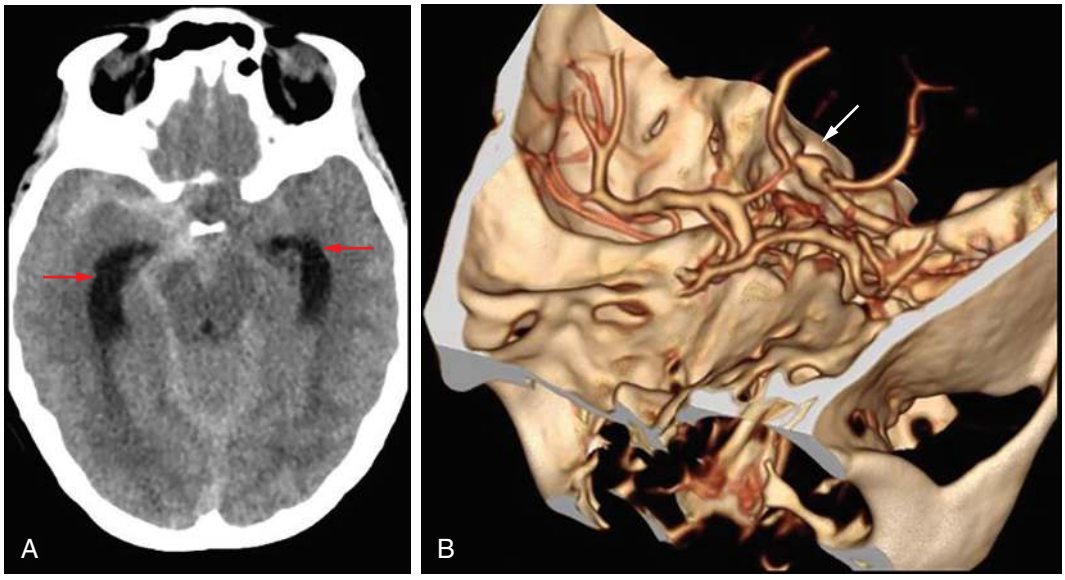

Fig. 52.13 Aneurysmal subarachnoid hemorrhage. A, Noncontrast CT shows acute hyperdense subarachnoid hemorrhage filling the perimesencephalic cisterns and extending laterally into the right sylvian fissure. The temporal horns of the lateral ventricles are dilated *(red arrows)*, representing acute hydrocephalus, which is a common complication of aneurysmal SAH. **B,** CTA in the same patient viewed using a volume-rendered reconstruction shows a complex saccular aneurysm arising from the tip of the basilar artery.

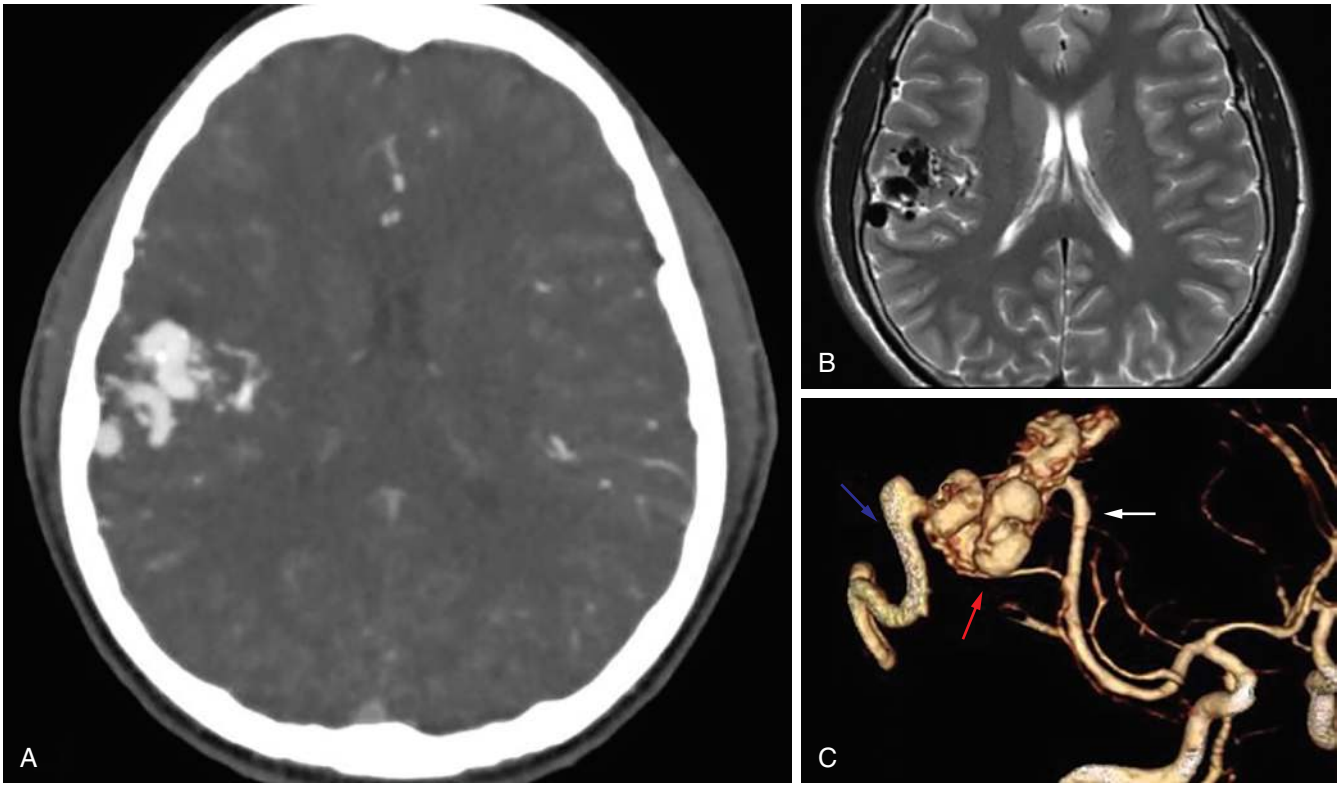

Fig. 52.14 Arteriovenous malformation. A, CT with contrast shows hyperdense tubular structures in the right frontal lobe representing the enlarged enhancing vessels of an arteriovenous malformation. **B,** T2-weighted MRI shows the vessels to be hypointense and devoid of signal. This lack of MRI signal is the result of rapid flow of blood. **C,** CTA of the head viewed as a volume-rendered reconstruction demonstrates the arterial feeders *(white arrow)*, nidus *(red arrow)*, and draining vein *(blue arrow)* of the arteriovenous malformation. Identification of these components is important for treatment planning and surgical approach.

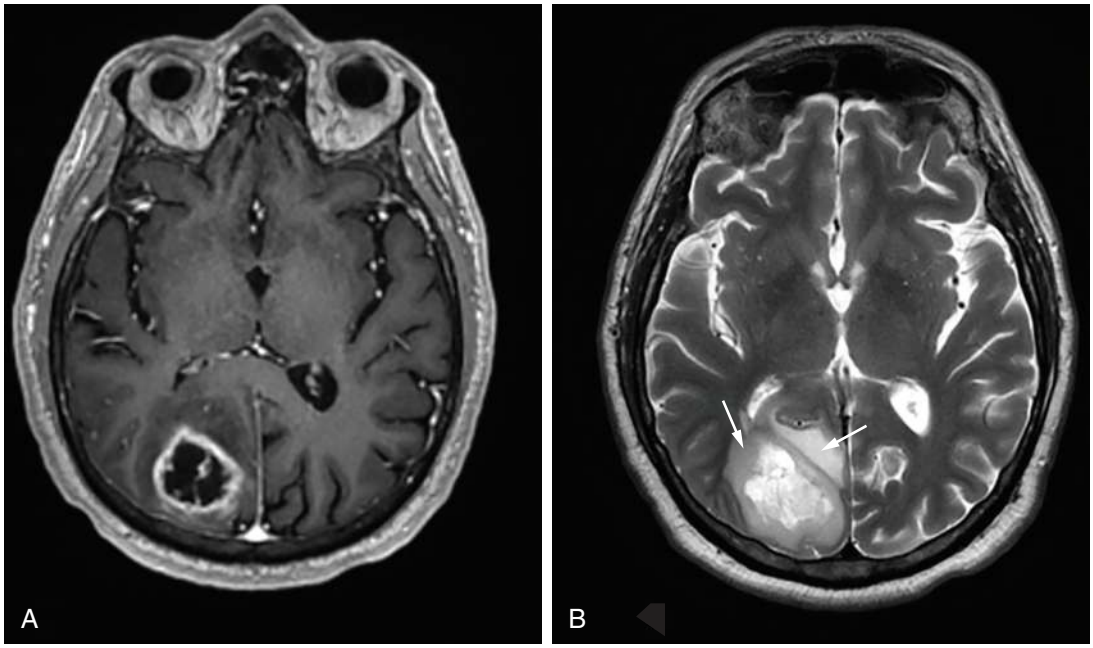

Fig. 52.15 MRI appearance of high-grade glioma. A, T1-weighted MRI with contrast shows a peripherally enhancing intraaxial mass in the medial right occipital lobe. This mass was resected, and pathology returned glioblastoma (WHO grade IV). **B,** T2-weighted MRI shows extensive surrounding vasogenic edema. Vasogenic edema is commonly seen surrounding intraaxial brain tumors and results from disruption of the blood–brain barrier by the neoplastic process.

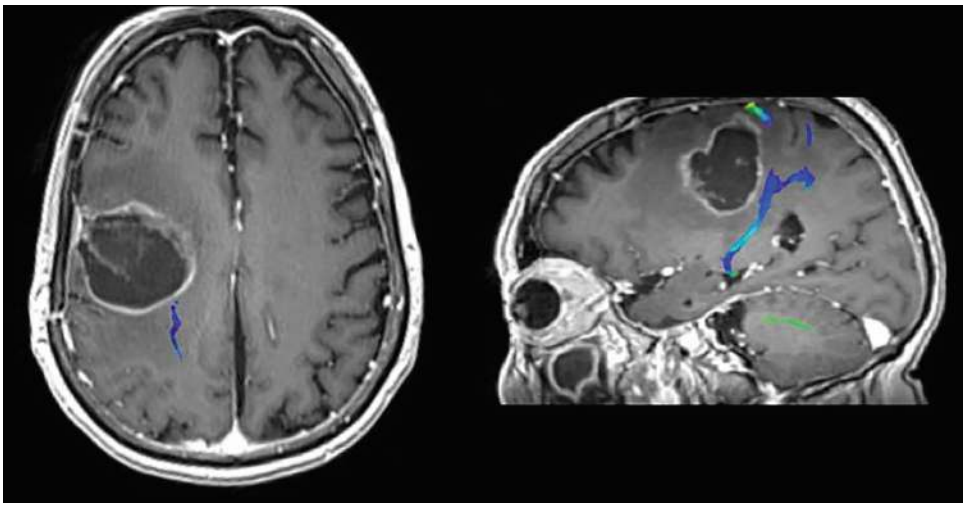

Fig. 52.16 MR tractography using DTI technique. DTI imaging was performed to localize the right corticospinal tract in this patient with a right frontal lobe glioblastoma. This tractography data was fused to the T1-weighted contrast-enhanced MRI to demonstrate the precise anatomic relationship of the corticospinal tract to the tumor.

laboratory evaluation and may be classified as infectious or noninfectious. Although CT and MRI may show evidence of meningeal inflammation, the role of imaging in cases of known or suspected meningitis is to evaluate for complications, such as hydrocephalus, abscess, and ischemia. The inflammatory exudate of meningitis may present as increased density of the involved CSF spaces on CT. Leptomeningeal inflammation produces a cellular and proteinaceous exudate that is seen as hyperintense signal within sulci and the basal cisterns on FLAIR sequences where normal CSF signal should be suppressed. Contrast administration will show abnormal enhancement of the leptomeninges on CT and MRI.[31]

Pyogenic infection of the brain parenchyma presents on a spectrum from cerebritis to abscess. Abscess presents on CT and MRI as a peripherally enhancing lesion with extensive surrounding vasogenic edema. Several findings on MRI may help distinguish abscess from other peripherally enhancing brain lesions such as high-grade glioma and metastases. Abscesses commonly show hypertense signal centrally on T2-weighted images and a hypointense rim, which represents the

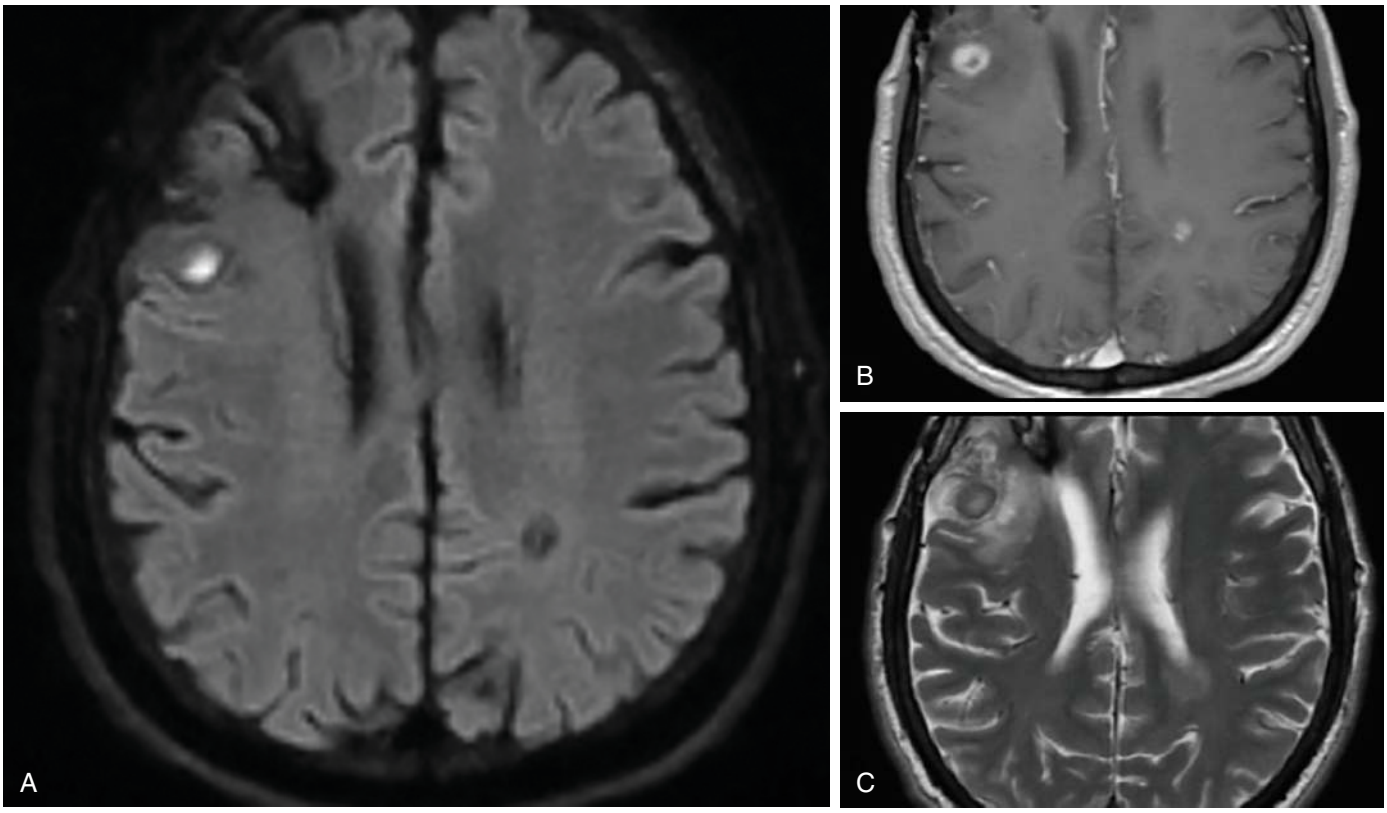

Fig. 52.17 Cerebral abscess. A, Diffusion-weighted image shows a round lesion in the right frontal lobe with central hyperintensity representing restricted diffusion. Central diffusion restriction is a classic finding in cerebral abscess. **B,** T1-weighted MRI with contrast shows the abscess to demonstrate a pattern of peripheral contrast enhancement. **C,** T2-weighted MRI shows the characteristic hypointense rim of a cerebral abscess representing a fibrotic-like reaction. There is surrounding vasogenic edema related to blood–brain barrier disruption from the local inflammatory process.

fibrotic-like reaction surrounding the abscess (Fig. 52.17B and C). DWI classically shows restricted diffusion (hyperintensity) within the central portion of the abscess cavity (see Fig 52.17A).[32]

Encephalitis refers to an inflammatory parenchymal process that may be infectious or noninfectious. Herpes encephalitis results from infection of brain parenchyma with herpes simplex virus-1 (HSV-1), typically as a result of reactivation of a latent infection. HSV has a predilection for the limbic system (mesial temporal lobes, insula, subfrontal region, and cingulum) and causes a hemorrhagic necrotizing infection. CT and MRI may be normal early in the course of the disease. Eventually, cortical and subcortical edema will become apparent in the involved parenchyma, commonly in the medial temporal lobes. SWI sequences will show foci of hypointensity representing areas of hemorrhage. Postcontrast images and DWI may show patchy areas of enhancement and restricted diffusion, respectively.[33]

Miscellaneous White Matter and Metabolic Diseases

Numerous disease processes present with abnormalities in the cerebral white matter. Posterior reversible encephalopathy syndrome (PRES) is a disorder of cerebrovascular autoregulation and has many proposed etiologies, all with hypertension as a common component. Common associations include acute systemic hypertension, preeclampsia/eclampsia, drug toxicity, uremia, and systemic infection.[34] PRES presents with vasogenic edema centered in the white matter predominantly involving brain parenchyma perfused by the posterior circulation. Parietal and occipital lobe involvement is common, as is involvement of the cerebellum. The brainstem, particularly the pons, and basal ganglia may also be involved. The edema is vasogenic, not cytotoxic, and therefore DWI rarely shows regions of restricted diffusion. Contrast-enhanced imaging may show patchy areas of contrast enhancement secondary to blood–brain barrier disruption.[35]

Disorders of metabolism often present with abnormal brain imaging. Wernicke encephalopathy results from thiamin deficiency and is commonly seen in alcoholics. MRI shows T1 hypointensity and T2/FLAIR hyperintensity in the medial thalami, mammillary bodies, and periaqueductal gray matter (Fig. 52.18). These regions also demonstrate restricted diffusion and contrast enhancement.[36]

SPINE

Trauma

CT is the initial imaging modality used to assess suspected spine injury. CT demonstrates exquisite detail of the osseous structures and is therefore the modality of choice to evaluate for spine fractures. Displacement of fracture fragments and their protentional encroachment on the spinal canal and neural foramina are best delineated on CT. Alterations in vertebral alignment are also well demonstrated on CT and can be used to infer injury to ligamentous structures (Fig. 52.19A and B).

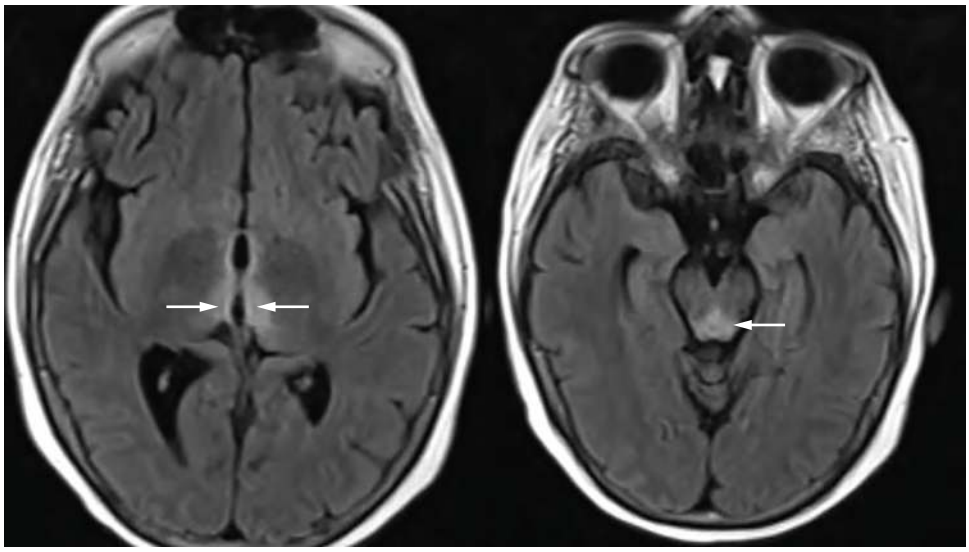

Fig. 52.18 Wernicke encephalopathy. FLAIR MR images show hyperintensity in the medial thalami and periaqueductal gray matter *(white arrows)* in this patient presenting with altered mental status and oculomotor dysfunction.

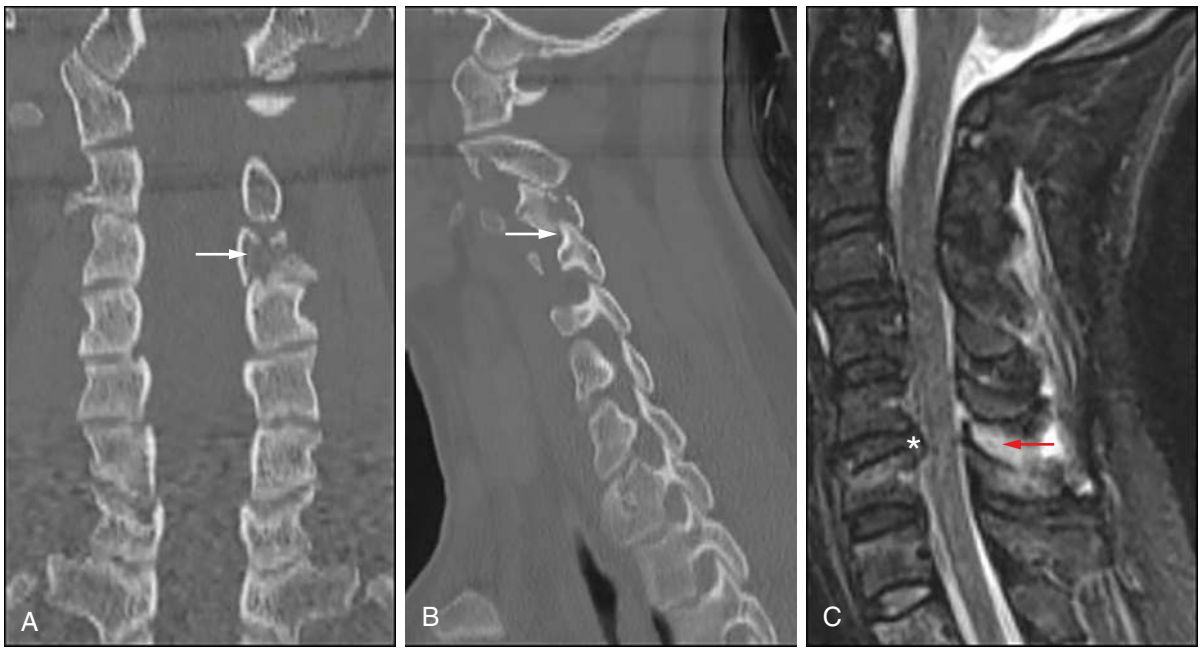

Fig. 52.19 Cervical spine trauma. A and B, CT of the cervical spine viewed in coronal and sagittal reconstructions shows an acute comminuted fracture of the C3 left articular pillar with subluxation, or perching, of this pillar on the C4 articular pillar *(white arrows)*. **C,** Short-tau inversion recovery (STIR) MR image in the same patient shows a traumatic C5–C6 intervertebral disc herniation *(white asterisk)* and injury to the C5–C6 interspinous ligament, as evidenced by hyperintense signal *(red arrow)*. These soft tissue injuries were not suspected based on the findings of CT and demonstrate the utility of MRI for detecting additional soft tissue injuries.

MRI provides improved visualization of the soft tissue structures, including ligaments, intervertebral discs, nerve roots, and the spinal cord. MRI is pursued to evaluate for etiology of a neurologic deficit or to assess for evidence of ligamentous injury that may predispose to spinal instability. Findings on MRI often direct care toward surgical or nonsurgical pathways (see Fig. 52.19C). Acute traumatic injury to the spinal cord may be inferred by the presence of increased T2 signal, with the substance of the cord representing edema. Chronic cord injury shows volume loss and T2 representing axonal loss and gliosis. Gradient echo sequences, which are sensitive to blood products, may show foci of hypointensity within a region of cord injury representing hematomyelia.[37] This portends a poor neurologic prognosis.

Infection

Spondylodiscitis is characterized by infection of the intervertebral disc space and adjacent vertebral bodies. Infection destroys the

intervertebral disc and may extend into the epidural space, placing the spinal cord and nerve roots at risk for injury. MRI is more sensitive than radiography and CT for spondylodiscitis, particularly early in the disease course.[38] MRI shows T2 hyperintense fluid signal in the disc space with associated contrast enhancement in addition to marrow edema and enhancement in the adjacent vertebral bodies. There is disc space height loss, and the vertebral body endplates are irregular from erosions. Extension of infection into the epidural space may result in epidural abscess formation, which presents as a peripherally enhancing collection (Fig. 52.20).[39]

Neoplasia

Tumors of the spine can be broadly categorized anatomically as extradural, intradural extramedullary, and intradural intramedullary. Extradural tumors are the most common and include lesions of the osseous vertebral column, which is the third most common site for metastatic disease.

MRI is the most sensitive imaging modality for detection of vertebral metastases and other spinal lesions. Normal vertebral bone marrow should appear brighter than the adjacent intervertebral discs on T1- and T2-weighted sequences. Infiltration of the vertebral marrow by tumor will show replacement of the normal hyperintense marrow signal by hypointense soft tissue on T1-weighted images. Metastases will often demonstrate contrast enhancement. DWI is more commonly being incorporated into spine imaging and has proved to be of significant benefit in evaluating vertebral metastatic disease and multiple myeloma.[40]

KEY POINTS

- CT is fast, safe, and sensitive and serves as the imaging modality of choice for initial evaluation of the brain and spine in cases of suspected or known neurologic illness or injury. MRI is more sensitive than CT for detection and characterization of most neurologic pathology and is used to answer specific clinical questions.
- Cerebral edema is a common response to brain pathology. Accurate characterization of the edema pattern as cytotoxic, vasogenic, or interstitial is useful in generating a differential diagnosis.
- Intracranial hemorrhage and cerebral ischemia evolve in a predictable manner on CT and MRI. Understanding this pattern of evolution can help in determining the chronicity of the underlying pathologic process.
- The role of neuroimaging in TBI is to identify treatable primary injuries and to monitor for the development of secondary injury.
- MRI is useful in characterizing tumors as low-grade or high-grade tumors and for differentiating neoplastic from infectious pathology.
- Advanced MRI techniques are more commonly being used to image neurologic function and interconnectivity, which are inapparent on standard morphologic imaging.
- CT is useful in characterizing abnormalities of bone and alignment in suspected spine pathology. MRI is the modality of choice to assess the soft tissue structures of the vertebral column and the neural elements within the spinal canal and neural foramina.

References for this chapter can be found at expertconsult.com.

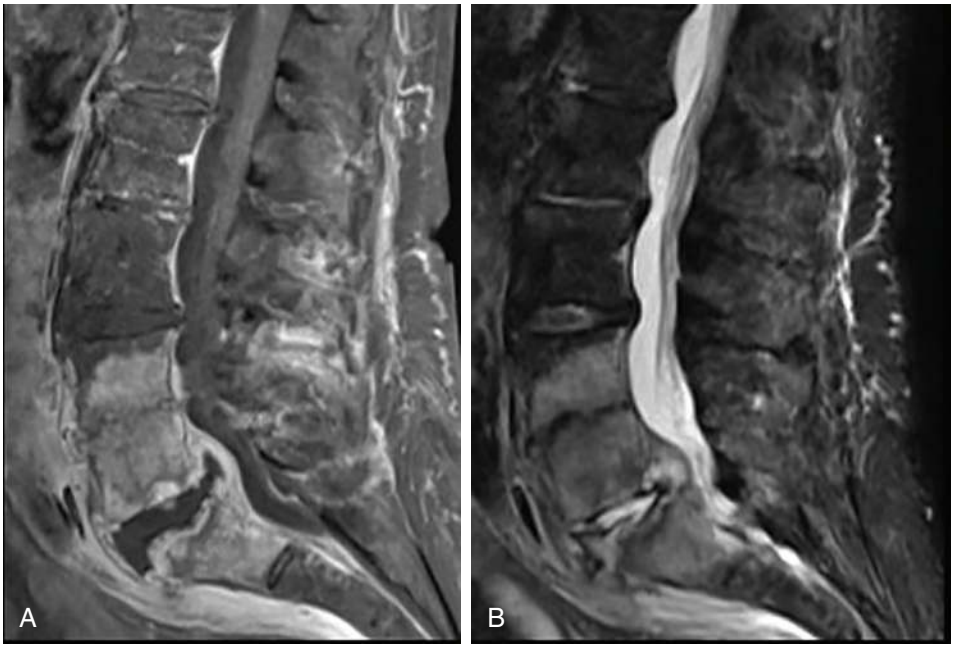

Fig. 52.20 **Spondylodiscitis of the lumbar spine. A,** T1-weighted MRI of the lumbar spine with contrast shows abnormal contrast enhancement of the L5 and S1 vertebral bodies, representing osteomyelitis. There is a hypointense collection in the L5–S1 intervertebral space, which extends posteriorly into the ventral epidural space, resulting in a peripherally enhancing epidural abscess. **B,** Short-tau inversion recovery (STIR) MR of the lumbar spine shows abnormal hyperintense fluid signal in the L5–S1 intervertebral disc space, representing infected material within the disc space, and hyperintensity throughout the L5 and S1 vertebral bodies, representing marrow edema.

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53

Core Principles of Respiratory Physiology and Pathophysiology in Critical Illness

John J. Marini and Luciano Gattinoni

INTRODUCTION

Understanding physiology underpins the logical decisions of critical care practice. Although facts and knowledge of literature findings and recommendations for specific problems clearly help inform good management, bedrock principles of physiology and pathophysiology translate across patients; awareness of them is a salient trait of the expert clinician. Providing respiratory support is among the defining features of intensive care, and to execute this effectively, an understanding of the rationale and consequences of related interventions is required. It follows that the fundamentals of respiratory mechanics and gas exchange must be mastered. Rather than detail specific respiratory conditions or ventilatory approaches, this chapter aims at surveying the indispensable physiologic elements that are vital to making appropriate decisions at the bedside. Our discussion of respiratory physiology rests on its two pillars: mechanics and gas exchange.

RESPIRATORY MECHANICS

What are Respiratory Mechanics and How are They Measured?

Because the lung is a flexible but passive structure, gas flows to and from the alveoli driven by differences between airway and alveolar pressures—no matter how they are generated. The total pressure gradient expanding the respiratory system is accounted for in two primary ways: (1) driving gas between the airway opening and the alveolus and (2) expanding tissue against the recoil forces of the lung and chest wall. The pressure required for inspiratory flow dissipates against friction, whereas the elastic pressure that expands the respiratory system is stored temporarily in its tissues until dissipated in driving expiratory flow.

The mechanical properties of the respiratory system are those characteristics that influence the energy cost of breathing. Because pressure provides the forces driving gas flow and counterbalancing elastic recoil, assessing respiratory mechanics involves the measurement of flows, volumes (flow integrated over time), and pressures. In simplified form, the expression of these relationships, the equation of motion of the respiratory system, can be written: $P = RV' + V/C + Pex$. In this equation P is the pressure applied across the entire respiratory system, R is inspiratory resistance to flow, C is inspiratory compliance, V' and V are flow rate and the volume inspired in excess of the end-expiratory value, and Pex is end-expiratory alveolar pressure—applied positive end-expiratory pressure (PEEP) and any supplemental end-expiratory pressure generated as a result of the ventilatory pattern itself (auto-PEEP, discussed later). Although regional mechanics are of unquestioned importance in determining ventilation, gas exchange, and tissue strain, the technology available at most bedsides currently limits measurements and monitoring to the global properties of the integrated respiratory system, composed of the lungs encased by the surrounding chest wall. Pressure changes relevant only to the lungs must be assessed as the difference between the airway pressure (Paw) and the pleural pressure (Ppl) that surrounds them (defined as the transpulmonary pressure, Ptp). The esophagus provides a convenient site from which to measure the changes of intrapleural pressure that occur during tidal ventilation with a balloon-tipped catheter.[1] It may also measure with reasonable accuracy the absolute pleural pressure across the same horizontal gravitational plane.[2] With the airway occluded and flow stopped, pressure measured at the airway opening estimates gas pressure at the alveolar level.

Transpulmonary Pressure

For any expandable compartment, such as the chest, the absolute volume and volume change depend on its flexibility (compliance) and the pressure difference inside and outside the structure (Fig. 53.1). For the lung, this transmural pressure is $Ptp = Paw - Ppl$. Under passive conditions the corresponding transmural pressure for the integrated respiratory system is the airway pressure minus atmospheric pressure, or Paw. For the passive chest wall alone, transmural pressure is simply the average pleural pressure. Pleural pressure is not helpful in assessing chest wall compliance during spontaneous breathing, however, as its embedded musculature generates the negative pleural pressure deflections that drive tidal movement. During muscular effort, the transmural pressure acting across the lung remains the airway pressure minus intrapleural pressure difference; therefore the actual transstructural pressure to which the lung is exposed is less than the measured Paw under passive conditions and greater than the measured Paw during spontaneous or patient-assisted breathing (Fig. 53.2). Because the lungs are inherently passive, their mechanical properties can be assessed during any form of spontaneous, patient-triggered but machine-assisted, or controlled, ventilation. The mechanical properties of the chest wall, in contrast, can only be directly evaluated during controlled ventilation

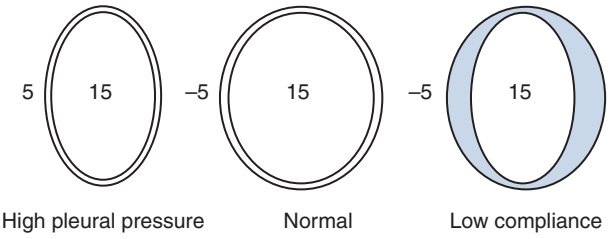

Fig. 53.1 Importance of transpulmonary pressure and compliance to volume of a nonrigid, expandable structure such as a lung unit or alveolus.

when the actual pleural pressure acting to distend that structure can be estimated by a balloon-tipped esophageal catheter.

Key Differences Between Active and Passive Breathing

It is sometimes taught that regarding the lung itself, there are few perceptible differences in mechanical behaviors between passive and active inflation.[3] Although that statement holds approximately true for global transmural pressures and volume measurements made in healthy excised lungs, it is not precisely accurate in vivo—especially not for acutely injured lungs. Active contraction of the diaphragm decreases the local transmural pressures of nearby alveoli somewhat more than average, whereas the nondependent zones within a passive chest may be surrounded by lower pleural pressures and therefore experience greater resting transpulmonary pressures and lesser swings of transpulmonary pressure during tidal inflation.[4] Such regional differences are accentuated by conditions that increase lung weight and produce heterogeneous mechanics, such as acute respiratory distress syndrome (ARDS) (Fig. 53.3). Not only does regional expansion and distribution of volumes differ in accordance with modifications of *effective* local compliance by spontaneous breathing efforts, but the filling and distention of the pulmonary blood vessels are significantly different as well[5] (Fig. 53.4). Negative pleural pressure swings and lower mean pleural pressures promote venous return and pulmonary vascular filling, whereas positive pleural swings and higher

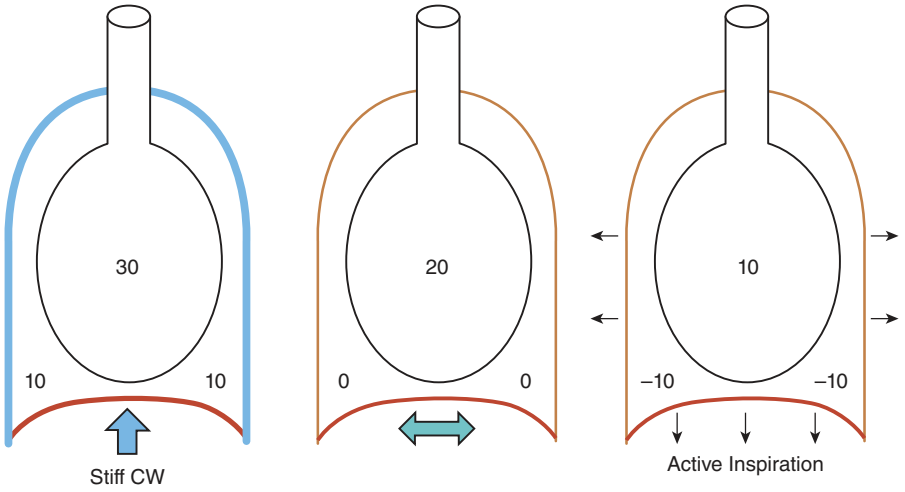

Fig. 53.2 Equal lung unit volumes are produced by the same transpulmonary pressures. The airway (alveolar) pressures that are externally recorded differ remarkably, depending on the elastance of the chest wall (*CW*) and the intrapleural pressures.

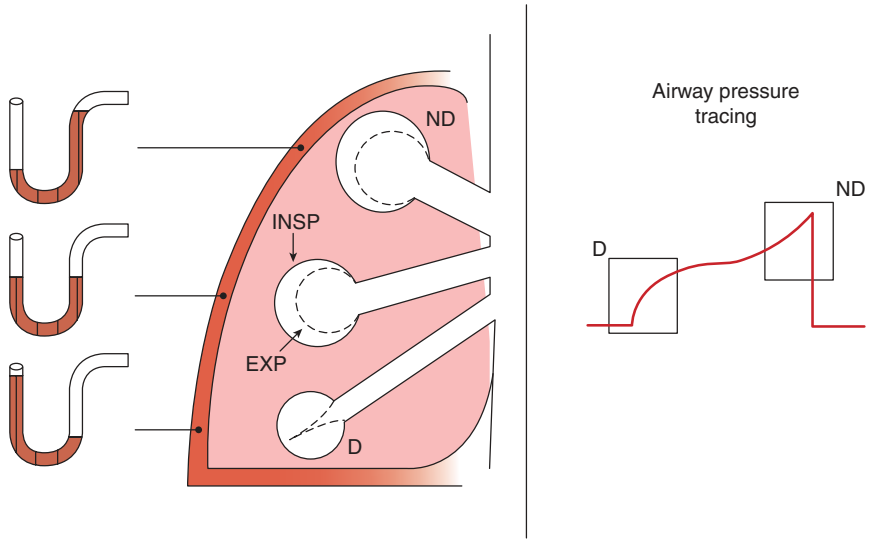

Fig. 53.3 Regional transpulmonary pressures vary with the local pleural pressures. Dependent lung units (*D*) have reduced transpulmonary pressures compared with nondependent ones (*ND*) and may be subject to reopening and collapse. Recruitment and overdistention of regional units contribute to the changing contours of the airway pressure-volume curve recorded in the external ventilator circuit.

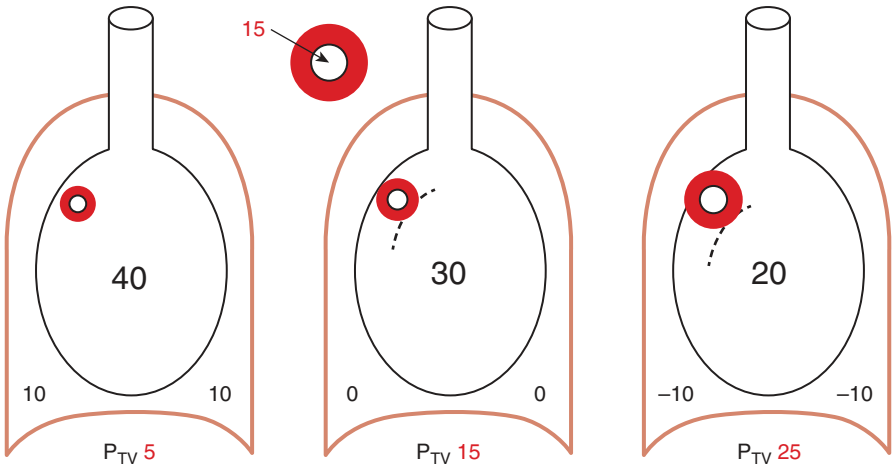

Fig. 53.4 Given the same intraluminal blood pressure (15 cm H_2O in this hypothetical example), the transmicrovascular pressures (P_{TV}) that influence edema formation vary with the surrounding interstitial pressure that surrounds them. Intrapleural pressure is often used as a measurable surrogate for the unmeasured interstitial pressure.

mean pressures impede venous return and pulmonary vascular filling. Greater vascular filling tends to reduce the compliance of the lung parenchyma.

Pulmonary Elastance and Compliance

In the clinical setting, the global mechanical properties of the chest are assessed during passive mechanical ventilation by the pressures and volume changes measured at the airway opening. One routinely used value that characterizes the capacity and stiffness of the respiratory system is termed *compliance,* the ratio of a volume change to the static pressure difference that caused it. Compliance, C, is the inverse of elastance, E, defined as the ratio of pressure change required to produce a volume change.[6] Because the lungs are enclosed by the chest wall, they share equivalent volumes. Consequently, under passive conditions the total positive alveolar pressure partitions itself into two components that expand the lungs and chest wall. The corresponding elastance components add in series: Ers = El + Ew[7] (Fig. 53.5). In contrast, compliances of the lungs and chest wall add in parallel: 1/Crs = 1/Cl +1/Cw. Therefore even though Crs is often used clinically to assess the elastic properties and capacity of the lung, the relationship of Crs to Cl is not entirely straightforward: Crs = (Cl × Cw) / (Cl + Cw). It should be noted here that the surface tension of the alveolar lining liquid film, increased by inflammation and attenuated by functional surfactant, may dramatically affect the lung's flexibility.[8]

The Crs and Cl can be reduced by depleting the *number* of open lung units available to ventilate and by altering their individual mechanical properties. This dual interpretation of compliance assessed at the airway opening is reflected in the sigmoidal shape of the inflation pressure-volume curve, which becomes more pronounced in the setting of acute parenchymal disorders, such as acute respiratory distress syndrome (ARDS) (Fig. 53.6). Under such conditions, increases of airway pressure made from low values near relaxation tend to impressively recruit previously collapsed alveoli, improving the Crs measured at the airway opening. As pressure builds to higher levels, however, this recruiting tendency progressively diminishes.[9] At the same time, greater transpulmonary pressures applied to units already open may

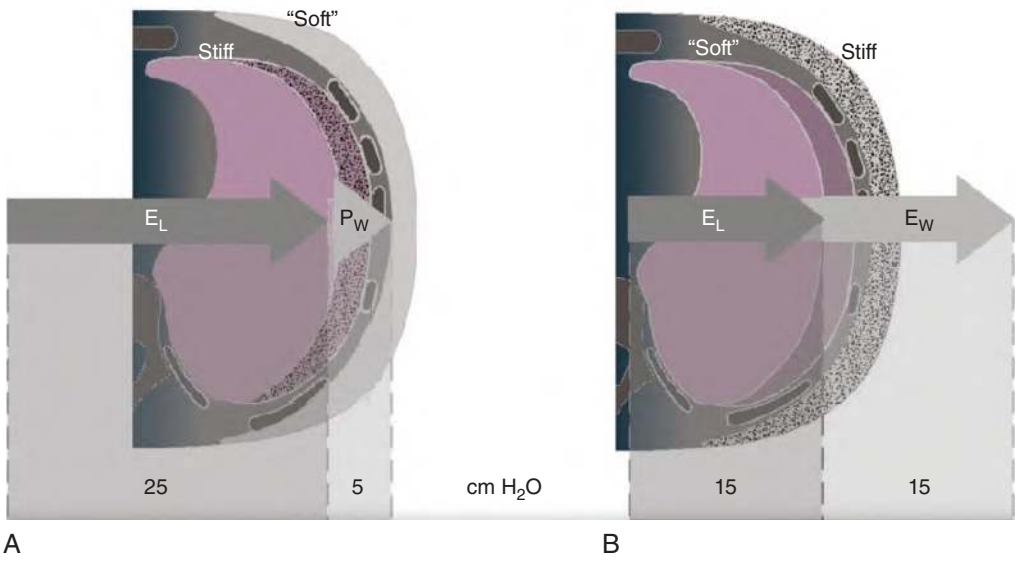

Fig. 53.5 Partitioning of an alveolar pressure of 30 cm H_2O across the lung and chest wall as a function of their elastance values (E_L and E_W). The lung and chest wall share an identical volume.

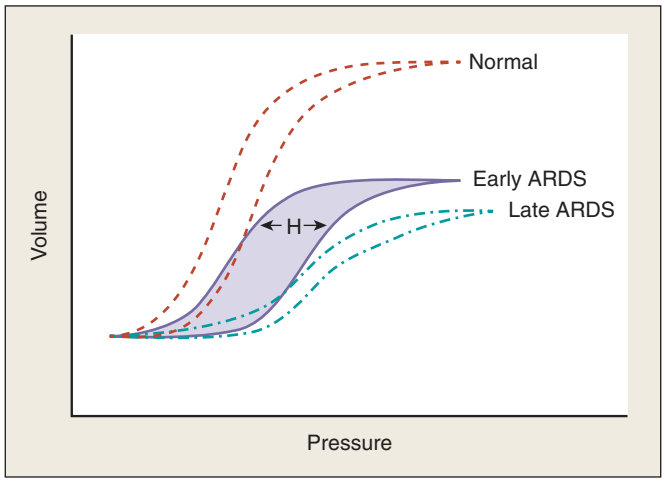

Fig. 53.6 Static pressure-volume loops for the respiratory system under normal conditions and under two severities of acute lung injury (early and late acute respiratory distress syndrome [*ARDS*]). Hysteresis (*H*) is reflected in the pressure difference that separates the inflation and deflation recoil characteristics.

stretch them into a less compliant range. This trade-off between recruitment in some zones (which often occurs disproportionately in the gravitationally dependent regions with higher surrounding pleural pressures) and stretching of open units eventually favors the latter at high volumes, bending the pressure-volume curve of the respiratory system toward the airway pressure axis.

Massive obesity is a prevalent condition in well-developed, adequately resourced countries. The increased body weight of such patients gives rise to a less compliant chest wall.[10] Apart from the load imposed by the mass of soft tissue that overlies the chest, one important reason for this apparent noncompliance is raised intraabdominal pressure. Because the flexible diaphragm forms the caudal boundary of the chest cavity, approximately half of each increment of abdominal pressure that exceeds ~6 cm H_2O is reflected the pleural space[11] (Fig. 53.7). It deserves emphasis that the *overall* effect of massive obesity resembles that of a static load or weight, rather than a true increase of elastance that raises pressure in direct proportion to increments of lung volume.

Energetics of Inflation

When a pressure difference is applied to the passive respiratory system, that total pressure (Paw) must be accounted for by its dynamic component that overcomes flow resistance (Pr) and its "elastic" components that expand the chest. At end inflation, the latter is composed of the elastic pressure that corresponds to the tidal volume, known as the *driving pressure* (DP = Vt/C), and the pressure above the ambient baseline, known as *positive end-expiratory pressure (PEEP)*. Expressed as an equation, end-inspiratory pressure is:

$$\text{Paw} = \text{Pr} + \text{DP} + \text{PEEP} \qquad \textbf{(Eq. 1)}$$

The mechanical energy (or work, W) delivered to cause a volume change of the passive respiratory system is the product of total airway pressure and volume—on a two-dimensional surface, a pressure × volume area.[12] This equivalence between energy and P × V area is made more intuitive by recalling that energy is a force-length product, where length is the distance moved by an unbalanced force. Pressure is force per unit area, and volume is the product of area and length. Consequently, the P × V product has the dimensions of force × length. Assuming constant inspiratory flow, the individual expenditures of

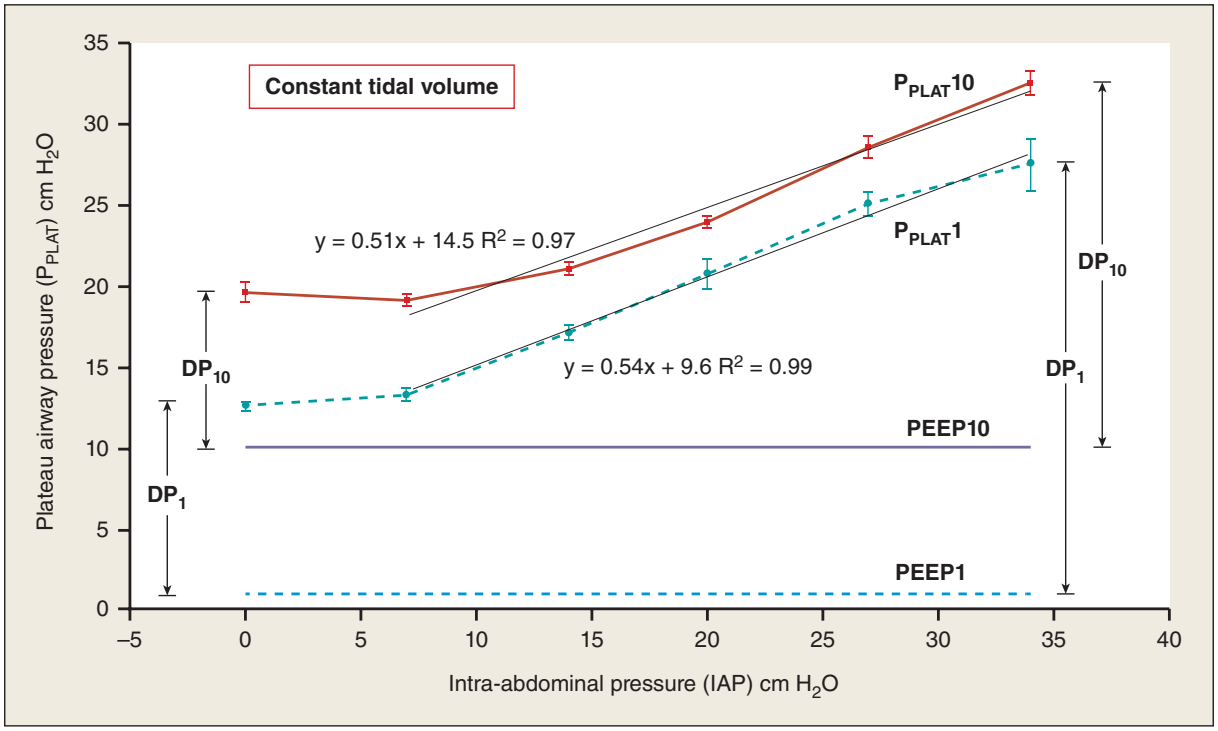

Fig. 53.7 Influence of increasing intraabdominal pressure (*IAP*) on the externally measured end-inspiratory static airway pressure (P_{PLAT}) and the corresponding driving pressures (*DP*) at two levels of positive end-expiratory pressure (*PEEP*, 1 and 10 cm H_2O). Tidal volume is unchanged. (Adapted from Cortes-Puentes GA, Gard KE, Adams AB, et al. Value and limitations of transpulmonary pressure calculations during intra-abdominal hypertension. *Crit Care Med.* 2013;41[8]:1870–1877.)

energy against the components that make up total inflation pressure are therefore approximated:

$$W = Vt(Pr) + Vt(Dp/2) + Vt(PEEP)$$

A transmural pressure × volume plot inscribes a tracing whose area quantifies the work and energy of tidal inflation (Fig. 53.8). For the entire passive respiratory system, this is Paw vs. V, and under conditions of constant inspiratory flow, time is a linear analog of inflation volume. Inflation work can be further partitioned into the P × V areas that correspond to the energy required to overcome flow resistance, to deliver volume increments, and to offset PEEP[13] (Fig. 53.9). Because the same total mechanical energy is required under passive and patient-assisted conditions for flow controlled, volume-cycled breaths, the area deficit between passive and active conditions reflects the energy contribution from the patient[14] (Fig. 53.10). Similar principles of energy expenditure apply selectively to the lung when transpulmonary pressure (Paw − Ppl, rather than Paw) is substituted.

Mechanical Power

Power, a measure of the rate of energy expenditure, is defined as the amount of energy per unit of time of any duration. Instantaneous power (Pi) may vary within the span of an individual inflation half-cycle by altering the flow profile (Fig. 53.11). Thus the intracycle power (ICP) being applied to the passive respiratory system at volume V above the unpressurized resting value is expressed as the product of airway pressure and flow: Pi = Paw × V′, or Pi = V′(V′R) + V′ ([V/VT] × DP) + V′ (PEEP).[15] On a longer time scale, mechanical power, as the term is currently understood in the clinical setting, is the product of the total inflation energy per cycle (Paw × V) area and the cycling frequency.[16] Defined in this way, power is a cumulative measure of repetitive energy pulse applications per minute. Experiments indicate that if the tidal strains of each inflation cycle exceed a certain threshold, the amplitude and duration of such power exposures may be a fundamental determinant of the extent of damage that results from that ventilation pattern (ventilation-induced lung injury [VILI]).[3]

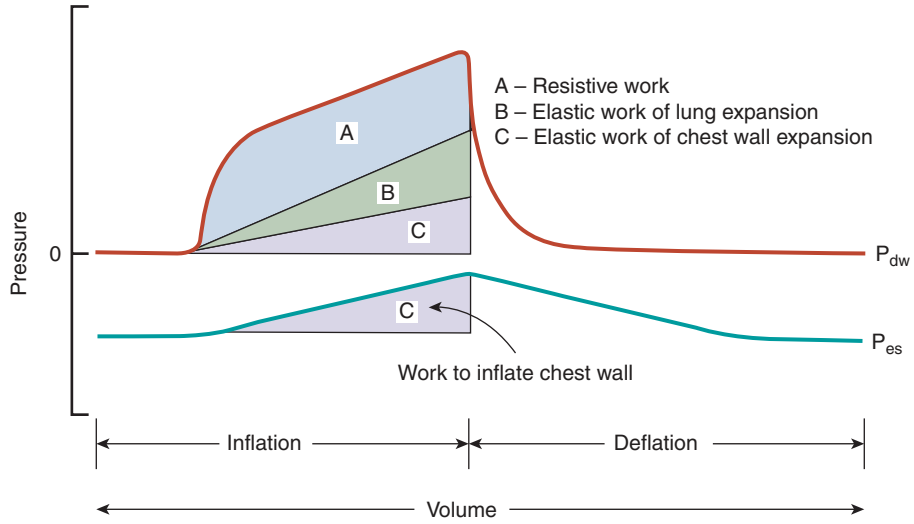

Fig. 53.8 Partitioning of the work (energy cost) of passively inflating the structures of the respiratory system without positive end-expiratory pressure (*PEEP*) applied. The pressure-volume areas quantify the work components. *Paw,* Airway pressure; *Pes,* esophageal (pleural) pressure.

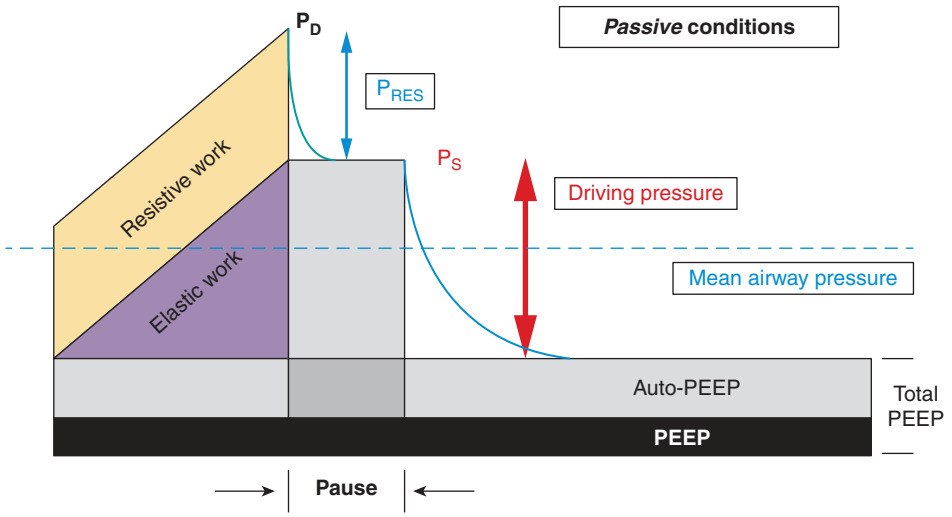

Fig. 53.9 Partitioning of inflation work under passive conditions of constant inspiratory flow. The horizontal axis is time. During constant flow, time is an analog of volume. Total positive end-expiratory pressure (*PEEP*) the sum of applied and auto-PEEP, has an associated energy cost during inflation.

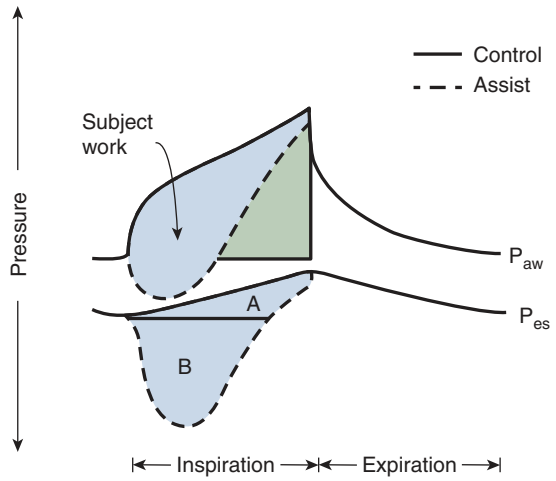

Fig. 53.10 Subject work of breathing under conditions of constant inspiratory flow provided under full control and patient-assisted breathing. Because the total mechanical task of inflation is the same, the pressure-volume area difference in machine work indicates the subject's contribution. Pressures can be inscribed either at the airway pressure (*Paw*) or esophageal pressure (*Pes*) sites. A, Chest wall work; B, lung inflation work.

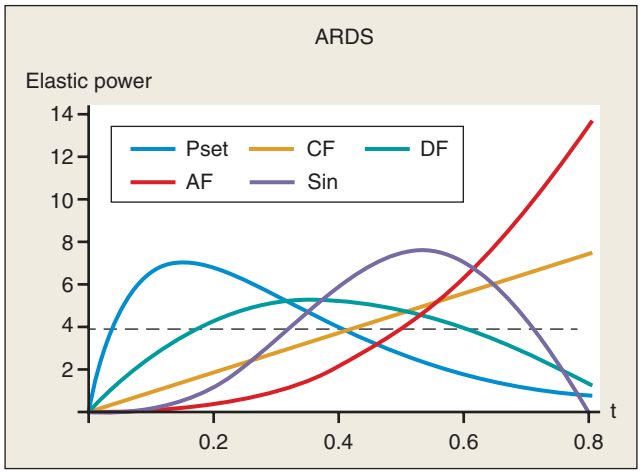

Fig. 53.11 Intracycle elastic power applied to the lung as a function of time for five flow patterns of ventilation. *AF,* Accelerating flow; *CF,* constant flow; *DF,* linearly decelerating flow; *Pset,* pressure control; *Sin,* sinusoidal pattern of unassisted breathing.

Influence of Body Position on Lung Volume

Modification of body position is too often neglected as a therapeutic tool. Gravitational forces exert an important influence on lung volume, on ventilation distribution, and on respiratory system compliance. Under most circumstances, more upright positioning substantially increases functional residual capacity (FRC). In normal subjects, reclining decreases FRC, primarily because of the upward pressure of the abdominal contents on the diaphragm and dorsal lung compression by the heart.[17] Normally, the FRC declines by approximately 30% (or approximately 600–900 mL for healthy persons) in shifting from the sitting to the horizontal supine position and by less in shifting from the sitting to lateral decubitus position[18] (Fig. 53.12). The magnitude of these reductions is somewhat less in older than in younger patients. Raising end-expiratory pressure with PEEP or continuous positive airway pressure (CPAP) elevates FRC. A simple calculation based on

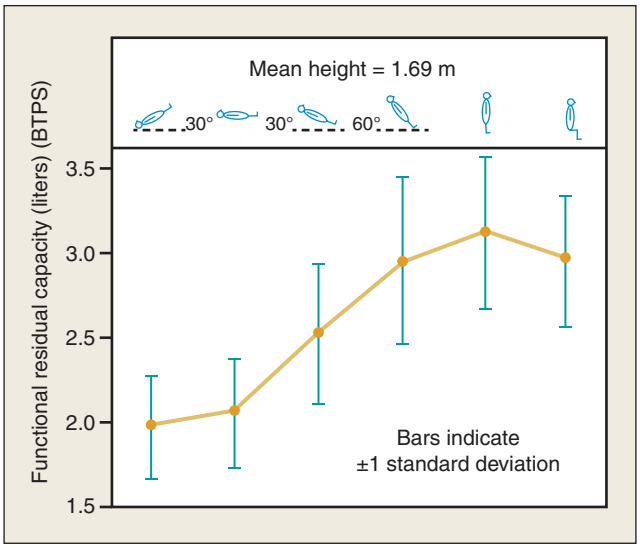

Fig. 53.12 Resting lung volume (functional residual capacity [FRC]) as a function of body positioning. *BTPS,* body temperature pressure saturated with water vapor.

these positional losses of volume and assuming normal supine respiratory system compliance (~80 mL/cm H_2O) suggests that 5–8 cm H_2O of PEEP may be necessary in healthy persons simply to offset the sitting-to-supine reduction of FRC. Patients of similar age with severe airflow obstruction generally lose much less volume than do normal healthy subjects when assuming supine recumbency. In massive obesity, the expiratory reserve volume (the FRC minus residual, "empty gas tank" volume) may nearly disappear even when fully upright. Sitting-to-supine changes of end-expiratory lung volume may be minimal not only for this reason but also because of positional airway closure and gas trapping.[19]

Recumbency redistributes lung volume because it alters the geometry of the thorax. When supine, the heart directly compresses the left lower lobe bronchi, and its weight is partially supported bilaterally by the lung tissues beneath. This anatomy helps account for the tendency for atelectasis to develop commonly in the left lower lobe in postoperative and bedridden patients—especially in those with cardiomegaly.[20] The pleural pressures in gravitationally dependent zones are less negative than at the apex. The vertical gradient of transpulmonary pressure (alveolar minus pleural pressure) is approximately 0.25 cm H_2O per centimeter of vertical height for normal subjects in the erect position and approximately 0.17 cm H_2O per centimeter for normal subjects in recumbency; consequently, local alveolar volumes are greatest in the nondependent regions.[17] For semi-recumbent patients with edematous lungs, an intensified gravitational gradient of pleural pressure accentuates the tendency for dorsal and peri-diaphragmatic atelectasis and consolidation.

The gradient of pleural pressure is less in the prone than in the supine position, in part because of reshaping of the thoracic cavity and shifting of the weight of the heart and mediastinal contents.[17] The supporting surface compresses the anterior chest and abdomen when prone, causing chest wall compliance to decline. Although conversion from the supine to the prone position is usually accompanied by marginal net changes of resting lung volume (<15%), there is usually a major shift of aerated lung volume toward dorsal regions (Fig. 53.13).

The lateral decubitus position causes the upper lung to assume a resting volume nearly as large as it has in the sitting position, whereas the lower lung is compressed to a size similar to or less than in the supine position. *Total* resting lung volume is somewhat greater in the lateral decubitus than in the supine horizontal orientation.[18]

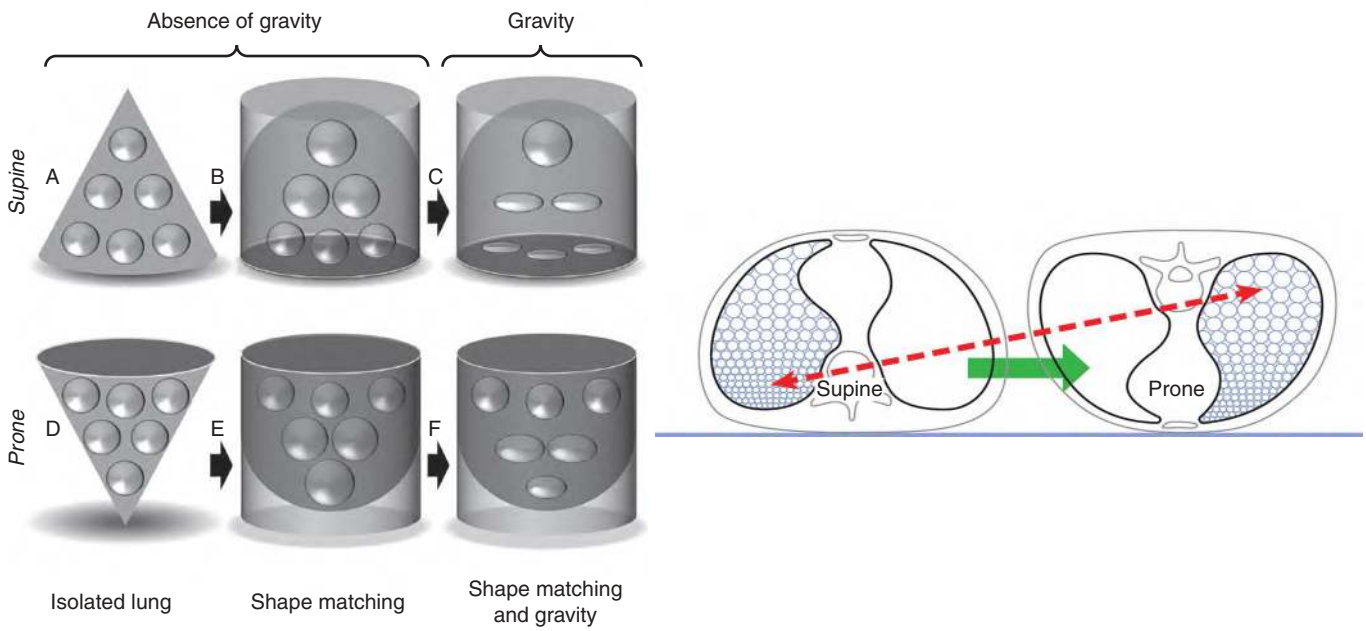

Fig. 53.13 Combined effects of gravity and shape matching on regional alveolar dimensions in the supine and prone positions.

Distribution of Ventilation. During spontaneous breathing, ventilation distributes preferentially to the dependent lung zones in the supine, prone, and lateral positions.[21,22] To avert atelectasis, the healthy subject typically breathes with low tidal lung volumes at rest, takes "sigh" breaths two to four times deeper than the average tidal volume multiple times per hour, and postural changes are unconsciously made frequently. Microatelectasis and arterial O_2 desaturation tend to develop if breathing remains shallow and uninterrupted by these periodic sighs or variations of position.[22–24]

Mechanics in Disease States

Management details regarding specific diseases are provided elsewhere in this volume. Yet certain basic features of mechanics for two common classes of breathing disorders are of such fundamental importance as to deserve emphasis here.

Acute Lung Injury

Acute lung injury ranks among the most challenging problems confronted in intensive care practice. ARDS may arise from diverse causes, most of which generate inflammation and high-permeability edema from pneumonia or sepsis. Mechanical ventilation provides indispensable life support but simultaneously holds the potential to injure lung tissue by applying excessive forces and tidal energy. Adverse consequences stem primarily from lung tissue's vulnerability to excessive stretching and mechano-signaling of inflammation, amplified by topographically heterogeneous mechanical properties and forces that act within the injured lungs.[25]

Despite the regional nonuniformity of transpulmonary pressures, only one airway pressure and/or one flow rate and flow profile can be selected and monitored at the airway opening. The low measured compliance that helps define ARDS was originally visualized as resulting from diffuse stiffening of all lung units, but now it is understood that compliance relates inversely to the number of units having relatively normal inflation properties. In other words, during the early phase of the process, *specific* compliance of each ventilated unit may be relatively normal and therefore susceptible to overstretching by high transalveolar pressure. This low-capacity condition has become known as the "baby lung"[26] (see Fig. 53.13). The degree to which that normality and vulnerability persists into the later stages of the ARDS process is not entirely clear. The gravitational gradient of transpulmonary pressure in ARDS is heightened by the increased weight of the lung, and the tendency for collapse of gravitationally dependent lung units is accentuated by the instability of surfactant-depleted air-liquid interfaces. As a consequence, sufficient PEEP is needed to generate a transpulmonary pressure at end expiration adequate to prevent their collapse. Not only does preserving alveolar patency help with gas exchange but also it prevents repeated tidal opening and closure of small airways—a process that accentuates potentially damaging stresses. Even when unit patency is preserved, focused stresses and high shearing forces arise at the interfaces between open and nonaerated tissues.[27] In this "amped up" environment, the repetitive application of relatively high tidal transpulmonary pressures may inflict damaging strain. These injurious transpulmonary forces may result from vigorous spontaneous efforts alone (patient self-induced lung injury [P-SILI]), from high airway pressures alone, or from any combination of both.[28] Even when it does not dramatically improve dorsal recruitment, prone positioning is currently thought to reduce VILI risk primarily by evening the distribution of transpulmonary pressures, thereby damping maximal tissue stresses and strains.

Acute Airflow Obstruction

Alveolar pressure at the end of passive tidal expiration may exceed set PEEP when the expiratory phase cannot be completed to the fully relaxed position of the respiratory system before the next inspiration begins (Fig. 53.14). The resulting pressure *gradient* driving end-expiratory flow (auto-PEEP, from the Greek word *autos* for "self") persists until interrupted by inspiratory forces generated by the patient or ventilator.[29] Total end-expiratory alveolar pressure (total PEEP) is the sum of the applied PEEP and auto-PEEP (AP). Unlike applied PEEP, AP local values (and therefore total PEEP) among lung units with diverse mechanical properties may not be the same throughout the diseased lung, and regional gas trapping may occur at higher pressures

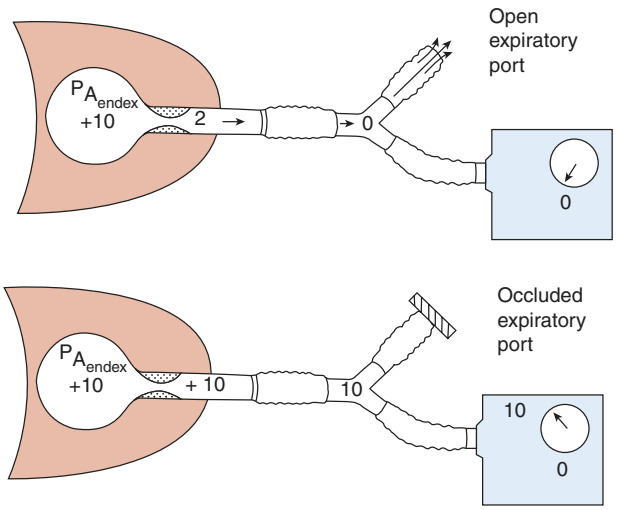

Fig. 53.14 The auto-PEEP effect and its measurement. Note that the true alveolar pressure (total PEEP) can only be estimated by the ventilator circuit when end-expiratory flow is stopped . In this case, no applied PEEP was present, and auto-PEEP was 10 cm H_2O. *PEEP,* Positive end-expiratory pressure. (From Pepe PE, Marini JJ. Occult positive end-expiratory pressure in mechanically ventilated patients with airflow obstruction (the auto-PEEP effect). *Am Rev Respir Dis.* 1982;126:166–170.)

than measured at the airway opening[30] (Fig. 53.15A). For this reason, the end-inspiratory static (plateau) airway pressure is generally a better indicator of hyperinflation than is the end-expiratory measurement of AP itself. Under passive conditions the detectable presence of AP and end-expiratory flow is invariably linked to increased end-expiratory distention, usually termed *dynamic hyperinflation (DH).* However, regional compliance determines the degree of lung unit expansion that corresponds to AP.

Determinants of Dynamic Hyperinflation and Auto-PEEP

Under passive conditions, the addressable variables that tend to increase DH and auto-PEEP are increased airway resistance, long inspiratory duty cycles (Ti/Ttot), and high minute ventilation (VE). Among these targets for therapy, perhaps the most effective strategy is to reduce ventilation requirement.[31] Lessening VE and accepting associated hypercapnia was adopted as a lifesaving approach for the treatment of intubated asthmatics well before permissive hypercapnia was implemented for ARDS.[32] Manipulation of the ventilatory *pattern* (frequency and VT combination) also influences DH, but reducing Ti/Ttot is generally of limited effectiveness when VE remains unchanged. Many who require ventilatory assistance for airflow obstruction have biphasic flow curves during tidal exhalation, with the second flow-limited phase much slower than the first.[33,34] Such

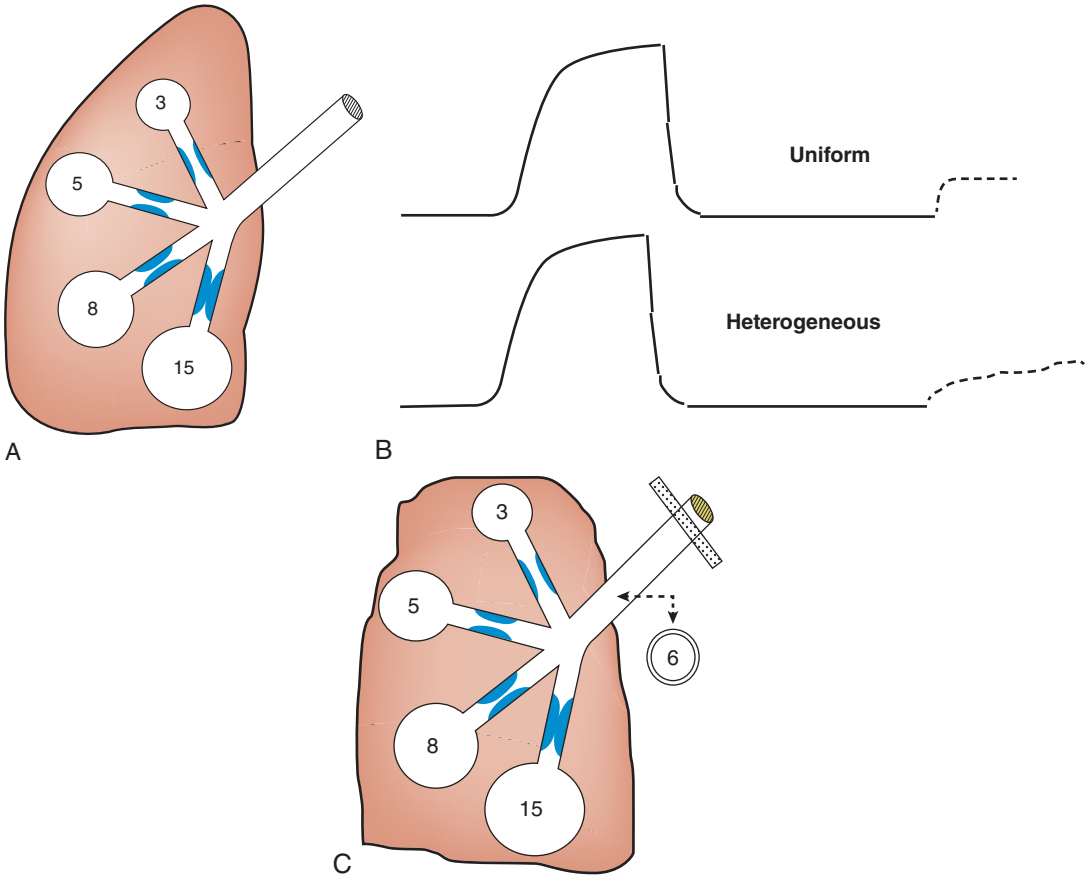

Fig. 53.15 A, Diverse regional values of auto-PEEP in a nonhomogeneous lung. Note that some lung units seal before the end of the deflation interval. **B,** Comparison of airway pressure profiles for a mechanically uniform and a mechanically nonuniform (*heterogeneous*) lung. At the point of end-expiratory flow stoppage *(arrow),* the slowly rising pressure profile at the airway opening reveals the mechanically heterogeneous lung as the varied alveolar pressures redistribute and equilibrate. **C,** Underestimation of maximal hyperinflating pressures by the auto-PEEP measured during end-expiratory port occlusion. Some of the most obstructed units seal before the end of expiration. The end-inspiratory (plateau) pressure provides a more reliable quantitative indicator of tidal hyperinflation. *PEEP,* Positive end-expiratory pressure.

biphasic deflation patterns are more often observed in chronic obstructive pulmonary disease (COPD) than in acute asthma, but do occur in both conditions.

Dynamic Hyperinflation

End-expiratory flow reliably implicates auto-PEEP during passive ventilation; however, the magnitude of flow bears little relation to the level of auto-PEEP that drives it through an undetermined upstream resistance.[30,31] At present, measuring static airway pressure after airway occlusion timed at end exhalation remains the method most commonly used to quantify *total* PEEP and to index global DH during *passive* ventilation. Under passive conditions, total PEEP can be measured by delaying the next breath as precisely timed airway occlusion terminates flow at the very end of the usual expiratory period. The contour of the resulting occlusion pressure helps reflect the uniformity or nonuniformity of auto-PEEP distribution (see Fig. 53.15B). Unfortunately, this maneuver cannot be performed reliably when the patient controls the breathing rhythm because of variations in the expiratory cycle length and/or muscular effort. This occlusion estimate is neither the highest nor lowest regional end-expiratory alveolar pressure during tidal breathing, but rather the *measurable* volume-averaged value (see Fig. 53.15C).

Consequences of Dynamic Hyperinflation and Auto-PEEP

Auto-PEEP associated with DH may affect hemodynamics, predispose to barotrauma, increase work of breathing, cause dyspnea, disrupt patient-ventilator synchrony, confuse monitoring of hemodynamics and respiratory system mechanics, and interfere with the effectiveness of pressure-regulated ventilation.[31] Barotrauma risk and the hemodynamic and energetic costs of auto-PEEP largely relate to any accompanying expansion of lung and chest wall volumes (DH)—not to alveolar pressure per se. Therefore as with the end-inspiratory plateau pressure, AP that occurs in association with stiff lungs or chest wall is less likely to be consequential than the same value measured in a setting of better respiratory system compliance.

Practical Bedside Indicators of Respiratory Mechanics

Compliance and resistance of the respiratory system can be easily estimated at the bedside under passive conditions during constant inspiratory flow. An end-inspiratory pause is applied to hold the inspired tidal volume trapped before exhalation is begun. Tidal compliance is the quotient of tidal volume and the difference between static plateau pressure (Ps) and PEEPtot, the so-called *driving pressure* (Δ) (see Fig. 53.8).[35] This contribution to stored elastic pressure, which is built up during inflation, drives expiratory flow. Importantly, calculations of Ps and Δ are valid for any inspiratory flow profile. Unless an automated estimate is provided by the ventilator, constant flow conditions flow conditions are required to estimate resistance, the difference between peak dynamic pressure (PD) and plateau pressures, divided by the rate of constant flow (see Fig. 53.8). The difference between PD and the pressure at which flow first becomes zero after the pause is applied (P_{ZF}) reflects the least resistance pressure because it excludes most stress relaxation, ventilation redistribution (pendelluft), and viscoelastic pressure adjustments that naturally occur during the pause. Finally, the slope of the airway pressure tracing at the end of inspiration obtained under constant flow conditions reflects elastance of the respiratory system ($1/C_{RS}$).

Mean Airway Pressure

Mean airway pressure is an easily observed and underused clinical tool. Under passive conditions, mean alveolar pressure and its only measurable analog, mean airway pressure (mPaw), relate intimately to the average forces that drive ventilation and hold the lung distended. When the nonelastic pressures dissipated in inspiration and expiration are identical, the airway pressure averaged over the entire ventilatory cycle should be the same everywhere, including the alveoli (mPalv) (Fig. 53.16). This mean pressure obtained in the absence of breathing effort is the pressure averaged over both phases of the tidal cycle. It distends the alveolus and passive chest wall and therefore correlates with alveolar size and with mean intrapleural pressure.[4] It follows that changes in mean airway (mean alveolar) pressure, when measured without patient effort, influence lung size and arterial oxygenation in the setting of pulmonary edema and lung injury. As a key determinant of mean intrapleural pressure, it also correlates under passive conditions with the "backpressure" to venous return. Mean airway pressure can be raised by increasing VE, by raising end-expiratory pressure, or by extending the inspiratory time fraction. To avoid serious and unanticipated problems in the passive patient, mean airway pressure is a key variable to monitor when the clinician changes minute ventilation or alters the mode of ventilation, breathing pattern, or PEEP setting. Although the relationship between mPalv and mP_{AW} is a close one, these pressures are not identical.[4] Any such pressure difference that generally

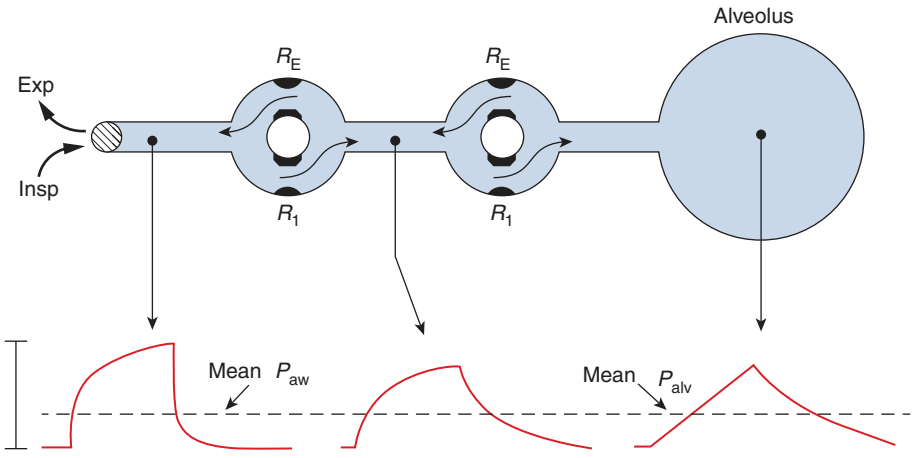

Fig. 53.16 Mean pressures along the path from airway opening to alveolus. When averaged over the entire tidal cycle, the mean airway pressures are theoretically very similar wherever they are measured; therefore mean alveolar pressure may be approximated by mean airway pressure in the external circuit. Note that when expiratory flow resistive losses exceed inspiratory flow resistive pressure losses (not illustrated), mean alveolar pressure may significantly exceed mean airway pressure.

favors a more positive Palv, may be striking in the setting of severe airflow obstruction that generates high levels of auto-PEEP.

Stress Index

Noticeable curvature of the inspiratory pressure tracing during passive inflation with constant flow suggests that disproportionate recruitment (concave to the time axis) or disproportionate overdistention (convex to the time axis) is taking place during the tidal cycle (Fig. 53.17). From the standpoint of lung protection, both are undesirable. During constant flow, the relationship between pressure and time can be expressed: $P_{AW} \alpha (t^s + [RV' + PEEP_{TOT}])$.[36] In this expression P_{AW} is airway pressure, t is inspiratory time since inflation onset (a correlate of volume), R is inspiratory resistance, and s is the "shaping" coefficient, or stress index (see Fig. 53.17). When s = 1.0, the Paw contour is linear. When it is significantly less than 1 or greater than 1, the stress index suggests undesirable degrees of tidal recruitment or overdistention, respectively (see Fig. 53.13). Adjustments to PEEP and/or VT are advisable, accordingly. Although the stress index is conceptually useful and often helpful, it is important to note that in practice its potential utility as an indicator of lung mechanics may be influenced strongly by the presence of a pleural effusion, abnormal chest wall properties, variations of auto-PEEP, and body position.[37] Any inspiratory muscular effort essentially invalidates its inferences.

Assessing Mechanics During Patient Effort

Although esophageal pressure measurement is seldom undertaken in clinical practice and therefore cannot be considered a basic skill, it deserves brief mention here because it provides the only direct and relatively noninvasive means for tracking lung mechanics during nonpassive breaths and for separating the forces applied to the lung and chest wall.[5] By noninvasively measuring the pressure in the pleural space that surrounds the lungs, the esophageal balloon catheter enables estimation of the transpulmonary pressure acting on the lung during all patient-initiated breaths (spontaneous or machine-assisted) and allows partitioning of transthoracic pressure into its lung and chest wall components during passive inflation (Fig. 53.18). The Pes

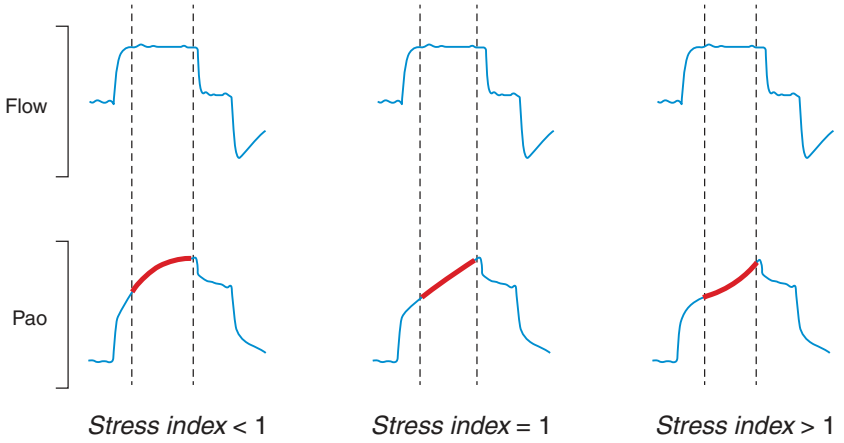

Fig. 53.17 Concept of the stress index. During constant inspiratory flow, the profile of the airway opening pressure (*Pao*) versus time indicates whether net tidal recruitment (<1) or net tidal overdistension (>1) are occurring with that combination of tidal volume and total PEEP. Significant departures from the ideal linear stress index of 1.0 are concerning.

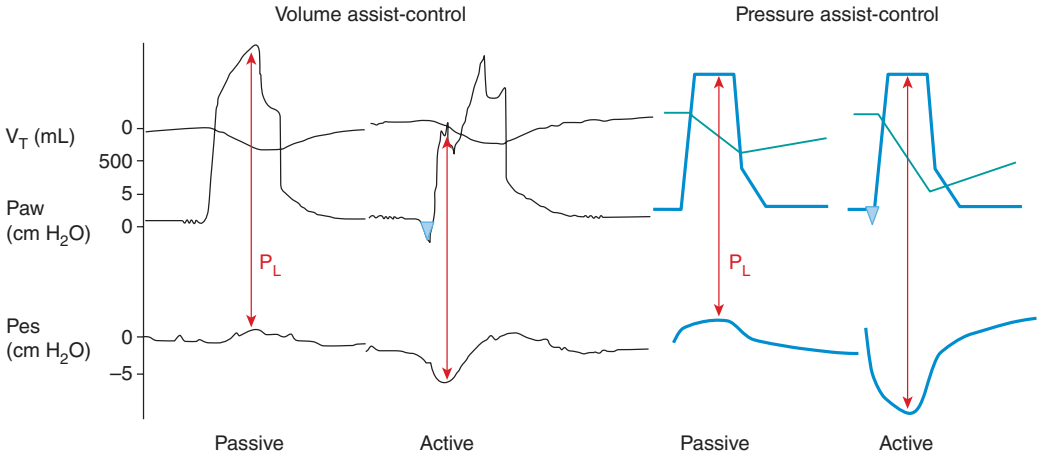

Fig. 53.18 Importance of the patient's contribution to the transpulmonary pressure under conditions of flow-regulated, volume-controlled ventilation *(left panels)* versus pressure regulated inflation *(right panels).* Note the potential for unregulated and greater transpulmonary pressure (P_L) during active breathing under the pressure assist-control condition. *Paw,* Airway pressure; *Pes,* esophageal (pleural) pressure. (From Akoumianaki E, Maggiore SM, Valenza F, et al., for the PLUG Working Group [Acute Respiratory Failure Section of the European Society of Intensive Care Medicine] The application of esophageal pressure measurement in patients with respiratory failure. *Am J Respir Crit Care Med.* 2014;189[5]:520–531, Fig. 2.)

provides a valuable indicator for detecting excessive effort, patient-ventilator asynchrony, lung stress, and weaning tolerance.[6,7,38] Having an intrapleural pressure permits direct calculation of lung compliance and airway resistance during spontaneous breathing, and Pes also can be used to compute the work of breathing. Finally, knowing the transpulmonary lung stress applied by a given plateau pressure may help to prevent VILI by guiding PEEP selection and by estimating lung-relevant transpulmonary stresses and driving pressures. Such information may prove influential during management of the massively obese[8] and during vigorous breathing.

GAS EXCHANGE

Oxygenation:

Directly Measured Variables

Partial oxygen pressure. The partial pressure of oxygen (PO_2) is the pressure exerted by the free oxygen molecules present in a gas or a fluid (in the form of unbound oxygen). The equilibrium between gas and fluid is the condition in which an equal number of oxygen molecules flow from the fluid to the gas and from the gas to the fluid. This equilibrium between oxygen in the alveoli and the free and unbound blood oxygen is defined by the solubility coefficient, which is equal to 0.0031 mL/mm Hg of oxygen/dL of blood.

Hemoglobin oxygen saturation. The hemoglobin oxygen saturation represents the fraction of hemoglobin to which the oxygen is bound. One molecule of hemoglobin, in which four binding oxygen sites are present, may only have a saturation fraction of 0%, 25%, 50%, 75%, or 100%. Therefore the clinically measured hemoglobin saturation is the weighted mean of the saturation of the single molecules (for example, if we assume that in a given patient 10% of the hemoglobin molecules are saturated at 50%, 20% at 75%, and 70% at 100%, the measured saturation will be 95%).

Indirectly Computed Variables

Alveolar PO_2. The alveolar PO_2 (PAO_2) is a key variable in the oxygenation process, as all blood perfusing an alveolus with a given PAO_2 will leave the lungs with the same oxygen tension (i.e., alveolar PO_2 = pulmonary capillary PO_2 [$PccO_2$]). Establishing the value of PAO_2 is a challenging task because of the cyclic nature of breathing and, furthermore, the values of PAO_2 differ significantly in distinct regions of the lung. This variation precludes accurate direct measurement of PAO_2 and has led to the development of indirect techniques for PAO_2 assessment, or in general, the assessment of all alveolar gases, by introducing the concept of the "ideal gases."[9]

The ideal PAO_2 may then be considered the average PO_2, which fully justifies the observed gas exchange, that is, which satisfies the following equation for a given respiratory quotient (RQ):

$$VO_2 = (FiO_2 - FAO_2) * VA = (CcO_2 - CvO_2) * Qc \qquad \textbf{(Eq. 2)}$$

$$\text{note: } VA = VE * \left(1 - \frac{Vd}{Vt}\right) \text{ and } Qc = Qt * \left(1 - \frac{Qs}{Qt}\right)$$

where VO_2 is the oxygen consumption per minute, FiO_2 the inspired fraction of oxygen, FAO_2 the alveolar fraction of oxygen, VA the alveolar ventilation, CcO_2 and CvO_2 the capillary and venous contents of oxygen, and Qc is the nonshunted perfusion of the lung. VE is the minute ventilation, Vd and Vt the dead space and the tidal volume, Qt is the total cardiac output, Qs is the shunted blood flow, and Qs/Qt the shunt fraction.

Equation (2) is consistent with a simple three-compartment model of pulmonary gas exchange: one ventilated and not perfused (Vd/Vt), one perfused but not ventilated (Qs/Qt), and one both perfused and ventilated. As illustrated by the equation, all oxygen *exchange* (VO_2) occurs in the ideal compartment having both Va and Q. (The same can be shown for CO_2 exchange.)

Although the "ideal" PAO_2 may be computed in different ways, one of the ones most used in the daily practice of mechanical ventilation is the following:

$$PAO_2 = FiO_2 * (P_B - P_{H_2O}) - \frac{PACO_2}{RQ} \qquad \textbf{(Eq. 3)}$$

where P_B is barometric pressure, P_{H_2O} is water vapor pressure at 37°C, $PACO_2$ is the alveolar PCO_2, and RQ is the respiratory quotient.

Although Eq. 3 accounts for the RQ—that is, the difference between oxygen consumption (VO_2) and CO_2 production (VCO_2)—it ignores the discrepancy between inspired and expired tidal volumes. This is evident after rearrangement of Eq. 3 into Eq. 4:

$$RQ = \frac{VCO_2}{VO_2} = \frac{FACO_2 * VA}{(FiO_2 - FAO_2) * VA} = \frac{FACO_2}{(FiO_2 - FAO_2)} \qquad \textbf{(Eq. 4)}$$

The earlier alveolar-gas equation (Eq. 3) is then derived by solving Eq. 4 for FAO_2 and expressing it as a partial pressure, according to the following general relationship:

$$P_p = F_g * (P_B - P_{H_2O}) \qquad \textbf{(Eq. 5)}$$

where P_p is the partial pressure of the gas and F_g is the fraction of the gas in the total gas volume.

As shown, the alveolar PAO_2 depends on the barometric pressure (P_B, which changes with altitude), on the $PACO_2$ (which depends on VCO_2 production and ventilation), and on the RQ (in the critical care setting it is usually approximated as 0.8).

A word of caution, however, is mandatory when assessing the alveolar PAO_2 in the setting of extracorporeal respiratory support; as an example, when using the extracorporeal CO_2 removal technique, the RQ disproportionately eliminates CO_2, causing RQ to be extraordinarily low, with remarkable effects on the computed PAO_2 and gas equilibrium.

Oxygen content. Essential information in the acutely critical patient is the blood content of oxygen, CnO_2, whose defining equation can be applied to arterial blood, central venous blood, or mixed venous blood:

$$CnO_2 = Hb * 1.39 * SatO_2 + 0.0031 * PO_2 \qquad \textbf{(Eq. 6)}$$

We may wonder why different coefficients are used in the literature: 1.35, 1.36, or 1.39 mL of oxygen per gram of fully saturated hemoglobin. The classical molecular weight of hemoglobin is 64,500 Da (or g/mol, if expressed as molar mass); therefore because 1 mole of fully saturated hemoglobin binds 4 moles of oxygen (at 760 mm Hg and 0°C) and the volume to mass relationship of ideal gases is 22.414 L/mol, fully saturated hemoglobin binds 4 * 22.414 = 89.656 L/mol. The ratio between 89,656 mL/mol and 64,500 g/mol equals 1.39 mL/g of Hb. The correction for the body temperature would give a higher coefficient (1.54 mL/g of Hb), whereas the coefficients used in literature are usually lower than 1.39 mL/g.

This adjustment is a result of the different molecular weights associated with the different strains of hemoglobin present within the erythrocytes.

Oxygen consumption. The oxygen consumption may be computed through the Fick method as the product between the cardiac output and the arterial-venous content difference:

$$VO_2 = (CaO_2 - CvO_2) * Qt * 10 \quad \textbf{(Eq. 7)}$$

Under normal conditions, the fraction of the oxygen transported from the arterial blood to the periphery is computed as follows:

$$DO_2 = Qt * CaO_2 \quad \textbf{(Eq. 8)}$$

As a consequence, the amount of oxygen returning to the right heart (vDO_2) amounts to:

$$vDO_2 = Qt * CvO_2 \quad \textbf{(Eq. 9)}$$

In normal conditions, the oxygen transported to the periphery is approximately 20 mL/dL of blood (for 5 L/min of cardiac output, it would amount to 1000 mL O_2 per minute). If the oxygen subtracted in the periphery (i.e., the oxygen consumption) is equal to 250 mL/min, the blood returning to the central venous compartment will be 750 mL/min. The ratio between returned and delivered oxygen in this example is 0.75, the approximate saturation. This underlines the importance of the mixed venous oxygen saturation, SvO_2, or its surrogate, the central venous saturation, as a key assessment tool in intensive care practice. Indeed, proceeding from the concept described earlier:

$$SvO_2 = SaO_2 - \frac{VO_2}{Qt * 1.39 * Hb} \quad \textbf{(Eq. 10)}$$

As shown, SvO_2 depends on arterial saturation, oxygen consumption, cardiac output, and hemoglobin concentration. Hence, any change in SvO_2 from baseline should immediately alert the intensive care physician that something potentially important is happening, either in the respiratory system (SaO_2), in the metabolic status (VO_2), in hemodynamics (Qt), or in the oxygen transporter (hemoglobin). Although SvO_2 is an unspecific tool, a sudden change of its value should immediately prompt the physician to evaluate all components that determine it.

Oxygenation assessment. Hypoxemia is defined by an oxygen partial pressure below the normal values. In subjects breathing in room air at normal atmospheric pressure, the PaO_2 is a function of age and may be approximated as:

$$PaO_2 = 100 - age * 0.3 \quad \textbf{(Eq. 11)}$$

where age is expressed in years.

As the partial pressure of a gas is equal to the total gas pressure times the fraction of the gas, and assuming that the oxygen exchange is in equilibrium between blood and alveoli, it follows that the arterial oxygen concentration is strongly related to (but not entirely determined by) the inspired oxygen fraction (FiO_2) and the barometric pressure. This must be taken into account under conditions of high altitude, as the P_B varies accordingly. The general equation to assess the inhaled PO_2 (PiO_{2new}) according to the external pressure is the following:

$$PiO_{2new} = FiO_2 * P_{Bnew} \quad \textbf{(Eq. 12)}$$

where P_{Bnew} is the barometric pressure at the new altitude.

In this setting, the alveolar oxygen pressure will be the following:

$$PAO_2 = (PiO_{2new} - 47) - \frac{PACO_2}{RQ} \quad \textbf{(Eq. 13)}$$

where 47 mm Hg represents the normal value of water vapor pressure at 37°C times the FAO_2.

PaO_2 and PaO_2/FiO_2 ratio. The simplest means by which to assess the efficacy of patient oxygenation is the direct measurement of arterial PO_2. However, because this value does not account for the fraction of inhaled oxygen, it cannot be used to assess the lung's oxygen exchanging status. The ratio between PaO_2 and FiO_2 was proposed decades ago as a tool for the assessment of the oxygenation status and the severity of hypoxemia; generally, mild hypoxemia is defined as a PaO_2/FiO_2 ratio of 200–300 mm Hg, mild to moderate hypoxemia as a PaO_2/FiO_2 ratio between 150 and 200 mm Hg, moderate to severe hypoxemia as 100–150 mm Hg, and severe hypoxemia below 100 mm Hg. The limitations of the PaO_2/FiO_2 ratio are twofold. First the relationship between FiO_2 and PaO_2 is not linear, and this nonlinearity implies that for a given degree of true oxygenation impairment, the PaO_2/FiO_2 ratio may vary depending on the FiO_2 at which it is determined. Second, a given FiO_2 results in a different alveolar partial pressure of oxygen, depending on the barometric pressure and, more importantly, on the RQ. This is especially relevant in patients under extracorporeal support, in which the RQ may be far different from the usual values. To overcome the first limitation of the PaO_2/FiO_2 ratio, it would be appropriate to compute the PaO_2/PAO_2 ratio, which takes into account the values of $PaCO_2$ and usually assumes an R equal to 0.8. The second limitation relating to distortions of RQ could only be overcome by measuring the actual VO_2/VCO_2 occurring in the natural lung.

Right-to-left shunt. This variable was introduced by Riley and colleagues in 1949 as a surrogate for directly measuring the ventilation-perfusion ratio (Va/Q).[9] As noted earlier, Riley and colleagues proposed a three-compartment model: one (ideal) ventilated and perfused, one (dead space) ventilated but not perfused, and one (right-to-left shunt, or more correctly, venous admixture) not ventilated but perfused.

The blood and gas leaving the ideal compartment have the same PaO_2, $PaCO_2$, and RQ as the body as a whole. In other words, the gas exchange (i.e., the oxygen transferred from the lung to the blood and the carbon dioxide removed by the lungs) occurs in this ideal compartment. In contrast, the blood leaving the right-to-left shunt compartment has the same PaO_2 and $PaCO_2$ of the mixed venous blood. The gas leaving the dead-space compartment has the same composition of the gas that enters it (CO_2 close to zero) and no blood comes out. In Fig. 53.19 we reproduce the original scheme of Riley and colleagues.

To understand the computations relating to the shunt compartment, it is convenient to consider gas content instead of pressure. Indeed, the oxygen content flowing per minute in the arterial blood [Qt * CaO_2] is the sum of that coming from the ideal compartment [(Qt − Qs) × CcO_2] and the blood [Qs] coming from the right-to-left shunt compartment:

$$Qt * CaO_2 = (Qt - Qs) * CcO_2 + Qs * CvO_2 \quad \textbf{(Eq. 14)}$$

where Qt is the cardiac output and Qs is the shunt flow. Rearranging the equation by dividing the two sides of the equation by Qt leads to the following equation:

$$CaO_2 = \left(1 - \frac{Qs}{Qt}\right) * CaO_2 + \frac{Qs}{Qt} * CvO_2 \quad \textbf{(Eq. 15)}$$

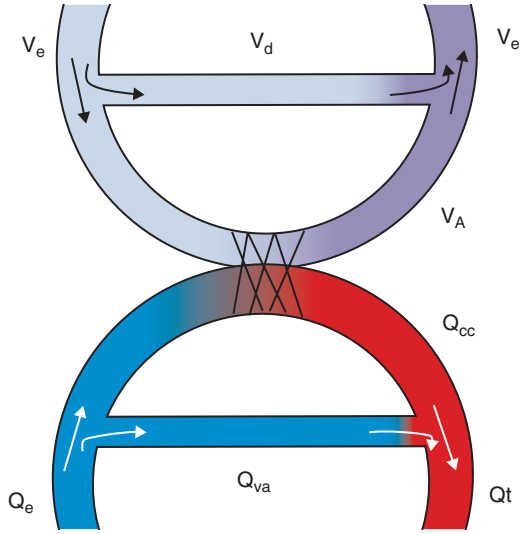

Fig. 53.19 Schematic representation of ventilation and perfusion exchange. *Upper part of the figure:* The gas entering the lungs (minute ventilation) splits in two compartments: dead space ventilation and alveolar ventilation. After the gas-exchange process within the pulmonary capillary, the CO_2-enriched alveolar gas is in part diluted, after leaving the perfused alveoli, by the dead space gas. *Lower part of the figure:* The blood entering the lungs (cardiac output, venous, in *blue color*) splits in two compartments: venous admixture flow (Q_{va}) and capillary blood flow (Q_{cc}). After the gas exchange the O_2-enriched capillary flow is in part diluted, after leaving the ventilated alveolar units, by the venous admixture. *Qt,* Cardiac output; *VA,* alveolar ventilation; *Vd,* dead space; *VE,* minute ventilation. (Adapted from Riley RL, Cournand A. Ideal alveolar air and the analysis of ventilation-perfusion relationships in the lungs. *J Appl Physiol.* 11949;1[12]:825–847.)

The variable of interest, the right-to-left shunt (Qs/Qt), can be then computed as follows:

$$\frac{Qs}{Qt} = \frac{CcO_2 - CaO_2}{CcO_2 - CvO_2} \qquad \textbf{(Eq. 16)}$$

It is noteworthy that Va/Q equal to zero is formally defined as a "true" right-to-left shunt. Using Riley and colleagues' model, however, all blood flowing in lung regions with Va/Q values intermediate between ideal and zero is assigned in proportion to the ideal or to the dead-space compartments. When perfused but low Va/Q units contribute to the Qs/Qt calculation, as they virtually always do to some extent, the appropriate terminology is "venous admixture" instead of right-to-left "shunt."

Oxygenation index and ROX index. The Oxygenation Index (OI) was introduced several decades ago by Bartlett and colleagues[10] as a composite measure for assessing the need of extracorporeal support in a pediatric population. It is calculated as follows:

$$OI = FiO_2 * \frac{MAP}{PaO_2} \qquad \textbf{(Eq. 17)}$$

where MAP is the mean airway pressure The MAP under passive conditions correlates with average aerated lung size and with lung unit recruitment. (MAP is discussed in the section on mechanics in this chapter.) Actually, rather than the adequacy of oxygenation, the OI assesses the costs of compensating for impaired oxygenation. Indeed, a high FiO_2 or MAP (which includes PEEP) are well-known potential boosters for VILI development and/or impaired venous return.

The ROX index has been recently introduced into daily clinical practice as an easy-to-apply tool for assessing patient oxygenation efficiency.[11] It is calculated as follows:

$$ROXi = \frac{SpO_2}{FiO_2} * \frac{1}{RR} \qquad \textbf{(Eq. 18)}$$

where SpO_2 is expressed as a percentage (0%–100%), FiO_2 is expressed as a fraction (0–1), and RR is the respiratory rate.

The ROXi normalizes the SpO_2 (using pulse oximetry as a surrogate of PaO_2) to the inspired FiO_2 and introduces the respiratory rate as an indicator of severity. Its advantages are ease of application, low cost, and potential for continuous monitoring. However, it is well-known how variations of temperature, pH and erythrocyte 2.3-diphosphoglycerate, and so on, shift the oxygen-hemoglobin dissociation curve, potentially leading to values of SpO_2 of 100% with values of PaO_2 ranging from 100 to 500 mm Hg. Consequently, the ROX index may be associated with unnecessarily high PaO_2 and, by contrast, cannot detect PaO_2 worsening until oxygen saturation decreases.

Clinical Applications

The arterial oxygen saturation of hemoglobin is the most widely used method of monitoring oxygenation, as it mirrors changes in arterial PaO_2 values below 90–100 mm Hg. Because values of PaO_2 higher than 100 mm Hg will be associated with a hemoglobin oxygen saturation of 100%, it is convenient to adjust FiO_2 in order to obtain a baseline oxygen saturation less than 100%. In doing so, any change in arterial oxygenation is immediately reflected by a modification in hemoglobin saturation. It is prudent to remember that a saturation of 50% is usually associated with a PaO_2 of approximately 25 mm Hg, whereas 90% usually corresponds to a PaO_2 of around 60 mm Hg. Within the range of 50% and 90%, oxygen saturation and PaO_2 are almost linearly related (i.e., any point change of saturation corresponds to ~1 mm Hg of PaO_2). Although these guidelines are obviously imprecise, they do help estimate blood oxygenation status.

Although the PaO_2/FiO_2 ratio is the most widely used indicator for classifying oxygenation impairment, its limits include the lack of linearity between PaO_2 and FiO_2. This implies that the PaO_2/FiO_2 ratio may change for a given shunt fraction, depending on the FiO_2 at which it is determined. The same occurs if the hemoglobin arterial oxygen saturation/FiO_2 ratio is used, as shown in Fig. 53.20.

In our opinion, the venous admixture and the dead space are the best assessment tools to assess any impairment of gas exchange (dead space will be discussed in detail later in this chapter). It must be noted, however, that venous admixture relates strongly to the cardiac output: an increased cardiac output promotes right-to-left shunt, whereas a decrease of cardiac output may raise PaO_2. This phenomenon becomes especially relevant when the airway pressures are high; indeed, an increased PaO_2 in a setting of high airway pressure may be the result of a decrease in cardiac output rather than increased recruitment.[39]

Finally, whereas hemoglobin saturation, PaO_2/FiO_2 ratio, and venous admixture account for the severity of oxygenation impairment, the OI and the ROX index include variables that reflect the conditions required to obtain a specific gas-exchange level. The OI includes the MAP and the FiO_2, and the ROX index incorporates the respiratory rate. Consequently, these indices are primarily indicated to help decide the level of intervention: extracorporeal support in the case of OI and tracheal intubation in the case of ROX index.

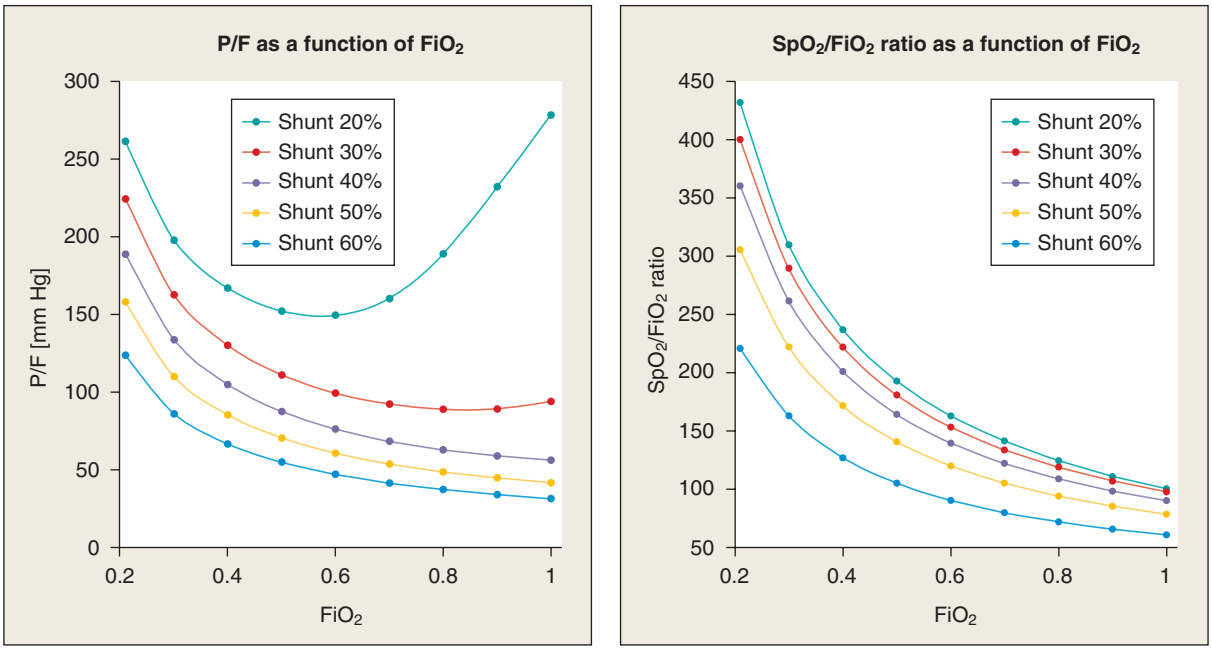

Fig. 53.20 *Left panel,* partial pressure of oxygen/fraction of inspired oxygen (PaO_2/FiO_2) ratio as a function of FiO_2 at different levels of shunt fraction. As shown, the same shunt may result in sharply different PaO_2/FiO_2 ratios, depending on FiO_2 at which the measurement has been performed. *Right panel:* SpO_2/FiO_2 as a function of FiO_2. As shown, the SpO_2/FiO_2 ratio is even less effective in reflecting the shunt fraction than the PaO_2/FiO_2 ratio. As an example, a shunt fraction of 40% may result in an SpO_2/FiO_2 ratio of 250 vs. <150, depending on the FiO_2 applied when making the measurement.

Carbon Dioxide Removal

Directly Measured Variables

Partial pressure of PCO_2. The partial pressure of carbon dioxide (PCO_2) is the pressure exerted by the free CO_2 molecules present in the gas or in a fluid. Carbon dioxide is characterized by a solubility coefficient of 0.0306 mmol/L*mm Hg. Note that the carbon dioxide solubility coefficient is measured as mmol/mm Hg per liter, whereas the oxygen coefficient refers to mL/mm Hg per deciliter. As 1 mmol of gas corresponds to 22.4 mL, it follows that the solubility of CO_2 compared with the oxygen is significantly higher when expressed with the same unit of measure: 0.0306 vs. 0.0074.

pH. The pH scale is used to assess acidity or alkalinity (basicity) of an aqueous solution by measuring the concentration of free H^+ protons in the solution, according to the following relationship:

$$pH = -\log[H^+] \qquad \textbf{(Eq. 19)}$$

where $[H^+]$ is the concentration of protons, in mmol/L.

In blood, at pH 7.4, the concentration of H^+ is 39.8×10^{-9} mol/L, or 39.8 nanomoles per liter. Remarkably, the magnitude of hydrogen ion concentration is on the order of nanomoles (10^{-9}), compared with the mmol (10^{-3}) of the other ions. An equilibrium constant (Kw) characterizes the process of water dissociation ($2H_2O \rightarrow H_3O^+ + OH^-$):

$$Kw = [H_3O^+] * [OH^-] \qquad \textbf{(Eq. 20)}$$

Accordingly, any increase or decrease of H^+ corresponds to an equal and opposite change of OH^-. For a better understanding of the relationship between CO_2 and pH, the concept of "electrical-charge equilibrium" needs to be introduced: the number of positive and negative charges in plasma must be equal. Directly Measured and Indirectly Computed are subcategories under Oxygenation. Electric charges originate from the dissociation of different substances. A strong ion is a substance that is always completely dissolved in a solution: that is, it always has an electric charge (e.g., sodium, chlorine, potassium, and lactate). Under normal conditions, the number of positively charged strong ions is higher than of the negatively charged anions; this difference is called the *strong ions difference (SID),* and it amounts to approximately 40 mmol. As a consequence, to maintain the electrical neutrality, 40 mmol of negative charges must be present in the system.

The weak acids, or buffers, are the substances that provide such missing negative charges, and they are present in two forms: dissociated (electrically charged) or undissociated (electrically neutral). Buffers can be conceptually divided into two groups, one represented by the total CO_2, which may be present as HCO_3^- (dissociated) or CO_2 (undissociated), and the other enclosing all the remnant weak acids, collectively called A_{tot}, primarily represented by albumin and phosphates. Again, A_{tot} may be either dissociated (A^-) or undissociated (AH) (Fig. 53.21).

To maintain the electrical-charge equilibrium, CO_2 and A_{tot} must dissociate in a way such that the sum of their dissociated forms is equal to the SID (i.e., $SID = HCO_3^- + A^-$). If a negative strong ion is added to the system, the SID decreases and, as a consequence, the sum of HCO_3^- and A^- should decrease by the same amount. Part of the HCO_3^- will convert to carbonic acid and eventually to CO_2 plus H_2O, and part of the A^- will become AH. Therefore in a condition of metabolic acidosis, the decrease of SID will lead to a decrease of HCO_3^- and A^-. Noteworthy, other than the decrease of HCO_3^- and A^-, the OH^- will decrease too, and because the product of OH^- and H^+ is constant, any decrease in OH^- will result in an increase of free H^+ (i.e., acidosis).

In respiratory acidosis the increase of pCO_2 leads to a higher HCO_3^-. Because the sum of HCO_3^- and A^- maintains the SID

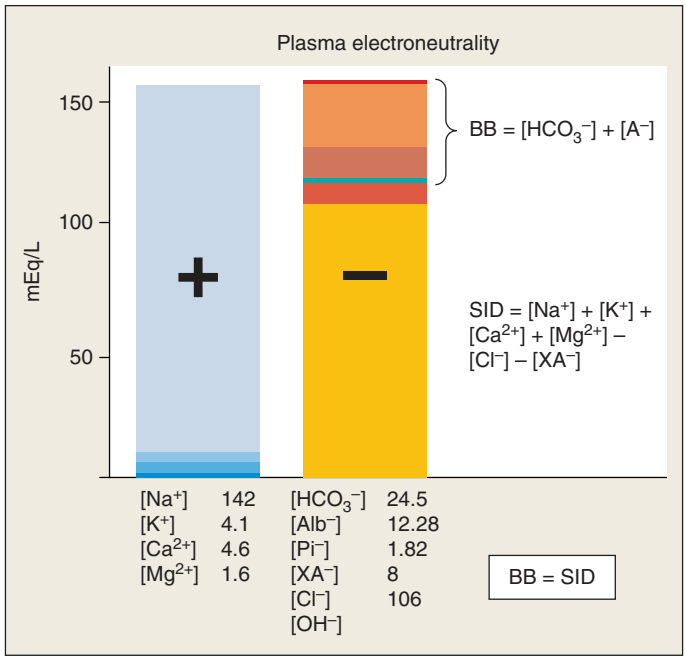

Fig. 53.21 Principle of plasma electroneutrality. As shown, electroneutrality (the height of the two columns) is reached when the 150 mEq/L of always-positive charges (strong ions always present with a positive charge) are neutralized by the 150 mEq/L of ions with negative charges. Of this 150 mEq/L, 108 mEq/L are always present with negative charges (strong ions), whereas 42 mEq/L may lose their negative charges if other negative ions are added to the system. In this case, part of $H_2CO_3^-$ will become $H_2O + CO_2$ and part of these anions (A^-) will become AH. Note that these "weak" ions are known as the buffer base (*BB*) and quantitatively equal the difference between strong positive and strong negative ions. *SIS,* Strong ions difference.

constant, any increase of HCO_3^- is matched by a decrease of A^-, which is then converted to AH. Again, a fraction of OH^- decreases, producing H^+ and therefore promoting respiratory acidosis.

Indirectly Measured Variables

Bicarbonates. Bicarbonate (HCO_3^-) is the dissociated part of carbon dioxide and the main form of transporting CO_2 in the blood; its equilibrium with the free CO_2 is classically represented by the Henderson-Hasselbalch equation:

$$pH = pk + \log \frac{HCO_3^-}{0.0306 * PCO_2} \qquad \textbf{(Eq. 21)}$$

Isolating bicarbonate on the left side of the equation results in the following expression:

$$HCO_3^- = 10^{pH-pk} * PCO_2 * 0.0306 \qquad \textbf{(Eq. 22)}$$

It is evident how any change of PCO_2 is followed by a change of HCO_3^- in the same direction. Furthermore, the proportionality constant () dictates the magnitude of this change. It should be noted that the algorithms used to compute bicarbonates are slightly different. Consequently, especially at pH values far from 7.4, the same $PaCO_2$/pH couple may result in bicarbonate differences as high as approximately 2 mmol.

Alveolar PCO_2. Alveolar PCO_2 ($PACO_2$) is the partial pressure of CO_2 in the alveolar space. Because of the complexity of alveolar gas assessment, it is again convenient to refer to the "ideal compartment" model we discussed earlier.

In a perfect gas exchanger, the alveolar PCO_2 equals the PCO_2 measured in the pulmonary venules and arterial blood ($PcCO_2$ and $PaCO_2$). If shunt is present, the blood coming from the ideal compartment is mixed with the blood coming from the shunted compartment, relatively rich with PCO_2. As a result, the $PaCO_2$ is higher than the $PACO_2$. On the other hand, in the perfect gas exchanger, the alveolar PCO_2 is equal to the end-tidal PCO_2 ($PetCO_2$), which is the pressure exerted by CO_2 within the exhaled gases. If dead space is present, the end-tidal PCO_2 will reflect the admixture of CO_2-free gas that never contacted blood and therefore will be lower than arterial PCO_2. In the perfect gas exchanger the ratio between end-tidal PCO_2 and $PaCO_2$ equals 1, whereas it varies in the presence of shunt or alveolar dead space.

For the sake of simplicity, however, in the clinical setting the alveolar PCO_2 is usually considered equal to the arterial $PaCO_2$. This difference is limited to no more than 2 mm Hg in the presence of shunt fraction lower than 20% and becomes more relevant at higher levels of shunt.

CO_2 content. The CO_2 content in the plasma is the sum of the dissolved PCO_2, bicarbonate, carbonate, and carbon dioxide bound to plasma proteins. However, the total plasma CO_2 content measured by blood gas-analysis machines only takes into account the sum of dissolved PCO_2 and bicarbonate:

$$PCO_2 + bicarbonate\ plasma\ CCO_2 = PCO_2 * 0.0306 * (1 + 10^{pH.rbc - pK}) \qquad \textbf{(Eq. 23)}$$

where $plasmaCCO_2$ is the total plasma content of CO_2.

It is important to realize that the CO_2 content of whole blood is markedly different from the total CO_2 content of plasma, as the pH of the red cells is lower than the pH of plasma, and pH influences CO_2 content. Therefore the total CO_2 in blood is:

$$bloodCCO_2 = plasmaCCO_2 * (1 - Ht) + Ht * 0.0254 * PCO_2 (1 + 10^{pH.rbc - pK}) \qquad \textbf{(Eq. 24)}$$

where Ht is the hematocrit, 0.0254 is the solubility of CO_2 within red blood cells (rbc), and pH.rbc is the intra-erythrocyte pH value.

Several formulas[40,41] have been proposed to compute the total CO_2 amount in the blood. However, for practical purposes, no one of these is really satisfactory because even a small error in the measurement of PCO_2, pH, or hematocrit may significantly change the computation. What is important to underline is the relationship between PCO_2, CO_2 content, and pH. Indeed, as shown in Fig. 53.22, for a given CO_2 content, any addition of strong ions leads to a decrease of base excess and pH and is eventually associated with an important rise of PCO_2.

At equilibrium, a given amount of carbon dioxide is produced and a given amount of oxygen is consumed, their relationship being equal to the RQ:

$$RQ = \frac{VCO_2}{VO_2} = \frac{Qt * (CvCO_2 - CaCO_2)}{Qt * (CaO_2 - CvO_2)} \qquad \textbf{(Eq. 25)}$$

where VCO_2 is the production of CO_2 per minute, VO_2 is the minute oxygen consumption, Q is the cardiac output, and Cv and Ca are the venous and arterial contents of CO_2 and O_2.

In critically ill patients this ratio is usually assumed to be 0.8. If a strong ion (lactate or chloride) is added to the venous blood, the pH suddenly decreases and the CO_2 content remains equal but the PCO_2 increases markedly, as shown in Fig. 53.23. This is the "Coca-Cola"

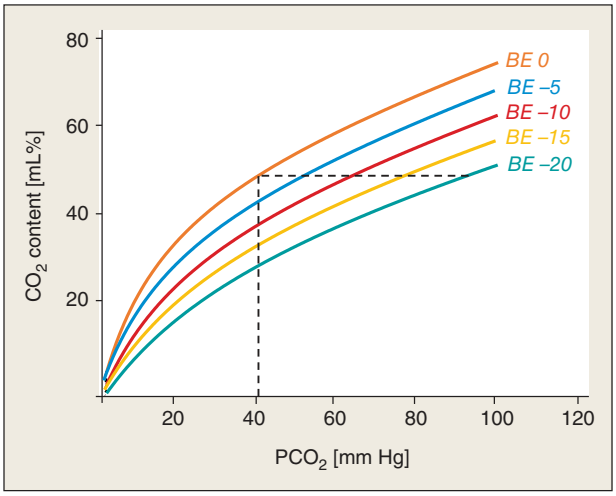

Fig. 53.22 CO_2 content as a function of partial pressure of carbon dioxide (PCO_2), according to different levels of base excess. For the same content of CO_2, the decrease of base excess may cause a sharp increase in PCO_2. In this case, in a closed system that contains 50 mL of CO_2 in 1 liter, adding, as an example, 20 mmol of lactates (strong negative ions) will cause PCO_2 to rise from 40 mm Hg to almost 100 mm Hg.

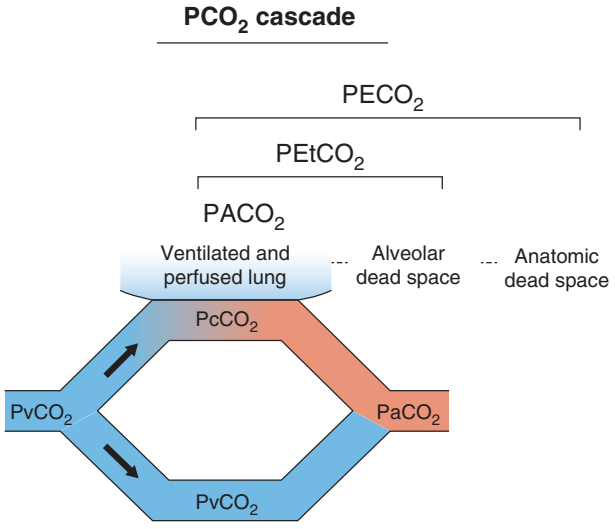

Fig. 53.23 Schematic representation of the cascade of CO_2. As shown, part of the free unbound CO_2 molecules ($PvCO_2$) leaves the blood phase and enters the alveoli. After CO_2 is removed by ventilation, the alveolar PCO_2 ($PACO_2$) and the PCO_2 in the pulmonary capillary leaving the alveoli are the same. The capillary PCO_2, however, mixes with the shunt flow (with higher PCO_2, the $PvCO_2$) after the venous admixture, thus generating the arterial PCO_2. If the shunt fraction is zero, $PaCO_2$, $PcCO_2$, and $PACO_2$ are equivalent. The $PACO_2$, present in the alveolar gases, is first diluted by the alveolar dead space, generating the $PEtCO_2$, and subsequently, by the anatomic dead space (airways plus circuit dead space), generating the $PECO_2$. If the alveolar dead space is equal to zero, the $PEtCO_2$ and $PECO_2$ are the same. It follows that $PEtCO_2/PECO_2$ are equal if both dead space and shunt fraction are zero.

effect, where an increased bubbling appears after squeezing a lemon (citric acid) into a soda. Of course, the bubbles are composed of free molecules of CO_2. The delta pCO_2 compared with the delta arteriovenous difference is therefore a suitable indicator for a strong negative ion addition.

CO_2 production. Although several methods have been described to measure the production of CO_2, the most reliable is based on the analysis of the exhaled gases. The carbon dioxide production (VCO_2) equation is as follows:

$$VCO_2 = VE * FECO_2 \quad \textbf{(Eq. 26)}$$

where VE is the minute ventilation and $FECO_2$ is the fraction of expired CO_2.

If CO_2 pressure is measured, it can be converted in fractions (FCO_2) according to the following formula:

$$FCO_2 = \frac{PCO_2}{P_B - 47} \quad \textbf{(Eq. 27)}$$

where PCO_2 is the partial pressure of CO_2, P_B is the barometric pressure, and 47 mm Hg is the pressure exerted by the water vapor at 37°C.

Several ventilators provide the capnographic curve, so they automatically measure the VCO_2 value. In this setting, VCO_2 is computed as the integral of the area below the capnographic curve. Despite being an extremely informative variable, VCO_2 is rarely assessed in the intensive care setting. It is worth noting that the level of mechanical ventilation required relates strictly to the amount of CO_2 to be cleared. Because a high intensity of mechanical ventilation is associated with a higher degree of VILI, a high VCO_2 is a main trigger for lung damage associated with mechanical ventilation.

CO_2 stores. Differently from oxygen, for which the body resources are limited to the oxygen dissolved in plasma and oxygen bound to the hemoglobin, carbon dioxide is present in large amounts in different body compartments. Indeed, CO_2 is stored in the blood, as discussed earlier, in the interstitium, where it is dissolved in the same form of blood, and in tissues, primarily in the bones. Here, it is accumulated in different chemical forms, on the whole bicarbonates and carbonates.[42]

The blood reserves are about 2.5%, interstitium accounts for an 8.5%, and the remaining CO_2 in the peripheral tissues amounts to 89%.[12] Traditionally, the extracellular compartment is considered "fast," as its CO_2 content may rapidly reduce by increasing the minute ventilation. Conversely, the CO_2 stored in tissues constitutes the "slow" compartment.

When measuring CO_2 production, or better, CO_2 clearance, the presence of mobilizable stores of CO_2 must be always taken into account. Indeed, the clearance of CO_2 may (1) be equal to the metabolic production, in which case the CO_2 store remains unmodified; (2) be increased, for example, during hyperventilation, leading to a decrease of the store of CO_2; or (3) be decreased, for example, in hypoventilation, associated with an increase of CO_2 stores. It must be remembered that despite the fact that arterial PCO_2 almost reaches the steady state in 5 minutes during hyperventilation and in 30 minutes during hypoventilation, the equilibrium, in terms of CO_2 depletion, is not reached even after 48 hours.

CO_2 assessment. The direct measurement of arterial PCO_2 allows one to classify any patient into normocapnic (35–45 mm Hg), hypocapnic (<35 mm Hg), or hypercapnic (>45 mm Hg). The determinants of arterial PCO_2 are the following:

$$PaCO_2 = \frac{VCO_2 * 863}{VA} \quad \textbf{(Eq. 28)}$$

where VCO_2 and VA (alveolar ventilation) are measured in L/min; 863 is a coefficient that converts the volume of a gas from a standard

temperature and pressure and dry (STPD) condition (0°C and 760 mm Hg, dry) to the body temperature pressure saturated with water vapor (BTPS) condition. In other words, a gas volume at 0°C (standard temperature, Ts) and 760 mm Hg (standard pressure, Ps) must be converted to body temperature (Tb = 37°C) and body pressure (Pb = 713 mm Hg).

The gas volume in BPTS conditions is equal to:

$$V\,btps = \frac{Ps * Tb}{Pb * Ts} * V\ stpd \qquad \textbf{(Eq. 29)}$$
$$\frac{760\ mmHg}{713\ mmHg} * \frac{310\ K}{273\ K} = 1.21$$

where body and standard temperatures are expressed in Kelvin degrees.

To convert the gas volume from STPD to BTPS, it must be multiplied by 1.21. Finally, to convert BTPS volume into a pressure, one must multiply the volume times the difference between barometric pressure (usually 760 mm Hg) and water vapor pressure (usually 46 mm Hg). Briefly: 760 minus 47 equals 713; multiplying by 1.21, the final result is 863.

According to Eq. 28, arterial PCO_2 increases either when VCO_2 increases or, more frequently, it increases when alveolar ventilation decreases. Alveolar ventilation is equal to:

$$VA = VE * \left(1 - \frac{Vd}{Vt}\right) \qquad \textbf{(Eq. 30)}$$

where VE is the minute ventilation, and Vd/Vt is the fraction of dead space over tidal volume. As a consequence, any increase of dead space or decrease in minute ventilation leads to an increase of PCO_2.

Therefore to fully understand PCO_2 behavior, its three determinants must be considered: carbon dioxide production, minute ventilation, and the BTPS converting factor.

Dead space and $PEtCO_2/PaCO_2$ ratio. The dead space is defined as the proportion of each breath that fails to take part in gas exchange, either because it remains in the conducting airways (anatomic) or because it ventilates regions of the lung that are not perfused adequately (alveolar). The physiologic dead space is the sum of the anatomic and the alveolar dead spaces.

To estimate the physiologic dead space, one should understand the relationship between alveolar and minute ventilation and arterial and exhaled pressure of carbon dioxide:

$$VCO_2 = \frac{VA * PACO_2}{863} = \frac{VA * PECO_2}{863} \qquad \textbf{(Eq. 31)}$$

Rearranging Eq. 31, we obtain:

$$\frac{VA}{VE} = \frac{PECO_2}{PACO_2} \qquad \textbf{(Eq. 32)}$$

where VA/VE is the fraction of the inspired air reaching the perfused alveoli. Noteworthy, the complement of this fraction is the dead space. Consequently:

$$DS = 1 - \frac{VA}{VE} = 1 - \frac{PECO_2}{PACO_2} = \frac{PACO_2 - PECO_2}{PACO_2} \qquad \textbf{(Eq. 33)}$$

where DS is the physiologic dead space.

For sake of simplicity, alveolar PCO_2 is usually substituted by the arterial PCO_2; however, in the presence of right-to-left shunt, the alveolar and the arterial PCO_2 values are different.

The alveolar dead space is calculated as follows:

$$VCO_2 = PACO_2 * VA_{perf} = PEtCO_2 * (VA_{perf} + VA_{unperf}) \qquad \textbf{(Eq. 34)}$$

As shown, the alveolar ventilation was divided into the alveolar ventilation of the perfused and the nonperfused regions of the lungs. $PEtCO_2$ is the pressure exerted by the carbon dioxide in the exhaled air:

$$\frac{VA_{perf}}{VA_{perf} + VA_{unperf}} = \frac{PEtCO_2}{PACO_2} \qquad \textbf{(Eq. 35)}$$

The ratio $PEtCO_2/PACO_2$ represents the fraction of the alveolar ventilation that actually performs the gas exchange. Conversely, the fraction of alveolar dead space (DSalv) is the following:

$$DSalv = 1 - \frac{VAperfused}{VAperfused + VAunperfuesd} = 1 - \frac{PEtCO_2}{PACO_2}$$
$$= \frac{PACO_2 - PEtCO_2}{PACO_2} \qquad \textbf{(Eq. 36)}$$

Remarkably, if alveolar PCO_2 is substituted with arterial PCO_2, the alveolar dead space also includes the shunt effect, and the $PEtCO_2/PaCO_2$ ratio becomes a measure of the adequacy of the gas exchange: any increase of alveolar dead space or true shunt will decrease the ratio. Fig. 53.24 shows the PCO_2 cascade.

Most of these variables are provided by some ventilator machines: the anatomic dead space is derived from the analysis of the capnographic curve, as described by Fowler, whereas the physiologic and alveolar dead spaces require the addition of the $PaCO_2$ value.

Ventilatory ratio. The ventilatory ratio (VR) was developed as a surrogate for dead space.[13] Ideally, it should provide the same information as dead space without the need to measure gas PCO_2. It is calculated as follows:

$$VR = \frac{VE * PaCO_2}{100 * BW * 37.5} \qquad \textbf{(Eq. 37)}$$

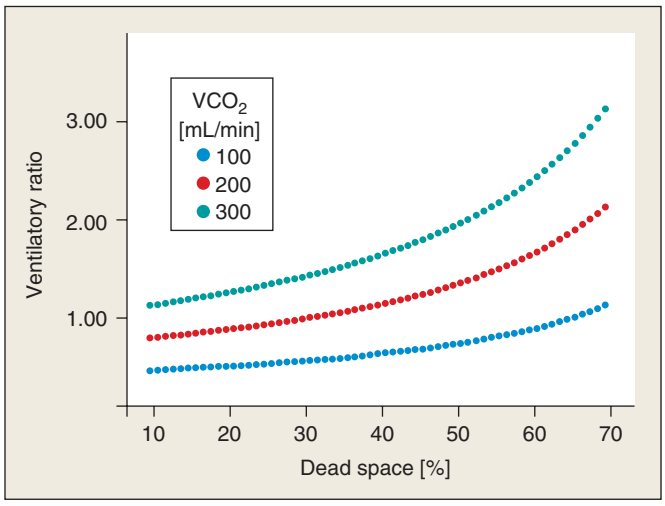

Fig. 53.24 Ventilatory ratio as a function of the dead space, at different levels of VCO_2. As shown, the same dead space may be associated with markedly different values of ventilatory ratio, depending on the VCO_2, whereas for the same VCO_2, the ventilatory ratio shows a near-exponential trend, according to the value of dead space. *VCO_2*, Production of CO_2 (mL/min).

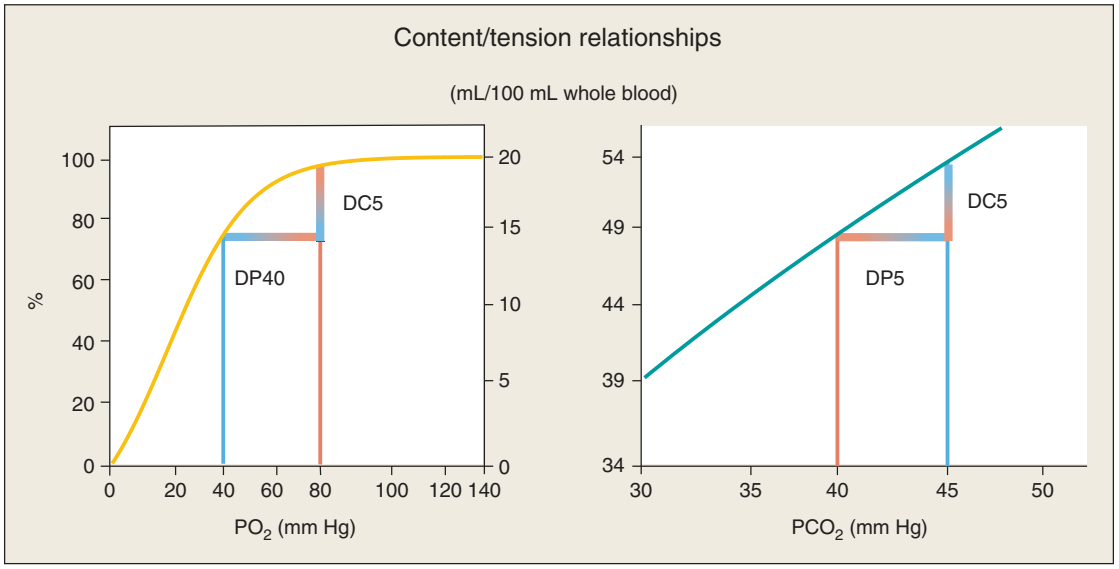

Fig. 53.25 Dissociation curve of oxygen and CO_2. Because of the different solubilities and different shapes of oxygen and CO_2 dissociation curves, the same gas transfer per liter is associated with a markedly different gas tension of partial pressure of oxygen (PO_2) and partial pressure of carbon dioxide (PCO_2). In the figure, 5 mL/100 mL of gas volume transferred from venous to arterial sides is associated with 55 and 5 mm Hg for PO_2 and PCO_2, respectively. That is, any change of 1 mm Hg of PCO_2 corresponds to the same gas-content change of approximately 10 mm Hg of oxygen.

where BW is the body weight, 100 mL is the "standard" value of ventilation for each kilogram of weight, and 37.5 mm Hg is the "standard" ideal value of arterial PCO_2. The value of 37.5 is often substituted with 40 mm Hg.

To fully understand the strengths and limitations of the VR, it is convenient to rearrange the defining VR equation (Eq. 37). The arterial PCO_2 in the numerator is substituted by its determinants (Eq. 28), and the alveolar ventilation contained in Eq. 28 is again substituted by its determinants (Eq. 30). The resulting equation is the following:

$$VR = \frac{VCO_2 * 863}{1 - \frac{Vd}{Vt}} * \frac{1}{k * BW} \qquad \textbf{(Eq. 38)}$$

where k is equal to 4 when ventilation is expressed in liters. Consequently, the VR is directly related to the CO_2 production and to the dead space. This is shown in Fig. 53.24, where the VR is expressed as a function of the dead space for a given VCO_2. As shown, the VR is markedly different for the same dead space if the VCO_2 is different.

Clinical Applications

The immediate assessment of the CO_2 clearance is best obtained by the direct measurement of the arterial PCO_2. However, in most instances, the central venous PCO_2 may be used as a surrogate, being usually 3–5 mm Hg greater than the arterial PCO_2. The presence of hemodynamic impairment or sepsis, in which the metabolic acidosis may lead to a rise of central venous PCO_2 with venous-arterial difference exceeding their normal range. The assessment of $PaCO_2$ alone, however, although allowing the definition of normocapnia, hypocapnia, or hypercapnia, is of limited value if not considered together with its determinants (VCO_2 and VE) and the CO_2 stores (primarily the bicarbonate levels).

When the CO_2 clearance equals the metabolic CO_2 production, the system is at steady state, and this may occur either with hypercapnia or hypocapnia, if the product of alveolar ventilation and the $PACO_2/713$ remains constant. It is important to realize if a given CO_2 gas-exchange pattern represents a steady state or if it reflects an actual disequilibrium, where the cleared CO_2 is lower or higher than the metabolic production. The first condition would be associated with a progressive rise of PCO_2 and CO_2 reserves (primarily bicarbonate), associated with a decrease of pH, whereas the second will be characterized by a decrease of CO_2 reserves and increased pH. The process will continue until the VA and $PACO_2$ product again equals the metabolic VCO_2 production. The VCO_2 changes resulting from changes of metabolism must be taken into account, although the primary CO_2 alterations are caused by changes of alveolar ventilation, either the result of impairment or overdrive of the respiratory centers or disruption of lung parenchyma with ventilation-perfusion mismatch, in acute or chronic conditions. In this case, measuring and monitoring the dead space, particularly in critical patients under mechanical ventilation, is of paramount importance.

The $PEtCO_2/PaCO_2$ ratio and ventilatory ratio are also useful tools for the assessment of dead space. However, they are both affected by a significant number of variables, including VCO_2, which in turn is influenced by many pulmonary and extrapulmonary conditions. Furthermore, all scores or tools that are calculated as ratios are prone to mathematical pitfalls with the potential to distort them.

In the routine clinical practice, in our opinion, the knowledge of $PACO_2$ and total ventilation is already a strong indicator of the lung condition if the basic principles of physiology are known. Finally, it should be reminded that in terms of gas exchange, 1 mm Hg change of $PaCO_2$ is equivalent to approximately 10 mm Hg change of PaO_2. This may appear surprising, but we must remember that in normal gas-exchange conditions, 200 mL/min of oxygen consumption are associated with a PaO_2 change from 40 to 100 mm Hg (normal arterial-venous PO_2 difference), whereas the same amount of CO_2 clearance is associated with an arterial-venous PCO_2 difference of approximately 5 mm Hg (from 45 to 40 mm Hg). This underlines the importance of monitoring the PCO_2 levels, whose modest changes as 1/2 mm Hg being the total ventilation unmodified are strong indicators of lung structural damage.[14,43]

CONCLUSION

Personalized mechanical ventilation is rooted in a mastery of basic physiologic principles.[44] As the COVID-19 pandemic has reminded us, this approach, rather than reliance on population- based evidence, guidelines, and tables, makes a lifesaving difference. Although new knowledge may reshape our understanding, the elements of physiology will always be the unshakable foundation of rational and effective ICU management.

KEY POINTS

- For any expandable compartment, such as the lung, volumes depend on flexibility (compliance) and the pressure difference inside and outside the compartment—the transstructural pressure. Regional properties may vary considerably site to site within the chest, both for the lung and the chest wall.
- Because the lungs are inherently passive, their mechanical properties can be assessed during any form of spontaneous, patient-triggered but machine-assisted, or controlled, ventilation by the transpulmonary pressure. The mechanical properties of the chest wall, in contrast, can only be directly evaluated during controlled ventilation when the actual pleural pressure acting to distend that structure can be estimated.
- The compliances of the lung and respiratory system can be reduced by depleting the *number* of open lung units available to ventilate and by altering their individual mechanical properties. This dual interpretation of compliance assessed at the airway opening is reflected in the sigmoidal shape of the inflation pressure-volume curve, which becomes more pronounced in the setting of acute parenchymal disorders, such as ARDS.
- When a pressure difference is applied to the passive respiratory system, that total airway pressure (Paw) must be accounted for by its dynamic component that overcomes flow resistance and its "elastic" components that expand the chest. At end inflation the latter comprises the elastic pressure that corresponds to the tidal volume, known as the driving pressure, and the pressure above the ambient baseline (PEEP).
- Modification of body position is too often neglected as a therapeutic tool. Gravitational forces exert an important influence on lung volume, on ventilation distribution, and on respiratory system compliance. The gradient of pleural and transpulmonary pressures is lower in the prone than in the supine position, in part because of reshaping of the thoracic contents by stiffening of the ventral chest wall surface and by the shifting weight of the heart and mediastinal contents. Even when it does not dramatically improve dorsal recruitment, prone positioning is currently thought to reduce VILI risk primarily by evening the distribution of transpulmonary pressures, thereby damping maximal tissue stresses and strains.
- Unlike PEEP that is intentionally applied, auto-PEEP (and therefore total PEEP) among lung units with diverse mechanical properties may not be the same throughout the diseased lung. The end-inspiratory static (plateau) airway pressure is generally a better indicator of hyperinflation risk than is the end-expiratory measurement of total PEEP itself.
- Essential information in the acutely critical patient is the blood *content* of oxygen, which is affected by hemoglobin concentration and oxygen saturation percentage. The defining equation for oxygen content can be applied to arterial blood, central venous blood, or mixed venous blood.
- The simplest means by which to assess the efficacy of patient oxygenation is the direct measurement of arterial PO_2. However, because this value does not account for the fraction of inhaled oxygen, it cannot be used to assess the lung's oxygen-exchanging status. The ratio between PaO_2 and FiO_2, although flawed, is preferable for that purpose.
- The often-neglected mixed venous oxygen saturation, SvO_2, or its surrogate, the central venous saturation, is a key assessment tool for intensive care practice.
- The ROX index normalizes the SpO_2 (using pulse oximetry as a surrogate of PaO_2) to the inspired FiO_2 and introduces the respiratory rate as an indicator of severity. Although imprecise, its advantages include ease of application, low cost, and potential for continuous monitoring.
- Venous admixture and dead space are valuable tools to assess impairment of pulmonary gas exchange. It must be noted, however, that venous admixture relates strongly to the cardiac output: an increased cardiac output promotes right-to-left shunt, whereas a decrease of cardiac output may raise PaO_2. The ratio of end-tidal PCO_2 of exhaled gas to $PaCO_2$ (the $PEtCO_2/PaCO_2$ ratio) and the ventilatory ratio are readily available and useful correlates of dead space.

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54

Patient–Ventilator Interaction

Tommaso Tonetti, Raffaele Merola, Cesare Gregoretti, and V. Marco Ranieri

Clinical management of patients with acute respiratory failure is based on the concept that significant changes in respiratory mechanics, respiratory muscle performance, and control of breathing are the underlying mechanisms responsible for acute respiratory failure.[1] The effects of mechanical ventilation on gas exchange, respiratory muscle load, and dyspnea depend on the matching between the ventilator settings and the patient's respiratory physiology. However, mechanical ventilation is rarely optimized, which would require ventilator settings based on accurate and reproducible measurements of lung and chest wall mechanics, respiratory muscle function, and respiratory drive.[2–5]

RESPIRATORY PHYSIOLOGY

The goal of the intrinsic ventilatory control system is to integrate the timing and intensity of the phrenic nerve signal, inputs from chemoreceptors and pulmonary stretch receptors, and variations in metabolic demands. Contraction of the respiratory muscles leads to the generation of flow and volume to provide adequate alveolar ventilation with tolerable work of breathing.[6] During spontaneous breathing,[7] the respiratory muscles generate pressure (P_{mus}) to produce flow against the resistive properties (R_{RS}), deliver volume against the elastic properties (E_{RS}) of the respiratory system, and overcome any intrinsic positive end-expiratory pressure (PEEPi, known better clinically as *auto-PEEP*). Under these circumstances, the act of spontaneous breathing can be described at any instant as follows:

$$Pmus = Pres + Pel + PEEPi \qquad \textbf{(Equation 1)}$$

where *Pres* represents the resistive pressure and is a function of flow (Pres = Flow × R_{RS}) and *Pel* represents the elastic recoil pressure generated by lung expansion and is a function of volume (Pel = Volume × E_{RS}). Assuming that R_{RS} and E_{RS} are linear, the equation becomes:

$$Pmus = (Flow \times R_{RS}) + (Volume \times E_{RS}) + PEEPi \qquad \textbf{(Equation 2)}$$

In patients with acute respiratory failure requiring ventilatory support, pressure generated by the ventilator (Pappl) is added to the pressure generated by the contraction of the respiratory muscles according to the following equation:

$$Pmus + Pappl = (Flow \times R_{RS}) + (Volume \times E_{RS}) + PEEPi \qquad \textbf{(Equation 3)}$$

The complex interaction among all the variables in Equation 3 can be summarized by the concept of neuroventilatory coupling (Fig. 54.1).[8] Under normal conditions, as well as at the onset of acute respiratory failure before mechanical assistance is delivered, the spontaneous contraction of the respiratory muscles suddenly generates flow and volume; the slope of the relationship between effort and ventilatory output is conditioned by the contractile properties of the respiratory muscles and the impedance of the respiratory system. When positive pressure is applied to assist the action of breathing using most modes of mechanical ventilation, the coupling between effort and output may be compromised.

During volume-targeted assist-control ventilation (ACV), flow and tidal volume remain unaffected by muscle contraction. During pressure-targeted flow-cycled (pressure support ventilation [PSV]) or time-cycled (assist-control pressure-targeted ventilation [AC/PCV]) ventilation, despite better coupling between inspiratory effort and the ventilator's output, any increase in respiratory impedance decreases the amount of delivered flow and volume.[8] During noninvasive ventilation (NIV), air leaks may further compromise the coupling between patient effort and ventilatory output.[9]

PATIENT AND VENTILATOR VARIABLES

Patient Variables

The patient interacts with the ventilator based on three physiologic variables[2,10,11]:

1. Respiratory drive[12]
2. Ventilatory requirements[5]
3. Timing of the breathing pattern[10]

Ventilator Variables

The ventilator interfaces with the patient's physiology based on three technologic variables:

1. Delivery mechanism (control variable); that is, the algorithm used by the ventilator to assist ventilation through the delivery of flow, volume, or pressure[13–18]
2. Inspiratory trigger (phase trigger variable), or the determinant of when the ventilator starts to deliver flow, volume, and pressure[19,20]
3. Cycle-off criterion (phase cycling variable), or the determinant of when the ventilator stops assisting inspiratory effort and opens the circuit to allow tidal deflation[16,17]

Features of ventilators, such as blowers and inspiratory, expiratory, and positive end-expiratory pressure valves, influence the interaction between patient and ventilator.[21–24]

To unload the respiratory muscles, restore adequate gas exchange, and relieve the patient from dyspnea, the clinician has two options: (1) total ventilator-controlled mechanical support or (2) partially patient-controlled support.

Total Ventilator-Controlled Mechanical Support

In this mode, flow, volume, and pressure are imposed by the ventilator, which thus totally replaces the patient's breathing pattern. Any pressure

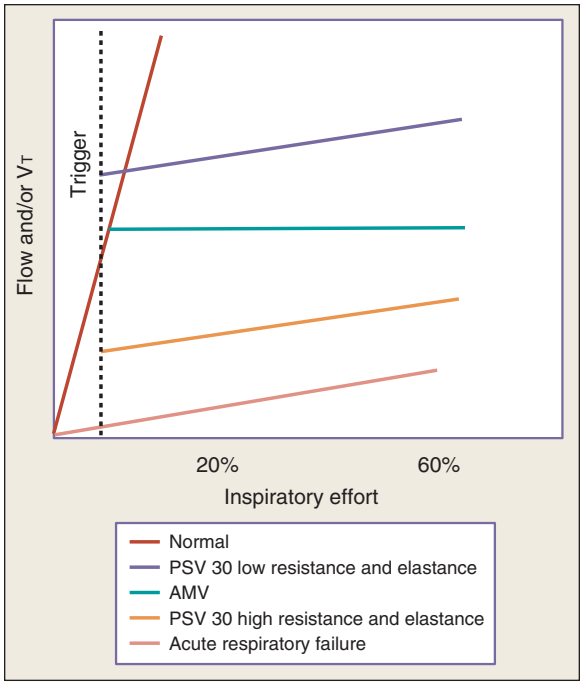

Fig. 54.1 Neuroventilatory Coupling. Under normal conditions, in addition to at the onset of acute respiratory failure, spontaneous contraction of respiratory muscles suddenly generates flow and volume. The slope of the relationship between effort and ventilatory output is conditioned by the contractile properties of the respiratory muscles and impedance of the respiratory system. When positive pressure is applied to assist the action of breathing in the most common modes of mechanical ventilation, the coupling between effort and output is compromised. During volume-targeted assist-control ventilation (ACV), flow and volume remain constant despite changes in muscle contraction. During pressure support ventilation (*PSV*), despite a sort of coupling between inspiratory effort and ventilatory output, any increase in respiratory impedance decreases the amount of delivered flow and volume. V_T, Tidal volume.

generated by the respiratory muscles is silenced or ineffectual. Although this passive condition can be achieved in some conscious patients (i.e., patients with neuromuscular diseases), it usually requires sedation and/or paralysis. The risk of patient-ventilator asynchrony is abolished, but there are potential risks associated with sedation and paralysis,[25] including respiratory muscle atrophy,[26] lung damage caused by overdistention,[27] patient discomfort,[28] retention of airway secretions, and difficulty weaning after prolonged controlled mechanical ventilation.[1]

Partial Patient-Controlled Mechanical Support

In this other type of assistance, spontaneous breathing activity is partially preserved,[29] with a decreased need for sedation and paralysis.[30] The ability to restore gas exchange, unload respiratory muscles, and relieve dyspnea with partial patient-controlled mechanical support depends strongly on the absence of patient-ventilator asynchrony.[31]

Although often unrecognized, underestimated, and inappropriately treated, patient-ventilator asynchrony is a common phenomenon associated with unfavorable outcomes.[3–5,18,31–39] Patient-ventilator asynchrony appears whenever a mismatch between the three physiologic variables characterizing spontaneous breathing (ventilatory drive, ventilatory requirements, and the duration and ratio of inspiratory time to total breath cycle duration) and the three technologic variables characterizing ventilator function (trigger function, the gas delivery algorithm [controlled variable], and cycling criterion) occurs.

RESPIRATORY DRIVE–VENTILATOR TRIGGER ASYNCHRONY

During partial ventilatory assistance, the inspiratory synchronization system (inspiratory trigger) detects the patient's inspiratory effort and activates a mechanical response. Therefore inspiratory effort is tracked to couple the patient's effort with the delivery of pressure, flow, or volume. The goal of an effective inspiratory trigger is to reduce the duration and intensity of the muscular effort as much as possible before the initiation of a mechanically supported breath.[40] It has been suggested that a trigger (independent of the algorithm) must have a response time of less than 100 ms. However, even then the inspiratory effort necessary to trigger a breath may remain a significant part of the total inspiratory effort, representing 17% and 12% of the total inspiratory effort during pressure and flow triggering, respectively.[13–21,32,33] Aslanian and coworkers found that although the time required for triggering was 43% shorter and the effort during the time of triggering was 62% less with flow triggering than with pressure triggering, effort for the posttriggering phase was equivalent for both these modalities.[41] Therefore the clinical benefit of flow triggering appears to be much less relevant than commonly stated.[3]

Inspiratory phase asynchrony may be correlated with respiratory drive. Phase lag quantifies the delay between the start of inspiratory muscle activity and the beginning of mechanical inflation (Fig. 54.2).[3,10,11] The presence of a threshold load, such as auto-PEEP (intrinsic PEEP), may further complicate the patient-ventilator interaction during the triggering phase.[19] Giuliani and colleagues suggest that effort during triggering determines patient effort during the remaining portion of inspiration.[42] Leung and coworkers demonstrated that the higher the level of ventilator-applied pressure, the lower the respiratory drive but the longer the time required to trigger the ventilator. As a result, respiratory muscles generate smaller inspiratory swings in intrathoracic pressure but over a longer inspiratory time.[2] Another problem is related to the fact that pressure is usually detected inside the ventilator, not

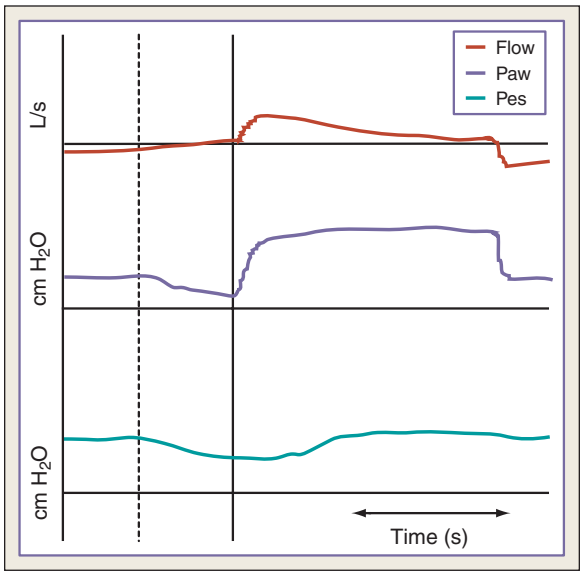

Fig. 54.2 Representative Tracings Show the Interaction Between Patient Effort and Triggering of the Ventilator. The delay between the beginning of inspiratory muscle activity *(dotted line)* and the beginning of mechanical inflation *(solid line)* can cause an inspiratory phase asynchrony. *Flow,* Flow generated at airway opening; *Paw,* the pressure applied at airway opening; *Pes,* esophageal pressure.

inside the patient. Therefore any resistive load (e.g., endotracheal tube or upper airways during NIV) reduces the ventilator trigger sensitivity in response to patient effort.[18]

Auto-triggering can be defined as a mandatory breath delivered in the absence of a patient's inspiratory effort.[22] The number of breaths monitored by the ventilator are higher than those initiated by the patient. Auto-triggering can be generated by too sensitive inspiratory triggers, air leaks, or an external signal, such as heart rate or water in the respiratory circuit.

Ineffective triggering is defined as an inspiratory effort that is not followed by ventilator activation, caused by the inability of the latter to detect the patient's "request" despite substantial inspiratory effort (Fig. 54.3). This asynchrony usually occurs with high levels of ventilator assistance and short expiratory times. Mechanical characteristics that may induce ineffective triggering include low elastance, high resistance, and PEEPi. Ineffective triggering is not correlated to an increase in the patient's inspiratory effort.[2] The application of external PEEP below the level of auto-PEEP can reduce the inspiratory effort required to trigger the ventilator.[43]

Double triggering, defined as the presence of two inspiratory cycles separated by a very short expiratory time, may result in breath stacking. Double triggering can be elicited by high patient ventilatory demand that causes two breaths to be triggered with a limited expiratory phase caused by too short of a ventilator inspiratory time (Ti) compared with the patient's neural time. This problem can be addressed by increasing Ti in time-cycled mode, by adjusting the expiratory threshold time in the flow-cycled mode, or by optimizing the pressure rise time (i.e., the *time taken to reach the targeted pressure set for the ventilator*).[44]

Reverse triggering is a recently discovered form of neuromechanical coupling that occurs in heavily sedated patients.[45,46] In this case, contrary to the usual triggering sequence (patient's effort switching on the ventilator-driven breath), mechanical insufflation triggers diaphragmatic muscle contraction. It has been conjectured that reverse triggering may be associated with an injurious inflation pattern, but this has never been confirmed. During reverse triggering, diaphragm contraction generates a deflection in pleural pressure confined to the dependent lung and draws gas from elsewhere in the lung (*pendelluft* effect) or from the trachea and ventilator toward the dependent lung. This phenomenon was observed in a swine model to cause regional overstretching of the dependent lung.[46]

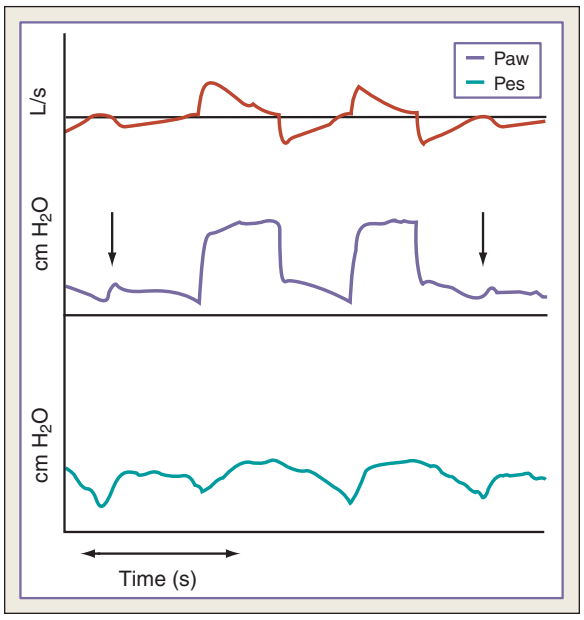

Fig. 54.3 Representative Tracings Show Ineffective Triggering Caused by the Ventilator's Inability to Detect the Patient's "Request" for an Assisted Breath. A substantial inspiratory effort *(arrows)* generates only a bump in the flow and pressure tracings instead of a mandatory assisted breath. *Flow,* Flow generated at airway opening; *Paw,* the pressure applied at airway opening; *Pes,* esophageal pressure.

New triggering algorithms aim to improve the patient-ventilator interaction during sudden changes in flow or respiratory rate and in the presence of air leaks during NIV. Volume triggers, triggers linked to flow waveform algorithms, combining pressure and flow signals in the same trigger algorithm, or using both pressure and flow triggers have been developed. However, all inspiratory trigger drawbacks may be overcome by using a neural trigger obtained using a dedicated nasogastric tube with multiple arrays of electrodes placed in the distal esophageal portion.[8,47,48]

VENTILATORY REQUIREMENT–GAS DELIVERY ASYNCHRONY

Gas delivery asynchrony occurs when ventilator-delivered flow, volume, and pressure are insufficient to meet the patient's ventilatory demand. Ward and coworkers confirmed the observations of Marini and colleagues[29] demonstrating that increasing the flow rate could reduce the patient's respiratory drive and active respiratory muscle work,[13] although this may exert an excitatory effect on the respiratory rate and the rate of rising of inspiratory muscle activity.[3,16,17,49–54] Laghi and coworkers demonstrated that the inspiratory time imposed during mechanical ventilation determined respiratory frequency, independent of inspiratory flow and tidal volume.[16] Pressure-targeted breaths may more effectively match the patient's ventilatory requirements because flow is the dependent (resultant) variable during constant pressure delivery. In addition, rapid pressurization of the airways is coupled with high inspiratory flow only at the beginning of inspiration, thus reproducing the physiologic flow profile.[55] However, during a pressure-targeted breath, the setting for the time of pressure increase may influence the patient-ventilator interaction because its modification determines the dependent flow output.[56,57]

INSPIRATORY TIMING–VENTILATOR CYCLING ASYNCHRONY

A breath can be pressure-, time-, volume-, or flow-cycled.[57] Although volume and pressure cycling are no longer used, a breath is defined as time-cycled when it is terminated after a given preset inspiratory time is reached (e.g., pressure- or volume-controlled time-cycled breaths). The breath is flow-cycled when the generated inspiratory flow decays from its peak by a fixed percentage (e.g., PSV mode).

Ventilator-patient asynchrony occurs when the patient is trying to exhale, but the ventilator is still delivering gas.[35,58,59] Parthasarathy and coworkers demonstrated that prolonging mechanical inflation into neural expiration reduces the time available for unopposed exhalation, resulting in the need for a greater inspiratory effort to trigger the ventilator.[58] Younes and colleagues showed that the delayed opening of the exhalation valve in ventilator-dependent patients exacerbates dynamic hyperinflation.[60]

In patients ventilated with time-cycled breaths, expiratory phase asynchrony occurs when the patient's neural inspiratory time is shorter or longer than the ventilator inflation time. For proper cycling of the ventilator and optimal patient-ventilator synchrony, the patient's inspiratory flow and ratio of inspiratory time–to–total breath cycle duration must be tracked.

During flow-cycled breaths, as in pressure-support mode, inspiratory time is determined exclusively by the time taken for the exponentially declining flow to reach the flow threshold value (the "off trigger" point for cycling between inspiration and expiration).[32,61] The inspiratory flow threshold value, also called the *expiratory trigger,* thus controls the inspiration-to-expiration switch in these modalities under the postulate that the very end of patient inspiration is tracked by inspiratory flow decay.[56,62]

The goal of these ventilatory modes is to optimize the synchronization between spontaneous patient inspiratory time and ventilator inspiratory time. However, for proper cycling-off and optimal patient-ventilator synchrony, the ventilator must always track the patient's inspiratory flow.[58,63,64]

PATIENT-VENTILATOR ASYNCHRONY DURING PRESSURE SUPPORT VENTILATION

Three phases may influence patient-ventilator interaction during PSV: (1) the threshold value of inspiratory flow decay (expiratory trigger), (2) the pressure ramp (pressure slope), and (3) the level of PSV.

(1) The expiratory trigger sensitivity can be fixed (default at 25% of peak flow) or can vary from 1% to 90% or from 5 to 25 L/min in some old ventilator software (Fig. 54.4).[65] It can also be linked to algorithms where there is a ranking logic of expiratory cycling criteria that links cycling to expiration. Setting the expiratory trigger at a higher percentage of peak inspiratory flow (i.e., 40%–70% of decay of the peak inspiratory flow) in patients with obstructive pulmonary disease improves patient-ventilator synchrony and reduces inspiratory muscle effort.[66] In addition, the modification of the cycling-off criteria may have a beneficial effect on reducing the dynamic hyperinflation and inspiratory effort in chronic obstructive pulmonary disease (COPD) patients, especially at low levels of pressure support.[67]

The proper adjustment of the expiratory trigger threshold may be important in improving patient-ventilator synchrony and in decreasing the work of breathing during acute lung injury. Unlike in obstructive pulmonary disease, setting the threshold at 5% of the peak inspiratory flow might be the optimal value for patients with acute respiratory distress syndrome or acute lung injury.[68] Indeed, Chiumello and colleagues found that in patients recovering from acute lung injury during PSV at 15 cm H_2O, the lowest cycling-off criteria reduced the respiratory rate and increased the tidal volume without modifying the work of breathing.[69]

The expiratory sensitivity setting is crucial when ventilators are used to deliver NIV, because air leaks may cause an abnormal prolongation of the mechanical inspiratory time at the expense of a patient's expiration requirements (inspiratory hang-up) (Fig. 54.5).[70–75]

(2) The setting of the pressure rise time (pressure slope) can affect the expiratory threshold by modifying the dependent inspiratory flow.[69,76–79] Although there is some evidence that rapid pressure rise times might reduce a patient's work of breathing,[77] a fast pressure increase may lead to particularly high peak inspiratory flow, which may then cause premature termination of inspiration when the fixed percentage criterion for expiratory cycling is reached (Fig. 54.6).[18,67,79]

Prinianakis and collagues assessed the effects of varying the rate of pressure change during noninvasive PSV on the breathing pattern of patients with COPD, in addition to inspiratory effort, arterial blood gases, tolerance to ventilation, and the amount of air leakage. No significant changes were observed in breathing pattern and arterial blood gases between the differing pressure slopes, but the pressure-time product of the diaphragm—an estimate of its metabolic consumption—significantly decreased with increasing the rate of pressurization. Interestingly, air leaks increased and the patients' tolerance of ventilation was significantly poorer with the fastest rate of pressure change.[80]

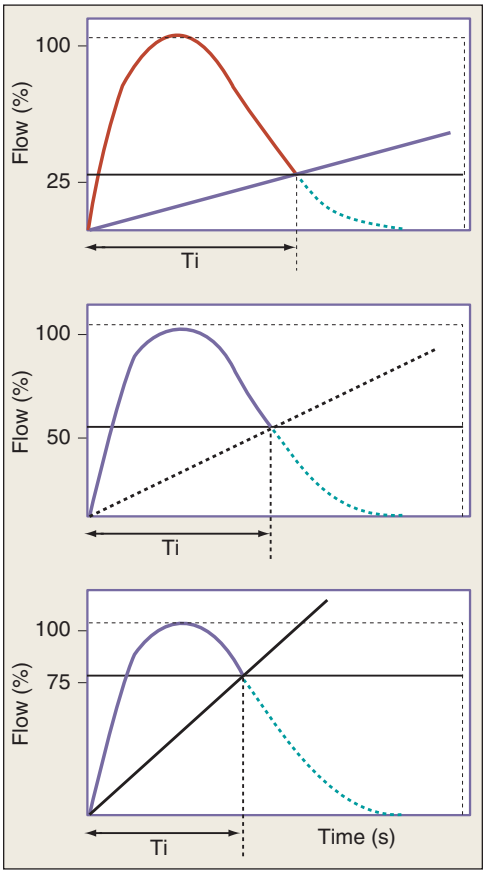

Fig. 54.4 Representative Tracings Show Different Settings for Expiratory Trigger Sensitivity on a Flow-Time Plot. *Top to bottom,* Expiratory trigger set at 25%, 50%, and 75% of peak flow. Ventilator inspiratory time is influenced by preset flow expiratory trigger sensitivity, at which point the ventilator switches to expiration.

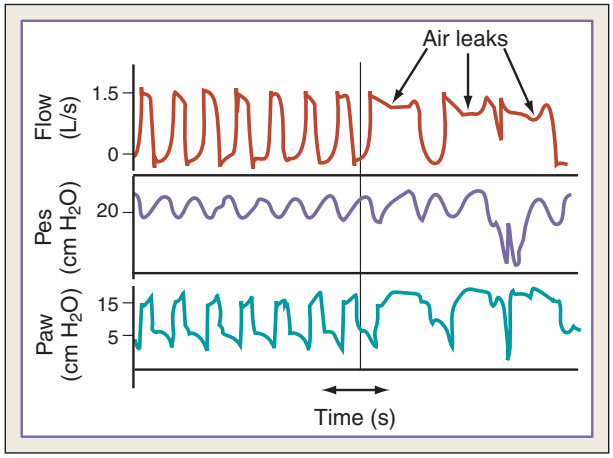

FIG. 54.5 Representative Record of Air Leaks During Noninvasive Face Mask Pressure Support Ventilation. The presence of air leaks causes prolonged ventilator inspiratory time *(arrows). Flow,* Flow generated at airway opening; *Paw,* the pressure applied at airway opening; *Pes,* esophageal pressure.

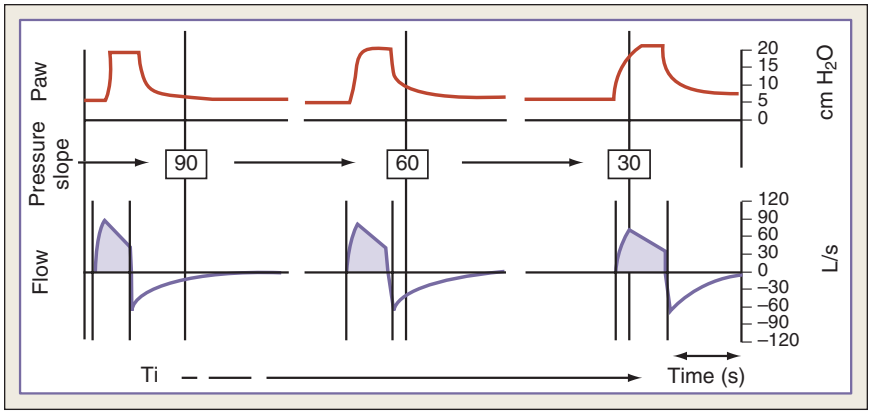

Fig. 54.6 Representative Tracings Show Different Pressure Rise Time Sensitivities on a Flow-Time Plot. *Left to right,* Pressure rise time set at 90%, 60%, and 30% of maximal pressurization time. Ventilator inspiratory time *(shaded area)* is influenced by preset pressure-slope sensitivity that generates a different peak inspiratory flow. *Flow*, Flow generated at airway opening; *Paw*, the pressure applied at airway opening.

(3) During NIV, the pressure support level affects patient-ventilator interactions, mainly through effects on the generation of air leaks.[9,71] Because air leaks may determine modifications in the inspiratory flow profile (see earlier), their reduction by lowering to a PSV level of 1 or 2 cm H_2O has been demonstrated to improve patient-ventilator asynchrony.[9]

In conclusion, dyssynchrony at the termination of a PSV breath can be corrected by varying the cycling-off criteria (e.g., the expiratory trigger threshold) or modulating the inspiratory flow (e.g., modifying the pressure slope or varying the set pressure level).[9] Automated modes designed to achieve an optimal expiratory cycling during PSV are available, but their added value deserves further investigation.[81,82]

TOTAL PATIENT-CONTROLLED MECHANICAL SUPPORT

Optimization of patient-ventilator interactions can be attained only by continuously matching the triggering, flow delivery, and cycling functions of the ventilator with the patient's ventilatory drive, spontaneous inspiratory flow demand, and ratio of inspiratory time to the total breath cycle. This implies a continuous measurement of physiologic variables and continuous adaptation of the ventilator to spontaneous variations in these variables. Future development in ventilator technology should be oriented toward systems with the capability to automatically interface between physiologic parameters and ventilator output. Such technology will be based on closed-loop algorithms able to achieve total patient-controlled mechanical support.[4]

The design features of an automatic control system in a mechanical ventilator include (1) what activates the system (the input), (2) what the system produces (the output), and (3) the protocol used to link input and output (the controlling algorithm). In a closed-loop system, the output will activate and condition the input. When changes in output are opposite to changes in input, the closed loop is said to be negative. The closed loop is positive when variations in output mirror variations in input. The most common example of a negative closed-loop control system in a clinical setting is the ventilator humidifier. In this case, the input is the temperature inside the chamber, and the output is the temperature of the gas being delivered to the patient. The controlling algorithm is designed to keep the latter constantly above a value set by the operator. If the output (i.e., the temperature of gas delivered to the patient) is lower than the preset level, the algorithm will increase the input (i.e., the temperature in the chamber). If the output is higher than the preset level, the algorithm will decrease the input. Closed-loop systems are hence able to stabilize and limit the performance of a mechanical system.

In the case of acute respiratory failure, the patient is unable to provide sufficient output (i.e., minute ventilation). Therefore the ventilator should be able to detect the input from the patient and continuously adapt the output. If the input is increasing (i.e., ventilatory requirements are increasing), the ventilator will increase the output (i.e., apply more positive pressure). If the input is decreasing (i.e., ventilatory requirements are decreasing), the ventilator will decrease the output (i.e., apply less positive pressure). The controlling closed loop eventually applied by the ventilator must be positive. Positive closed-loop control systems are inherently unstable in the sense that they tend to "run away" with ventilatory assistance. If the pressure generated by the ventilator is higher than the pressure required to offset the passive properties of the respiratory system, the ventilator will continue to deliver flow and volume even while the patient stops his or her inspiratory effort and tries to initiate expiration and "extinguish" ventilatory assistance. If the patient does not produce any inspiratory effort, the ventilator will not produce any ventilatory support.

Based on closed-loop algorithms, new modes of mechanical ventilation have been proposed. Such approaches represent modifications of PSV and are characterized by the patient's ability to control the amount of assistance provided by the ventilator. They are differentiated by the patient-related variables used to close the loop.

PROPORTIONAL ASSISTED VENTILATION, PROPORTIONAL PRESSURE SUPPORT, AND PROPORTIONAL ASSISTED VENTILATION PLUS

During proportional assisted ventilation (PAV) and proportional pressure support (PPS), the ventilator generates pressure in proportion to the patient-generated flow and volume[83,84]; the ventilator amplifies patient effort without imposing any ventilatory or pressure targets; and ventilator-generated pressure rises as long as inspiratory muscle effort is produced by the patient. During these modes of mechanical support, the clinician adjusts the percentage of flow-assisted or volume-assisted ventilation after determining the patient's resistance and elastance, with the goal of reducing the load imposed by the patient's inspiratory workload.[85–87] Despite the exciting potential of these techniques[87-90] applied either invasively or noninvasively,[81–99] no large-scale studies have demonstrated an improvement in patient outcome with

PAV or PPS compared with other modes of ventilation. Several studies performed during invasive ventilation showed that PAV improves patient-ventilator synchrony at the start of inspiration[32,92,94] but not necessarily at the end.[84–92]

Compared with PAV, proportional assisted ventilation plus (PAV+) provides a continuous measurement of the patient's elastance and resistance according to the method described by Younes and coworkers.[85–87,95–99] This option requires that the physician set only a given percentage of the overall pressure requirement. During invasive ventilation, PAV+ appears to reduce the incidence of patient-ventilator asynchronies considerably compared with conventional PAV[100] (Fig. 54.7). When compared with PSV, PAV+ decreases the setting time and responds automatically to changes in sedative doses.[101]

NEURALLY-ADJUSTED VENTILATORY ASSISTANCE

With neurally-adjusted ventilatory assistance (NAVA), the electrical activity of the diaphragm is measured using an electrode array inserted into a nasogastric tube placed in the lower esophagus; this information is then used to control the ventilator to generate flow, volume, and pressure by applying pressure in proportion to diaphragm electrical activity.[8,44,45,102,103] A representative tracing of NAVA is shown in Fig. 54.8. With NAVA, therefore, the patient retains full control of the breathing pattern.[104] Unlike the proportional assist mode just described, estimates of respiratory mechanics are not needed. With NAVA, the patient's respiratory center controls the assisted positive breaths in all phases of the ventilation cycle, from triggering to cycling-off of inspiration. Any change in patient ventilatory output

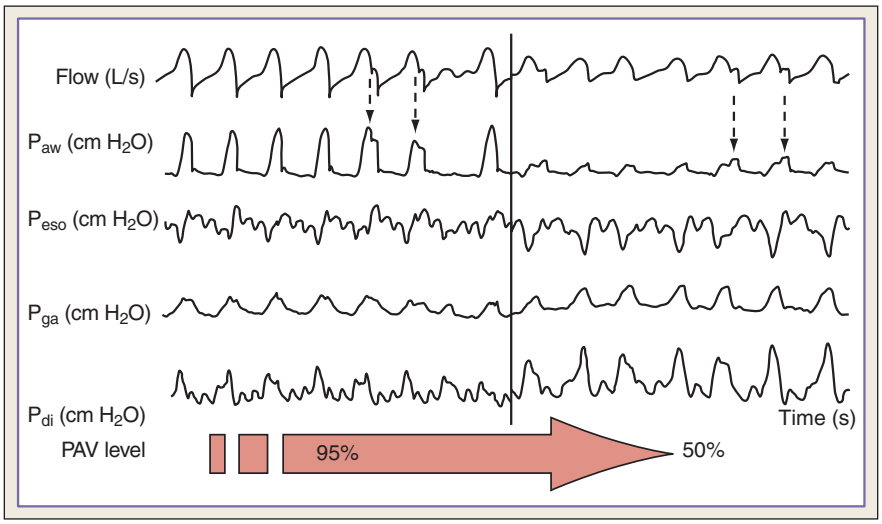

Fig. 54.7 Representative tracing of flow (*Flow L/s*), airway pressure (P_{aw} *cm* H_2O), esophageal pressure (P_{eso} *cm* H_2O), gastric pressure (P_{ga} *cm* H_2O), and transdiaphragmatic pressure (P_{di} *cm* H_2O) during proportional assisted ventilation plus (PAV+) ventilation. *Directional arrow (bottom)* going from left to right shows that the gain is reduced from 95% to 50% with a subsequently increased inspiratory effort. *Dotted arrows (top)* indicate the measurement of respiratory mechanics automatically computed by the ventilator.

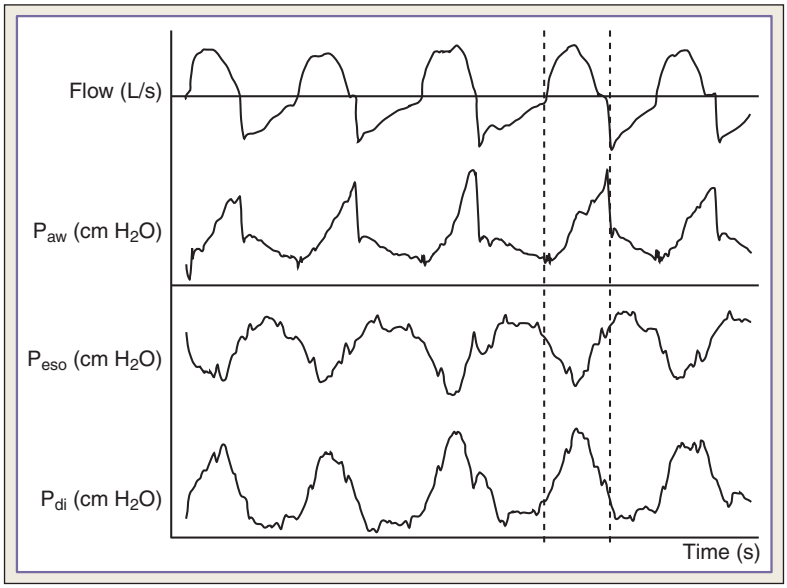

Fig. 54.8 Representative tracing of flow (*Flow L/s*), airway pressure (P_{aw} *cm* H_2O), esophageal pressure (P_{eso} *cm* H_2O), and transdiaphragmatic pressure (P_{di} *cm* H_2O) during NAVA ventilation. *The two dotted lines* define the beginning and end of the patient's inspiratory effort.

is matched within the breath by the ventilator, even in the presence of variations in respiratory mechanics.

NAVA has been shown to decrease ineffective efforts (trigger asynchrony) and premature and delayed cycling (cycle asynchrony) compared with pressure-controlled, flow-cycled ventilation (i.e., PSV).[105–107] Furthermore Vignaux and colleagues showed that compared with pressure support via NIV, NAVA improves patient-ventilator synchrony even in infants and children. It does so by reducing both triggering delay and the number of asynchrony events.[108] NAVA also appears to improve patient-ventilator synchrony during helmet ventilation.[109] NAVA has one major advantage compared with PAV, as air leaks do not interfere with its correct functioning.[110]

Recently, it has been reported that NAVA reduced micro-asynchronies (inspiratory trigger delay, premature and late cycling) in tracheostomized patients, despite no reduction in macro-asynchronies (ineffective, double, and auto-triggering) when compared with PSV.[111]

In conclusion, recent meta-analyses reported that NAVA improves patient-ventilator synchrony; however, its beneficial effect on clinical outcomes is still uncertain, and more studies are needed.[112,113]

ADAPTIVE SUPPORT VENTILATION

Compared with PAV and NAVA, adaptive support ventilation is a time-limited, pressure-targeted mode of ventilation (pressure-controlled ventilation) that relies on a negative closed-loop system of regulating ventilator settings across multiple breaths in response to changes in respiratory impedance (elastance and resistance), spontaneous efforts, and end-tidal PCO_2.[114] The basic principle relies on the work of Otis and colleagues[115] and Mead and coworkers[6] demonstrating that for a given level of minute alveolar ventilation, there is a respiratory rate that is least costly regarding respiratory work. With adaptive support ventilation, the operator enters the patient's body weight and sets the desired minute ventilation. The expiratory time constant is determined by analysis of the tidal expiratory flow-volume curve.[116] Adaptive support ventilation adjusts for inspiratory pressure, inspiratory-expiratory time ratio, and the mandatory respiratory rate to maintain the target minute ventilation and respiratory rate within a framework designed to avoid rapid, shallow breathing; excessive inflation volumes; and dynamic hyperinflation. Spontaneous breathing triggers either a pressure-controlled or a spontaneous breath with inspiratory pressure support, the level of which is adjusted to meet the target respiratory rate–tidal volume combination.

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KEY POINTS

- Patient-ventilator asynchrony occurs commonly during mechanical ventilatory support. It is often unrecognized, underestimated, and inappropriately treated in a clinical setting.
- Patient-ventilator asynchrony occurs when the three physiologic variables of the patient's breathing pattern, ventilatory drive, driving, and timing components of the breathing cycle do not match ventilator trigger, ventilator-delivered flow, and ventilator cycling criteria, respectively.

KEY POINTS—cont'd

- Clinical optimization of patient-ventilator interactions can be obtained only by continuously matching the triggering, flow delivering, and cycling functions of the ventilator with the patient's physiologic variables.
- Optimization of patient-ventilator interactions during invasive or noninvasive ventilation implies a continuous measurement of physiologic variables and continuous adaptation of the ventilator to the spontaneous variations in these physiologic variables.
- Future developments in ventilator technology should be oriented toward a system with the capability to interface automatically and seamlessly between physiologic parameters and ventilator outputs. Such technology will be based on closed-loop algorithms able to achieve total patient-controlled mechanical support.

References for this chapter can be found at expertconsult.com.

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Akoumianaki E, Lyazidi A, Rey N, et al. Mechanical ventilation-induced reverse-triggered breaths: a frequently unrecognized form of neuromechanical coupling. *Chest.* 2013;143:927–938.
This physiologic study reported that reverse triggering is frequently present in deeply sedated, mechanically ventilated patients with acute respiratory distress syndrome (ARDS). It underlines this often unrecognized or overlooked phenomenon and its potential importance for the ventilation of ARDS patients.

Appendini L, Purro A, Gudjonsdottir M, et al. Physiologic response of ventilator-dependent patients with chronic obstructive pulmonary disease to proportional assist ventilation and continuous positive airway pressure. *Am J Respir Crit Care Med.* 1999;159(5):1510–1517.
In difficult-to-wean patients with chronic obstructive pulmonary disease, proportional assisted ventilation (PAV) appeared to improve ventilation and decrease inspiratory muscle effort. The study also found that the combination of PAV and continuous positive airway pressure can unload the inspiratory muscles to values close to those in normal subjects.

Beck J, Sinderby C, Lindström L. Effects of lung volume on diaphragm EMG signal strength during voluntary contractions. *J Appl Physiol.* 1998;85(3):1123–1134.
These authors found that variations in end-expiratory lung volume between breaths can affect the transformation of respiratory muscle activation into mechanical output (neuromechanical coupling).

Calderini E, Confalonieri M, Puccio PG, et al. Patient-ventilator asynchrony during noninvasive ventilation: the role of the expiratory trigger. *Intensive Care Med.* 1999;25(7):662–667.
This article describes the loose patient-ventilator synchrony in the presence of air leaks and noninvasive pressure support ventilation.

Laghi F, Karamchandani K, Tobin MJ. Influence of ventilator settings in determining respiratory frequency during mechanical ventilation. *Am J Respir Crit Care Med.* 1999;160(5):1766–1770.
These authors reported that during the assist-control mode, ventilator inspiratory time can determine respiratory frequency independently of inspiratory flow and tidal volume.

Leung P, Jubran A, Tobin MJ. Comparison of assisted ventilator modes on triggering, patients' effort, and dyspnea. *Am J Respir Crit Care Med.* 1997;155(6):1940–1948.
This study found that when receiving assist-control ventilation or high levels of pressure support, one-quarter to one-third of a patient's inspiratory efforts may fail to open the inspiratory valve triggering the machine. The number of ineffective triggering attempts increases in proportion to the level of ventilatory assistance and is not correlated with the magnitude of inspiratory effort at a given level of assistance.

Parthasarathy S, Jubran A, Tobin MJ. Cycling of inspiratory and expiratory muscle groups with the ventilator in airflow limitation. *Am J Respir Crit Care Med.* 1998;158(5):1471–1478.

The continuation of a mandatory mechanical breath into neural expiration was associated with a waste of inspiratory effort, defined as failure of the subsequent inspiratory attempt to trigger the ventilator.

Parthasarathy S, Tobin JM. Effect of ventilator mode on sleep quality in critically ill patients. *Am J Respir Crit Care Med.* 2002;166(11):1423–1429.
Inspiratory assistance during pressure support causes hypocapnia, which combined with a lack of a backup rate and wakefulness drive, can lead to central apneas and sleep fragmentation, especially in patients with heart failure. A backup rate, as during assist-control volume-targeted ventilation, prevents the development of apneas and perhaps decreases arousals.

Sinderby C, Navalesi P, Beck J, et al. Neural control of mechanical ventilation in respiratory failure. *Nat Med.* 1999;5(12):1433–1436.
This article describes a completely new mode of breathing assistance regulated by detecting inspiratory effort, based on the measurement of electrical activity of the diaphragm using an electrode array inserted into a nasogastric tube and placed in the lower esophagus. The output generated from the electrodes, filtered for sources of electrical interference, is used to control the ventilator that finally generates the respiratory output.

Tobert DG, Simon PM, Stroetz RW, et al. The determinants of respiratory rate during mechanical ventilation. *Am J Respir Crit Care Med.* 1997;155(2):485–492.
The authors examined the rate response of eight normal volunteers during both quiet wakefulness and non–rapid eye movement (non-REM) sleep in the setting of mechanical ventilation through a nasal mask in an assist-control mode with a machine backup rate of two breaths per minute. They found that both tidal volume and inspiratory flow settings affect the respiratory rate and can affect carbon dioxide homeostasis. During non-REM sleep, hypocapnia resulted in wasted ventilator trigger efforts. Thus ventilator settings appropriate for wakefulness may cause ventilatory instability during sleep.

Younes M, Webster K, Kun J, et al. A method for measuring passive elastance during proportional assist ventilation. *Am J Respir Crit Care Med.* 2001;164(1):50–60.
A noninvasive method to continuously measure elastance of the respiratory system during proportional assisted ventilation is described.

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55

Noninvasive Positive-Pressure Ventilation

Anas A. Ahmed and Nicholas S. Hill

Noninvasive ventilation is defined as the provision of ventilatory assistance to the lungs without an invasive artificial airway. Noninvasive ventilators consist of a variety of devices, including negative- and positive-pressure units. Until the early 1960s, negative-pressure ventilation in the form of tank ventilators was the most common type of mechanical ventilation used outside the anesthesia suite.[1] However, during the Copenhagen polio epidemic of 1952, it was observed that the survival rate improved when patients with respiratory paralysis were treated with invasive positive-pressure anesthesia devices. Subsequently, invasive positive-pressure mechanical ventilation gradually became the preferred means of treating acute respiratory failure.[2] Negative-pressure and other so-called body ventilators remained the mainstay of ventilatory support for patients with chronic respiratory failure until the mid-1980s.[1]

With improving mask and ventilator technology and recognizing the many advantages of positive- over negative-pressure ventilation,[1] noninvasive positive-pressure ventilation (NIV) displaced negative-pressure ventilation as the treatment of choice for chronic respiratory failure in patients with neuromuscular and chest wall deformities.[3] Over the past 30 years, NIV has spread from the outpatient to the inpatient setting, where it is now used to treat certain forms of acute respiratory failure (ARF). Studies involving large clinical databases show that NIV use for patients with ARF resulting from chronic obstructive pulmonary disease (COPD) and non-COPD diagnoses increased several-fold during the first decade of the millennium.[4] A survey in Massachusetts found that NIV is used very frequently in the acute care setting, constituting up to 40% of initial ventilator starts.[5] This chapter discusses the rationale for the increased use of NIV in critical care, in addition to appropriate indications, practical applications, and monitoring.

RATIONALE

The most important advantage of NIV is the avoidance of complications associated with airway intubation and invasive mechanical ventilation. These hazards include upper airway trauma, the bypass of the upper airway defense mechanisms, increased risk of nosocomial pneumonia, and interference with upper airway functions, including the ability to eat and communicate normally.[6] By avoiding airway intubation, NIV leaves the upper airway intact, preserves airway defenses, and, during breaks, allows patients to eat and vocalize normally and to expectorate airway secretions. Compared with invasive mechanical ventilation, NIV reduces infectious complications, including pneumonia, sinusitis, and sepsis.[7–9] Strengthening the rationale for its use is evidence that NIV lowers the morbidity and mortality rates of well-selected patients with ARF and may shorten hospital length of stay or avoid hospitalization altogether,[10] thus reducing costs.

The main indication for mechanical ventilatory assistance is to treat respiratory failure, either type 1 (hypoxemic), type 2 (hypercapnic), or both. Fig. 55.1 shows that airspace collapse, surfactant abnormalities, and airway narrowing and closure contribute to ventilation-perfusion abnormalities and shunt, which cause hypoxemia. By opening the collapsed air spaces and narrowed airways, sustained positive airway pressure reduces shunt and improves ventilation-perfusion relationships, ameliorating hypoxemia. In addition, positive airway pressure can reduce the work of breathing by improving lung compliance as a consequence of opening collapsed air spaces. Another potential benefit of positive airway pressure is enhanced cardiovascular function via the afterload-reducing effect of increased intrathoracic pressure. Conversely, deleterious cardiovascular effects may occur if the preload-reducing effect outweighs the afterload-reducing effect, as may be observed in patients with reduced intravascular fluid volume.

MECHANISMS OF ACTION

Fig. 55.2 shows the pathophysiologic mechanisms that contribute to ventilatory failure. Increased airway resistance, reduced respiratory system compliance, and intrinsic positive end-expiratory pressure (PEEP) contribute to the increased work of breathing, predisposing patients to respiratory muscle fatigue. In patients with COPD, the increased radius of the diaphragmatic curvature, which increases muscle tension and thereby increases impedance to blood flow, exacerbates the situation. By counterbalancing intrinsic PEEP with extrinsic PEEP and by augmenting tidal volume with intermittent positive-pressure ventilation (IPPV), NIV reduces the work of breathing and avoids the vicious cycle leading to respiratory failure. Work of breathing measurements, including transdiaphragmatic pressure, diaphragmatic pressure-time product, and diaphragmatic electromyographic amplitude, are all decreased when NIV is delivered to patients with exacerbations of COPD. In such patients, continuous positive airway pressure (CPAP) and pressure-support ventilation (PSV) both reduce the work of breathing, but the combination of the two (PSV + PEEP) is more effective than either alone.[11]

INDICATIONS

A number of causes of ARF are now considered appropriate for NIV therapy and are listed in Box 55.1. Evidence supporting these indications is rated and briefly discussed here; guidelines for patient selection are discussed later. The European Respiratory Society/American Thoracic Society (ERS/ATS) Task Force for NIV offered recommendations and suggestions on clinical applications of NIV in 2017,[12] which are incorporated into the discussion that follows. At the outset, it is imperative to emphasize that the interface used to apply NIV may be crucial to its efficacy in any individual patient.

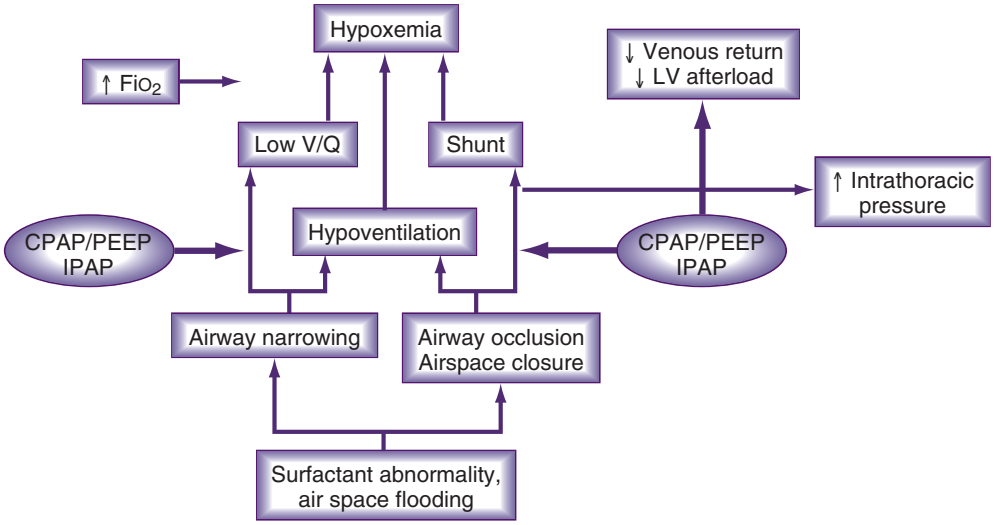

Fig. 55.1 Pathophysiology of acute hypercapnia and points where continuous positive airway pressure (*CPAP*), positive end-expiratory pressure (*PEEP*), and pressure support (PS) interrupt the process *(large arrows).* Hypercapnia (increased partial pressure of carbon dioxide in arterial blood [$PaCO_2$]) occurs when respiratory muscles fail to ventilate alveoli adequately to maintain homeostasis with carbon dioxide production. Respiratory muscle failure occurs when the work of breathing is normal (e.g., acute or chronic neuromuscular disease) or increased (e.g., patients with chronic obstructive pulmonary disease, asthma, or obesity hypoventilation syndrome), presumably because of inadequate oxygen delivery to the respiratory muscles (e.g., approximately one-third of patients presenting with cardiogenic pulmonary edema). Strategies to counter these pathophysiologic mechanisms include applying CPAP or PEEP to counterbalance intrinsic PEEP (PEEPi), increasing alveolar ventilation by augmenting tidal volume (V_t), using intermittent positive-pressure ventilation (IPPV), and reducing CO_2 production by decreasing the work of breathing. *FiO_2*, Fraction of inspired oxygen; *IPAP*, inspiratory positive airway pressure; *LV*, left ventricular.

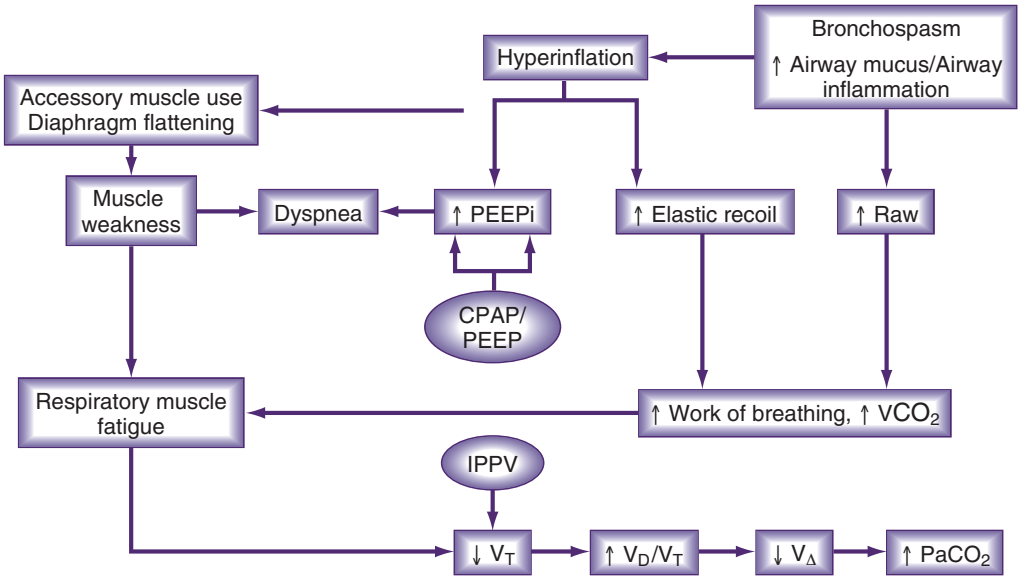

Fig. 55.2 Pathophysiology of acute hypoxemic respiratory failure and points where positive-pressure and oxygen supplementation interrupt the process. Low ventilation-perfusion ratios, shunt, and alveolar hypoventilation cause hypoxemia. Hypoxemia is treated by increasing the fraction of inspired oxygen (FiO_2) (limited benefit with shunt) and applying positive pressure (continuous positive airway pressure [*CPAP*] or positive end-expiratory pressure [*PEEP*]) to increase the residual functional capacity, open collapsed alveoli and narrowed airways, and enhance compliance. An additional beneficial effect of CPAP may occur in patients with cardiogenic pulmonary edema because it reduces both venous return and left ventricular afterload, which may enhance cardiovascular performance in patients with dilated, hypocontractile left ventricles. *IPPV,* Intermittent positive-pressure ventilation; *$PaCO_2$*, arterial partial pressure of carbon dioxide; *PPPi*, intrinsic PEEP; *VCO_2*, production of carbon dioxide.

BOX 55.1 Indications for Use of Noninvasive Ventilation in the Acute Care Setting

Airway Obstruction
COPD (A)*
Asthma (B)
Cystic fibrosis (C)
Obstructive sleep apnea or obesity hypoventilation (B)
Upper airway obstruction (C)
Facilitation of weaning in COPD (A)
Extubation failure in COPD (B)

Hypoxemic Respiratory Failure
ARDS (C)
Pneumonia (C)
Trauma or burns (B)
Acute pulmonary edema (use of CPAP) (A)
Immunocompromised patients (A)
Restrictive thoracic disorders (C)
Postoperative patients (B)
Do-not-intubate patients (C)
During bronchoscopy (C)

ARDS, Acute respiratory distress syndrome; *COPD,* chronic obstructive pulmonary disease; *CPAP,* continuous positive airway pressure.
*Letters in parentheses indicate the level of evidence supporting the use of noninvasive ventilation: *A,* multiple randomized controlled trials: recommended; *B,* at least one randomized controlled trial: weaker recommendation; *C,* case series or reports: can be attempted, but with close monitoring.

Airway Obstruction

Chronic Obstructive Pulmonary Disease

Randomized controlled trials[13,14] and meta-analyses[15] have consistently shown that compared with conventional therapy, NIV improves vital signs, gas exchange, and dyspnea scores; reduces the rates of intubation, morbidity, and mortality; and shortens hospital length of stay in patients with moderate to severe exacerbations of COPD. Thus NIV is considered the ventilatory mode of choice in selected patients with acute exacerbations of COPD. Some studies suggest that the addition of heliox to NIV further improves the work of breathing and gas exchange during COPD exacerbations,[16] but a subsequent multicenter trial found no improvement in other outcomes compared with NIV alone.[17] The ERS/ATS Task Force gave a strong recommendation for use of NIV as the ventilatory modality of first choice for patients with hypercapnic respiratory failure caused by COPD exacerbations.[12] More recent clinical practice guidelines suggest the use of nocturnal NIV in the home in addition to usual care for patients with chronic stable hypercapnic COPD (arterial partial pressure of carbon dioxide [$PaCO_2$] ≥52 mm Hg) given several desirable effects of NIV, including possible reductions in mortality and hospital admissions, improved quality of life (QOL), reduced dyspnea, and produced improvements in functional capacity, awake blood gases, and exertion tolerance.[18,19]

Asthma

Uncontrolled studies have reported improvements in gas exchange and low rates of intubation after the initiation of NIV in patients with severe asthma attacks. Two controlled trials have demonstrated a more rapid improvement in expiratory flow rates with NIV,[20,21] and one showed a decreased hospitalization rate in acute asthma patients treated with NIV compared with a sham mask.[21] Neither study was powered adequately to assess intubation or mortality rates. Nonetheless, these data support a trial of NIV in asthmatics responding poorly to initial bronchodilator therapy. NIV can be combined with continuous nebulization and heliox, although the added value of these latter therapies has not been established in controlled trials. In a more recent study using a large medical record dataset, 13,588 admissions for acute asthma were identified in 58 hospitals.[22] Use of NIV for acute asthma was widely variable between hospitals, with 36% not using it at all, and one hospital using it in 16.3% of such patients. Overall, NIV was used in 4.0% of patients with acute asthma and invasive mechanical ventilation (IMV) in another 5.7%. NIV failure rate was only 4.9%, and the case-fatality rate of patients using NIV was only 2.3%. Despite these low rates, use of NIV was not associated statistically with lower mortality rate than IMV after risk standardization, but hospital length of stay was slightly shorter. Based on the tentativeness of the evidence, the ERS/ATS Task Force made no recommendation regarding the use of NIV for acute asthma.[12]

Cystic Fibrosis

Uncontrolled studies indicate that NIV is useful to stabilize gas exchange in the treatment of acute episodes of respiratory failure in end-stage cystic fibrosis patients and can serve as a bridge to transplantation.[23]

Obesity Hypoventilation Syndrome

Acute hypercapnic respiratory failure related to obesity hypoventilation (OHS) is becoming more prevalent given the high and increasing obesity rates in the general population. A single-center prospective observational study was conducted to examine the use of NIV in these patients. Using COPD patients with acute hypercapnic respiratory failure for comparison, the authors found no change in the rate of NIV failure between the two groups and found lower rates of late NIV failure, readmission to the intensive care unit (ICU), and ICU and hospital mortality in the OHS group. Their conclusion was that NIV can be used safely and efficaciously in acute hypercapnic respiratory failure related to OHS in the ICU.[24] Furthermore, a recent systematic review found that hospital discharge with positive airway pressure devices reduces mortality risk in OHS patients admitted with acute-on-chronic hypercapnic respiratory failure compared with those not discharged on such devices.[25]

Upper Airway Obstruction

Anecdotally, NIV can be used effectively to treat patients with reversible upper airway obstruction, such as that caused by glottic edema after extubation. In this situation, NIV can be combined with aerosolized medications or heliox, but no controlled trials have demonstrated the efficacy of this approach. If therapy with NIV is considered, patients should be selected with great caution and monitored closely, because upper airway obstruction can lead to precipitous deterioration. The use of NIV in patients with tight, fixed upper airway obstruction is inappropriate because it delays the institution of definitive therapy.

Hypoxemic Respiratory Failure

Hypoxemic respiratory failure is defined as severe hypoxemia (arterial oxygen partial pressure to fraction of inspired oxygen [PaO_2/FiO_2] ratio less than 200) combined with an unassisted respiratory rate >30 breaths per minute and a non-COPD diagnosis, including acute pneumonia, acute lung injury (ALI), acute respiratory distress syndrome (ARDS), pulmonary edema, or trauma. Controlled trials of NIV to treat patients with acute hypoxemic respiratory failure have

shown statistically significant reductions in the rate of intubation, length of hospital stay, incidence of infectious complications,[8,26] and in one study, ICU mortality.[26] However, because of the heterogeneity of causes, these studies fail to demonstrate that all patient subgroups with hypoxemic respiratory failure benefit equally from NIV. Furthermore, when patients are stratified according to the acuity of illness, those with a Simplified Acute Physiologic Score (SAPS II) less than 35 fare considerably better with NIV than do those with higher scores.[27] Thus the selection of patients with less severe disease is likely to enhance the success of NIV in treating hypoxemic respiratory failure, and studies that examine individual subgroups within the larger category are likely to be more useful clinically.

Acute Cardiogenic Pulmonary Edema

Use of NIV to treat acute cardiogenic pulmonary edema (CPE) is the second main indication for NIV among causes of ARF, and the ERS/ATS Task Force recommended its use.[12] Meta-analyses of randomized controlled trials demonstrated that compared with oxygen therapy, CPAP (though not a true mode of ventilatory support) is highly effective at relieving respiratory distress, improving gas exchange, and averting intubation when used to treat patients with acute cardiogenic edema.[28,29] Inspiratory assistance combined with expiratory pressure can reduce the work of breathing and alleviate respiratory distress more effectively than CPAP alone. However, several uncontrolled trials and two controlled trials found that NIV and CPAP were equally effective in improving vital signs and avoiding intubation. The current recommendation is to use CPAP alone or NIV as an initial therapy; if CPAP is used initially, inspiratory pressure support should be added if the patient has persistent hypercapnia or dyspnea.[29]

Pneumonia/Acute Respiratory Distress Syndrome

One controlled trial showed that NIV in patients with severe community-acquired pneumonia lowers the rate of endotracheal intubation and shortens the length of ICU stay compared with conventional therapy; however, a subgroup analysis revealed that the benefits occurred only in patients with underlying COPD.[30] No benefit was apparent in the non-COPD patients with severe pneumonia. A subsequent uncontrolled trial in non-COPD patients with severe pneumonia found that two-thirds of such patients treated with NIV eventually required intubation.[31] Although the latter authors deemed a trial of NIV in non-COPD patients with severe pneumonia to be a reasonable approach, controlled data to support such a recommendation are currently lacking. According to the Berlin definition,[32] patients with ARDS have oxygenation defects, bilateral radiographic infiltrates, and no heart failure to explain the infiltrates. Thus many patients hospitalized with severe pneumonia are diagnosed with ARDS as well. Earlier studies on the use of NIV for pneumonia/ARDS patients yielded conflicting findings, and meta-analyses were inconclusive.[33] A prospective cohort study,[34] using NIV as a "first-line" intervention for ARDS, found that ventilator-associated pneumonia and mortality were greatly reduced when patients succeeded rather than failed NIV, and a SAPS score of 34 or less and PaO_2/FiO_2 ratio above 175 within the first hour predicted the success of NIV. However, only 15% of the ARDS patients entered into this study actually succeeded with NIV. More recently, the LUNG SAFE ARDS database found that among 506 ARDS patients in their observational cohort treated with initial NIV,[35] those with a $PaO_2/FiO_2 \leq 150$ had a mortality of 36% compared with 25% in those treated with initial IMV, suggesting that NIV might increase the risk of poor outcomes in patients with more severe oxygenation defects. Based on the weakness of the data, the (ERS/ATS) Task Force made no recommendation on the use of NIV to treat pneumonia/ARDS ("de novo acute respiratory failure") but did allow that a trial of NIV might be considered in selected patients as long as they were closely monitored to avoid any delay in needed intubation.[12]

Coronavirus Disease-19 Pneumonia

The COVID-19 pandemic has created waves of patients entering hospitals with pneumonia and acute hypoxemic respiratory failure around the world and generated debate about the efficacy and safety of NIV as an initial therapy. Given concerns about spreading disease via aerosolization of virus, there was hesitancy about using NIV in this setting, and many centers favored early intubation to limit dispersion of aerosol.[36,37] However, this created shortages of ICU beds, and initially reported outcomes of invasively managed patients were poor.[38] Consequently, many centers gave trials of NIV or high-flow nasal cannula (HFNC) to patients not needing immediate intubation to see if some of these patients could be managed noninvasively outside of the ICU.[39] Guidelines on how to manage patients with COVID-19 pneumonia varied widely,[40] but most discouraged use of NIV except for patients with COVID-19 pneumonia complicated by COPD exacerbations or CPE (i.e., the usual indications). The pandemic encouraged the use of the helmet interface, a clear plastic hood that fits over the head, because of the theoretically superior containment of aerosol if the neck seal is tight. This became the predominant interface at some centers in Italy,[39] but was used infrequently, if at all, at other centers in Europe and the United States.[41] Another innovation of the pandemic was the use of NIV (and HFNC) in combination with awake prone positioning to improve oxygenation and avoid the need for intubation,[42] although the efficacy of this approach has been questioned.[43] Despite an increasing number of reports on the use of noninvasive approaches for treating patients with COVID-19 pneumonia,[39,41,44] NIV failure rates have remained high (usually >50%), and at present, the quality of the evidence base remains low. It therefore remains unclear how efficacious or safe NIV is compared with the more aggressive approach favoring earlier intubation. Notably, the ERS/ATS Task Force made no recommendation for use of NIV during a viral pandemic based on data accrued during the earlier H1N1 and SARS-CoV-1 pandemics in which efficacy of NIV was unclear and concerns were raised about viral spread.[12]

Immunocompromised States

The dismal prognosis of invasively ventilated immunocompromised patients makes NIV an appealing alternative ventilatory mode, with its demonstrated ability to decrease the rate of nosocomial infection.[7] In earlier studies of both solid organ transplantation[45] and neutropenic patients (most of whom had hematologic malignancies)[46] who developed acute hypoxemic respiratory failure, NIV reduced the rates of intubation, nosocomial infection, and ICU mortality compared with conventional therapy. However, more recent studies suggest that the benefit of NIV is difficult to demonstrate, and randomized controlled studies comparing NIV with conventional oxygen therapy, with IMV added if needed, showed no reduction in intubation, mortality rate, or length of hospital stay.[47,48] In immunocompromised patients with *Pneumocystis carinii* pneumonia resulting from acquired immunodeficiency syndrome (AIDS), NIV appears to yield benefit when compared with IMV in physiologically and demographically matched patients.[49] Thus the current suggestion is to reserve NIV for milder cases of acute respiratory failure in immunocompromised patients but resort to intubation without undue delay if progressive deterioration occurs.[50,51] The ERS/ATS Task Force gave a conditional recommendation for use of NIV in immunocompromised patients with hypoxemic respiratory failure,[12] but acknowledged that accruing evidence suggests that HFNC may have efficacy advantages over NIV in this population of patients.[52]

Postoperative Respiratory Failure

NIV and CPAP alone have been studied in postoperative patients who develop respiratory failure after various kinds of surgeries. In particular, they reduce extravascular lung water and improve lung mechanics and gas exchange after coronary artery bypass surgery.[53] Controlled trials show that CPAP or NIV averts postoperative complications compared with oxygen supplementation after high-risk procedures like thoracoabdominal aortic procedures[54] or abdominal surgery.[55,56] NIV improves oxygenation, reduces the need for reintubation, lowers the mortality rate after lung resectional surgery,[57] and enhances pulmonary function after gastroplasty.[58] Thus NIV should be considered in selected postoperative patients at a high risk of pulmonary complications or with frank respiratory failure, especially in the setting of underlying COPD or pulmonary edema.

Trauma and Burns

Trauma patients develop respiratory failure for a multitude of reasons, but some have chest wall injuries, such as flail chest or mild ALIs that might respond favorably to NIV. In a retrospective survey of 46 trauma patients with respiratory insufficiency who had been treated with NIV, Beltrame and coworkers found rapid improvements in gas exchange and a 72% success rate; however, patients with burns responded poorly.[59] More recently, a randomized trial of NIV versus high-flow oxygen in thoracic trauma patients with PaO_2/FiO_2 <200 was stopped early after the enrollment of 50 patients because of significant reductions in the intubation rate (12% vs. 40%) and hospital length of stay (14 vs. 21 days) in the NIV group.[60] The (ERS/ATS) Task Force "suggested" the use of NIV in patients with chest trauma, especially flail chest.[12]

Restrictive Lung Disease

The use of NIV in patients with underlying restrictive disease and acute deterioration of respiratory status has not been studied extensively because they constitute only a small portion of patients admitted to acute care hospitals. Patients with restriction related to an underlying neuromuscular disease and superimposed ARF may benefit from a trial of NIV. Small case series have reported that using NIV in patients with myasthenic crises may avoid intubation.[61,62]

Patients with restriction caused by end-stage pulmonary fibrosis in respiratory extremis have been reported to respond poorly to mechanical ventilation.[63] However, in selected patients with interstitial lung diseases, NIV may play a role in preventing intubation and improving survival. A prospective observational study revealed that patients with APACHE II scores <20 and mixed interstitial lung disease requiring noncontinuous NIV had a higher survival rate than those requiring continuous NIV or invasive ventilation.[64] Similarly, a small retrospective observational study in patients with ARF secondary to idiopathic pulmonary fibrosis (IPF) showed a poor overall prognosis, but for those who survived, NIV helped to shorten the ICU stay and improve the 90-day survival rate.[65] Interestingly, this study also found that patients with IPF and a higher NT-proBNP at baseline appeared to have a greater chance of NIV failure.

Do-Not-Intubate Patients

Although controversial, NIV may be a useful tool in patients with ARF who do not wish to be intubated. There are several reports of good outcomes (>50% survival to discharge) with NIV in this subset of patients, especially those with COPD, congestive heart failure,[66] and end-stage malignancy. NIV may also be used as a palliative technique to reduce dyspnea, preserve patient autonomy, and provide time for the finalization of affairs for some terminal patients.[67,68] However, there is concern that this may merely prolong the dying process, and patients and their families must be informed that NIV is being used as a form of life support in this setting and should be given the option to refuse it. By virtue of its comfort and tolerance advantages, HFNC may be a better choice than NIV for some patients with respiratory failure requiring palliation.

Facilitation of Weaning and Extubation

Patients who require IMV initially and fail to wean promptly are potential candidates for NIV to facilitate extubation, thus reducing the complications related to prolonged intubation. Several randomized controlled trials and subsequent meta-analyses have demonstrated that transitioning to NIV may significantly shorten the duration of IMV, reduce the length of ICU stay, and improve survival when compared with patients weaned in the routine fashion.[69–71] The benefit of NIV in ventilator weaning seems to be highest in patients intubated for acute exacerbations of COPD.[72,73]

Another potential application of NIV in the weaning process is to avoid reintubation in patients with extubation failure, a complication of IMV associated with a high mortality rate. Data for this use of NIV are variable and inconclusive. Earlier studies investigating the role of NIV in this situation showed promise, but one randomized trial found that NIV may delay required intubation in this setting, resulting in an increased ICU mortality rate.[74] More recent studies have demonstrated that patients at high risk of extubation failure,[75] especially those with hypercapnia,[76] have a reduced need for reintubation and mortality if treated with NIV as opposed to oxygen supplementation alone. Subsequent meta-analyses have demonstrated that NIV used prophylactically after planned extubation has decreased reintubation rates.[77,78] However, its effect on ICU and hospital mortality remains unclear. Thus although the use of NIV to facilitate weaning and extubation appears to benefit hypercapnic patients with COPD or congestive heart failure, its overzealous application could lead to delayed reintubation and other adverse consequences.

Bronchoscopy

Both CPAP and NIV can be used to support oxygenation and ventilation during bronchoscopy in patients "at risk" for being stressed by the procedure, such as those with severe COPD. A specially designed open CPAP system has been used during bronchoscopy in patients with marginal oxygenation to maintain adequate gas exchange and avoidance of respiratory failure.[79] Also, a controlled trial demonstrated equivalent oxygenation and complication rates in patients undergoing bronchoscopy and supported with either noninvasive or invasive mechanical ventilation.[80] Thus NIV often provides an effective means of providing ventilation and oxygenation support to patients undergoing bronchoscopy.[80]

ROLES OF HFNC VS. NIV

The increasing use of HFNC over the past decade throughout the world has raised questions about when to use HFNC vs. NIV. HFNC refers to the delivery of heated, humidified (to body conditions), and oxygenated gas via loose-fitting nasal prongs at high flow rates usually ≥20 L/min up to 40–80 L/min, depending on the manufacturer. The interface permits unimpeded speaking and eating, and the heat and humidity make the high flows tolerable. Patients sense HFNC as more comfortable than standard mask oxygen or NIV. The heat and humidity also hydrate mucus in the airways and preserve mucocilliary function better than standard oxygen. Oxygenation is also better with HFNC than with standard oxygen delivery techniques because the higher flow rates reduce the entrainment of room air and promote the delivery of a higher FiO_2 to the lungs. In addition, the higher flow rates flush the upper airways, lowering dead space and improving efficiency

of ventilation. There is also a small and unregulated positive airway pressure applied by HFNC, but this is less than with NIV at the usual settings. Consequently, on average, oxygenation with NIV is better than with HFNC.

The influential FLORALI study[52] randomized patients with acute hypoxemic respiratory failure, mainly caused by pneumonia or ARDS, to NIV, standard oxygen, or HFNC. In patients with $PaO_2/FiO_2 \leq 200$, intubations were fewer in the HFNC group compared with the other groups, and in the overall population, ICU and 90-day mortality rates were less with HFNC. A subsequent systematic review that included the FLORALI results found that HFNC, compared with standard oxygen, slightly reduced escalation of care and intubations but could not substantiate its mortality benefit.[81]

These results and the ease of application and high tolerance of HFNC compared with the other modalities have made it the preferred initial noninvasive modality over NIV to treat hypoxemic respiratory failure at many centers, but as yet, the evidence base isn't adequate to recommend this practice. Furthermore, with regard to the established indications for NIV (i.e., ARF associated with COPD exacerbations and CPE), NIV should still be considered the modality of first choice unless the respiratory failure is mild or the patient is intolerant of NIV. HFNC may be preferred for palliation of do not intubate/do not resuscitate (DNI/DNR) patients because of its superior tolerability, and the two—NIV and HFNC—may be used in tandem, with HFNC performing better than standard oxygen during breaks from NIV.[82]

PRACTICAL APPLICATION

Patient Selection

NIV should be viewed as a "crutch" that assists patients through a period of ARF while reversible factors are being treated, helping them avoid IMV and its attendant complications. To optimize the chance of success, NIV should be used early, when patients first develop signs of incipient respiratory failure. In addition, predictors of success are useful in identifying patients most likely to benefit (Box 55.2). The selection process might be viewed as taking advantage of a "window of opportunity": the window opens when the patient first requires ventilatory assistance and closes when the patient becomes too unstable.

Based on the predictors of success and criteria used in prior controlled trials, we recommend the following three-step selection process: (1) ensure that the patient has an etiology of respiratory failure likely to respond favorably to NIV and (2) identify patients in need of ventilatory assistance by using clinical and blood gas criteria. Patients with mild respiratory distress and only mild gas exchange abnormalities are likely to do well without ventilatory assistance. Good candidates are those with moderate to severe dyspnea, tachypnea, and impending respiratory muscle fatigue, as indicated by the use of accessory muscles of breathing or abdominal paradox. The level of tachypnea used as a criterion depends on the underlying diagnosis. With COPD, candidates for NIV usually have respiratory rates exceeding 24 breaths per minute, but with hypoxemic respiratory failure, respiratory rates are usually higher, in the range of 30–35 breaths per minute. The third step excludes patients for whom NIV would be unsafe. If respiratory arrest is imminent, the patient should be promptly intubated because the successful initiation of NIV requires some time for adaptation. Patients who are medically unstable with hypotensive shock, uncontrolled upper gastrointestinal bleeding, unstable arrhythmias, or life-threatening ischemia are better managed with IMV. Additionally, NIV should not be used for patients who are uncooperative, are unable to adequately protect their airways or clear secretions, or are intolerant of masks. The use of NIV merits caution after recent upper gastrointestinal or airway surgery.

BOX 55.2 Predictors of Noninvasive Ventilation Success in Patients With Acute Respiratory Failure

- Lower acuity of illness (Acute Physiology and Chronic Health Evaluation [APACHE] score)
- Ability to cooperate; better neurologic score
- Ability to coordinate breathing with ventilator
- Less air leakage; intact dentition
- Hypercarbia, but not too severe ($PaCO_2$ between 45 and 92 mm Hg)
- Acidemia but not too severe (pH between 7.1 and 7.35)
- Improvements in gas exchange and heart and respiratory rates within the first 2 hours

$PaCO_2$, Arterial partial pressure of carbon dioxide.

Initiation of Noninvasive Ventilation

After identification of an appropriate candidate for NIV, a ventilator and interface must be chosen, initial settings must be selected, and the patient must be monitored closely in an appropriate location until stabilized. The roles of physicians, respiratory therapists, and nurses are of paramount importance in explaining the process and gaining the confidence of the patient. NIV can be initiated wherever patients present with acute respiratory distress, but they should be transferred to a location with sufficient monitoring (usually an ICU or step-down unit) until stabilized. During transfers, ventilatory assistance and monitoring should be continued.

Ventilator Selection

Selection of a ventilator is based largely on availability, practitioner experience, and patient comfort. Critical care ventilators with NIV modes and devices designed specifically for administration of NIV are acceptable, and the latter often have internal batteries and can be used for transport. Pressure-limited modes, including pressure support and pressure control, are available on most critical care ventilators. Pressure control ventilation (PCV) delivers time-cycled, preset inspiratory and expiratory pressures with adjustable inspiratory/expiratory ratios at a controlled rate. This mode also permits patient triggering and the selection of a backup rate. PSV delivers preset inspiratory and expiratory pressures to assist spontaneous breathing efforts without a backup rate. Nomenclature and the specific characteristics of these modes may differ between ventilators, and this must be taken into account to avoid errors. For example, with some ventilators, pressure support is the amount of inspiratory assistance added to the preset expiratory pressure. Others require the independent selection of inspiratory and expiratory positive airway pressures, with the difference between the two determining the level of pressure support.

PSV is a flow-triggered and flow-cycled procedure, and patient effort determines tidal volume and duration of inspiration. Pressure-support modes have the potential to match breathing pattern quite closely and have been rated by patients as more comfortable for NIV than volume-limited ventilation.[83] However, leaks during NIV can interfere with the detection of reduced inspiratory flow at the termination of inspiration, causing expiratory asynchrony.

Traditional bilevel positive airway pressure (BiPAP) devices designed for home use have limited pressure-generating capability ($\leq$30 cm H_2O) and lack oxygen blenders or sophisticated alarm or battery backup systems and are not suitable for use in patients who require high oxygen concentrations or inspiratory pressures. Bilevel devices designed specifically for the acute setting are equipped with

sophisticated alarm and monitoring capabilities, graphic displays, and oxygen blenders. These devices are capable of enhancing synchrony by offering ways to limit the inspiratory duration and an adjustable "rise time"—the time to reach the targeted inspiratory pressure. Most critical care ventilators include an "NIV" mode that enhances leak compensation capabilities and silences "nuisance" alarms.[84] If desired, volume-limited ventilation can be delivered using critical care ventilators, but a higher tidal volume than that commonly used for IMV is recommended to compensate for air leakage.

Initial ventilator pressure settings are usually set in low ranges to facilitate patient acceptance, but can be set higher if necessary to alleviate respiratory distress. Typical pressures are an inspiratory positive airway pressure in the range of 12 cm H_2O and a PEEP (or expiratory positive airway pressure) of 5–6 cm H_2O.[85] L'Her and colleagues[86] demonstrated that increases in inspiratory pressure are helpful to alleviate dyspnea, whereas increases in expiratory pressure are preferable to improve oxygenation. For volume ventilation, initial tidal volumes range from 6 to 7 mL/kg. The ventilator is set in a spontaneously triggered mode, with or without a backup rate. Pressures commonly used to deliver CPAP in patients with acute respiratory distress range from 5 to 12.5 cm H_2O. CPAP can be applied using compressed air with a regulator system, blower-based CPAP device, bilevel device, or critical care ventilator.

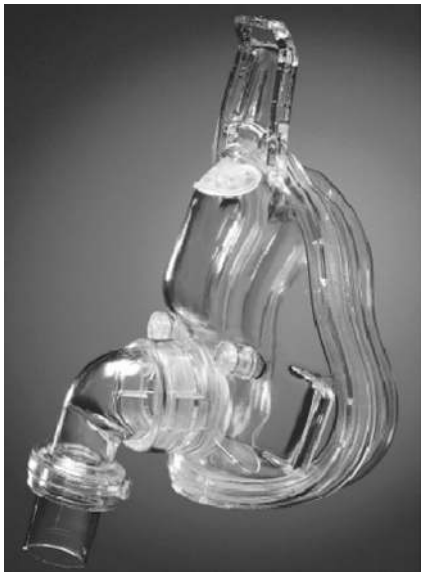

Fig. 55.3 Full-face mask with soft silicon seal to minimize pressure on the nasal bridge. A disposable version of this mask is widely used in the acute care setting.

Interfaces

The major difference between invasive and noninvasive ventilation is that with the latter, pressurized gas is delivered to the airway via a mask rather than via an invasive artificial airway. The open breathing circuit of NIV permits air leaks around the mask or through the mouth, rendering the success of NIV dependent on ventilators designed to deal effectively with air leaks and to optimize patient comfort and acceptance. Interfaces—the devices that connect the ventilator tubing to the nose, mouth, or both—enable pressurized gas to enter the upper airway during NIV. Commonly used interfaces in the acute setting include nasal and full-face (or oronasal) masks.

Nasal masks are widely used for the administration of CPAP or NIV, particularly for chronic applications. Nasal masks are usually better tolerated than full-face masks for long-term applications because they cause less claustrophobia; enhance comfort; and allow eating, conversation, and expectoration. The standard nasal mask is a triangular or cone-shaped clear plastic device that fits over the nose and uses a soft cuff that forms an air seal over the skin. The mask exerts pressure over the nasal bridge, often causing skin irritation and redness, and occasionally ulceration. Pharyngeal gas pressures may decline during mouth opening.

Full-face masks cover both the nose and the mouth (Fig. 55.3) and are preferable to nasal masks in the acute setting. The efficacy of both nasal and oronasal masks in lowering $PaCO_2$ and avoiding intubation is similar in the acute setting, but a randomized controlled trial[87] observed better patient tolerance with full-face masks because of reduced air leakage through the mouth. More recently, "total" face masks have become available; they seal around the perimeter of the face and resemble a hockey goalie's mask or a snorkel mask. Made of optical-grade plastic, they are easy to apply and cause no more claustrophobia than standard face masks.[5] Mouthpieces are seldom used to administer NIV in the acute setting but are occasionally used during initiation when the patient holds the mouthpiece in place to adapt to the sensation of positive-pressure ventilation.

Helmets are clear plastic, inverted, bucket-shaped devices that fit over the entire head and seal over the shoulders and neck.[88] These have achieved popularity in some European countries and were the most commonly used interface for patients with hypoxemic respiratory failure caused by COVID-19 pneumonia at certain Italian centers during the recent pandemic,[39] but not in most other countries where availability and experience are less. A randomized controlled trial performed before the COVID-19 pandemic at a single center in Chicago found a much lower need for intubation and lower mortality rate when patients with ARDS used the helmet as opposed to the standard full-face mask, but this study awaits replication.[89]

Selection of a comfortable interface that fits properly is key to the success of NIV. With the full-face mask, which is the first choice at many centers, the patient should be allowed to hold the mask in place initially if possible. The mask straps are tightened with the least amount of tension necessary to avoid excessive air leakage. Excessive tightening causes discomfort and skin trauma and may lead to NIV failure. Some air leakage is acceptable, and even obligatory with bilevel ventilators, because of the need to flush carbon dioxide from the single-channel ventilator circuit. However, excessive air leakage through the interface can lead to NIV failure with any ventilator.

Oxygenation and Humidification

Oxygen is titrated to achieve the desired oxygen saturation, usually greater than 90%–92%, either by using the oxygen blenders used for critical care applications and for most bilevel ventilators or by adjusting the liter flow (up to 15 L/min) delivered via oxygen tubing connected directly to the mask or ventilator circuit. Bilevel ventilators designed for home use have limited oxygenation capabilities (maximal inspired oxygen fraction, 0.45–0.5) and are not suitable for use in patients with hypoxemic respiratory failure. A heated humidifier should be used to prevent drying of the nasal passage and oropharynx when the duration of application is anticipated to be more than a few hours.

Monitoring

Once NIV is initiated, patients should be closely monitored in a critical care or step-down unit until they are sufficiently stable to be moved to a regular medical floor. The aim of monitoring is to determine whether the main goals are being achieved, including the relief of symptoms, reduced work of breathing, improved or stable gas exchange, good

BOX 55.3 Monitoring of Patients Receiving Noninvasive Ventilation in Acute Care Settings

Location
Critical care or step-down unit
Medical or surgical ward if able to breathe unassisted for >20–30 min

"Eyeball" Test
Dyspnea
Comfort (mask, air pressure)
Anxiety
Asynchrony
Leaks

Vital Signs
Respiratory and heart rates
Blood pressure
Continuous electrocardiography

Gas Exchange
Continuous oximetry
Arterial blood gases (baseline, after 1–2 h, and as clinically indicated)

patient-ventilator synchrony, and patient comfort (Box 55.3). A drop in the respiratory rate with improved oxygen saturation or improving pH with a lower $PaCO_2$ within the first 1–2 hours indicates a successful outcome.[90] Abdominal paradox, if present initially, subsides, and the heart rate usually falls. The absence of these propitious signs indicates a poor response to NIV and the need to make further adjustments. Excessive leaks should be sought and corrected, and patient-ventilator synchrony should be optimized. Pressures may need to be adjusted upward to relieve respiratory distress and achieve a reduction in $PaCO_2$. If these adjustments fail to improve the response within a few hours, NIV should be considered a failure, and the patient should be promptly intubated if it is still clinically indicated. Excessive delay in intubation may precipitate a respiratory crisis and add to the morbidity and mortality.

ADVERSE EFFECTS AND COMPLICATIONS

When applied by experienced caregivers to appropriately selected patients, NIV is usually well tolerated and associated with minimal complications. The most frequent adverse effects and complications are related to the mask, ventilator airflow or pressure, patient-ventilator interaction, or airway secretions. A potentially serious concern raised in recent years is that of excessive tidal volumes generated by some patients, mainly with hypoxemic respiratory failure, who are breathing at excessive tidal volumes (>9.5 mL/kg) that have been associated with poorer outcomes.[91] This is thought to predispose to patient self-induced lung injury (PSILI). Some advocate lowering NIV pressures or earlier intubation in such patients, but neither the need to do so nor the efficacy of these interventions has been tested.

Common adverse effects of NIV depend on the type of mask and include discomfort and erythema or skin ulcers on sealing surfaces, usually on the nasal bridge, related to pressure from the mask seal. Proper fitting and attachment, consistent use of artificial skin over the nose, and newer masks with softer silicone seals help minimize these problems. Adverse effects related to airflow or pressure include conjunctival irritation caused by air leakage under the mask into the eyes and sinus or ear pain related to excessive pressure. Refitting the mask or lowering the inspiratory pressure may ameliorate these problems. Nasal or oral dryness caused by high airflow is usually indicative of air leaking through the mouth. Measures to minimize leakage may be useful, but nasal saline or emollients and heated humidifiers are often necessary to relieve these complaints. Gastric insufflation occurs commonly, may respond to simethicone, and is usually tolerated.

Patient-ventilator asynchrony is a common occurrence during NIV. Failure to adequately synchronize compromises the ventilator's ability to reduce the work of breathing and may contribute to NIV failure. The asynchrony may be related to patient agitation, which can be treated with the judicious use of sedatives. Failure to synchronize can also result from inadequate ventilator triggering or the inability to sense the onset of patient expiration because of air leakage. This can be corrected by minimizing air leaks and using ventilator modes that permit a limitation of maximal inspiratory duration. Even with the best efforts to optimize settings and comfort, a minority of patients still fail. This may be partly because of the progression of the underlying disease process or the patient's inability to tolerate NIV, but every effort should be made to ascertain that it is not the result of technologic problems that could be corrected by mask or ventilator adjustments. Therefore intubation should not be delayed if improvement is not apparent within a few hours.

KEY POINTS

- The use of NIV is established in patients with certain forms of ARF, including as a result of COPD exacerbations and acute CPE.
- For these entities, NIV delivered by nasal or oronasal masks reduces the need for endotracheal intubation, decreases the length of stay in the ICU and hospital, and reduces mortality.
- The efficacy of NIV has also been demonstrated for mild to moderate respiratory failure in immunocompromised patients and to facilitate extubation in COPD patients.
- Patients who develop respiratory failure and who refuse intubation are potentially good candidates for NIV, but all patients must be selected carefully.
- Several factors are vital to the success of NIV: careful patient selection; properly timed initiation; comfortable, well-fitting interface; coaching and encouragement; and careful monitoring.
- NIV should be used to avert endotracheal intubation rather than as an alternative to it. One should not persist in the use of NIV if it leads to a delay in necessary intubation.
- A trial of NIV should be instituted in properly selected patients with ARF before a respiratory arrest is imminent to provide ventilatory assistance while the factors responsible for the respiratory failure are aggressively treated.
- NIV is an important option to assist patients with ARF and, if properly applied in selected patients, improves patient outcomes in the critical care setting compared with conventional oxygen therapy with IMV if necessary.
- Although HFNC is often better tolerated than NIV and is favored as initial therapy for hypoxemic respiratory failure at many centers, NIV is still the favored initial choice to treat ARF caused by COPD exacerbations or cardiogenic pulmonary edema

References for this chapter can be found at expertconsult.com.

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Ferrer M, Sellares J, Valencia M, et al. Non-invasive ventilation after extubation in hypercapnic patients with chronic respiratory disorders: Randomized controlled trial. *Lancet*. 2009;374:1082–1088.
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One hundred and ten patients with COVID-19 pneumonia and moderate to severe hypoxemic respiratory failure were randomized to receive continuous helmet NIV for 48 hours followed by HFNC vs. HFNC alone. Days free of respiratory support within 28 days (the major outcome variable) were 20 in the helmet group and 18 in the HFNC group (P = NS). Intubation rate was 30% in the helmet group and 51% in the HFNC group (P = .03). In-hospital mortality was 24% in the helmet group and 25% in the HFNC group (P = NS). Although the intubation rate was lower in the helmet group, the major outcome variable and mortality were similar between the groups.

Jaber S, Lescot T, Futier E, et al. Effect of noninvasive ventilation on tracheal reintubation among patients with hypoxemic respiratory failure following abdominal surgery: A randomized clinical trial. *JAMA.* 2016;315(13):1345–1353.
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Lindenauer PK, Stefan MS, Shieh MS, et al. Outcomes associated with invasive and noninvasive ventilation among patients hospitalized with exacerbations of chronic obstructive pulmonary disease. *JAMA Intern Med.* 2014;174(12):1982–1993.
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Patel BK, Wolfe KS, Pohlman AS, et al. Effect of noninvasive ventilation delivered by helmet vs face mask on the rate of endotracheal intubation in patients with acute respiratory distress syndrome: A randomized clinical trial. *JAMA.* 2016;315(22):2435–2441.
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Advanced Techniques in Mechanical Ventilation

Richard D. Branson

INTRODUCTION

Physiologic closed-loop controlled (PCLC) systems run the gamut from simple negative feedback controllers to fully automated control of airway pressure, tidal volume (V_T), minute ventilation (V_E), fraction of inspired oxygen (FiO_2), and positive end-expiratory pressure (PEEP).[1] Proposed advantages of PCLC systems include maintenance of evidence-based treatment, rapid response to changes in patient condition, reduced necessity for clinician-machine interaction, and less undesirable variation in clinical practice. Disadvantages include reduced of caregivers to clinical changes, loss of situational awareness, and complacency.

Definitions

Wysocki and others have classified closed-loop systems based on the level of sophistication into simple, physiologic signal based, and explicit computerized protocols.[2] Table 56.1 provides examples of closed-loop systems as described by Chatburn and colleagues.[3] This classification method describes operation during traditional and closed-loop control using seven terms describing the targeting schemes for ventilator modes. These are set point, dual, servo, adaptive, bio-variable, optimal, and intelligent.[3] Aside from the added complexity, the use of engineering terms, although consistent with the literature, may seem to infer a value judgment. For instance, "intelligent" implies a system that is perhaps superior to "optimal." In some ways, however, this too is a classification system based on increasing sophistication. Evidence is required to conclude that "intelligent" is superior to "set-point" targeting. As an example, volume control, continuous mandatory ventilation (VC-CMV), a set-point targeting scheme, is the only method to date that has been demonstrated unequivocally to affect clinical outcome in terms of control of V_T during ventilatory support for acute respiratory distress syndrome (ARDS).[4]

ADVANCED MODES

Development of new modes of ventilation can be traced to the current limitations of conventional ventilation and a desire for a competitive edge between manufacturers. Despite marked changes in the understanding of mechanical ventilation in the last 20 years, improvements are still needed. These typically include provision of lung-protective ventilation by limiting driving pressure, power, airway pressures, and volume; encouraging safe spontaneous breathing; improving patient-ventilator synchrony; balancing lung recruitment (avoiding collapse and overdistention); and limiting the hemodynamic interference.

Adaptive Pressure Ventilation: Adaptive Control

Adaptive pressure ventilation (APV) was one of the first closed-loop systems introduced in mechanical ventilation. Also called by various manufacturers by the terms *pressure-regulated volume control, autoflow, volume support,* and *volume control* +, this mode provides a pressure-limited, time-cycled breath while constrained by a tidal volume (V_T) target.[5] APV is classified as an adaptive targeting scheme.

Proposed advantages of APV typically include a more consistent V_T, lower peak airway pressure, and fewer alarms compared with volume control ventilation (VCV).[6] These findings are easily explained by the nature of pressure-limited ventilation. The most frequent ventilator alarm during VCV is high pressure, which is eliminated by pressure-regulating the breath. And although V_T is the target, APV guarantees a minimum V_T, but allows the patient to receive a larger V_T than set during an aggressive inspiratory effort.[7]

Importantly, Jaber and colleagues have shown that aggressive effort during APV can result in an offloading of respiratory work from the ventilator to the patient.[8] Despite automated control of V_T, an increase in patient effort (greater Pmus) results in a reduction in set pressure, as the patient effort contributes to volume delivery. This has been confirmed by other investigators.[9–11]

Comparisons of APV and VCV or pressure control ventilation (PCV) have demonstrated some changes in physiologic parameters (oxygenation, lung mechanics), which may be partially explained by the characteristics of the control group, but these have failed to produce meaningful outcome differences, regardless of disease state.[7,12–19] APV is commonly used in many intensive care units (ICUs), as it does pragmatically reduce ventilator alarms and obviates the need to choose and modify the inspiratory flow setting during VCV. However, this likely results in unrecognized offloading of work to the patient, asynchrony, and imprecise control of V_T and may compromise the objectives of a lung-protective strategy. Use of APV should accompanied by close monitoring of V_T and patient response.

Servo Control Modes: NAVA and PAV+

Two modes of ventilation are considered "servo control" modes. Each allows the patient to control V_T, delivers pressure in proportion to the patient's effort, and requires intact respiratory drive. Both systems can be considered to have closed-loop characteristics, with the changes in output occurring within the breath. Neurally adjusted ventilatory assist (NAVA) delivers inspiratory pressure in proportion to the electrical activity of the diaphragm (EAdi) as a surrogate for neural respiratory drive. EAdi is measured via a nasogastric tube constructed with an embedded array of electrodes.[20] Proportional assist ventilation with load-adjustable gain factors (PAV+) delivers pressure in proportion to the instantaneous flow and volume generated by the patient's inspiratory demand, or Pmus. PAV+ performs programmed, random measurements of respiratory mechanics (elastance and resistance), solving the equation of motion of the respiratory system to determine the level

TABLE 56.1 Targeting Schemes for Mechanical Ventilation as Described by Chatburn et al.[3]

Name (abbreviation)	Description	Advantage	Disadvantage	Example Mode Name
Set point	The operator sets all parameters of the pressure waveform (pressure control modes) or volume and flow waveforms (volume control modes).	Simplicity	Changing patient conditions may make settings inappropriate	Volume control CMV
Dual	The ventilator can automatically switch between volume control and pressure control during a single inspiration.	Can adjust to changing patient conditions and ensure either a preset V_T or peak inspiratory pressure, whichever is deemed more important.	It may be complicated to set correctly and may need constant readjustment if not automatically controlled by the ventilator.	Volume control
Servo	The output of the ventilator automatically follows a varying input.	Ventilator support is proportional to inspiratory effort.	Requires estimates of artificial airway and/or respiratory system mechanical properties.	PAV+, NAVA
Adaptive	The ventilator automatically sets target(s) between breaths in response to varying patient conditions.	Maintains stability of V_T delivery with pressure control for changing lung mechanics or patient inspiratory effort.	Automatic adjustment may be inappropriate if algorithm assumptions are violated or if they do not match physiology.	Adaptive pressure ventilation, PRVC
Bio-variable	The ventilator automatically adjusts the inspiratory pressure or V_T randomly.	Stimulates the variability observed during normal breathing and may improve oxygenation or mechanics.	Manually set range of variability may be inappropriate to achieve goals.	Variable pressure support
Optimal	The ventilator automatically adjusts the targets of the ventilatory pattern to either minimize or maximize some overall performance characteristic (e.g., work rate of breathing).	Adjusts to changing lung mechanics or patient inspiratory effort.	Automatic adjustment may be inappropriate if algorithm assumptions are violated or if they do not match physiology.	ASV, AVM
Intelligent	This is a targeting scheme that uses artificial intelligence programs such as fuzzy logic, rule-based expert systems, and artificial neural networks.	Adjusts to changing lung mechanics or patient inspiratory effort.	Automatic adjustment may be inappropriate if algorithm assumptions are violated or if they do not match physiology.	SmartCare Intellivent ASV

ASV, adaptive support ventilation; *AVM*, adaptive ventilation mode; *CMV*, continuous mandatory ventilation; *NAVA*, neurally adjusted ventilatory assist; *PAV+*, proportional assist ventilation with load-adjustable gain factors; *PRVC*, pressure-regulated volume control; V_T, tidal volume.
Modified from Chatburn RL, El-Khatib M, Mireles-Cabodevila E. A taxonomy for mechanical ventilation: 10 fundamental maxims. *Respir Care*. 2014;59(11):1747–1763.

of assistance.[21,22] Both techniques deliver a variable pressure, and all breaths are patient triggered. Both are intended to speed the transition to spontaneous breathing and avoid the overassistance commonly encountered with pressure support ventilation (PSV). Importantly, neither mode regulates respiratory rate or tidal volume and as such is indicated only when spontaneous breathing is restored or in transition from controlled ventilation.[23,24]

There are some important distinctions between NAVA and PAV+. NAVA uses the EAdi signal to trigger, control, and cycle the ventilator breath. Inspiratory airway pressure is determined by the proportionality gain (NAVA level, in cm H_2O/microvolt) set by the clinician using the equation:

$$\text{Paw} = (\text{NAVA level} \times \text{EAdi}) + \text{PEEP}$$

The NAVA breath is cycled when the EAdi amplitude falls to 70% of the peak value. NAVA triggering is independent of traditional measures of pressure and flow, therefore reducing the impact of intrinsic PEEP or the presence of leaks. Triggering during NAVA may also be accomplished by pressure or flow on a "first come first served" basis if EAdi thresholds are not met.[20]

PAV+ is triggered using a traditional flow or pressure trigger; intrabreath pressure is provided based on solving for the equation of motion, and cycling is based on flow.

$$\text{Paw} = \text{Pmus} \times \%\text{assist} / (100 - \%\text{assist})$$

The machine-delivered pressure during PAV+ is a percentage of the total pressure, based on the gain. If the gain is set to 80%, the ventilator provides 80% of the pressure required to solve the equation of motion, with the remainder provided by patient effort (Pmus).

The primary basis of the advantage for proportional modes is the variable intracycle pressure delivery, compared with a constant fixed pressure, as in PSV. The delivered V_T during PSV is primarily a function of pressure setting and pulmonary compliance.[25,26] During PSV, overassistance occurs commonly, often resulting in excessive V_T, reduced diaphragm activity, hyperinflation, missed triggers, and central apnea events during sleep.[26–31] Fig. 56.1 describes the differences

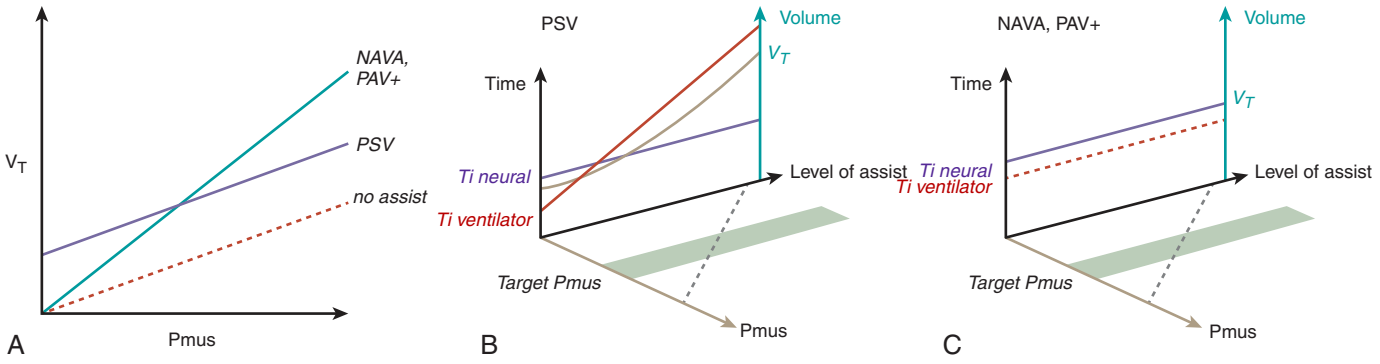

Fig. 56.1 A, The relationship between patient effort (respiratory muscle pressure, *Pmus*) and tidal volume (V_T) in unassisted spontaneous breathing *(dashed line),* during pressure support ventilation (*PSV*) and proportional modes such as proportional assist ventilation with load-adjustable gain factors (*PAV+*) and neurally adjusted ventilatory assist (*NAVA*). **B,** Patient-ventilator interaction during PSV. Increasing the pressure support level increases V_T *(tan line)* and ventilator inspiratory time (Ti, *red line*), whereas patient effort (Pmus, *gray dotted line*) is *downregulated.* In addition, neural Ti *(purple line)* remains unaltered with increasing levels of assist, which results in late cycling. **C,** Patient-ventilator interaction during NAVA and PAV+. Ventilator assist is delivered proportional to the patient's demand over the full inspiratory cycle (neural Ti = ventilator Ti, note that *dashed red and purple lines* overlap). Increasing the inspiratory assist level (NAVA level or PAV+ gain), downregulates Pmus *(gray dotted line).* Because the patient's brain stipulates the desired V_T, changing the level of assist often has only minimal effects on the V_T, as shown by the *horizontal purple line* on the volume vs. level of assist curve. (From Jonkman AH, Rauseo M, Carteaux G, et al. Proportional modes of ventilation: Technology to assist physiology. *Intensive Care Med.* 46[12]:2301–2313.)

that occur in spontaneous breathing, PSV, NAVA, and PAV+ with respect to changes in support level and demonstrates their impact on V_T, level of assistance, and timing.[23]

Proportional modes of ventilation are overwhelmingly associated with improved patient-ventilator interaction and reduced asynchronies compared with PSV.[32–36] NAVA supports respiratory muscle unloading while preventing neuromuscular decoupling.[29] Asynchronies are reduced primarily by a reduction in missed triggers, but NAVA and PAV+ both reduce late cycling by better matching ventilator inspiratory time with neural inspiratory time.[31,33,37] Published studies suggest that preservation of diaphragmatic activity may improve distribution of volume to basilar lung regions, thereby improving gas exchange.[38,39]

Overassistance commonly observed during PSV may be linked to diaphragmatic injury.[40] Proportional modes require maintenance of diaphragmatic contraction throughout inspiration, helping to reduce the risk of this complication. Several studies have shown that proportional modes reduce the risk of overdistention.[29] Leiter and Manning describe the impact of the Hering-Breuer reflex inflation inhibition on downregulation of respiratory drive to avoid hyperinflation.[41] In this instance, Pmus and EAdi are reduced, suggesting an advantage for proportional modes. At increased end-expiratory lung volumes, the diaphragm shortens, and its disadvantaged position results in weaker effort. Patients receiving PAV+ at appropriate gain levels spent >95% of time at a driving pressure <15 cm H_2O and V_T <11 mL/kg. Higher driving pressures are often associated with severely reduced compliance.[42,43] Auto-triggering is also reduced with proportional modes, and in the presence of auto-triggering, delivered pressures and volumes are less when compared with PSV set at customary levels.[44]

The principle of operation of proportional modes reduces the risk of overinflation and ventilator-induced lung injury (VILI) while preventing both disuse atrophy of the diaphragm and excess work that favors fatigue. Jonkman and colleagues suggest caution when using proportional modes in patients with excessive levels of respiratory drive over concern that lung-protective reflexes might be overwhelmed in this scenario.[23] The major advantages of proportional modes are shown in Box 56.1.

Compared with PSV, proportional modes have been reported to reduce weaning duration and increase the chance of the patient continuing to require a patient-triggered mode.[36,45] Faster liberation from mechanical ventilation with proportional modes might be facilitated by reduced asynchronies, improved patient comfort, and fewer sleep interruptions.[36,46–49] Demoule and colleagues demonstrated no differences in weaning duration or other outcomes comparing NAVA with PSV.[50] However, Kacmarek and colleagues reported a randomized controlled trial of patients requiring mechanical ventilation for >72 hours, comparing NAVA with standard lung-protective ventilation. They found that ventilator free-days were increased by 4 days in the NAVA group (22 vs. 18 days), although no differences in mortality or other safety outcomes were identified.[51]

The shortcomings of proportional modes appear to relate to clinician understanding.[35] The interplay of gain and NAVA level on patient effort, Pmus, respiratory rate, and tidal volume is moderately complex are not always understood by bedside clinicians. Appropriate selection of both NAVA level and of gain during PAV+ likely changes with the

BOX 56.1 Potential Advantages of Proportional Modes Compared With PSV

- Avoiding overassistance
- Avoiding excessive V_T and overdistention
- Reducing asynchrony
- Preserving breath-to-breath variability
- Preserving diaphragmatic function—diaphragmatic-protective ventilation
- Facilitate weaning

progression of illness and therefore requires titration. This probably has reduced the adoption of these modes, despite clear advantages regarding synchrony. Additionally, proportional modes require an intact respiratory drive, and poor selection of patient candidates may result in dissatisfaction by clinicians. Monitoring of EAdi, separate of NAVA, may prove useful in titrating other modes of ventilation, a concept that requires further study.

CONTROL OF VENTILATION

A number of modes have been developed to maintain a desired level of minute ventilation and to automatically select ventilation parameters. These include mandatory minute volume, auto-mode, adaptive support ventilation (ASV), and adaptive ventilation mode (AVM).[52–54]

Adaptive Support Ventilation

Adaptive support ventilation is a closed-loop mode of mechanical ventilation designed to titrate ventilator output on a breath-by-breath basis, with the level of ventilatory support determined by respiratory mechanics and breathing effort. The goal of ASV is to provide a preset level of minute ventilation (V_E) while minimizing the work of breathing during ventilator support. Under normal conditions, the minute volume setting is 100% of a "normal" minute volume that is based on predicted body weight of 0.1 L/kg/min. Thus a 70-kg patient would receive a V_E of 7.0 L/min; at a setting of 150%, V_E would be 10.5 L/min.

ASV adjusts inspiratory pressure to achieve a respiratory pattern (V_T and frequency) that minimizes the work of breathing based on the Otis equation.[55] Importantly, however, the range of available V_T is controlled by the maximum pressure (Pmax) setting selected by a clinician. Breaths alternate between pressure-controlled and pressure-supported breaths, based on the presence or absence of spontaneous breathing efforts. Conceptually, ASV can provide synchronized intermittent mandatory ventilation (SIMV) + PSV, but in my experience, breaths are most commonly either all mandatory or all spontaneous. During mandatory breaths, ASV controls the inspiratory time and I:E based on measurement of the expiratory time constant (the product of resistance and compliance). Lower compliance results in a short I:E, whereas high resistance results in a longer I:E to avoid air trapping. ASV requires the clinician to set levels for FiO_2 and PEEP.

Clinical Studies of ASV

ASV can be used during the initiation, maintenance, and weaning of mechanical ventilation. It has been used in a number of studies evaluating time to discontinuation of ventilatory support after coronary artery bypass surgery.[56–63] Studying this large, relatively homogeneous, readily available population is attractive; however, this population requires ventilation primarily as a "casualty of anesthesia" and under normal circumstances has limited pulmonary dysfunction. Studies report faster weaning in half of the trials and no change in the other half. Of note, these studies find that ASV required fewer clinician/ventilator interventions, fewer arterial blood gases, and fewer ventilator alarms and reduced the incidence of postoperative atelectasis on radiograph.[63]

Choosing the appropriate minute volume target to promote weaning in this scenario has not been extensively studied and requires clinician input.[64–67] The selected V_T during ASV can exceed lung-protective limits, and the potential for VILI after surgery is a concern.[67]

Several recent trials have evaluated ASV for weaning patients with acute respiratory failure off machine support. Chen and colleagues reported their experience with ASV in a 16-bed ICU in China staffed daily by a single respiratory therapist with no coverage at night.[68] They compared management of patients with ASV with a matched historical control using SIMV + PSV. Under these rather unique circumstances the authors demonstrated that patients in the ASV group achieved extubation readiness within 1 day of enrollment more often and achieved weaning within 21 days. However, there were no differences in ICU duration or hospital stay. These findings must be considered in light of the staffing model. However, one potential advantage of closed-loop ventilation is the ability to continue appropriate care in the absence of caregivers, and this study seems to support this thesis. Recent findings during the COVID-19 pandemic suggest that in a situation where large numbers of patients with ARDS are managed by too few caregivers, the use of ASV might improve safety and efficacy of ventilatory support, especially during a surge.[69]

Kirakli and colleagues compared ASV with PSV for weaning chronic obstructive pulmonary disease (COPD) patients from ventilation.[70] They found that patients ventilated with ASV had shorter weaning times and equivalent weaning success. However, the total duration of ventilatory support did not change. The use of ASV has been reported for weaning after recovery from acute respiratory failure and after liver transplantation.[71]

ASV has been successfully used as a primary mode of ventilator support during acute respiratory failure. The algorithm, which was based on the expiratory time constant, was shown to select I:E and respiratory frequency appropriately for both obstructive and restrictive disease. Certain reports have found a reduction in manual ventilator adjustments with similar gas exchange and perhaps improved CO_2 elimination for a given combination of V_T and respiratory frequency.[72–74] Patients with obstructive disease, however, have received V_T levels outside the suggested range of current "lung-protective" guidelines.

One criticism of ASV has been the finding that V_T may approach 9–10 mL/kg in some patients.[65,75] This limitation can be overcome by appropriately setting the Pmax and V_T limits. ASV has been commercially available for over 20 years, and widespread adoption has not occurred. Although ASV may facilitate weaning when the % minute volume value is appropriately set, it appears to have no clear advantage over manual techniques. Closed-loop techniques can reduce practice variation through appropriate selection of "hard rules," such as a Pmax chosen by the operator. I have previously argued that techniques like ASV may provide the most benefit in resource-limited environments, and the work by Chen and colleagues and Wendel-Garcia and colleagues appears to support this opinion.[68,69]

Adaptive Ventilation Mode

Adaptive ventilation mode is a modification of ASV on a new ventilator platform. It includes the traditional determination of % minute volume, but also includes automated titration of rise time and flow termination of pressure support breaths. A modified version, AVM 2, differs from ASV in that rather than determining the optimal frequency and V_T based on values observed in spontaneously breathing patients, AVM 2 determines the optimal variables based on assisted ventilation. In a bench and model study, AVM 2 was associated with lower driving pressure and power.[76] Clinical trials are not currently available.

iASV

Intellivent ASV (iASV) is the logical extension of ASV to include the automated selection of FiO_2 and PEEP. The PEEP/FiO_2 controller uses the PEEP tables from the ARDS Network's Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome (ARMA) and Assessment of Low tidal Volume and elevated End-expiratory volume to Obviate Lung Injury (ALVEOLI) trials. The ARMA trial

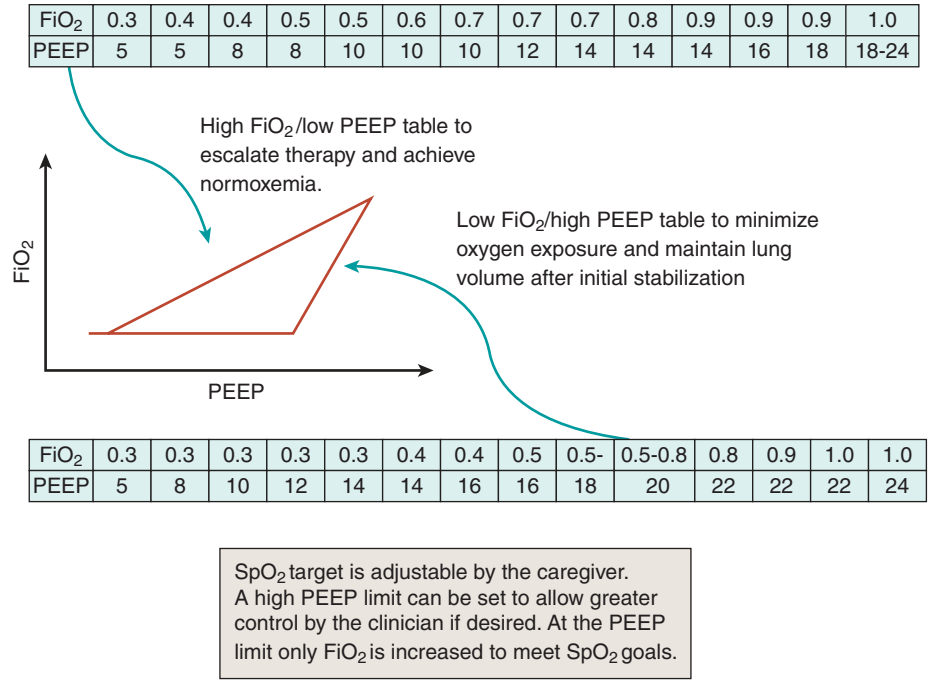

Fig. 56.2 Combination of the PEEP-FiO_2 tables from the ARDSnet ARMA and ARDSnet ALVEOLI trials used for increasing and decreasing oxygenation support during iASV. *iASV,* Intellivent adaptive support ventilation; *FiO_2,* fraction of inspired oxygen; *PEEP,* positive end-expiratory pressure; *SpO_2,* blood oxygen saturation. (From Branson RD. Modes to facilitate ventilator weaning. *Respir Care.* 2012;57[10]:1635–1648.)

used an aggressive FiO_2 strategy, whereas the ALVEOLI trial was PEEP-intensive. An integral pulse oximeter provides the input signal to the ventilator, into which the clinician can set the desired blood oxygen saturation (SpO_2). Pulse volume variability from the oximeter can also provide information regarding patient hemodynamic status, limiting the use of PEEP in favor of FiO_2 during hemodynamic compromise. As of 2021, Intellivent is not commercially available in the United States.

The minimum PEEP is 5 cm H_2O, and at initiation the controller uses the ARMA PEEP/FIO_2 table to reach the desired SpO_2. After stabilization, the FiO_2 and PEEP are weaned using the ALVEOLI table. Fig. 56.2 provides a pictograph of the PEEP/FiO_2 tables used with Intellivent.

Clinical Studies of iASV

In a preliminary trial of sedated patients with acute respiratory failure, Arnal and colleagues demonstrated that during a 2-hour crossover trial, iASV provided ventilation at lower airway pressures, tidal volumes, and FiO_2 while producing the same oxygenation results as ASV.[77] Tidal volumes were slightly lower with iASV and $PaCO_2$ was higher. In a follow-up crossover trial, iASV applied for 24 hours compared with PSV demonstrated improved oxygenation. In this study, PEEP was higher and more variable during iASV, as one might expect.[78] The authors suggested that the bio-variability of PEEP might explain the improved oxygenation. De Bie and colleagues demonstrated fewer hypoxemic events in subjects after coronary bypass and quicker return to spontaneous breathing with iASV.[79]

Clavieras and colleagues applied iASV in a wide range of patient populations ventilated for <24 hours and found that ventilator settings were selected appropriately based on the lung condition, particularly in passive patients. However, like traditional ASV, spontaneously breathing subjects (breathing with adaptive pressure support) have less variability in volume and pattern.[80] A randomized trial of iASV compared safety and efficacy with modes chosen by the attending physician as the time spent within previously defined ranges of nonoptimal and optimal ventilation. Interestingly, iASV was more likely to be in the suboptimal range for Pmax. As in previous trials, iASV made more manipulations but required fewer clinician interactions, and the variability of volumes and airway pressures were greater.[81] Fot and colleagues evaluated iASV compared with protocolized weaning and SIMV + PSV after coronary bypass grafting. They found that iASV and protocolized weaning had similar outcomes and shortened weaning compared with traditional methods. The authors noted the reduction in clinician interaction with the ventilator, but no other advantages.[82] Arnal and others compared iASV with either PSV or VC-CMV in 60 subjects with respiratory failure. They concluded that iASV reduces the number of manual ventilator setting changes with no difference in the number of arterial blood gas analyses or sedation use. Using a Likert scale, caregivers rated iASV as easier to use compared with conventional ventilation modes.[83] More recently, Arnal and colleagues demonstrated that across a wide variety of patients, iASV provided a lower driving pressure and lower mechanical power than traditional ventilation.[84] Work by Buiteman-Kruizinga and colleagues confirmed this finding.[85,86]

Smartcare PS

SmartCare PS describes control of PSV where the pressure support level is based on the patient's V_T, respiratory frequency, end-tidal carbon dioxide ($ETCO_2$), and a series of presets based on the patient condition (e.g., presence of COPD or neurologic injury). SmartCare PS adjusts pressure support to maintain the patient in a "normal" range of ventilation, which is typically defined as a V_T 300 mL, a respiratory frequency between 12 breaths/min and 30 breaths/min, and $ETCO_2$ <55 mm Hg (this can be adapted for subjects with COPD or neurologic injury). Outside of the normal range, SmartCare PS defines other conditions and manipulates the pressure support based on the

current value, the clinician input parameters, and the patient's historical breathing pattern. SmartCare PS is intended for weaning and therefore not used clinically for the supported phase of acute respiratory failure.[11]

Clinical Studies of Smartcare PS

Introduced in 1996, SmartCare PS has been evaluated in a number of weaning trials.[87–92] The original trial simply compared the duration of ventilation in the specified ranges of comfort with clinician-selected PSV. This study found that SmartCare PS maintained patients in the clinician-desired ranges far more frequently.[89] In 2006 Lellouche and coauthors published the first and largest randomized trial compared with traditional weaning in five European centers. This report found significantly shorter weaning times with SmartCare PS compared with traditional weaning. However, in at least two centers, spontaneous breathing trials were not used in the control arm.[87] This may be viewed as a limitation of the study, but does represent a pragmatic trial. Across the world, the use of protocolized weaning clinical practice guidelines are espoused but not routinely implemented.

Subsequent trials of SmartCare PS have found both advantage and no advantage compared with traditional weaning based on patient condition (sepsis vs. COPD vs. cardiac surgery), the type and staffing of ICU, and patient age (adults vs. pediatrics).[93,94] Cochrane reviews of automated weaning routinely find that automated weaning demonstrates approximately a 30% reduction in weaning time compared with traditional weaning. However, the lack of standards in the control arms of trials, trial heterogeneity, and small numbers limit the strength of these conclusions.[91,95] Large multicenter trials are still needed to determine the value of SmartCare PS in routine practice.

Automated Control of Inspired Oxygen

Despite being initially described in neonates nearly 50 years ago, closed-loop control of inspired oxygen is not Food and Drug Administration (FDA) approved.[96] iASV includes closed-loop control of FiO_2 with and without PEEP control. Claure and others introduced a closed-loop FiO_2 system for neonates over two decades ago.[97] The system is a negative feedback controller that adjusts the FiO_2 in an effort to maintain the set SpO_2 target. Numerous studies have demonstrated reduced numbers and durations of desaturation events, less frequent hyperoxemia, and reduced staff burdens in the neonatal intensive care unit (NICU).[98–106] In the NICU, where the consequences of both hyperoxemia and hypoxemia have been known for decades, the introduction of closed-loop control of FiO_2 is overdue.

In adults, automated FiO_2 control has also been shown to reduce hyperoxemia, reduce the duration of hypoxemia, reduce clinician interventions, and conserve oxygen resources.[107]

Concerns with Automated Control of Ventilation

Automation of mechanical ventilation offers a number of advantages, as previously described. The potential disadvantages are less frequently discussed but require additional research. As an example, if the ventilation system increases PEEP and/or FiO_2 rapidly in response to hypoxemia and prevents the typical desaturation events that routinely alert caregivers to worsening lung function, this must be communicated to the staff. Increases in PEEP and airway pressures that may result in hemodynamic compromise also require additional safety measures. As clinicians, we consider heart rate, blood pressure, filling pressures, vasopressor therapy, and fluid status during manipulation of mean airway pressures. At present, no ventilation system has the ability to include these additional inputs into the ventilator decision process. It may be that limiting PEEP is needed and that increases beyond a certain value (e.g., to <12 cm H_2O) must be approved by a clinician with knowledge of hemodynamic performance and current therapy.

As seen with several of these techniques, certain situations can result in excessive V_T and pressure delivery, perhaps leading inadvertently to VILI. Alarm settings and alert settings require additional enhancements.

CONCLUSION

Simple closed-loop control of mechanical ventilation is widely deployed and operates behind the ventilator interface. More complex systems, described as intelligent control, are commercially available but have yet to gain widespread acceptance.[108] New trials demonstrating cost/benefit advantages that accrue to automated ventilation are required. Simply reducing the number of caregiver interactions is not an advantage for the patient or the staff. In fact, automated systems causing lack of situational awareness of the ICU are a concern. Along with these autonomous systems, monitoring and displays that easily inform the staff of the patient's current condition and response to therapy are required. Alert notifications for sudden escalation of therapy are required to assure patient safety.

The use of automated ventilation clearly has utility in remote settings that lack the timely input of experts. There are over 1000 critical access hospitals in the United States, most with fewer than 50 beds, that are the entry point to the healthcare system in rural America. These hospitals typically lack ICUs, trained onsite critical care providers, and respiratory care expertise. Remote care in disaster and military medicine is another area where local expertise may not match the severity of patient illness. These environments represent a natural fit for automated ventilation. Experiences from the COVID-19 pandemic will further expand the use of automated systems. Whether automated ventilation will be accepted in large academic medical centers remains to be seen.

KEY POINTS

- Closed-loop control modes of mechanical ventilation modify ventilator output based on respiratory mechanics and gas exchange variables.
- Automated control of ventilation and oxygenation can provide safe and effective ventilatory support while maintaining evidence-based lung protection.
- Disadvantages of automated modes include loss of situational awareness and reduced attention by caregivers.
- Automated modes of ventilatory support have been shown to reduce the interaction of caregivers and ventilator, perhaps decreasing workload, but this has not been demonstrated as a patient benefit.
- In the absence of expert oversight, automated ventilatory support may improve safety.
- Automated control of inspired oxygen has been demonstrated to reduce the incidence of hypoxemia and hyperoxemia in infants and adults.
- Closed-loop control of PEEP poses challenges related to ongoing assessment of hemodynamics.
- Closed-loop systems, including NAVA and PAV have been demonstrated to reduce asynchrony.

References for this chapter can be found at expertconsult.com.

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Chatburn RL, El-Khatib M, Mireles-Cabodevila E. A taxonomy for mechanical ventilation: 10 fundamental maxims. *Respir Care*. 2014;59(11):1747–1763.
This paper provides a cogent scheme for classifying modes of mechanical ventilation with particular attention to automated systems. It is clear that one of the largest impediments to the introduction of new techniques is lack of understanding by bedside clinicians. Automated systems, by virtue of frequent automated titration, can further distance the staff from the settings. The paper suggests a change in paradigm, focusing on the current response of the patient versus the settings on the ventilator.

Claure N, Bancalari E. Targeting arterial oxygen saturation by closed-loop control of inspired oxygen in preterm infants. *Clin Perinatol*. 2019;46(3):567–577.
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Goligher EC, Jonkman AH, Dianti J, et al. Clinical strategies for implementing lung and diaphragm-protective ventilation: Avoiding insufficient and excessive effort. *Intensive Care Med.* 2020;46(12):2314–2326.
Excellent review of the causes and prevention of Ventilator induced diaphragmatic dysfunction (VIDD). The impact of ventilator mode and breath type, in addition to controlling patient effort, is detailed. The role of proportional modes of support, including theoretical and realized advantages, are provided.

Jonkman AH, Rauseo M, Carteaux G, et al. Proportional modes of ventilation: Technology to assist physiology. *Intensive Care Med.* 2020;46(12):2301–2313.
This paper is an extensive and detailed review of PAV+ and NAVA. Important specifics on setting and monitoring ventilator and patient parameters are detailed. Proportional modes are compared with pressure support ventilation, and the impact on asynchrony, comfort, and the risk of lung/diaphragmatic injury are reviewed.

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Weaning from Mechanical Ventilation

Ferran Roche-Campo, Hernán Aguirre-Bermeo, and Jordi Mancebo

THE CONCEPT OF LIBERATION AND EXTUBATION

Weaning from mechanical ventilation refers to the transition period from total ventilatory support to spontaneous breathing. Approximately 70% of intubated mechanically ventilated patients are extubated after the first spontaneous breathing trial (SBT), either by ventilator disconnection or after breathing at low levels of pressure support for short periods ranging from 30 to 120 minutes.[1,2] The remaining patients (about 30%) require progressive withdrawal from artificial ventilatory support. In half of these patients, mechanical ventilation can be withdrawn in less than 1 week; however, the other half of patients require more than 1 week of mechanical ventilation. Importantly, in this latter group, the prognosis is markedly worse.[3,4]

Early liberation from mechanical ventilation and removal of the endotracheal tube is clinically important. Unnecessary prolongation of mechanical ventilation increases the risk of complications, including infections (particularly of bronchopulmonary origin), barotrauma, cardiovascular compromise, tracheal injuries, and muscle deconditioning. To maximize patient outcomes, clinicians should attempt to hasten the process that ultimately leads to removal of the endotracheal tube.[5] Every additional day that passes after the first weaning attempt increases the risk of death.[3]

Liberation and extubation are different concepts.[6] Liberation refers to weaning from mechanical ventilation, meaning that the patient no longer requires ventilatory support. When liberation has been achieved, the clinician must consider a different question: "Is the patient able to breathe spontaneously and protect the airway without the endotracheal tube?" Removal of the endotracheal tube is referred to as *extubation.* The extubation failure rate is variable, ranging from 5% to 20% of extubated patients.[1,7–9]

MECHANISMS THAT EXPLAIN LIBERATION FAILURE

Respiratory Pump Failure

The most common reason for weaning failure is respiratory pump insufficiency, which is caused by an imbalance between the patient's endurance capabilities and respiratory demands.[10–13] Jubran and Tobin[14] investigated the progression of respiratory mechanics during SBT in patients with chronic obstructive pulmonary disease (COPD). At the very beginning of the trials, patients who subsequently failed had a slightly higher airway resistance, respiratory system elastance, and intrinsic positive end-expiratory pressure (PEEP) compared with those who succeeded. However, during the trials, respiratory mechanics progressively worsened in patients who failed to achieve ventilator liberation. Subjects who failed quickly developed rapid, shallow breathing, and most also developed (but more slowly) an increase in partial pressure of carbon dioxide ($PaCO_2$). Together, these abnormalities of mechanics and chemical drive resulted in increased inspiratory muscle effort. Breathing exertion was likely close to the threshold of muscle fatigue in some patients.

Laghi and Tobin[15] studied 19 intubated patients during weaning from mechanical ventilation; of these, 11 patients failed and 8 succeeded. Several physiologic indices were measured before and 30 minutes after SBT. Before the SBT, the transdiaphragmatic twitch pressure, elicited by magnetic bilateral phrenic stimulation, did not differ between the patients who failed or succeeded at ventilator liberation, and this variable did not decrease after the trial in either group. Patients failing the SBT were reconnected to the ventilator because of clinical signs of intolerance. It was concluded that weaning failure was not accompanied by low-frequency diaphragmatic fatigue. Weaning failure patients did, however, exhibit severe diaphragmatic weakness, because twitch pressures were always low.

Common Disorders That Alter the Balance of Capacity and Load in Critical Illness

Reduced Neuromuscular Capacity and Reserve

Traditionally, peripheral muscular dysfunction—known as *critical illness polyneuropathy*—was associated with difficult weaning.[16] However, in recent years, respiratory muscle dysfunction (mainly the diaphragm)—known as *critical illness–associated diaphragm weakness*[17]—is a condition whose existence has become recognized and its properties better characterized. We now know that respiratory muscle dysfunction is independent of peripheral polyneuropathy and twice as prevalent (present in up to 60% of ventilated patients), exerting a greater impact on weaning.[18] Diaphragm weakness is mainly associated with muscle disuse or a low level of effort associated with controlled ventilation modalities,[19] but it has also been associated with a high breathing effort because of insufficient respiratory assistance.[20] The optimal balance between diaphragm overuse and underuse is difficult to determine. However, it stands to reason that the appropriate level of assisted ventilation could prevent diaphragm atrophy.[21]

Increased Muscle Loads

The increased work of breathing results from increased mechanical loads (elastic and/or resistive). Increased elastic workloads occur when lung and chest wall compliance are reduced (e.g., pulmonary edema, extreme hyperinflation during an acute asthmatic attack, pulmonary fibrosis, abdominal distention, severe obesity, trauma, or thoracic deformities).[15] The presence of intrinsic PEEP is another example of increased elastic workload, and this phenomenon is relatively common, especially in patients with COPD.[22,23] Resistive work of breathing during critical illness may increase as a result of bronchospasm, excessive secretions, endotracheal tube resistance (which increases with kinking and deposition of secretions), and ventilator valves/circuits and

humidifiers, especially when conditioning of inspired gases is provided with heat and moisture exchangers. The latter also increase the dead space posed by the external apparatus.

CARDIOVASCULAR DYSFUNCTION

The presence of cardiovascular dysfunction can contribute to weaning failure by augmenting the loads on the respiratory system and reducing neuromuscular capacity.[24,25] Cardiovascular dysfunction can result from physiologic changes that occur during the resumption of unassisted spontaneous breathing.[26] When spontaneous breathing resumes, the intrathoracic pressure during inspiration is negative, leading to increased left ventricular preload and afterload. Increased heart loads augment myocardial oxygen demand and may precipitate myocardial ischemia in patients with coronary artery disease.[27] Pulmonary vascular congestion may also increase.

Jubran and colleagues[28] examined hemodynamics and mixed venous saturation in patients during weaning trials. Successfully weaned patients demonstrated increases in the cardiac index and oxygen transport compared with values observed during mechanical ventilation. Patients who failed weaning did not increase oxygen delivery to the tissues because, in part, of elevated right and left ventricular afterloads. Consequently, these abnormalities have the potential to jeopardize respiratory muscle function.

In intensive care unit (ICU) patients, congestive heart failure in predisposed patients may occur as a consequence of an increase in venous return, volume overload, or catecholamine release induced by physiologic stresses, such as weaning. Impairment of cardiovascular function can be magnified in cases with a positive fluid balance.[29]

Studies have shown that using a T-tube (instead of pressure support and PEEP) to perform an SBT in difficult-to-wean patients may elicit an adverse cardiovascular response; when support is added (in the form of pressure support and PEEP), respiratory and cardiovascular function both improve.[30]

In the ICU setting, noninvasive tools are available (e.g., echocardiography and measurement of plasma B-type natriuretic peptide [BNP]) to help diagnose cardiovascular dysfunction. Up to 50% of patients who fail a weaning test exhibit cardiogenic pulmonary edema (based on BNP measurements and/or echocardiography), which is more common in patients with COPD and in patients with underlying cardiac dysfunction.[31]

Mekontso-Dessap and colleagues showed that BNP-guided administration of diuretics can reduce weaning time, particularly in patients with left ventricular systolic dysfunction.[32] That same group of authors has also shown that isolated diastolic dysfunction may be associated with a longer weaning time and increased filling pressures, with impaired left ventricular relaxation potentially being a key mechanism for failure of the weaning trial.[33]

PREDICTION OF WEANING AND EXTUBATION OUTCOMES

Yang and Tobin[34] studied the predictive power of several weaning indices, finding that the rapid shallow breathing index (f/VT) had the best predictive value. In their study, 95% of patients with an f/VT ratio >105 failed an SBT. The rapid shallow breathing index appears to be the most useful bedside method of screening for liberation readiness. If the f/VT value is less than 105, then an SBT of 30–120 minutes should be used to confirm the patient's capacity to breathe spontaneously without assistance. However, because the f/VT has a low specificity (the test is positive in a relatively large proportion of weaning failure subjects), the f/VT alone is insufficient to predict weaning failure. From a practical point of view, the information conveyed by weaning indices and clinical judgment should be considered together in making clinically important decisions regarding extubation.

Patients incapable of protecting their airway and clearing secretions with an effective cough are at an increased risk of extubation failure. Traditional assessment has consisted of demonstrating a cough reflex when the airways are stimulated with a suction catheter and by the absence of excessive secretions. Smina and colleagues[35] found that patients with a peak expiratory flow equal to or below 60 L/min were five times more likely to have an unsuccessful extubation than patients with expiratory flows greater than 60 L/min.

EXTUBATION FAILURE

Extubation failure can be defined as the need to reintubate and reinstitute ventilatory assistance within the first 24–48 hours and up to 7 days afterwards. The reintubation rate ranges from 10% to 20%.[3,7]

Mechanisms explaining extubation failure include the presence of abnormalities not diagnosed at the time extubation was performed (e.g., pneumonia, unaddressed cardiac dysfunction, or new arrhythmia precipitated by the physiologic stress that accompanies spontaneous breathing effort) and the inability to maintain the tracheobronchial tree free of copious secretions.[9,36,37]

Extubation failure results in a marked increase in the duration of mechanical ventilation, ICU and hospital stay, need for tracheostomy, and hospital mortality.[3,7,9,38–40] Further studies are needed to understand and detail the pathophysiologic mechanisms of extubation failure.

PROGRESSIVE WITHDRAWAL OF MECHANICAL VENTILATION

When patients fail SBTs, pressure support ventilation (PSV) is the modality most often used for the progressive withdrawal of mechanical ventilation.[4,41] Two prospective multicenter randomized clinical trials have shown that the implementation of synchronized intermittent mandatory ventilation (SIMV) is generally less efficacious than other techniques.[1,2]

Sedation and analgesia are important components of care for mechanically ventilated patients. An important study found that daily interruption of sedation significantly reduced the duration of mechanical ventilation.[42] Because sedation and weaning from mechanical ventilation cannot be separated from one another, the results are more effective when these two strategies are combined (i.e., daily interruption of sedation plus systematic use of SBTs) to hasten liberation from the ventilator than when used separately.[43]

PRESSURE SUPPORT VENTILATION

Clinical experience[1,2] and data from clinical trials[44,45] suggest that the "optimal" initial levels for PSV are those that provide respiratory rates between 25 and 30 breaths/min. In this setting, it is particularly important to rule out the existence of asynchronous breathing or ineffective respiratory efforts. A ventilator setting with an unnecessarily high level of pressure support can be the cause of patient–ventilator dyssynchrony. Patients who show ineffective triggering are on mechanical ventilation for longer periods, and tracheostomy is also more often indicated in these patients.[46] A subsequent study found a decrease in the number of ineffective respiratory efforts without changes in the work required for breathing and without modifications in the respiratory rate when pressure support levels were reduced.[47] These studies[46,47] indicate that some patients receive excessive levels of mechanical ventilation during the weaning process. These findings are vital, because they indicate that there are modifiable causes (i.e., excessively high levels of assistance) of detrimental patient–ventilator interactions.

The level of external PEEP used in patients with clinically suspected dynamic hyperinflation and dynamic airway collapse should be adjusted with great caution, because the measurement of dynamic intrinsic PEEP in spontaneously breathing patients is not easily performed. To that end, it has been suggested that external PEEP can be titrated according to the changes in airway occlusion pressure.[48]

During weaning, the PSV levels are decreased according to the patient's clinical tolerance, usually by steps of 2–4 cm H_2O at least twice a day. In general, clinical tolerance to a level of PSV of about 8 cm H_2O without PEEP is required before performing extubation, although this level may vary according to a given patient's overall clinical status and endotracheal tube diameter.

NEW MODALITIES

Several novel weaning modalities have been examined, including those that use closed-loop PSV[49–51] or proportional modes, such as proportional assist ventilation (PAV),[52,53] to provide a continuous adaptation of ventilator assistance to the patient's needs 24 hours a day.

Lellouche and colleagues examined automated weaning with the semi-closed-loop PSV system in two groups of patients during the weaning period.[54] In the control group, weaning was performed as per usual care based on written weaning guidelines. In the study group, weaning was performed using a computer-driven weaning protocol. In the study group, weaning time was significantly shorter compared with usual weaning (3 vs. 5 days; $P = .01$). This decrease in weaning time was associated with a decrease in both the total duration of mechanical ventilation (7.5 vs. 12 days; $P = .003$) and ICU length of stay (12 vs. 15.5 days; $P = .02$).

A subsequent study by Rose and colleagues[55] comparing weaning duration with a semi-closed-loop mode versus usual care (weaning managed by experienced specialized critical care nurses using a 1:1 nurse-to-patient ratio) found no differences between the two strategies. Schadler and colleagues[56] found that the semi-closed-loop system decreased the duration of mechanical ventilation in a specific subgroup of patients (cardiac surgery). Finally, a study by Burns and colleagues[57] compared automated weaning with the semi-closed-loop mode versus a standardized protocol in critically ill patients, finding that patients on automated weaning had significantly shorter median times to first successful SBT (1 day vs. 4 days; $P < .001$) and to successful extubation (4 days vs. 5 days; $P = .01$).

In the meta-analysis carried out by Burns and colleagues, the authors concluded that, compared with nonautomated weaning strategies, weaning with semi-closed-loop PSV significantly decreased weaning time without increasing the risk of adverse events.[58] A pilot study compared PAV with conventional PSV and found that PAV is both safe and feasible.[59]

Despite these positive results, in actual clinical practice, the use of these techniques remains quite limited and their success largely a matter of operator skill and familiarity.[4]

SPONTANEOUS BREATHING WITH A T-TUBE

Tolerance to breathing through a T-tube represents a good test to evaluate a patient's capacity to maintain autonomous, spontaneous breathing.[60] The optimal duration of a T-tube trial is at least 30 minutes and no more than 120 minutes.

One disadvantage of the T-tube trial is related to the absence of a connection to a mechanical ventilator. Because patients are not monitored by the alarms on the ventilator, they need to be closely supervised. Moreover, the unassisted breathing through the resistance of the endotracheal tube is a "stress test" for the cardiorespiratory system that, although informative, may itself predispose to weaning failure.

Fernandez et al.[61] showed that in patients who successfully passed the SBT, reconnection to mechanical ventilation for 1 hour, using the same parameters in place before the SBT, significantly reduced reintubation rates in the 48 hours after extubation (5% vs. 14%).

Traditionally, SBTs with pressure support or a T-tube have been considered suitable methods for evaluating a patient's capacity for spontaneous breathing.[7] Nevertheless, Subirà and colleagues recently compared the relative effects of an initial SBT consisting of 30 minutes of PSV with 8 cm H_2O (a less-demanding approach for the patient) to an SBT consisting of 120 minutes of T-tube (a more-demanding approach), finding that the less-demanding strategy resulted in higher rates of successful weaning.[62] These data support the view that in most patients (80%) who are extubated in the first SBT, 30 minutes of PSV may be sufficient to identify those who present a high probability of successful extubation. This concept may hold true in patients whose pretest likelihood suggests a high probability of successful extubation.[63] However, we believe that the use of T-tube weaning trials in difficult-to-wean patients should be considered as an alternative to PSV that induces greater changes in the breathing pattern, inspiratory muscle effort, and cardiovascular response than T-tube in this fragile population.[30]

VENTILATORY SUPPORT AFTER EXTUBATION

Noninvasive Ventilation and High-Flow Nasal Cannula

As discussed earlier, extubation is a crucial event in the management of patients on mechanical ventilation, and extubation failure is associated with higher mortality.[36] Numerous studies published in recent years have evaluated the use of noninvasive ventilation (NIV) and high-flow oxygen therapy as measures to facilitate extubation.

From a practical point of view, there are two different ventilatory support strategies. The first is a facilitative strategy, which permits early extubation in patients who meet criteria for an SBT but who do not pass the test. The second is a preventive strategy, aimed at preventing the emergence of post-extubation respiratory failure. Fig. 57.1 shows our proposed algorithm for ventilatory support.

1. Facilitative Strategy

Currently, NIV is the only approach recommended to facilitate early extubation in selected patients with hypercapnic respiratory failure, and it should only be applied in centers with experience with this technique.

Examples of patients suitable for NIV include those with acute-on-chronic respiratory failure who present with hypercapnia at the end of the weaning test. Various studies have shown that the early application of NIV to facilitate extubation in this patient population reduces the duration of invasive ventilation without increasing the reintubation rate, and it may even reduce mortality rates.[64–66]

At present, there are no firm recommendations on the facilitative use of NIV or high-flow nasal oxygen (HFNO) in patients with non-hypercapnic respiratory failure. Perkins and colleagues, in a group of patients with difficulty weaning and a failed SBT, compared two different approaches: (1) NIV with early extubation (despite the failed SBT) and (2) continued invasive mechanical ventilation until patients were able to pass the SBT.[67] Those authors found that early extubation with NIV did not reduce ventilation time (4.3 vs. 4.5 days in the invasive group, adjusted hazard ratio 1.1; 95% confidence interval [CI], 0.89–1.40). Despite the negative results of this study, these findings imply the wisdom of a change in the current paradigm under which patients who fail to pass an SBT should remain intubated. No studies have been conducted with HFNO in these conditions, but we can expect that such a study will performed in the near future.

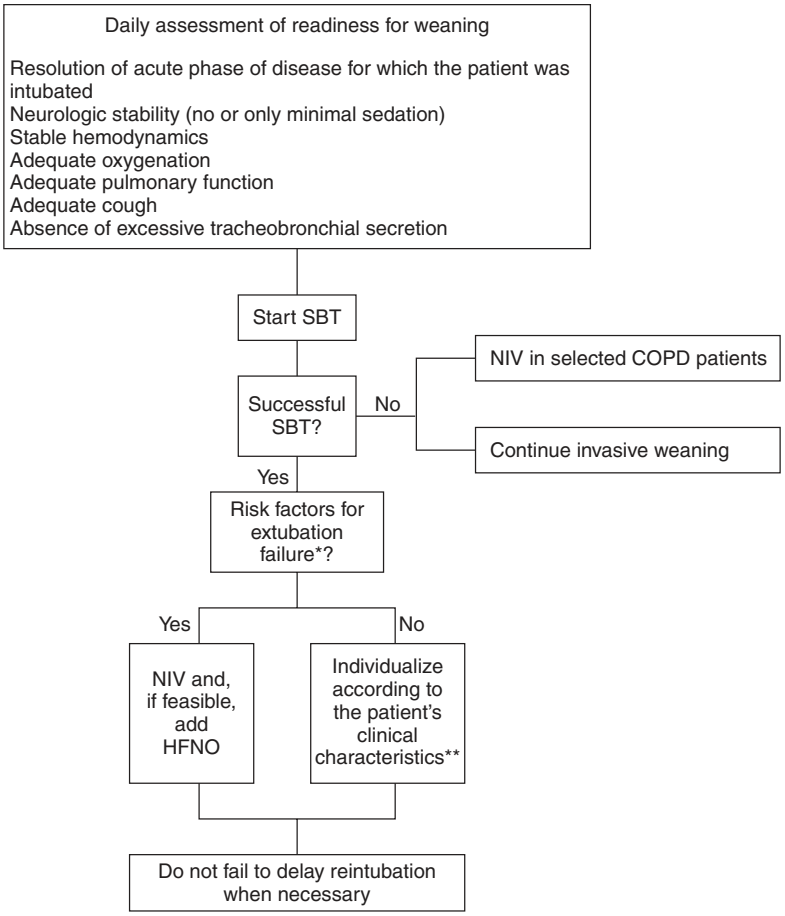

Fig. 57.1 Algorithm for Ventilator Support After Extubation in Critically Ill Medical Patients.
*Risk factors for extubation failure:
– Older than 65 years of age OR
– Presence of any underlying chronic cardiac disease (left ventricular ejection fraction ≤45%; history of cardiogenic pulmonary edema; documented ischemic heart disease; permanent atrial fibrillation).
– Presence of any underlying lung disease (chronic obstructive pulmonary disease; obesity hypoventilation syndrome; restrictive pulmonary disease).
A patient with pancreatitis and fraction of inspired oxygen (FiO_2) 40% is **NOT the same as a simple post-operative patient after 48 hours of ventilation.
COPD, Chronic obstructive pulmonary disease; *HFNO,* high-flow nasal oxygen; *NIV,* noninvasive ventilation; *SBT,* spontaneous breathing trial.

2. Preventive Strategy

In low-risk patients (under age 65 and/or with no underlying respiratory or cardiac pathology), there is evidence that high-flow oxygenation can prevent reintubation. Hernández and colleagues[68] conducted a randomized multicenter trial to compare the efficacy of 24 hours of high-flow versus conventional oxygen therapy after extubation and demonstrated that patients who received HFNO had a lower reintubation rate (5% vs. 12%, $P = .03$). The 12% reintubation rate in the control group in that study is surprisingly high for this population of low-risk patients, which is why we believe that it is premature to recommend the routine use of HFNO for all patients post-extubation. Confirmatory trials will be necessary.

In high-risk patients (older than age 65 or with any underlying chronic heart or lung disease), numerous studies have shown that NIV applied immediately after extubation reduces reintubation rates, which is why this approach is absolutely recommended for this patient population.[65,66,69,70] However, not all patients are able to tolerate NIV well. In this context, HFNO is an alternative strategy proven to be noninferior to NIV in preventing reintubation in high-risk patients.[68] Recently, Thille and colleagues[71] showed that NIV combined with HFNO for ≥48 hours is more effective than HFNO alone in reducing reintubation rates at day 7 (12% vs. 18%, $P = .02$).[71] The results of that study demonstrate, once again, the importance of NIV in at-risk patients and suggest that HFNO could be a complementary treatment that works synergistically with NIV.

CLASSIFICATION OF WEANING

A consensus conference on classification[72] defined three groups of weaning patients: (1) simple weaning (patients who proceed from initiation of weaning to successful extubation on the first attempt); (2) difficult weaning (patients who fail initial weaning and require up to 7 days from the first SBT to achieve successful weaning); and (3) prolonged weaning (patients who require more than 7 days from the first SBT to achieve successful weaning).

The objective of this classification system was to provide greater epidemiologic insight into the weaning process and its association with outcomes.[72] The simple weaning group represents 60%–70% of ventilated patients, whereas the difficult group accounts for 20%–25% of patients, and the prolonged group 5%–15% of patients.[73] Several

studies[74–78] have evaluated this classification system and the distribution of the groups, showing that simple weaning is the most common scenario and that prolonged weaning is associated with poorer outcomes.

Nevertheless, this simple classification system was not designed specifically for this purpose, nor does it tell us exactly what occurs in all patients who receive invasive mechanical ventilation. The WIND study[3]—a prospective, multinational, multicenter study—was designed to answer these questions. The WIND study included all patients on ventilation during a 3-month period, finding that 24% of these patients did not even start the weaning process. The authors classified the remaining patients into three different groups, as follows: simple weaning, comprising the 57% of patients who completed weaning in the first 24 hours; difficult weaning, consisting of the 10% of patients who experienced weaning difficulties lasting more than 1 day but less than 7 days; and prolonged weaning, which included the remaining 9% of patients, who presented with prolonged weaning (>7 days). The ICU mortality rates in the three groups were, respectively, 6%, 17%, and 29%. Clearly, the patients in the third group represent a special population that requires more hospital resources, and a different approach to weaning is probably necessary in these patients.

SUMMARY

The vast majority of intubated mechanically ventilated patients can be successfully liberated from the ventilator after passing an SBT. The best strategy to shorten the total time on mechanical ventilation is a simple clinical approach applied daily to determine the patient's ability to tolerate unassisted spontaneous breathing. Under this approach, at least one daily screening test should be performed, the first early in the day; if this test is positive, then a confirmatory SBT (30–120 minutes in duration) should be performed. In patients who fail multiple SBTs, different techniques for progressive withdrawal of mechanical ventilation can be applied. In this scenario, the most common technique is PSV. Automated systems seem to perform at least as well as usual care, and may even perform better. NIV and HFNO may be useful to hasten the weaning process and avoid reintubation in selected populations. Patients with a long weaning duration (>7 days from the first SBT) have poorer outcomes. Extubation failure is poorly understood and associated with a high mortality rate.

KEY POINTS

- In the vast majority of patients, weaning from mechanical ventilation is a simple process. In this scenario, patients are extubated at the first SBT attempt and outcomes are favorable.
- The implementation of a weaning strategy based on solid clinical and pathophysiologic knowledge improves outcomes in terms of the duration of mechanical ventilation and length of ICU stay. This positive effect is mainly attributable to daily screening to determine the patient's ability to maintain spontaneous breathing.
- A relatively small group of patients require prolonged weaning, which is associated with worse outcomes. These patients need to be carefully evaluated for neuromuscular and cardiovascular dysfunction and could benefit from adjunctive therapy.
- The underlying mechanisms for extubation failure remain poorly understood, and more research is needed in this area. One common cause of extubation failure is acute pulmonary edema, but it is also easy to treat. Patients with extubation failure have a higher mortality rate that varies according to the specific cause of the failure.
- Noninvasive ventilation (NIV) and high-flow nasal therapy are used to facilitate weaning and extubation. In some high-risk cases, NIV plus adjuvant high-flow nasal oxygen (HFNO) may be appropriate.

References for this chapter can be found at expertconsult.com.

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Adjunctive Respiratory Therapy

Sanjay Manocha and Keith R. Walley

Many critically ill patients are unable to effectively clear secretions that accumulate in the central and peripheral airways. This failure can be the result of factors such as increased secretion production, impaired cough reflex, weakness, and pain. An endotracheal tube prevents closure of the glottis and the high expiratory flows necessary for effective coughing, thereby promoting the retention of secretions. In addition, in critically ill patients, the cilia of the pulmonary tree are impaired in function and reduced in number.[1,2] This leads to an increased risk of aspiration, atelectasis, and pneumonia, which are all detrimental to a critically ill patient.

Adjunctive respiratory therapies aim to prevent and treat respiratory complications that are encountered in critically ill patients (Table 58.1).

METHODS TO IMPROVE PULMONARY MUCOCILIARY CLEARANCE

Percussion

Percussion of the chest can aid in secretion clearance. By clapping cupped hands over the thorax in a rhythmic fashion or using mechanical devices that mimic the same action, the pulsating force so generated is transmitted through the thorax to dislodge airway secretions. Used in conjunction with postural drainage, this action often provides an effective method to mobilize secretions from the pulmonary tract.[3]

High-Frequency Chest Compression

High-frequency chest compression (HFCC) enhances mucus clearance. Using an automated vest device worn by the patient that is attached to an air-pulse generator, small volumes of gas are introduced into the vest bladders at a rapid rate that ranges from 5 to 25 Hz, elevating pressures up to 50 cm H_2O. This technique, primarily used in cystic fibrosis patients, has efficacy equivalent to conventional chest physiotherapy techniques of percussion and postural drainage.[4,5] In an observational study comparing HFCC with percussion and postural drainage in nine long-term mechanically ventilated patients, no difference was seen in the amount of sputum production, oxygen saturation, or patient comfort.[6] HFCC was determined to be safe and felt to save staff time. In a small randomized trial of patients extubated after being ventilated for more than 21 days, the addition of HFCC improved sputum clearance but did not have a significant impact on weaning success rates.[7] In a larger randomized trial conducted in a heterogeneous patient population, HFCC was more comfortable than chest physiotherapy, but did not produce a measurable difference in hospital length of stay, resolution of lobar atelectasis, or risk of nosocomial pneumonia.[8] It is difficult to apply this technique to most critically ill patients because of the size of the vest, as covering the thorax may prevent adequate monitoring.

Manual Hyperinflation

Manual hyperinflation with an inflation bag aims to inflate the lungs slowly to 1.5–2 times the tidal volume or to peak airway pressures of 40 cm H_2O. An inspiratory pause allows for filling of alveoli with slow time constants. This pause is followed by a quick release to allow for rapid deflation. The goals are to recruit atelectatic lung regions, to improve oxygenation, and to improve clearance of airway secretions. Similar to recruitment maneuvers described with mechanical ventilators, manual hyperinflation leads to only transient improvements in oxygenation. Thus it may facilitate secretion clearance but without any identified long-term, clinically significant improvement in patient outcomes.[9–13] It also has the potential disadvantage of requiring a ventilator disconnect—this method can be mimicked by a mechanical ventilator without doing so.[14]

Contraindications to manual hyperinflation include hemodynamic compromise and elevated intracranial pressure. There is also a risk of barotrauma because of preferential inflation of open lung regions that are highly compliant compared with the collapsed regions.

Mechanical Insufflation–Exsufflation

Similar to manual hyperinflation, mechanical insufflation–exsufflation can assist in secretion clearance from the peripheral airways. It is commonly used in patients with chronic neuromuscular diseases to augment the cough. For the critically ill patient population, a recent systematic review judged the quality of evidence to be low.[15] A single small clinical trial found reduced chances of extubation failure when used with noninvasive ventilation and manual cough assistance.[16] Insufflation–exsufflation is generally well-tolerated, but side effects include hypotension, nausea, and abdominal distention. In those with respiratory compromise who require positive pressure ventilation, the disconnect or removal of ventilatory support needed to accomplish this intervention may lead to oxygen desaturation and de-recruitment, thereby limiting its use in the intensive care unit (ICU).

Positioning and Mobilization

Mobilization of patients in the ICU, either through active or passive limb exercises, may improve overall patient well-being and, in the long term, may lead to better patient outcomes. In one report, the addition of early physiotherapy and occupational therapy to daily interruption of sedation resulted in more ventilator-free days and improved functional capacity.[17]

The now standard default positioning of the patient with the head of the bed elevated to at least 30 degrees from horizontal appears to significantly reduce the risk of aspiration and ventilator-associated pneumonia.[18] Upright positioning of patients in whom there is no contraindication increases resting lung volumes and therefore has benefits for gas exchange and work of breathing, especially among

TABLE 58.1 Adjunctive Respiratory Therapies

Methods to Improve Pulmonary Mucociliary Clearance
Chest physiotherapy:
• Percussion
• Postural drainage
• Chest vibration
Suctioning:
• Oropharyngeal suctioning
• Nasopharyngeal suctioning
• Endotracheal suctioning
Continuous lateral rotation
Positive expiratory pressure devices
Forced expiration
Closed chest oscillation
Bronchoscopy
Manual hyperinflation
Mechanical insufflation–exsufflation
Bronchodilators
Mucoactive agents
Methods to Improve Lung Expansion
Deep breathing
Incentive spirometry
Intermittent positive ventilation
Optimum body position
CPAP therapy
Methods to Improve Oxygenation and Ventilation
Inhaled vasodilators:
• Nitric oxide
• Prostaglandins
Helium–oxygen (heliox)

CPAP, Continuous positive airway pressure.

those in whom the supine or semirecumbent position leads to an unusually increased work of breathing. In some individuals with unilateral lung disease, positioning with the affected side up can lead to improved ventilation/perfusion ($\dot{V}/\dot{Q}$) matching, in part by increasing perfusion to the dependent "good" side.[19,20] If atelectasis secondary to retained secretions is the cause, having the affected side up leads to improved drainage of airway secretions.

Postural drainage involves positioning the body to allow gravity to assist in the movement of secretions and is indicated in those rather unusual patients with sputum production volumes of more than 25–30 mL/day and who have difficulty clearing their secretions.[21]

Tracheal Suction

Used in conjunction with other techniques to mobilize secretions from the peripheral to the central airways, suctioning is an effective way of removing secretions to improve bronchial hygiene. Using an open method, the patient's artificial airway is disconnected from the ventilator and a disposable suction catheter is inserted through the tube. A closed system involves a suction catheter within a protective external sheath that is advanced into the trachea while direct connection to the ventilator continues uninterrupted. Because no disconnect is required, the risk of environmental cross-contamination is reduced. Routine changes of the in-line suction catheters are not required, and this restrained practice is cost-effective.[22,23] Overall, the risk of nosocomial pneumonia between the two systems is not different.[24–26]

Because of the anatomic arrangement of the large central airways, a suction catheter most often enters the right main bronchus preferentially, as opposed to the left side. Specially designed curved-tipped "left-sided" suction catheters increase the likelihood of their successful navigation into the left mainstem bronchus.

The uncomfortable practice of nasotracheal suctioning has fallen out of favor and should only be considered in spontaneously breathing patients with ineffective or suppressed cough who are able to protect the glottis. It is perhaps most effective when used in conjunction with assisted coughing and other forms of chest physiotherapy.

Complications with suctioning include hypoxemia (especially in the setting of a ventilator disconnect), increased intracranial pressure, mechanical trauma to the trachea, bronchospasm, and bacterial contamination. All patients should be preoxygenated with 100% oxygen for 1 or 2 minutes before suctioning. To reduce the risk of agitation, the patient should be informed before tracheal suctioning is performed. The suctioning should be limited to $<$15 seconds, and the suction port on the catheter should be opened and closed intermittently—not held closed for longer than 5 seconds at a time.

Continuous Rotation Therapy

Continuous rotational or kinetic therapy extends the practice of regular twice-hourly repositioning of patients from one side to the other by placing the patient on a bed specialized for this purpose that moves to preprogrammed angles on a more frequent basis. Air mattresses that deflate in alternating fashion from side to side also provide postural position changes. Most studies using such equipment demonstrate a lower incidence of nosocomial pneumonia or atelectasis.[27–33] Nonetheless, a systematic review did not demonstrate improvements in mortality or the duration of mechanical ventilation with kinetic therapy.[34]

Bronchoscopy

Fiberoptic bronchoscopy has the advantage of providing direct visualization of the airways and permits suctioning of specific segments where secretions may be retained. Bronchoscopy is a moderately effective technique for the treatment of atelectasis in critically ill patients, with success rates ranging from 19% to 89% depending on the extent of the atelectasis (lobar atelectasis responds better than subsegmental atelectasis).[35] In a recent retrospective review of hospitalized patients with near-complete or complete lung collapse, bronchoscopy is reported to have accelerated radiologic resolution and to have aided in determining causes, such as endobronchial lesions and infectious etiologies.[36] When compared with aggressive multimodal chest physiotherapy in the only randomized trial, no difference in the rate of resolution was observed between the two methods.[37] Bronchoscopy is a semi-invasive procedure that may confer only transient benefit if not followed by respiratory therapy measures directed at preventing recollapse. Furthermore, it is not without associated risks and complications: specifically, sedation required for the procedure, transient increases in intracranial pressure, hypoxemia, and hemodynamic consequences or arrhythmias. Therefore bronchoscopy is not recommended except in situations, such as extensive unilateral atelectasis, that lead to significant difficulties in oxygenating or ventilating and that have not resolved with other methods (e.g., suctioning).

Chest Physiotherapy

Chest physiotherapy is a multimodal therapy with the goal of improving pulmonary function (gas exchange, lung compliance, and pulmonary

mucus clearance). Techniques include percussive therapies (manual or mechanical chest percussion), postural drainage, chest vibration, manual hyperinflation, mobilization, suctioning, and rotational therapy. Overall, chest physiotherapy provides transient improvements in oxygenation and lung compliance, likely secondary to airway clearance and the recruitment of atelectatic regions. In specific situations, it may improve outcome and clinical course, such as preventing ventilator-associated pneumonia[38] or acute lobar atelectasis.[39] But there is insufficient evidence to support routine chest physiotherapy in ventilated patients without primary pulmonary disease.[40]

Aerosol Therapies

Aerosolization

Aerosolization of medications allows direct medication delivery and activity at the site of pathology in addition to the ability to deliver high concentrations with minimal systemic absorption and toxicity.

The two most used methods of delivery by aerosolization are via (1) nebulization or (2) metered-dose inhalers (MDIs). *Nebulization,* commonly with a pneumatic jet, uses a high flow of gas (usually 6–8 L/min) to produce small particles of a liquid medium that contains the medication of interest. In the spontaneously breathing patient, approximately 50% of the nebulized liquid is in the respirable range, with a mass median aerodynamic diameter (MMAD) of 1–5 μm. Approximately 10% reaches the lower respiratory tract and small airways. In mechanically ventilated patients, 1%–15% of the nebulized liquid and medication is delivered to the lower respiratory tract. Ultrasonic nebulization uses high-frequency ultrasonic waves on the surface of the liquid medium to generate high volumes of small, respirable particles.

MDIs are pressurized canisters with the drug suspended as a mix of propellants, preservatives, and surfactants. Upon activation, particles ranging in size from 1 to 2 μm are produced. An MDI used in conjunction with a chamber or spacing device significantly increases drug delivery in spontaneously breathing patients. The same is true when the MDI is attached to the ventilator circuit, either in direct proximity to the endotracheal tube or as part of an in-line device in the inspiratory limb of the Y-piece.

Factors that influence the efficacy of aerosol delivery in mechanically ventilated patients include[41,42]:

1. Administration position in the circuit. An MDI should be positioned closely to the endotracheal tube at the Y-piece and used with a spacer. A pneumatic nebulizer, however, should be positioned at least 30 cm from the Y-piece.
2. Humidification. An excess can decrease aerosol delivery to the respiratory tract because of ineffective deposition of the medication on the ventilator circuit. Higher doses may be required to achieve the desired effect.
3. Timing of delivery. Delivery should occur during the inspiratory phase to maximize drug delivery.
4. Flow rates. Slower inspiratory flow rates (and therefore longer inspiratory time) increase the delivery of nebulized medications. A decelerating flow pattern can also increase the delivery to the lower airways.
5. Tidal volumes. Larger tidal volumes (greater than 500 mL) help optimize delivery.
6. Endotracheal tube size. Tube sizes less than 7 mm reduce drug delivery.
7. Density of inhaled gas. Low-density gases, such as helium–oxygen mixtures, increase deposition to the lower airways by increasing the laminar flow and producing a smaller respirable particle size.

Bronchodilators

Bronchodilators are the most frequently administered aerosolized therapy in critically ill patients. Inhaled beta-2 agonists, such as albuterol or fenoterol, are generally well tolerated in a critically ill patient and improve lung mechanics in many patients with reversible airflow obstruction. In acute lung injury, beta-2 agonists may improve lung edema clearance and have additional antiinflammatory properties.[43,44] However, two multicenter randomized trials in acute respiratory distress syndrome (ARDS) did not show detectable clinical benefit and were associated with more adverse events.[45–47] In a randomized trial of postoperative esophagectomy patients, inhaled salmeterol did not prevent the onset of ARDS.[48] Adverse effects (e.g., arrhythmias, hypokalemia) can occur in patients receiving high doses that encourage significant systemic absorption. Anticholinergic bronchodilators, exemplified by ipratropium bromide, can also be effective in patients with increased airway reactivity, especially when used in conjunction with a beta-2 agonist. Bronchodilators administered via MDI are equally as effective as a nebulizer in spontaneously breathing patients.[41] In mechanically ventilated patients, nebulization is either equally effective[49] or less effective[50,51] than high doses of MDI used with a spacer. MDI administration has the advantage of easier use without the risk of bacterial contamination or the need to adjust flow rates.[41]

Antibiotics

Theoretical advantages of aerosolized antibiotics include directing therapy to the site of infection at higher concentrations with a low risk of systemic absorption and side effects. In chronic pulmonary infective states (e.g., cystic fibrosis and severe bronchiectasis),[52–54] aerosolized antibiotics have a role in reducing bacterial concentrations in the sputum, but they have only been shown to provide clinical long-term benefits in cystic fibrosis.[54] In the acute infective state, aerosolized antibiotics cannot be used alone and have not been shown to add benefit to parenteral antibiotics.[55–57]

In the intubated or tracheostomized patient, the colonization of the airway with potential pathogens routinely occurs, and the attendant risk is high for nosocomial pneumonia. As a preventive measure, a recent meta-analysis of prospective clinical trials of aerosolized aminoglycosides suggested a significant reduction in the development of ventilator-associated pneumonia but no difference in overall mortality.[58] The most recent Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) ventilator-associated pneumonia guidelines recommend that adjunctive inhaled antibiotic therapy be considered for those with ventilator-associated pneumonia caused by bacteria with susceptibilities limited to aminoglycosides or polymyxins (colistin or polymyxin B).[59] The European Society of Clinical Microbiology and Infectious Diseases ESCMID does not support the use of nebulized antibiotics in mechanically ventilated patients.[60] Bacterial resistance must also be considered. Side effects reported in spontaneously breathing patients treated with inhaled tobramycin include increased cough, dyspnea, and chest pain.[52] Further study is needed to better define the role in inhaled antibiotics as adjuvant therapy in critically ill patients.

Mucoactive Agents

In chronic inflammatory lung conditions such as chronic obstructive pulmonary disease (COPD), cystic fibrosis, bronchiectasis, and intubation/tracheostomy, the overproduction of mucus and impaired clearance results in complications such as airflow obstruction, atelectasis, and infection. Mucus is primarily composed of water, mucin glycoprotein, cellular debris, neutrophil-derived filamentous actin and DNA, and bacteria.[61]

Mucolytic agents reduce the viscosity of mucus by breaking down the mucin glycoprotein network or free DNA strands, thereby altering mucus rheology to improve clearance. Aerosolized *N*-acetylcysteine (NAC) breaks down the disulfide bonds of the mucin glycoprotein network and is associated with improved mucus clearance. However,

because of the increased incidence of bronchospasm with its use, therapy with NAC alone is not frequently initiated, but it may be used in conjunction with an inhaled bronchodilator.[61] Recombinant human DNase (rhDNase, dornase alpha) improves mucus viscosity and pulmonary function in cystic fibrosis patients but has no significant effect on their acute exacerbations.[62,63] In bronchiectasis not resulting from cystic fibrosis, rhDNase is not effective and may be harmful.[64] In mechanically ventilated patients with atelectasis, there is no significant improvement in clinical outcome.[65–67]

This was highlighted in the NEBULAE trial, a large randomized clinical trial that compared "on demand" NAC or salbutamol for thick secretions or wheezing with routine NAC and salbutamol given four times a day. There was no change in ventilator-free days, length of stay, or mortality between the groups. More tachycardia was noted in the routine NAC administration cohort, likely related to the coadministered salbutamol.[68]

Other Aerosol Therapies

Additional aerosol therapies include hypertonic saline, racemic epinephrine (for acute upper airway obstruction because of inflammation), surfactant, and corticosteroids. In the setting of ARDS, inhaled budesonide has been reported to improve oxygenation and reduce peak plateau pressures.[69] Nebulized heparin in smoke inhalation–associated lung injury can improve oxygenation and reduce airway pressures, but the effects on patient outcomes remain to be confirmed.[70,71]

METHODS TO IMPROVE LUNG EXPANSION

Lung expansion techniques that mimic normal sigh maneuvers may help reverse and prevent atelectasis. These techniques are often used in postoperative patients at high risk for pulmonary complications, such as those undergoing thoracic and upper abdominal surgery, and in patients with neuromuscular or chest wall disorders.

Deep breathing and incentive spirometry involve coached inspiratory maneuvers to voluntarily increase lung volumes greater than the vital capacity of the patient. Both are equally effective in reducing postoperative pulmonary complications compared with chest physiotherapy applied without them.[72] Methods to improve adherence can result in clinically important outcomes, as demonstrated in a study involving postoperative bypass surgery patients.[73]

A recent systematic review of continuous positive airway pressure (CPAP) in the postoperative setting for upper abdominal surgery suggested a reduction in atelectasis and the need for reintubation but no improvement in mortality or need for ICU admission.[74]

Intermittent positive pressure breathing to improve lung expansion has fallen out of favor as a preventive measure in postoperative patients because of the expense, lack of a difference in outcomes compared with deep breathing or incentive spirometry, and complications such as abdominal distention.[75]

METHODS TO IMPROVE OXYGENATION AND VENTILATION

Nitric Oxide

Nitric oxide (NO) is a vascular-derived relaxing factor that causes vasodilation via vascular smooth muscle relaxation. The main action of NO is mediated by activating guanylate cyclase, increasing intracellular cyclic guanylate monophosphate (cGMP), thereby causing smooth muscle and subsequent vasomotor relaxation.[76] The beneficial effects observed with inhaled NO are mediated primarily through pulmonary vasodilation that occurs predominantly in patent lung units. Additional observed benefits include a reduction in platelet aggregation and neutrophil adhesion/sequestration in the lungs.[77–79] NO is rapidly inactivated by binding to the heme moiety of hemoglobin. Because of its short half-life, NO does not enter the systemic circulation, making it an ideal selective pulmonary vasodilator.

The most common use of NO in the ICU is in the setting of ARDS. Randomized controlled trials of varying sample size in ARDS have demonstrated improvement in oxygenation by improving $\dot{V}/\dot{Q}$ mismatch. NO initially improved the partial pressure of oxygen (Pao_2) and Pao_2:FIO_2 ratios, but they were no different than control by 24–72 hours.[80,81] A reduction in mean pulmonary artery pressure was also observed in these trials with the use of NO. A beneficial trend was observed in a post hoc analysis in one trial involving higher-severity ARDS.[80] However, a meta-analysis of controlled trials did not support the routine use of inhaled NO in ARDS, and even suggested a possible increase in renal dysfunction.[82–84] With these results in mind, NO is a treatment option primarily in refractory cases of severe ARDS.[83]

NO can be considered a "rescue" therapy to possibly allow for the institution of more protective forms of ventilation, facilitating decreases of fraction of inspired oxygen (FIO_2) and mean airway pressures to maintain acceptable oxygenation. It might also be used in situations in which secondary pulmonary hypertension leads to compromised hemodynamic function from right ventricular failure.

Almitrine bismesylate enhances pulmonary vasoconstriction in areas of hypoxic vasoconstriction, thereby enhancing the redistribution of blood flow from shunt areas to lung units with normal $\dot{V}/\dot{Q}$ ratios.[85,86] This effect of almitrine therefore potentates the effects of inhaled NO on gas exchange. Almitrine is not readily available in North America.

In addition to ARDS, other clinical conditions where NO use may be beneficial are listed in Table 58.2. Inhaled NO has been used after heart and lung transplants as a method to reduce right ventricular afterload in the setting of elevated pulmonary artery pressures.[87] In lung transplants, NO has been described to reduce the risk of ischemia–reperfusion injury. However, this effect was not supported by a randomized clinical trial in which NO was instituted early after lung transplantation.[88]

Inhaled NO is typically initiated at low doses ranging from 1 to 2 ppm and gradually increased until the desired effect is achieved. One method recommended in the United Kingdom (based on American-European Consensus Conference on ALI/ARDS guidelines) is to perform a dose–response test starting at 20 ppm and reduce the concentrations to 10, 5, and 0 ppm to determine the lowest effective dose.[89] A significant response should be considered a 20% increase in the Pao_2:FIO_2 ratio or at least a 5 mm Hg decrease in the mean pulmonary artery pressure (PAP). Improvements in gas exchange are usually observed at lower doses than the reductions in PAP. The usual dose of inhaled NO ranges from 10 to 40 ppm. Doses greater than 80 ppm are associated with a higher risk for adverse effects.

TABLE 58.2 Clinical Conditions Where Inhaled Nitric Oxide May Be Used

Acute respiratory distress syndrome
Severe primary and secondary pulmonary hypertension
Congenital cardiac syndromes
Right ventricular failure in acute pulmonary embolism or after cardiac surgery
Pulmonary ischemic–reperfusion injury after a heart–lung or lung transplant
Sickle cell crisis

Adverse effects of NO include the formation of methemoglobin and spontaneous oxidation to nitrogen dioxide (NO_2). NO_2 is toxic and causes airway irritation and hyperreactivity with levels as low as 1.5 ppm, in addition to pulmonary edema and pulmonary fibrosis after exposure to higher levels. Despite these adverse effects, the development of methemoglobinemia or other toxicities related to NO_2 during acute or prolonged NO inhalation is unusual, especially when NO has been administered at concentrations less than 80 ppm.[90]

To reduce the risk of exposure to NO_2, NO should be stored at concentrations no higher than 1000 ppm in a pure nitrogen environment and only exposed to oxygen at the time of administration. NO should be delivered into the ventilator circuit as close to the patient as possible. NO and NO_2 levels should be monitored closely on the inspiratory side of the Y-piece when using doses above 2 ppm. Rebound pulmonary vasoconstriction can occur with sudden discontinuation, leading to a rapid worsening of $\dot{V}/\dot{Q}$ mismatch and pulmonary hypertension with a significant hemodynamic collapse.[91]

An absolute contraindication to NO therapy is a methemoglobinemia reductase deficiency (congenital or acquired). Relative contraindications include bleeding diathesis (secondary to reports of altered platelet function and bleeding time with inhaled nitric oxide [iNO]), intracranial hemorrhage, and severe left ventricular failure (New York Heart Association [NYHA] grade III or IV).[89]

Inhaled Prostaglandins

Inhaled prostaglandins I2 (PGI2) and E1 (PGE1) have effects similar to iNO, with minimal systemic effects.[92] PGE1 has the advantage of more rapid degradation by pulmonary endothelial cells, providing a selective advantage over PGI2 at higher doses.[93] A recent meta-analysis did not find improved outcome for its routine use in ARDS,[94,95] but the inhaled prostaglandins can be considered rescue therapy[96] when used for conditions similar to those treated with iNO. As with iNO, care must be taken to avoid the abrupt discontinuation of PGI2 or PGE1 because pulmonary hypertension and cardiovascular collapse are possible "rebound"' events.

Heliox

Helium is an inert gas with a significantly lower density than room air (1.42 g/L for oxygen versus 0.17 g/L for helium). By substituting helium for nitrogen, the degree of reduction in the density of the gas is directly proportional to the F_{IO_2} concentration in the mix. Heliox reduces the Reynolds number, increasing the laminar flow and reducing airflow resistance. Consequently, the work of breathing and dynamic hyperinflation associated with high airway resistance are reduced. Clinical situations where heliox may be used include conditions with high airflow resistance, such as severe acute asthma or COPD exacerbations, bronchiolitis, bronchopulmonary dysplasia, and extrathoracic or tracheal obstruction. Heliox has been used to improve lung compliance during noninvasive ventilation in COPD patients, to reduce the work of breathing, to avoid intubation, and to improve aerosolized drug delivery. In the management of moderate to severe asthma exacerbations, routine use of heliox is not supported by systematic reviews of the literature, but can be considered as an adjuvant for short-term use in severe cases not requiring concentrated inhaled oxygen. Most studies use helium/oxygen mixes of 80:20 or 70:30 to achieve a therapeutic benefit. At higher concentrations of oxygen, the effect of helium declines, and therefore heliox is limited to patients who are not severely hypoxemic. In COPD exacerbation, three multicentered trials found no difference in intubation rate or length of stay in the ICU when heliox was added to noninvasive ventilation.[97–99] However, there appeared to be a cost benefit resulting from a shorter overall hospital length of stay.[97] When used in conjunction with nebulized medications, higher flows of heliox may be required to ensure adequate delivery of the medication, though this may be offset by the smaller particle size generated in a heliox mixture. Ventilators also require a recalibration for measured F_{IO_2}, flows, and tidal volumes when using heliox.

SUMMARY

Pulmonary disease and complications are common in critically ill patients, especially those undergoing mechanical ventilation. It is important for the clinician to recognize these potential complications and the many forms of adjunctive respiratory therapies available to prevent further morbidity. Simple therapies, such as chest physiotherapy, suctioning, and positioning, should be used in most patients, with more advanced procedures and therapies used on a selective basis based on the underlying clinical condition.

KEY POINTS

- Inability to effectively clear secretions is common in critically ill patients, increasing the risk of aspiration, atelectasis, and pneumonia.
- Chest physiotherapy, positional therapy, and early mobilization should be considered in all critically ill patients.
- Other adjunctive forms of respiratory therapy should be considered on an individual basis based on the underlying clinical condition.
- Aerosolization of medications is an effective way of providing direct delivery to the lungs.
- MDIs are preferred over nebulization for the delivery of bronchodilators in both the spontaneously breathing and mechanically ventilated patient.
- iNO is associated with improved pulmonary and cardiac physiologic parameters when administered in a variety of clinical conditions encountered in the ICU.
- Heliox can be considered for adjuvant therapy in severe cases of airflow obstruction.

References for this chapter can be found at expertconsult.com.

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Intensive Care Unit Imaging

David E. Niccum, Firas Elmufdi, and John J. Marini

RECENT ADVANCES IN ICU IMAGING

Modern advancements in imaging modalities continue to provide an ever-increasing amount of diagnostic and interventional capabilities to aid in the care of critically ill patients. Continued advancement of bedside ultrasound (US) technology and training has allowed for a drastic increase in the availability and ease of performance of these examinations. As a result, guided bedside procedures, including central venous catheter (CVC) placement, arterial line placements, and percutaneous drainage procedures (i.e., thoracentesis or paracentesis), can be performed with relative ease and with a reduction in rates of complications.[1] Bedside US also serves as an indispensable adjunct to a provider's physical examination skills. US facilitates cardiac, vascular, renal, gallbladder, pleural, and lung assessment. The bedside availability of US has made thoracentesis and CVC placement safer and easier.

Additionally, interventional radiology plays an expanding role in performing repairs that once could only be addressed surgically.[1] Embolization of cerebral aneurysms, percutaneous aortic aneurysm grafting, embolization of life-threatening bleeding vessels, placement of intravascular filters, emergent stroke intervention, and pulmonary embolism (PE) lysis can be performed emergently and on patients often at high risk for open surgical procedures. These and many other specialized applications are discussed here and elsewhere in this text in conjunction with the specific diseases they help define. This chapter focuses on imaging applications relevant to the critical care setting: chest x-ray (CXR) and chest computed tomography (CT), abdominal plain film, intensive care unit (ICU) ultrasound, and interventional procedures.

Major advances have occurred in ICU radiology over the last two decades as technological progress has resulted in perfected digital filming techniques, accelerated image acquisition and processing speeds, deployed ultrasonography to the bedside, and dramatically improved imaging communications to and from the ICU point of care.[1] Clinical data and background information can be rapidly reviewed by both clinician and radiologist, and digital images can now be viewed remotely on almost any computer, portable x-ray machine, or handheld electronic device. This technological revolution has brought a host of improvements, including:

1. Physical films are no longer lost or found out of chronological order.
2. Delays in availability have decreased.
3. It is now possible to manipulate image brightness and contrast and to better compare new images side by side with previous ones.
4. Geographically separated physicians can simultaneously view a study.
5. Physicians no longer need to leave the ICU to view studies.

Physicians no longer need to physically travel to the radiology department to access hard copy x-ray films and are therefore less likely to interact directly with a consulting radiologist. As a result, they are more likely to practice in isolation without consulting the radiologist. Although "throughput" efficiency may be enhanced, such isolation is unquestionably detrimental. Failure to connect face to face often deprives the radiologist of important clinical information that would aid in effective consultation, may result in clinicians overlooking subtle but important findings, and eliminates a valuable educational function.

CHEST RADIOGRAPHY

Technique

Although chest CTs offer greater diagnostic capability than plain bedside radiography, there are many applications for which high-quality bedside CXRs retain great utility. Bedside portable anteroposterior (AP) CXR can be strongly affected by patient positioning and exposure technique. In order to obtain the most useful images, care should be taken to reposition devices that overlay the field of view such as electrocardiogram (ECG) leads and wires, pacer pads, intravenous (IV) tubing, and mechanical ventilator tubing. "Gravity-dependent" markers can be used to help identify patient positioning. The patient should be rotated as minimally as possible, as this can greatly affect the dimensions of intrathoracic structures. Rotation can also make diaphragms appear elevated or depressed. Finally, rotation can make diffuse infiltrative processes seem less symmetric by accentuating or diminishing parenchymal lung markings in general.

An AP film magnifies the anterior mediastinal structures and vessels by up to 20%. Obese patients present particular challenges in separating what is normal from what is not, especially when filmed supine (Fig. 59.1).

Positioning: Generally, supine radiographs amplify the heart's dimensions through augmented venous filling, elevated diaphragms, and lung volume reduction. For example, the azygous vein distends in the supine normal subject but collapses in the upright position (Fig. 59.2). Supine radiographs can also make the discovery of a small pneumothorax or effusion difficult or impossible.

Exposure: A properly exposed CXR will reveal vertebral interspaces in the retrocardiac region. If these are not visualized, the film is underpenetrated. Underpenetration will exaggerate parenchymal markings and make it difficult to observe air bronchograms in the setting of consolidation. Consistent exposure on repeat images allows for the day-to-day comparison of films.

Timing: Time films to capture the patient in inspiration, even those acquired on mechanical ventilation. Infiltrates will appear denser in the setting of partial inhalation or exhalation. Likewise, the application of high positive end-expiratory pressure (PEEP) will result in decreased density of infiltrates on a CXR.

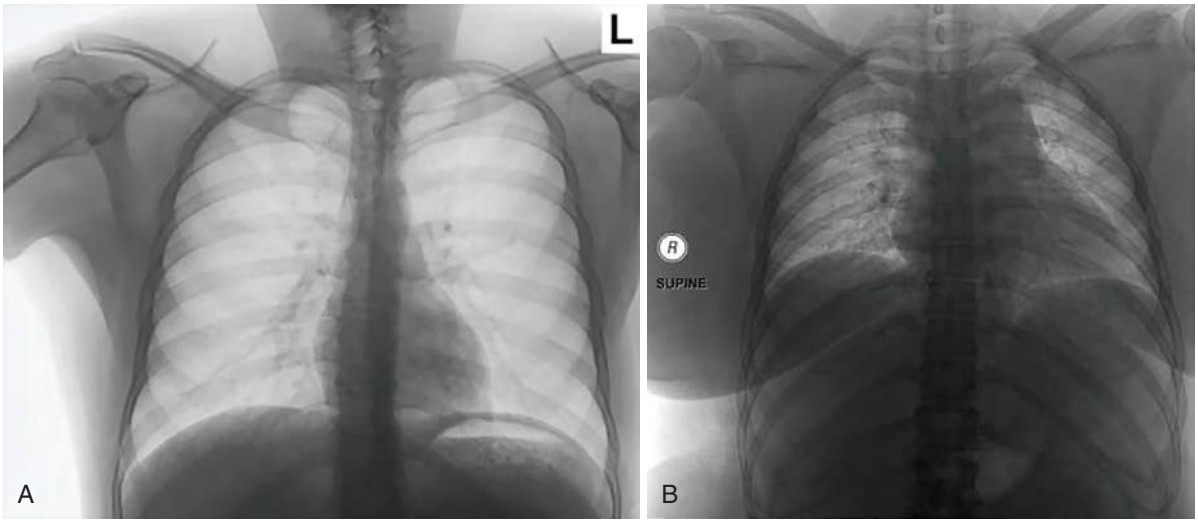


Fig. 59.1 **A,** Normal posteroanterior (PA) upright chest radiograph. Note the definition and dimensions of the heart and vascular structures. **B,** Supine anteroposterior (AP) chest radiograph in massively obese normal subject. Note the widened mediastinum, enlarged heart shadow, and symmetrically elevated hemidiaphragms.

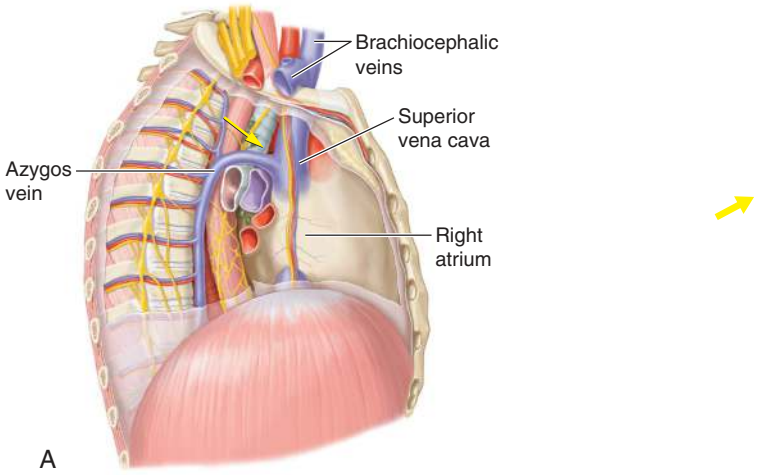


Fig. 59.2 **A,** Lateral view demonstrating the position of the azygous vein in the mediastinum. **B,** Distention of azygos vein, indicating higher-than-normal pressures in the superior vena cava (SVC), is seen on frontal chest film as a circular or lenticular shadow *(arrow)* at its point of anatomic insertion. (A, From Tank PW, Gest TR. *Lippincott Williams & Wilkins Atlas of Anatomy.* Baltimore, MD: Wolters Kluwer; 2009: Plate 4-35b; B, From Marini JJ, Dries DJ. *Critical Care Medicine,* 5th ed. Philadelphia, PA: Wolters Kluwer; 2019: Fig 11.2.)

Consistency: Ideally, compare images from the same patient with the same positioning, ventilator settings, and timing of the respiratory cycle. If this consistency is not possible, keep in mind the differences in technique when comparing films.

The appearance of infiltrates are also often affected by procedures such as bronchoalveolar lavage (BAL). A BAL will leave residual fluid and cause atelectasis (often in sections of the lung with preceding infiltrates) that will result in increased density of infiltrates for several hours postprocedure.

NORMAL PA CXR/NORMAL AP OBESE CXR

Film Timing

A majority of patients should be considered for CXR on arrival in the ICU. Patients who are generally at high risk for endotracheal tube (ET) tube or central line malposition, pneumothorax, or who may have changes in the appearance of their pulmonary parenchyma shortly after initiation of positive-pressure ventilation (such as cardiogenic pulmonary edema) will all benefit from early CXR.

The frequency with which follow-up CXRs are required in the ICU is controversial. Generally, CXRs should be considered after procedures invading the thorax such as ET tube placement, central line placement, feeding tube placement, thoracentesis, or transvenous catheter placement. These images are useful, as they ensure proper placement of the device and that no unintended complications occurred (i.e., pneumothorax). In all but emergency situations, a CXR should follow failed attempts at catheterization via the subclavian route before contralateral placement is attempted to ensure no pneumothorax is present.

Regularly scheduled CXRs are not necessary in all patients with cardiopulmonary disease in the ICU. Despite data indicating that a plurality of routine ICU CXRs demonstrate an abnormality or minor change,

many such findings are nonacute or inconsequential. Observable clinical examination changes typically accompany significant developments that would be observed on a CXR. A prospective study indicates that less than 10% of films demonstrate a new significant finding, and only a fraction of these are not anticipated by clinical examination.[2] Furthermore, meta-analysis of studies examining routine daily CXRs compared with on-demand imaging have failed to demonstrate improvement of patient outcomes, including mortality and ICU length of stay.

A reasonable compromise in practice would be to obtain daily "routine" radiographs on mechanically ventilated patients who have hemodynamic or respiratory instability. Examples would include patients with a significant pneumothorax with a persistent air leak or a patient with progressive hypoxic or hypercapnic respiratory failure. Otherwise, changes in patient clinical condition or procedures dictate the need for additional films. In a stable, mechanically ventilated patient, images can safely be obtained less frequently. Obviously, clinical deterioration should prompt reevaluation.

Placement of Tubes and Catheters

Tracheal Tube Position

ET positioning should be confirmed with a CXR because of the high frequency (25%) of suboptimal ET placements.[3] Ideally the tube should be positioned in the mid-trachea 5 cm above the carina, which is usually located just inferior to the level of the aortic arch. If the carina cannot be visualized on the CXR, the ET tube tip should be positioned overlying the T6 vertebra (Fig. 59.3). Another method to locate an unseen carina uses the intersection of the midline of the trachea with a 45-degree bisecting line, which passes through the middle of the aortic knob. Positioning of the ET tube too deeply usually leads to right mainstem bronchus intubation. This often will result in right upper lobe or left lung atelectasis. Left main intubations are uncommon because the left main bronchus is smaller and angulates sharply from the tracheal axis. If the tube is positioned too high in the trachea (above the level of the clavicles), there will be an increased risk of unintended extubation.

ET tubes move with flexion, extension, and rotation of the neck. An ET tube will generally move in the same direction that the neck flexes or extends (chin down = tip down or chin up = tip up). Head rotation away from the midline will elevate the ET tube tip. Total tip excursion can range up to 4 cm with extremes of head movement.

An ET or tracheostomy tube should occupy one-half to two-thirds of the tracheal width and should not cause bulging of the trachea in the region of the tube cuff. Bulging is indicative of cuff overinflation. This can result in tracheal wall ischemia and subsequent airway stenosis and should therefore be avoided. Gradual dilation of the trachea may occur during long-term positive-pressure ventilation and should be avoided by minimizing both ventilator cycling pressure and cuff sealing pressures.

Fig. 59.3 Location of the main carina on the frontal film. The separation between the right and left main bronchi *(arrow)* almost invariably occurs at the level of the sixth and seventh posterior ribs, directionally "southwest" of the aortic knob. (From Marini JJ, Dries DJ. *Critical Care Medicine,* 5th ed. Philadelphia, PA: Wolters Kluwer; 2019: Fig 11.3.)

In patients who are post-tracheostomy, a CXR may detect subcutaneous air, pneumothorax, pneumomediastinum, or malposition of the tube. However, routine use of a CXR after both surgical and percutaneously inserted tracheostomy placement is controversial.[4] It may best be reserved for patients with either emergent or technically difficult procedures or who have clinical decompensation after them.[5] The T3 vertebral level is considered the ideal position of the tracheostomy stoma. A tracheostomy tube tip should usually lie halfway between the stoma and the carina. Unlike an ET tube, a tracheostomy tube does not change position with neck flexion or extension.[6] Lateral radiographs are necessary for evaluation of AP angulation. Sharp anterior angulation of the tracheal tube is associated with the development of trachea-innominate fistulas, and continued posterior angulation risks erosion and tracheoesophageal fistula. Massive hemoptysis usually signals the former condition, whereas sudden massive gastric distention with air occurs in the latter. Fortunately, both complications are quite rare in modern practice.[7]

Tracheal Stenosis

Previous intubation or tracheostomy can be complicated by tracheal stenosis. Narrowing of the trachea can be seen at the level of the tracheal tube tip, at the cuff, or, most commonly, at the tracheostomy tube stoma. Stenosis must be substantial (luminal opening <4 mm) to be symptomatic. The typical hourglass-shaped narrowing can be hard to visualize on a single AP radiograph, so CT is best for establishing a definitive diagnosis.

Central Venous Catheters

The tip of a CVC should lie within the thorax, well beyond any venous valves. These valves are typically located in the subclavian and jugular veins, approximately 2.5 cm from their junctions with the brachiocephalic trunk (at the radiographic level of the anterior first rib).[8] Proximal placement will result in an inaccurate measurement of the central venous pressure and is also associated with increased risk of thrombus formation. Distal placement is associated with the risks of cardiac perforation and tamponade. To avoid this, CVCs should be placed with the catheter tip in the middle-superior superior vena cava (SVC), with the tip directed inferiorly. Radiographically, catheter tips positioned above the superior margin of the right mainstem bronchus are unlikely to rest in the atrium. There are some risks to positioning catheters in the middle SVC, including vascular abutment and potential perforation. This is especially notable with left-sided catheters which will enter the SVC at an oblique angle. Caution should be exercised, especially with more rigid hemodialysis lines placed from this approach. Such catheters may benefit from placement in the lower SVC to avoid this complication. Vascular perforation can result in air embolism, fluid infusion into the pericardium or pleural space, hemopneumothorax, and pericardial tamponade.[3]

Postprocedure radiographs reveal complications, including catheter misplacement, in around 10% of CVC placements.[3] For example, catheters inserted via the subclavian route can pass across the midline into the contralateral subclavian vein, or even turn cephalad, entering the internal jugular veins. Similarly, catheters inserted in the internal jugular veins may track into the subclavian vein of either side. This is more commonly seen in patients with proximal stenosis. To minimize this risk, ultrasound should be used to demonstrate collapsibility of the jugular vein before placement. The phenomenon of a subclavian catheter crossing the midline is most common when a triple-lumen catheter is

threaded through a larger-bore channel already in the right subclavian vein. Many clinicians are comfortable leaving CVCs, which terminate in the contralateral subclavian, in place provided there are no clinical effects, but are less at ease with CVCs terminating in the internal jugular vein. In addition to catheter malposition, the complications of CVC insertions include pneumothorax, arterial injury, stroke, and pleural cavity entry. Catheter-associated thrombosis can also occur with CVCs and peripherally inserted central catheter (PICC) lines.

The width of the mediastinal and cardiac shadows should be assessed after placement of CVCs because perforation of the free wall of the right ventricle (RV), although rare, has the potential to result in pericardial tamponade.

Pulmonary Artery (Swan-Ganz) Catheter

A properly inserted pulmonary artery catheter (PAC) should follow the same route as a CVC but continues through the right atrium, RV, and into a pulmonary artery. The tip of the PAC ideally overlies the middle third of a well-centered AP CXR 3–5 cm from the midline, within the mediastinal shadow, or at least not more than 2 cm past the hilum. Ideally, the tip should also lie below the level of the left atrium.

The PAC balloon is used both for placement and obtaining postcapillary wedge pressure (PCWP). Care should be taken to ensure that the balloon is left deflated except during these two procedures, as it can result in pulmonary infarct or pulmonary artery rupture. Unrelieved pulmonary arterial blockage has been a reported complication in 1%–10% of PAC placements. The most common radiographic finding is distal catheter tip migration, with or without pulmonary infarction. Distal migration is common in the first hours after insertion as the catheter softens, adding slack to the line. This slack results in the tip being propelled distally by repeated right ventricular contractions. If pressure tracings suggest continuous wedging, it is important to look for distal migration, a catheter folded on itself across the pulmonic valve, or a persistently inflated balloon (appearing as a 1-cm diameter, rounded lucency at the tip of the catheter). Inflating the balloon of an inappropriately distal PAC can result in immediate catastrophic pulmonary artery rupture or delayed formation of a pulmonary artery pseudoaneurysm. Pseudoaneurysms present as indistinct rounded densities on CXR 1–3 weeks after PAC placement. The diagnosis is easily confirmed by magnetic resonance imaging (MRI) or contrasted chest CT.

In addition to these pulmonary infarct and pulmonary artery rupture issues, PAC insertion can result in knotting or looping and entanglement with other catheters or pacing wires. The risk of knotting or entanglement of PACs can largely be avoided by following two simple steps. First, do not advance the catheter more than 20 cm before observing the next chamber's pressure tracing. For example, a right ventricular tracing should be seen within 20 cm of catheter advancement after obtaining a right atrial pressure tracing. This prevents the catheter from having enough length to form a large loop in the right atrium or ventricle. Second, if the PAC does become knotted or entangled with another device such as a pacing wire, it is essential to resist the temptation to pull on the catheter harder to extract it. Forceful pulling will only tighten the knot, making eventual extraction more difficult. Rather, knotted catheters can be "untied" under fluoroscopic guidance by an interventional radiologist by simply loosening the knot using a stiff internal guidewire.

Pacing Wires

On an AP view of the chest, a properly placed pacing catheter should have a gentle curve with the tip overlying the shadow of the right ventricular apex. To accurately assess the wire's position in three-dimensional space, a lateral film is required. On a lateral view, the tip of the catheter should lie within 4 mm of the epicardial fat stripe and point anteriorly. Posterior angulation suggests coronary sinus placement. Other common areas for malposition include the right atrium or pulmonary artery outflow tract.

In patients with permanent pacemakers, leads can fracture at the entrance to the pulse generator, a site that should be checked routinely. Pacing wires can also result in cardiac perforation, so it is important to examine the CXR for signs of tamponade and perform bedside cardiac US if it is suspected.

Chest Tubes

The optimal position for a chest tube depends on the reason for its placement. Inferior and posterior positioning is ideal for the drainage of free-flowing pleural fluid, whereas anterosuperior placement is preferred for pneumothorax. On an AP chest film, posteriorly placed tubes are closer to the film than those placed anteriorly. This proximity of the chest tube to the film results in a "sharp" or focused appearance of the catheter edge and its radiopaque stripe. Conversely, anteriorly placed chest tubes often have fuzzy or blurred margins. Chest tube location may appear appropriate on a single AP film, even though the tube actually lies within subcutaneous tissues or lung parenchyma. Unexpected failure to re-expand the pneumothorax or drain the effusion should be a clue to extrapleural placement. A chest CT may be necessary to confirm appropriate positioning. In a complicated pleural effusion, a CT can visualize loculations that a plain film can miss. On plain film, another clue to the extrapleural location of a chest tube is the inability to visualize both sides of the catheter. The radiopaque stripe on many tubes includes a break or "sentinel eye," which denotes the proximate port of entry for air or fluid. This should be included within the pleural cavity to achieve drainage and ensure no subcutaneous entry of air into the tube. After removal of a larger chest tube, fibrinous thickening may produce a persisting tube track, which mimics the visceral pleural boundary, suggesting pneumothorax.

Intraaortic Balloon

The intraaortic balloon (IAB) is an inflatable device placed in the proximal aorta to assist a failing ventricle. Diastolic inflation of the balloon produces a distinct, rounded lucency within the aortic shadow, but in systole, the deflated balloon is not visible (unlike its supporting catheter). Ideal positioning places the catheter tip just distal to the left subclavian artery (Fig. 59.4). Placed too cephalad, the IAB may occlude

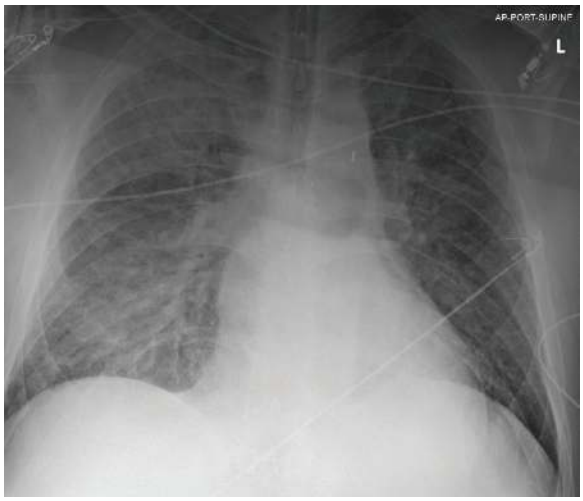


Fig. 59.4 Intraaortic balloon pump on portable anteroposterior (AP) chest x-ray. The position of the tip of the balloon can be seen at the level of the AP window. Note the pulmonary edema pattern in this patient after cardiac arrest in the setting of an ST-elevated myocardial infarction.

the carotid or left subclavian artery. Placed too caudally, the IAB may occlude the lumbar or mesenteric arteries and produce less effective counterpulsation. Daily radiographic assessment is prudent to detect catheter migration or a change of the aortic contour suggestive of IAB-induced dissection.

Temporary Ventricular Assist Devices

Temporary ventricular assist devices (VADs), such as Impella catheters, are also available to assist a failing left ventricle (LV). They are placed via a patient's femoral artery with the catheter extending through the aorta and aortic valve, with the catheter tip being visualized in the LV. Repositioning of the catheter requires visualization beyond a standard CXR, with bedside US or formal echocardiography being required at the time of placement and positioning. Like PACs, slack can develop in a temporary VAD catheter because of a patient's body heat, resulting in an inappropriate position (often too deep in the LV). Clinical signs of catheter malposition include hemolysis (potentially massive) with change in urinary color and blood counts, hypotension, and reduced variability in the motor current monitor tracing.

Gastric Access Tubes

Whether inserted through the nose (nasogastric [NG]) or mouth (orogastric [OG]), it is usually prudent to obtain a CXR or plain abdominal film to confirm appropriate gastric tube position before administration of medication, fluid, or feeding, even when clinical evaluation indicates proper positioning. Tube feeding or medication administration into the airway or pleura can result in severe complications. Even in intubated patients, a small number of tubes intended for the stomach do end up in the lung (usually the right mainstem bronchus). Vigorous insertion technique can force the gastric tube through the lung into the pleural space (Fig 59.5). Inadvertent airway entry is most likely to occur when using a small-bore, stylet-stiffened tube, especially when inserted in comatose or deeply sedated patients.

It is important to confirm that the tip of the tube not only overlies the stomach but also that there is no significant deviation of the tube from the midline esophagus until it has passed the level of the diaphragm. This will help avoid the rare but avoidable complications that can result from tubes that traverse the left mainstem bronchi and into the pleural space. When inserted via the esophagus, the side holes of the enteral tube should be fully advanced past the lower esophageal sphincter to minimize reflux. After similar safety precautions, an abdominal film should be obtained after placement of a percutaneous endoscopic gastric (PEG) tube to search for common complications, such as extragastric migration or peritoneal leakage.

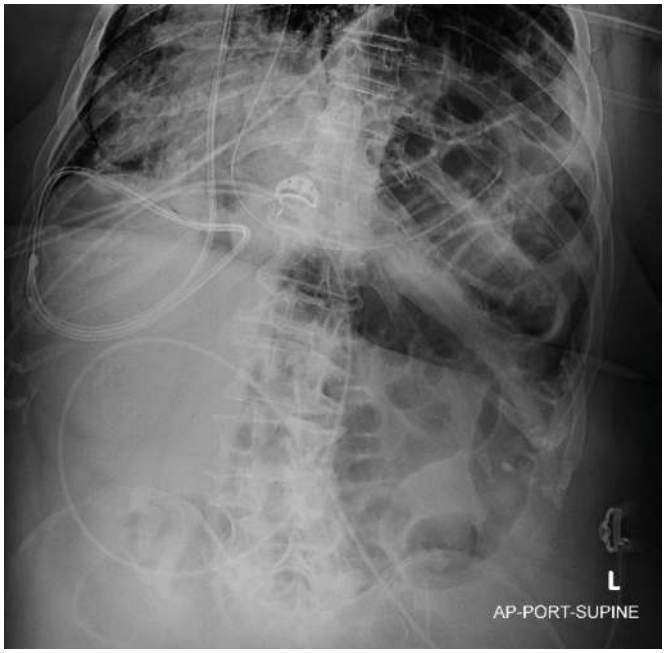


Fig. 59.5 Malpositioning of small-bore nasojejunal (NJ) feeding tube. This was found on abdominal imaging immediately after placement in an intubated patient with SARS-CoV-2 infection. The tube is seen clearly tracking down the right mainstem bronchus and then coiling in the right lower pleural space. Subsequent chest x-ray confirmed the presence of a pneumothorax. This imaging prevented further complications of administering nutrition or medication into the pleural space.

Specific Applications of Chest Radiography

Bedside CXRs retain several important advantages over chest CTs for patients in the ICU despite the greater diagnostic abilities of CTs. CXRs are faster, cheaper, expose the patient to less radiation, and most importantly, avoid a potentially hazardous trip to radiology. Already mentioned at the outset of this discussion, it must be recognized that the chest CT offers far greater diagnostic precision than the bedside radiograph. Yet, for many purposes, the humble bedside chest radiograph remains indispensable, as it is cheaper and quicker to obtain, presents less exposure to ionizing radiation, and spares the patient the hazards associated with transport from the ICU environment.

Atelectasis

Atelectasis is a frequent cause of densities on ICU CXRs. Findings range from invisible microatelectasis, through plate, segmental, and lobar atelectasis, to collapse of an entire lung. Differentiating between segmental atelectasis and segmental pneumonia is often difficult, and these conditions often coexist. Atelectasis can be differentiated by identifying its commonly found features of volume loss, rapid onset, and quick reversal.

Atelectasis tends to develop in dependent regions and by a 2:1 ratio more commonly in the left rather than the right lower lobe. CXR findings will include hemidiaphragm elevation, parenchymal density, vascular crowding (especially in the retrocardiac area), deviation of hilar vessels, ipsilateral mediastinal shift, and loss of the lateral border of the descending aorta or heart. Each lobe has a characteristic pattern of atelectasis that an experienced ICU provider should be able to recognize, and these are summarized in Figs. 59.6 through 59.10. Air bronchograms extending into an atelectatic area suggest that collapse continues without total occlusion of the central airway and that attempts at airway clearance by bronchoscopy or aggressive suctioning are therefore likely to fail to re-expand the involved lobe.

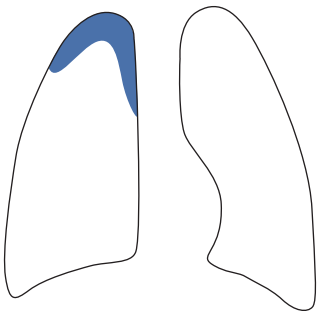


Fig. 59.6 Right upper lobe collapse. Apical density increases as the minor fissure rotates superior medially, producing an easily recognizable curvilinear arch extending to the mediastinum.

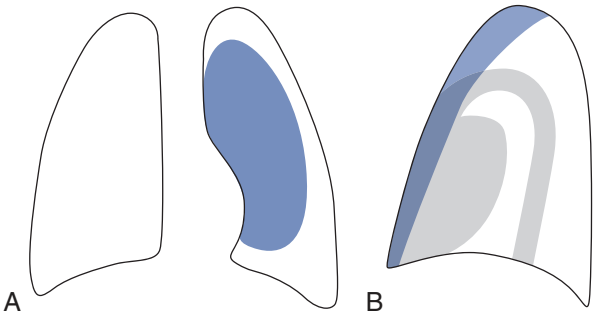


Fig. 59.7 Left upper lobe collapse. A, Because the left lung does not have a middle lobe or minor fissure, upper lobe collapse occurs anteriorly, producing a diffuse haziness of the hemithorax and loss of the upper left cardiac border. **B,** On a lateral film a more distinct region of collapse can be seen running along the anterior portion of the radiograph.

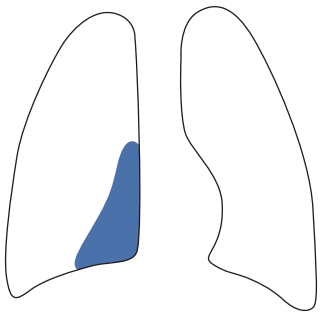


Fig. 59.9 Right lower lobe (RLL) collapse. On an anterior CXR, RLL partial lobar collapse is visualized as diaphragmatic "silhouetting." When lower lobe volume loss is extensive, a triangular posteromedial density can be seen with its base resting on the diaphragm. Contrary to popular belief, the "silhouette sign" is not always reliable on portable films, particularly in the presence of an enlarged heart or when the film was obtained in a lordotic or rotated projection.

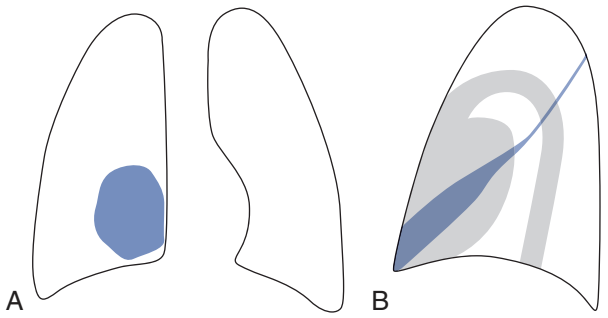


Fig. 59.8 Right middle lobe collapse. On lateral CXR, right middle lobe atelectasis appears as a prominent wedge with its apex directed toward the hilum. The minor fissure and major fissure move toward each other. Findings are more subtle on frontal films, manifesting as obscuration of the right heart border.

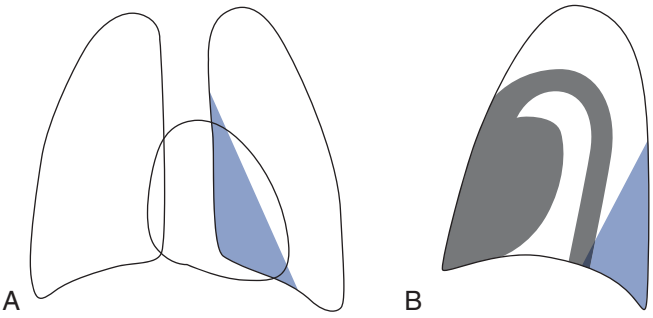


Fig. 59.10 Left lower lobe (LLL) collapse. On an anterior CXR, partial LLL collapse is visualized as diaphragmatic "silhouetting." When lower lobe volume loss is extensive, like in right lower lobe (RLL) collapse, a triangular posteromedial density can be seen with its base resting on the diaphragm.

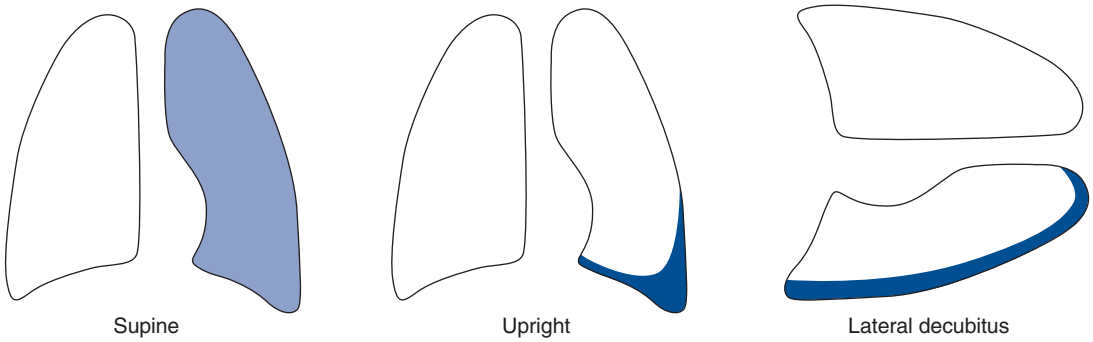


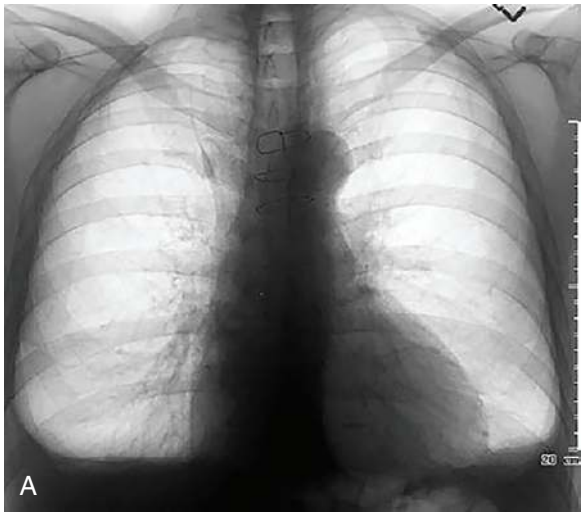
Fig. 59.11 Appearance of a mobile pleural effusion in three positions. In the supine position, a "ground-glass" lateralized diffuse density (with preservation of vascular markings) may be the only sign of layered pleural fluid. A changing appearance with position confirms the diagnosis. (From Marini JJ, Dries DJ. *Critical Care Medicine,* 5th ed. Philadelphia, PA: Wolters Kluwer; 2019: Fig. 11.4.)

Pleural Effusion and Hemothorax

Pleural effusions occur very commonly among ICU patients. Their appearance varies based on body positioning (Fig. 59.11).

Large effusions can redistribute on a supine AP CXR, causing a hazy density to overlie the entire hemithorax without loss of vascular definition (Fig. 59.12). Apical pleural capping is another radiographic sign of large collections of pleural fluid in the supine patient. Upright or lateral decubitus radiographs may help confirm the presence of an effusion (Fig. 59.13). If a large collection of pleural fluid obscures the lung parenchyma, a contralateral decubitus film often helps visualize the ipsilateral lung. Pleural fluid is not ordinarily visible until several hundred milliliters have accumulated. On lateral decubitus films, 1 cm of layering fluid suggests a volume that can usually be tapped safely. However, in the era of bedside US, the performance of decubitus films is becoming less common as point-of-care US (POCUS) offers a faster and cheaper alternative. US will also be able to provide specific localization and guidance for thoracentesis.

Fig. 59.12 Mobile right pleural effusion supine. Diffuse haziness with well-preserved outlines of the ipsilateral pulmonary arteries is characteristic. (From Marini JJ, Dries DJ. *Critical Care Medicine,* 5th ed. Philadelphia, PA: Wolters Kluwer; 2019: Fig. 11.5.)



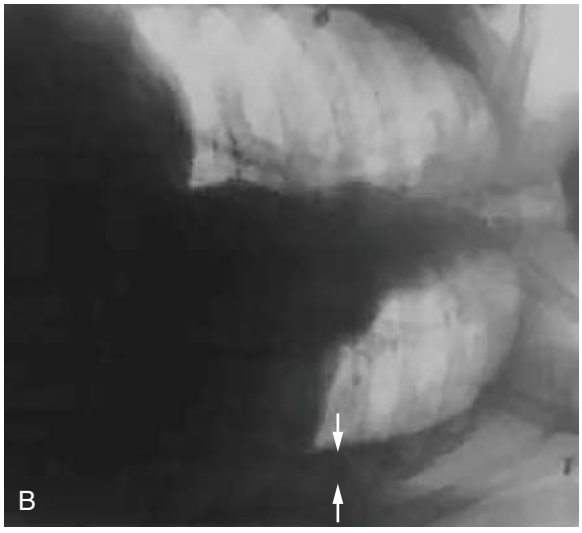


Fig. 59.13 A, Bilateral pleural effusions with characteristic crescentic blunting on the upright PA film. **B,** Mobile effusion in left lateral decubitus orientation. *Arrows* demarcate the fluid separating left lung from ribs.

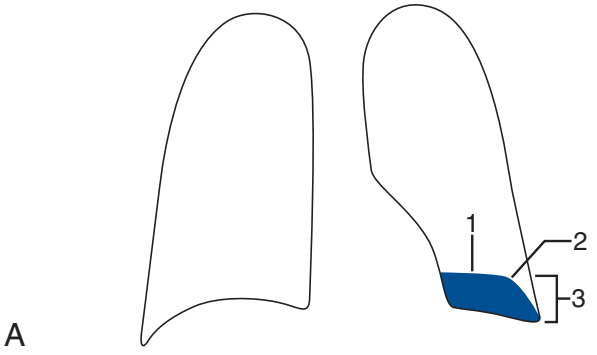
Bilateral Pleural Effusion (Decubitus)

Subpulmonic or loculated fluid may be difficult to recognize on a portable CXR. Hemidiaphragm elevation, lateral displacement of the diaphragmatic apex, abrupt transitions from lucency to solid tissue density, and increased distance from the upper left hemidiaphragmatic margin to the gastric bubble (on an upright film) are all signs of a subpulmonic effusion (Fig. 59.14). US and chest CT are useful adjuncts in detecting the presence of such collections of pleural fluid and in guiding drainage. US has the obvious advantages of portability, repeatability, cost-efficiency, safety, and real-time imaging for drainage.

Extraalveolar Gas/Barotrauma

Extraalveolar gas can manifest as interstitial emphysema, cyst formation, pneumothorax, pneumomediastinum, pneumoperitoneum, or subcutaneous emphysema.

Pulmonary Interstitial Emphysema. This condition is usually associated with positive-pressure ventilation and represents air in the lymphatic and interstitial system. Radiographic signs of gas in the pulmonary interstitium include lucent streaks that do not conform to air bronchograms and new cysts at the lung periphery, usually at the



B

Fig. 59.14 A, Radiographic signs of a subpulmonic effusion: *(1)* hemidiaphragm elevation with separation of lung from gastric bubble, *(2)* lateralization of the diaphragmatic dome, and *(3)* abrupt transition from lucency to soft tissue density. **B,** Left subpulmonic effusion in upright position. Note abrupt transition of density at the lung base and lateral displacement of what appears to be the hemidiaphragmatic dome. (From Marini JJ, Dries DJ. *Critical Care Medicine,* 5th ed. Philadelphia, PA: Wolters Kluwer; 2019: Fig. 11.7.)

bases. Interstitial emphysema may also generate small "target lesions" as air surrounds small peripheral pulmonary arterioles viewed *en face*. These signs, best seen when the parenchyma is densely infiltrated, can indicate the imminent development of pneumothorax.

Subpleural Air Cysts. Subpleural air cysts are a potential sign of impending pneumothorax in mechanically ventilated patients. They appear on a CXR as small (3- to 5-cm wide) basilar, rounded lucencies. They often appear abruptly and tend to rapidly increase in size (sometimes to as large as 9 cm). They can frequently progress to tension pneumothorax in the presence of continued high-pressure mechanical ventilation. When subpleural air cysts are noted, the clinician should reduce airway pressures to the extent possible and maintain a high level of vigilance with preparation to emergently insert chest tubes if needed. Fortunately, such catastrophic developments have become much less likely in the present era of lung-protective ventilation.

Pneumothorax. The identification of pneumothorax in ventilated patients remains of critical importance, despite the decreased incidence of this condition since the introduction of low tidal volume ventilation. When it does occur, pneumothorax commonly complicates the course of patients with necrotizing pneumonias, acute respiratory distress syndrome (ARDS), secretion retention, or expanding cavitary or bullous lesions.

Pneumothorax is often difficult to detect on portable CXRs. Fewer ICU patients exhibit the typical patterns seen on upright CXRs performed in noncritically ill patients. Proper upright positioning is very important in detection. At the bedside, an upright *expiratory* CXR is often the best film for detecting a pneumothorax. This view confines a fixed amount of intrapleural air within a smaller volume, accentuating the proportion of thoracic volume it occupies and the separation of the lung from the chest wall. On supine films or in patients with pleural adhesions, gas may collect exclusively in the basilar (anterior) regions of the thorax. In this case a pneumothorax will be positioned anterior to the heart or may mimic pneumomediastinum or pneumopericardium. Loculated pneumothoraces can be very difficult to detect without CT, and residual localized air collections are often found by CT among patients with one or more chest tubes. Radiographic signs of pneumothorax on the supine CXR include a "deep sulcus sign" and lucency over the upper portions of the spleen or liver. POCUS can greatly facilitate a diagnosis of pneumothorax and should be considered when doubt persists after CXR examination.

When observing a pneumothorax, the visceral pleura provides a specific marker: a radiodense (white) thin stripe of appropriate curvature, with lucency visible on both sides and absent lung markings beyond (Fig. 59.15). Skin folds often mimic the pleural edge but can be distinguished by the following features: (1) lucency present only on one margin, (2) poorly defined limits, and (3) extension beyond the confines of the rib cage. Because pneumothorax reduces blood flow to the collapsed lung, its density may be surprisingly normal, even with an extensive gas collection. Here again, failure to detect dynamic lung sliding and especially the presence of a "lung point" on US nicely complement or even supplant the radiographic evidence (see the section "Ultrasound" later).

Pneumothoraces are often characterized by the percentage of the hemithorax they occupy. This practice is highly imprecise, both because the frontal CXR is only two-dimensional and because apparent percentage changes occur with variations in breathing depth and position. As with pleural fluid, precise determination of the size of a pneumothorax is neither possible nor necessary. A tension pneumothorax is not defined by a specific size of gas collection in the pleural space. Both a tension pneumothorax, regardless of size, and a "large" pneumothorax require drainage—the former because of its immediate physiologic effects, the latter because it creates a pleural pocket that is unlikely to reabsorb spontaneously over an acceptable time. The reabsorption rate of a pneumothorax has been estimated to be 1%–2% per day, a crude rule of thumb that emphasizes the slowness of this process. A 15% pneumothorax would typically take 2 weeks to reabsorb.

Tension Pneumothorax. A tension pneumothorax should be suspected in intubated patients with sudden cardiopulmonary decompensation. This is especially true in patients with high peak inflation pressures. Pneumothorax has been shown to occur in up to 50% of patients with peak airway pressures exceeding 60 cm H_2O. Although action may need to be pursued purely on clinical grounds, imaging, including portable CXR and bedside US, often can be performed in a timely fashion to assist with diagnosis.

Tension pneumothorax can result in shifting of the mediastinum and can flatten or invert with the ipsilateral hemidiaphragm. Tension pneumothorax may not have a typical appearance in a patient's respiratory failure, resulting in uncertainty of diagnosis. Infiltrated or obstructed lungs fail to collapse completely, and an unyielding mediastinum may not shift noticeably, despite a marked pressure gradient. Comparison to past films and clinical correlation may be required. In general, a pneumothorax should be decompressed in a patient with cardiopulmonary decompensation with a new or enlarging pneumothorax. The clinician should rapidly consider and rule out acute hyperinflation (gas trapping) as an explanation before proceeding with any invasive measure.

Tension pneumothorax may be very difficult to distinguish from bullous disease under tension by plain radiograph alone. Although a chest CT can be revealing, patients in extremis cannot wait for a diagnostic CT scan. In such emergent settings, erring on the side of chest

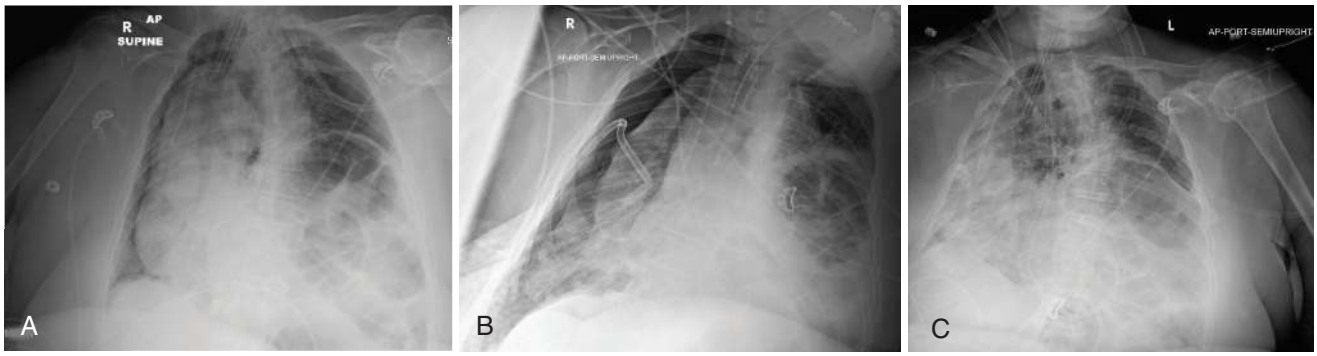


Fig. 59.15 **A,** Pneumothorax seen in a patient with SARS-CoV-2–related ARDS. **B,** Subsequent placement of a small-bore chest tube that, although appearing to be in a good position, has become kinked and is not evacuating the expanding pneumothorax. **C**, Repositioning of the same chest tube has resulted in evacuation of the pneumothorax.

tube insertion is probably the best course of action, even though rupturing a large bulla can create a bronchopleural fistula. A surgically inserted chest tube should be considered in patients with significant bullous disease, as it will help discriminate the pleural boundary better and minimize the likelihood of this complication.

Pneumomediastinum. After gaining access to the mediastinum, gas normally decompresses into adjacent soft tissues. Apart from discomfort or pain, pneumomediastinum itself rarely produces important physiologic effects in adults. Mediastinal gas may arise from neck injuries, from rupture of the trachea or esophagus, or most commonly from alveolar rupture and retrograde dissection of air along bronchovascular bundles. Pneumomediastinum appears radiographically as a lucent band around the heart and great vessels, reflecting gas within the space separating the parietal pleura from the mediastinal contents. On the heart's inferior border, this lucency can extend across the mediastinum, linking the two sides of the chest with a "complete diaphragm sign." An unnaturally sharp heart border is the first indicator of pneumomediastinum, a sign that must be distinguished from the "kinetic halo" seen at the heart or diaphragm border of an edematous lung. The mediastinal pleura, outlined by gas on both sides of a thin radiodense line, can often be detected. On a lateral film, pneumomediastinum usually appears as a thin crescent of gas outlining the ascending aorta. Not uncommonly, extrapleural gas extends from the mediastinum, lifting the parietal pleura off the diaphragm, or outlining the inferior pulmonary ligament. It also can surround and elevate the thymus, resulting in the "thymic sail sign." Pneumomediastinum may indicate, but does not correlate specifically, with pneumothorax, which follows in up to 30% of mechanically ventilated patients.[9] In doubtful cases where progression is feared, definitive diagnosis can be established by CT.

Subcutaneous Gas. Subcutaneous gas, also known as *subcutaneous emphysema,* usually has important diagnostic but little physiologic significance. It produces lucent streaks or bubbles in the soft tissues that contrast with the normal densities of the chest and neck. However, there is almost no limit to the path the gas may take, as it may track into the face, the retroperitoneum, the peritoneal cavity, and the scrotum. During mechanical ventilation, bilateral subcutaneous gas usually results from alveolar or bronchial rupture and medial gas dissection, indicating both a viable decompression pathway and an increased risk of pneumothorax. In patients with pneumothorax, progressive accumulation of subcutaneous gas can indicate the presence of a bronchopleural fistula or a malfunctioning chest tube, especially if the gas is bilateral. Ipsilateral subcutaneous gas detected shortly after chest tube placement generally entered via the tube track itself. Subcutaneous gas detected immediately after blunt chest trauma indicates possible tracheobronchial or esophageal disruption.

Pulmonary Edema

It is important, yet often difficult, to distinguish between normal permeability (fluid overload and congestive heart failure [CHF]) and high-permeability pulmonary edema (ARDS). Although considerable overlap exists in their radiographic findings, certain CXR findings may help distinguish these two etiologies. Patterns of infiltration, the size of the heart and great vessels, and distribution of vascular markings are among the characteristics that should be scrutinized to establish a diagnosis (Table 59.1).

CHF and volume overload are characterized by a widened vascular pedicle, an even or inverted pattern of vascular markings, and a tendency toward a gravitational distribution of edema ("bat wing" or basilar). Pleural effusions, often bilateral and particularly those of substantial size, are also more common with CHF than with ARDS. The vascular pedicle is measured at the point the superior vena cava crosses the right main bronchus to a parallel line dropped from the point of takeoff of the left subclavian artery from the aorta. It should be less than 60 mm in length in 90% of normal CXRs. Kerley B-lines, because of perilymphatic interstitial fluid, are common in established CHF (usually of several days' to weeks' duration), whereas crisp air bronchograms are unusual. Conversely, the less mobile infiltrates of ARDS are widely scattered, patchy, and often interrupted by distinct air bronchograms. These criteria are better for correctly classifying CHF and volume overload edema and less accurate for identifying ARDS.[10] Although useful, when applied with appropriate clinical correlation, widespread application of these criteria has shown them to be less reliable than stated in the original investigations. Because most of the radiographic deterioration seen in ARDS occurs within the first 5 days of illness, a worsening CXR appearance after this time suggests superimposition of pneumonia, fluid overload, CHF, or ventilator-induced lung injury (VILI) (Fig. 59.16).

TABLE 59.1 Radiographic Features of Pulmonary Edema

Characteristics	Cardiogenic or Volume Overload Edema	High-Permeability Edema
Heart size	Enlarged	Normal
Vascular pedicle	Normal/enlarged	Normal/small
Flow distribution	Balanced/cephalad	Basal/balanced
Blood volume	Normal/increased	Normal
Septal lines	Common	Absent
Peribronchial cuffing	Very common	Uncommon
Air bronchograms	Uncommon	Very common
Edema distribution	Even/central/gravitational	Patchy/peripheral/nongravitational
Pleural effusion	Very common/moderate to large	Infrequent/small

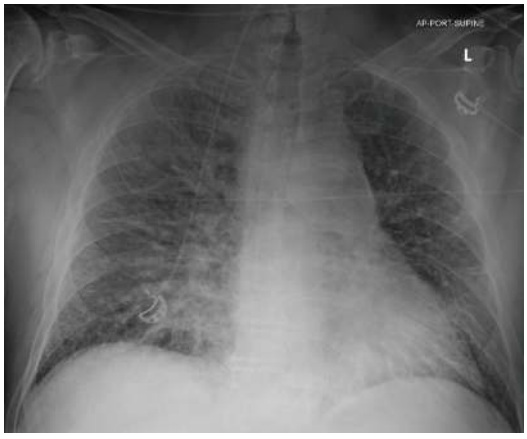


Fig. 59.16 Acute pulmonary edema seen in a 62-year-old man with a STEMI. Although pulmonary edema is usually bilateral and symmetric, it may collect asymmetrically when a mediastinal tumor, bronchial cyst, or massive thromboembolism diverts blood flow preferentially to one lung. A recently transplanted lung is also prone to developing unilateral pulmonary edema. Asymmetry may also be observed after unilateral aspiration, re-expansion pulmonary edema or in the presence of extensive bullous disease. Gravity may redistribute edema fluid and atelectasis to newly dependent lung regions over relatively brief periods after patient repositioning. *STEMI*, ST elevation myocardial infarction.

Mediastinal Widening

Mediastinal widening, particularly after chest trauma or an invasive procedure, should raise suspicion of aortic disruption. This should be determined only on a well-centered film, as a rotated or lordotic film may be misleading. In lower-risk patients, vascular anomalies, lobar atelectasis, and masses of the mediastinum should also be considered. Prior chest films should be examined for comparison if available.

A contrast-enhanced chest CT will provide a definitive diagnosis of aortic disruption. Obtaining a high-quality upright posteroanterior (PA) CXR, though desirable, is frequently not possible because of injuries or hypotension. Radiographic clues to aortic disruption include a widened superior mediastinum (the most sensitive sign), a blurred aortic knob, rightward deviation of an NG tube or aortic shadow, and tracheal deviation to the right and anteriorly. Inferior displacement of the left main bronchus, left-sided pleural effusion (with or without apical capping), and displacement of intimal calcifications of the aorta, provide other signs suggestive of aortic disruption. Mediastinal widening with vascular injury is frequently associated with traumatic fractures of the sternum, first two ribs, or clavicle. Widening of the cardiac shadow should prompt careful review of the aortic contour because blood may dissect from the aorta into the pericardium.

Although once considered the gold standard for imaging, catheter-based angiography is rarely used today. More safely performed contrast-enhanced CT scanning, MRI, and echocardiography almost always are sufficient for diagnosis.

Pericardial Effusion

Pericardial effusion is recognized radiographically by enlargement of the cardiac shadow. The classic "water bottle configuration" of the cardiac silhouette, although highly characteristic, is unusual. Serial enlargement of the cardiothoracic ratio can also be seen, as can cardiogenic-appearing pulmonary edema. An epicardial fat pad visible on the lateral CXR is sometimes referred to as the Oreo cookie sign, as it can result in two dense lines, which can be seen both anterior and posterior to the pericardial fat pad. POCUS can be performed to confirm any suspected effusion. Echocardiography is the procedure of choice for the detection and evaluation of pericardial effusions, and it simultaneously affords the opportunity to assess heart chamber size, contractile function, and vena caval diameter. When a transthoracic echocardiogram cannot obtain images of adequate quality because of patient weight or chest hyperinflation, a transesophageal echocardiogram is usually diagnostic. Although echocardiograms can have findings supportive of tamponade, this remains a clinical diagnosis, and cardiovascular compromise in the setting of a large or rapidly accumulating pericardial effusion should raise a high suspicion for this condition.

Air-Fluid Levels (Lung Abscess vs. Empyema)

Although CT scanning more reliably differentiates the location of air-fluid levels, several radiographic features help to distinguish whether an air-fluid level lies within the pleural space or within the lung parenchyma (Fig. 59.17). On an AP film, pleural fluid collections generate wide, moderately dense air-fluid levels. Lung abscesses and liquid-filled bullae are spherical in shape and as such, tend to project similar diameters on both AP and lateral films (Fig. 59.18, *top panels*). Lung abscesses generally have distinct, thick, shaggy walls with irregular contours, unlike most liquid-filled bullae and pleural fluid collections.

Intrapulmonary collections are usually smaller, denser, and rounded. The air-fluid level of pleural fluid collections must abut the chest wall on either AP or lateral film (see Fig. 59.18, *bottom panels*). Fluid collections that cross a fissure line on upright films are located within the pleural space. As body position is altered, pleural fluid collections frequently undergo marked changes in shape or contour.

Postthoracotomy Changes

After pneumonectomy, fluid will accumulate in the vacant hemithorax over days to months. The absolute fluid level is of little significance postpneumonectomy. However, changes in the level of fluid are important. A rapid decline in the fluid level can indicate a bronchopleural fistula, a complication that most commonly develops within 8–12 days of surgery. If a fistula develops earlier, failure of the bronchial closure should be suspected, prompting consideration of reoperation. Bronchopleural fistulas tend to displace the mediastinum to the contralateral side, an unusual occurrence during uneventful postoperative recovery. Small residual air spaces may remain for up to a year after pneumonectomy and do not necessarily imply the presence of a persistent fistula. Very rapid postoperative filling of the hemithorax suggests infection, hemorrhage, or malignant effusion.

Fistulous Tracts

Fistulas between the trachea and innominate artery develop most frequently when a tracheal tube angulates anteriorly and to the right in patients with a low tracheostomy stoma, persistent hyperextension of

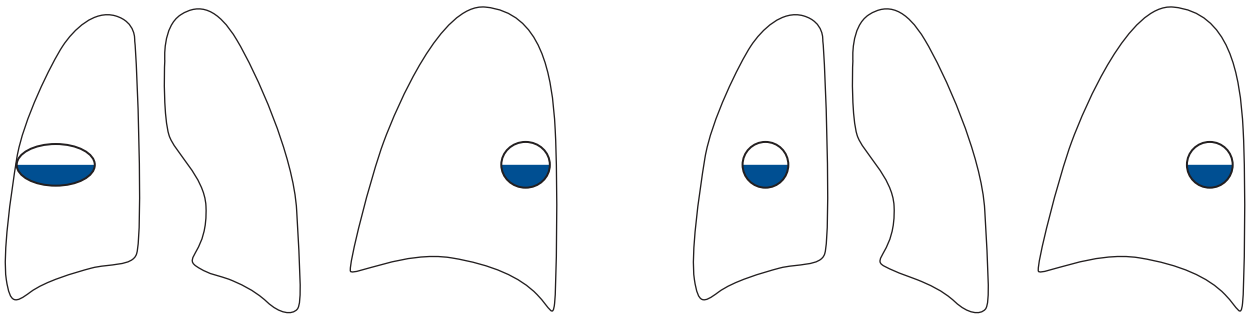


Fig. 59.17 Intraparenchymal versus intrapleural fluid collections. Fluid collections within the pleural space usually have a greater horizontal than vertical dimension, do not cross fissure lines, and may have sloping attachments to the pleural surface on one or more views. Furthermore, pleural collections typically have different dimensions on anteroposterior (AP) and lateral views. By contrast, intraparenchymal collections tend to be more spherical, with equal dimensions on AP and lateral views. (From Marini JJ, Dries DJ. *Critical Care Medicine,* 5th ed. Philadelphia, PA: Wolters Kluwer; 2019: Fig. 11.8.)

Fig. 59.18 Air-fluid levels (lung abscess vs. empyema). *Top:* Large right upper lobe lung abscess with thick cavity wall and air-fluid level indicating communication with the airway. *Bottom:* Loculated empyema of the right posterior pleural space. The lateral view demonstrates that the opacity is not rounded, abuts the ribs, and is not entirely encapsulated by aerated lung. (From Marini JJ, Dries DJ. *Critical Care Medicine,* 5th ed. Philadelphia, PA: Wolters Kluwer; 2019: Fig. 11.9.)

the neck, or asthenic habitus. Because of this association, anteriorly directed tracheal tubes should be repositioned. Fistulas also may form between the trachea and esophagus during prolonged ET intubation. These usually occur at the level of the ET cuff, directly behind the manubrium. Predisposing factors include cuff overdistention with simultaneous presence of an NG tube and posterior angulation of the tracheal tube tip. Tracheal stenosis often coexists. This creates pressure on the tissue separating the ET cuff and NG tube, resulting in ischemia. The sudden occurrence of massive gastric dilation in a mechanically ventilated patient provides an important clue to the presence of a fistula. A radiographic contrast agent may be introduced into the esophagus after cuff deflation or tube removal in an attempt to confirm the presence of a fistula.

Pulmonary Embolism

Although the plain CXR rarely, if ever, diagnoses PE, it is quite useful to detect other conditions in the differential diagnosis, including CHF, pneumothorax, and aspiration. A clear CXR in a patient with sudden cardiopulmonary decompensation should be met with suspicion for PE and warrants further evaluation. Even on plain CXR imaging, large PEs may give rise to suggestive findings: ipsilateral hypovascularity, pulmonary artery enlargement, and very rarely, abrupt vascular cutoff. Local oligemia (the Westermark sign) may be seen early in the course of PE, usually within the first 36 hours in only 10% of cases. "Hampton's hump," a pleural-based triangular density caused by pulmonary infarction, is seldom seen. About 50% of patients with PE have an associated pleural effusion.

For critically ill ICU patients with suspected thromboembolism, it often makes sense to begin the evaluation with a Doppler examination of the limbs, especially in patients too ill to transport or with acute or chronic renal disease. If the US examination reveals what appears to be fresh clots in any deep vein, thromboembolism is diagnosed and therapeutic anticoagulation should be considered. For ICU patients the legs, arms, and neck are potential sites of clots. Roughly half of all CVCs in place for a week or more are associated with at least a partially occlusive thrombus, and approximately 15% of these patients have concurrent PEs.[11] POCUS or formal echocardiography can also be performed in the right clinical context to evaluate for acute right ventricular failure, which can be seen in submassive or massive pulmonary emboli. It is important to note that the McConnell's sign of a dilated, hypoactive RV with relative sparing of the apex also is seen in other conditions that cause severe hypoxic respiratory failure (such as ARDS). Given this, the specificity of this finding is affected by the clinical context. One approach would be to evaluate for deep vein thrombosis (DVT) and the McConnell's sign on bedside US on patients with clinical suspicion for PE who are too unstable to transport or have other contraindications to a CT or ventilation/perfusion (V/Q) scan. If either of these two examinations are positive, one can proceed to treat them empirically for a

pulmonary embolism. When the patient becomes more stable and appropriate, a confirmatory CT angiogram should be pursued.

If the US is negative but the clinical suspicion of PE remains high, V/Q scanning or contrasted chest CT may be performed. The rarity of a normal CXR diminishes the value of V/Q scanning for critically ill patients. Nonetheless, normal perfusion scans are very helpful. The sensitivity and specificity of chest CT for the diagnosis of PE are now well established. In the right clinical context, it is safe to assume that a large filling defect seen in the pulmonary circuit of a technically adequate study represents a clot with ~96% specificity. Primary tumors of the pulmonary artery, primary lung tumors, cancers metastatic to the mediastinum, nonneoplastic mediastinal adenopathy, hydatid disease, and mediastinal fibrosis rarely can mimic PE. By contrast, because the sensitivity of CT varies among institutions, and even in the best centers is not 100% for subsegmental clots, a negative CT does not definitively exclude PE.[12] Sensitivity is optimized by a scanner with many rows of detectors, quick acquisition time, optimal contrast injection technique and gating, adequate breath-holding by the patient, and experienced interpretation of optimally reconstructed images, including three-dimensional views. Although there is controversy about the importance of subsegmental clots in healthy patients, in critically ill patients with impaired cardiopulmonary reserve, it is probably inadvisable to overlook such emboli. Echocardiogram may reveal right ventricular and pulmonary arterial dilation. If the Doppler US is negative, V/Q not practical, echocardiography unrevealing, and CT nondiagnostic while clinical suspicion remains high, angiography is the next, seldom-taken step. Frequently, CT and catheter angiography are both relatively contraindicated by renal insufficiency. Angiography can be safely performed in most critically ill patients, provided that (1) care is used in transport, (2) pulmonary artery pressures are not excessive at the time of contrast administration, and (3) selective injections guided by perfusion scanning are performed. Septic PE should be considered in patients with multifocal cavitary lesions of varying size.

Pneumonitis

Aspiration and Acute Pulmonary Edema

Although bacterial infection sometimes supervenes, gastric aspiration initially produces sterile chemical pneumonitis. When bacterial infection complicates aspiration in the intubated patient, the time from intubation to aspiration can provide valuable clues to the etiologic organism. Events occurring within 4 days of intubation are usually associated with *Staphylococcus, Streptococcus,* and *Haemophilus* infections, whereas later episodes are usually because of gram-negative rods. Massive aspiration, although position and volume dependent, typically appears as bilateral diffuse alveolar and interstitial infiltrates of rapid onset. The extent of the infiltrate does not correlate with outcome, and radiographic improvement often occurs quite rapidly. Aspiration in the supine position usually affects the posterior segments of the upper lobes and superior segments of the lower lobes. Patients who aspirate in a decubitus position often develop unilateral infiltrates (Fig. 59.19A). Patients who are upright tend to have basilar and right middle and right lower lobe opacities. When asymmetrical, the right lung is usually more involved. Significant atelectasis may occur when large pieces of solid food or foreign objects (e.g., teeth, dental appliances) are aspirated.

On occasion, massive symmetric aspiration and/or ARDS can be difficult to distinguish from acute pulmonary edema (see Figs. 59.19B and 59.20). As discussed earlier, several CXR cues may help in making that distinction. Blurred hilar structures and the virtual absence of air bronchograms characterize acute pulmonary edema and fluid volume overload.

Pneumonia

The diagnosis of pneumonia is a clinical one. However, a CXR may give a clue to the organism producing bacterial pneumonia. Bacterial pathogens typically produce patchy segmental or lobar involvement. Bulging fissures, although uncommon, suggest *Klebsiella*. A diffuse, patchy, ground-glass appearance suggests viral pneumonitis (e.g., influenza or COVID-19) or atypical organisms such as *Legionella, Mycoplasma,* and *Pneumocystis* (Fig. 59.21). Small, widely scattered nodular densities suggest miliary *Mycobacterium tuberculosis* as the etiologic organism. Larger nodular densities are associated with *Cryptococcus, Actinomycosis,* or *Nocardia. Aspergillus* often gives rise to peripheral wedge-shaped infiltrates caused by vascular invasion and secondary infarction or cavitary formation. Cavitation suggests neoplasm, tuberculosis, fungal infection (e.g., histoplasmosis, cryptococcosis, coccidioidomycosis), lung abscess, or septic PE. Pneumonitis that develops in preexisting areas of bullous emphysema often produces air-fluid levels that can be confused with lung abscess or empyema. The thinner contour of the cavity wall, the more rapid pace of development and resolution, and premorbid CXRs demonstrating bullae help to identify this problem.

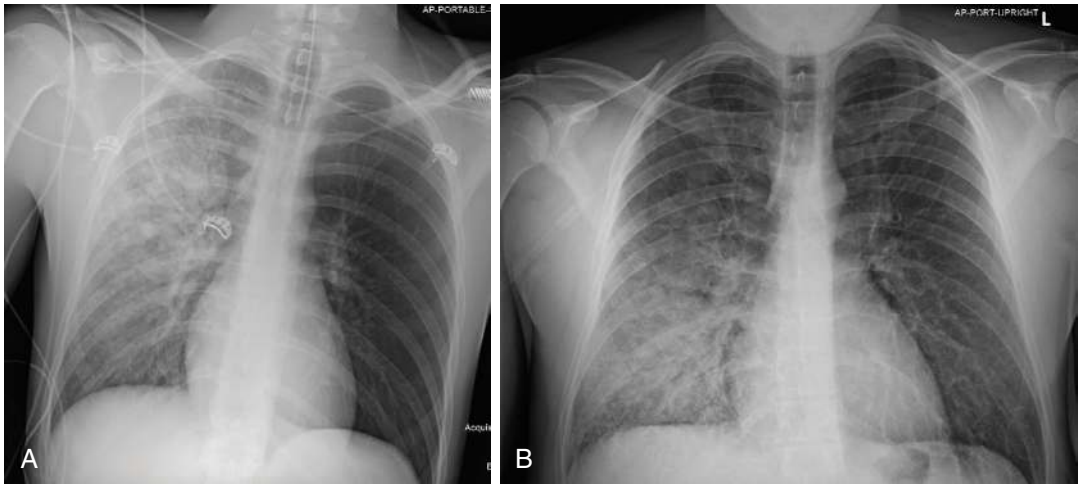


Fig 59.19 Aspiration pneumonitis. A, Aspiration pneumonitis seen in a young male who presented after being found down with an opiate overdose. Note the asymmetric distribution of his infiltrates. **B,** Note the asymmetric distribution of the infiltrates, the presence of air bronchograms, and blurring of the hilar structures.

Fig. 59.20 Radiographic appearance of pulmonary edema. Note the virtual absence of air bronchograms and the bilaterally indistinct hilar shadows. (From Marini JJ, Dries DJ. *Critical Care Medicine,* 5th ed. Philadelphia, PA: Wolters Kluwer; 2019: Fig. 11.10.)

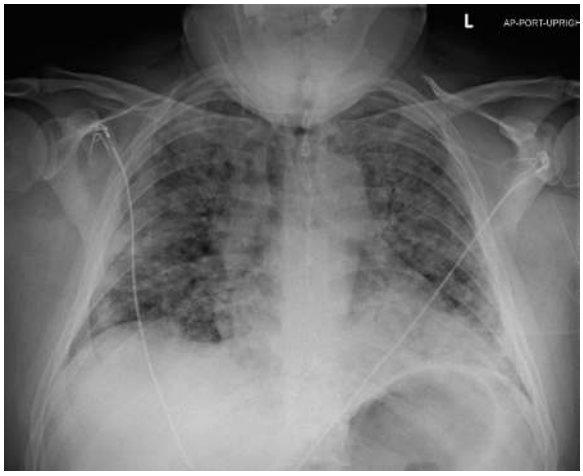


Fig. 59.21 Radiographic appearance of SARS-CoV-2 pneumonia.

Nosocomial or ventilator-associated pneumonia affects up to 30% of patients with ARDS but is difficult to detect with certainty because focal parenchymal densities may also represent edema, atelectasis, and infarction. Hence, radiographic abnormalities must be interpreted considering the clinical situation. A new unilateral infiltrate in a patient with a previously stable CXR is the best radiographic indicator of a superimposed infection; however, fever, increasing leukocytosis, rising procalcitonin, increased sputum production, and progressive hypoxemia are better indicators than the CXR alone. A focal wedge-shaped infiltrate (especially occurring distal to a PAC tip or in a patient with hemoptysis) is likely to represent pulmonary infarction.

Intraabdominal Conditions

An upright CXR can also help diagnose acute intraabdominal problems. Midline or paraesophageal hiatal hernias are easily visualized. Diaphragmatic disruption may allow abdominal contents to herniate into the chest after abdominal trauma, often displacing a gas-containing viscus into the left chest. Short of a trip to the CT scanner, the upright CXR also provides the most sensitive method of detecting free air within the abdominal cavity. (A cross-table film of the abdomen taken at least 5 minutes after decubitus positioning may serve a similar purpose.) Intubated patients frequently swallow air, producing gastric dilation. In the appropriate setting, massive gastric dilation can suggest the possibility of esophageal intubation or a tracheoesophageal fistula.

CT AND MRI

Reconstruction, Multiplanar, and Subtraction Views

Using a single acquisition of CT data, images obtained (preferably with contrast) can be reconstructed to view multiple planes—not only the traditional axial plane but also the coronal and sagittal ones, allowing improved diagnostic accuracy (Fig. 59.22). Additionally, subtraction techniques may highlight the vasculature (Fig. 59.23). Three-dimensional reconstructions may be developed from the CT

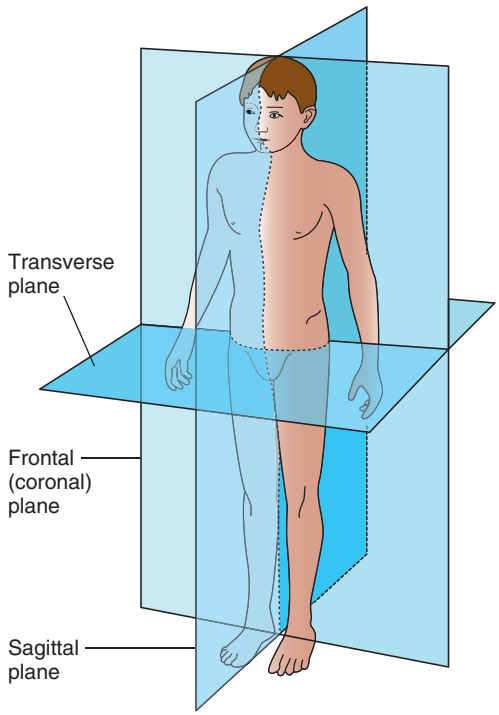


Fig. 59.22 *Top:* The two-dimensional imaging planes. The "transverse" plane is also termed "axial." *Bottom:* Three planes of view for head CT. (From Marini JJ, Dries DJ. *Critical Care Medicine*, 5th ed. Philadelphia, PA: Wolters Kluwer; 2019: Fig. 11.11.)

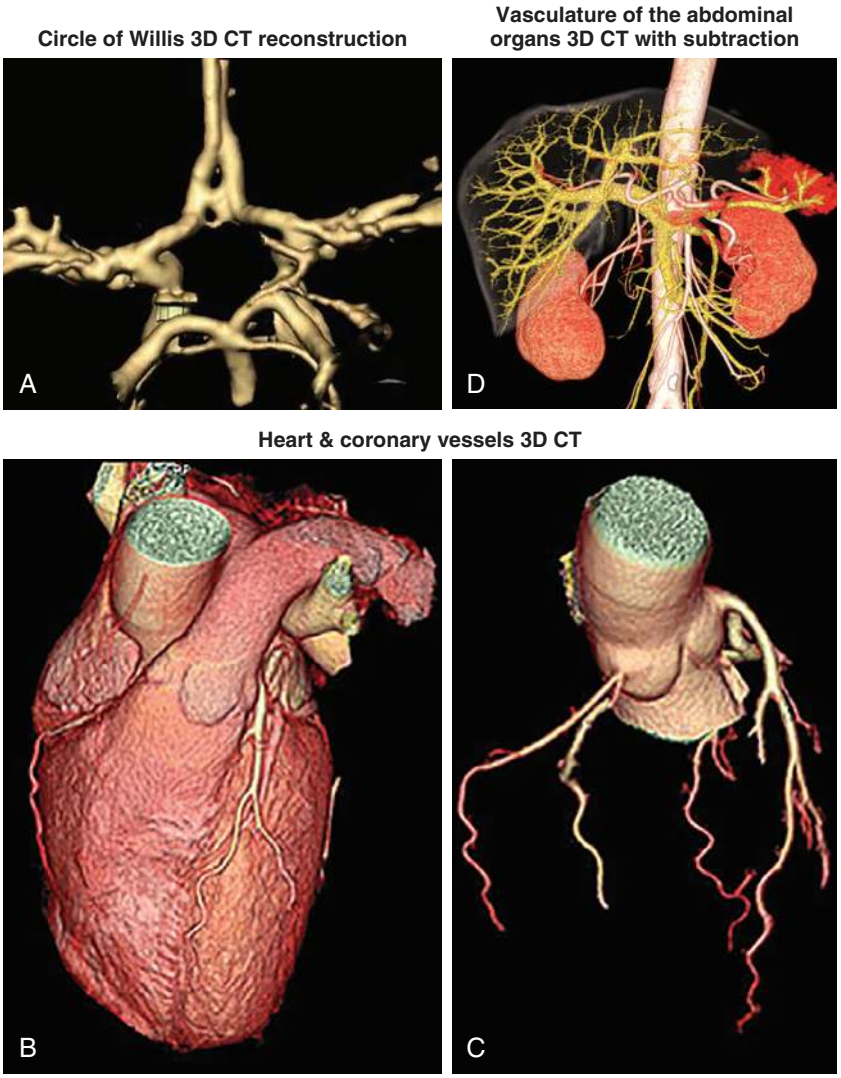


Fig. 59.23 **A,** Multiplanar three-dimensional (*3D*) reconstruction of circle of Willis using data from a single computed tomography (*CT*) study and subtraction technique. Such images can be rotated around a selected axis. **B,** Multiplanar reconstruction of the heart with electrocardiogram (ECG)-gated subtraction views of main coronary vessels. **C,** Multiplanar reconstruction of abdominal vasculature with subtraction, highlighting selected organ vasculature. (From Marini JJ, Dries DJ. *Critical Care Medicine*, 5th ed. Philadelphia, PA: Wolters Kluwer; 2019: Fig. 11.12.)

database that are valuable in detailing the anatomy of difficult cases. Such helpful innovations are available because of the accelerated development of digital radiography.

General Preparing of the Patient for Imaging Studies

Radiology staff performing these examinations will facilitate and help implement their preparation, depending on the study being performed. Ensuring accurate diagnostic suspicions on an examination order will help ensure the most beneficial diagnostic protocols are followed. Restricted angulation of the imaging table or gantry is often a limiting factor for patients who are not intubated and receiving mechanical support for ventilation. If the patient is to undergo a sedation-based procedure such as drain placement, then a prior coagulation profile and nothing by mouth (NPO) status are often prerequisites. With elective procedures, the clinician must plan ahead or defer transport in order to comply with these requirements and imaging suite schedules. It is wise to check verbally with the technical staff whenever there is doubt regarding the demands and timing of the study or procedure.

Computed Tomography

Establish urgency of examination (stat vs. routine). The examination protocol is usually determined by the radiologist, and the selected protocol defines the appropriate prep. Depending on the examination, the patient may need oral contrast (e.g., CT abdomen), which can be administered via enteric tube if necessary. Appropriate access for IV contrast administration should be established, provided that it is both indicated and not prohibited by allergy or renal insufficiency. If a computed tomography angiography (CTA) is ordered, then the type (and patency) of IV access catheter may need to be approved by CT staff, as this study requires a relatively high injection rate of the contrast with elevated risk of IV contrast extravasation/infiltration. Communication with the radiology staff before transport is usually advisable.

Magnetic Resonance Imaging

Because it invariably takes a relatively long time to complete, MRI is generally avoided in ICU patients unless both the clinician and radiology team believe it to be absolutely necessary. Unstable and tenuous patients are placed at particular risk because of the relative separation of patient from caregivers. If considering MRI, confer with the MR tech and/or radiologist to discuss how best to proceed. Individual patients may impose unique limitations. For example, metallic foreign bodies or certain medical devices may be incompatible with MRI. Also, the lengthy procedure may create anxiety in patients suffering from claustrophobia. Many ICU patients will require mechanical ventilatory support to remain both still and recumbent for the time required for these examinations.

Ultrasound

US imposes very few limitations other than having physically restricted access to appropriate acoustic windows from binders, wounds, and dressings. For many purposes, high-quality ultrasonic examinations are acquired by technicians at the bedside. Abdominal and pelvic imaging are preferably done in an NPO state to limit bowel gas from interfering with the imaging (see "Ultrasound" section later).

Chest CT and MRI

The chest CT finds many applications in ICU practice. Often CT is the only practical way to image the lung in very obese individuals, as the bedside CXR cannot adequately penetrate the chest wall to reveal the obscured lung characteristics. It is therefore prudent for all critical care unit practitioners to become familiar with the basic elements of axial chest CT interpretation (Fig. 59.24) and to be aware of coronal and sagittal plane reconstructions (Fig. 59.25A and B).

Although indispensable to modern critical care practice, CT scanning (and MRI for that matter) has significant limitations in the critically ill population.[13] Continuing technical advancements in modern

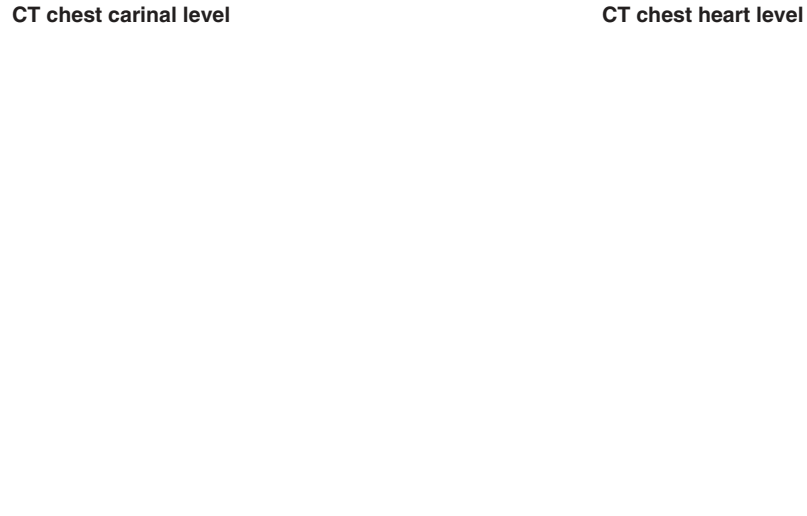


Fig. 59.24 *Left*, The normal structures visualized by a vascular-contrasted axial computed tomography (*CT*) image at the carinal level. *Right*, The normal cardiac structures visualized by a vascular-contrasted axial CT image at the midchest level. *LA*, Left atrium; *LA*, left ventricle; *RA*, right atrium; *RV*, right ventricle; *SVC*, superior vena cava. (From Marini JJ, Dries DJ. *Critical Care Medicine,* 5th ed. Philadelphia, PA: Wolters Kluwer; 2019: Fig. 11.13.)

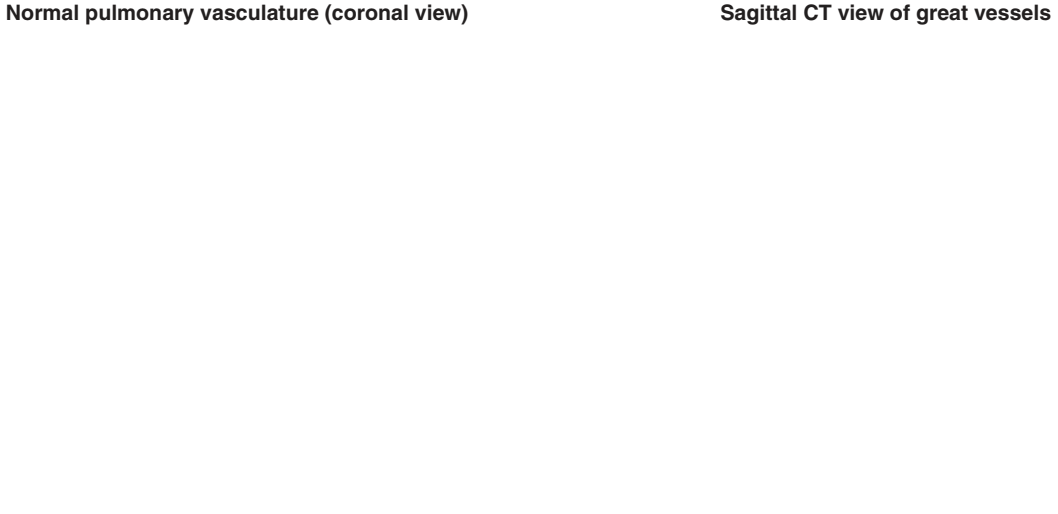


Fig. 59.25 *Left*, Radio-contrasted normal vasculature (coronal plane). *White* indicates pulmonary arteries. *Gray* indicates pulmonary venous, left atrial, and aortic vessels. Sagittal computed tomography (CT) of chest *(right)* and 3D-reconstructed image using the same data set obtained on that study *(middle).* (From Marini JJ, Dries DJ. *Critical Care Medicine,* 5th ed. Philadelphia, PA: Wolters Kluwer; 2019: Fig. 11.14.)

CT scanners expedite the process of image acquisition and in-suite interpretation. Appropriate concern has been voiced over the risks of moving patients out of the ICU for imaging studies; however, carefully arranged transport is routinely performed reasonably safely. The importance and urgency of any study requiring transport should be weighed against the risk of transport. Alternative studies should be considered that do not require transport if applicable (such as performing an extremity US to locate a DVT rather than CTA chest to evaluate for PE). Portable CT technology can also be used in the right clinical setting. The most important feature of safe transport is to ensure that all vital supports can be effectively maintained and that adequate equipment and personnel are immediately available to cope with any catastrophic event (e.g., accidental extubation or extraction of venous or arterial catheters or chest tubes, interruption of critical infusions, unanticipated cardiac arrest). Patients with bronchopleural fistula needing continual pleural drainage and those requiring vasopressors or high inspired oxygen concentrations or PEEP are at particular risk. It is important to be sure that the intubated patient is able to be adequately oxygenated and ventilated on the transport setup for several minutes before departure. Although now rarely used in transportable patients, interruption of inhaled nitric oxide or nebulized prostacyclin infusions during transport can precipitate calamitous physiologic deterioration. Metallic appliances create artifact on CT scans and may preclude the use of MRI because of the powerful magnetic fields involved. Furthermore, MRI studies are especially time consuming, and the inability of critically ill patients to remain adequately immobile may produce unacceptable motion artifact unless neuromuscular blocking agents are used. If neuromuscular blocking agents are initiated at the time of image acquisition, it is important to ensure that their ventilator settings provide a minute ventilation adequate enough to avoid catastrophic decompensation caused by respiratory acidosis.

CT scanning often requires the use of nephrotoxic contrast material. (Enteral contrast used for abdominal scanning does not carry this risk.) Iodixanol or Nonionix low-osmolality agents can reduce the risk of nephrotoxicity in at-risk patients. Otherwise, administration of IV fluids should be pursued in patients who are intravascularly volume deplete at the time of their examination. Sodium bicarbonate or lactated Ringer's may be preferable to the chloride load of saline. Acetylcysteine is no longer recommended for contrast-induced nephropathy prophylaxis. In years past, MRI was used in place of CT for patients with marginal renal function in an attempt to avoid contrast nephrotoxicity. Unfortunately, the use of some gadolinium-based MRI contrast media may be even more dangerous. Gadolinium has been associated with a rare but progressive and potentially devastating scleroderma-like syndrome known as *nephrogenic systemic fibrosis.* Gadolinium-containing contrast should be avoided in patients with acute kidney injury or who have a baseline estimated glomerular filtration rate (eGFR) of $<$30 mL/min (including patients with end-stage renal disease).

The financial aspects of imaging should not be overlooked. A chest CT scan typically costs three to four times as much as a portable CXR in addition to the costs of transport, which can be substantial. Because patients are placed at higher risk during travel and significant financial and manpower costs are involved, it is logical to plan ahead by bundling studies together when feasible. For example, if an elective head CT is planned tomorrow but an urgent chest CT must be done today, it may make sense to perform both studies today, avoiding the second trip. As a corollary, if an imaging study is likely to yield results that will prompt a radiology-based intervention (e.g., needle or catheter aspiration), it is common sense to confer with the radiologist in advance of the transport, so as to arrange rapid interpretation of the diagnostic study and subsequent intervention in a single trip. Simple preplanning can also avoid wasteful, redundant studies. For example, if a chest CT is to be performed today, there is little reason to do a "routine" morning CXR as well.

In neurocritical care applications, the noncontrasted CT excels for diagnosis of acute intracranial bleeding.[14] It is also helpful when determining if there is an intracranial mass before a lumbar puncture and for detecting sinus cavity opacification. However, detailed anatomic imaging of the brain, spinal cord, and other soft tissues is best performed by MRI (Fig. 59.26). Moreover, detection of acute ischemic strokes by noncontrasted CT is not reliable until many hours have passed after the event (Fig. 59.27A) (though CTAs of the head and neck can identify areas of acute thrombosis, which can be very useful in identifying patients who may benefit from endovascular recannulization), and inflammation of the meninges may evade notice. For these selected problems, MRI is better adapted, as it is immediately sensitive to both (see Fig. 59.27B). With different radiofrequency stimulation and pulsing sequences (so-called "weighting," Fig. 59.28), MRI can reveal inflammation and edema (T2 and fluid-attenuated inversion recovery [FLAIR] weighting) and perfusion adequacy (diffusion weighting). Despite limitations, the chest CT often provides information not otherwise available. It can better differentiate patterns of infiltration or nodularity in the pulmonary parenchyma. It can reveal a small or loculated pneumothorax in patients when previous CXRs are unrevealing. It can well visualize lung abscess or empyema and usually can differentiate between the two conditions. In patients with empyema and atypically distributed pleural effusions or with a persistent pneumothorax, the chest CT is invaluable to evaluate the location and effectiveness of thoracic drainage tubes. A CT better demonstrates the distribution of infiltrates and characteristics of nodules.

In summary, the chest CT represents one of the most useful diagnostic tests available to intensive care practitioners. A short summary list of indications for chest CT scanning includes (1) evaluation of thoracic trauma, (2) searching for occult or persistent sources of fever (empyema, lung, or mediastinal abscess), (3) guiding placement of drainage tubes for loculated or persistent pneumothorax or pleural effusions, (4) detecting

Fig. 59.26 Sagittal magnetic resonance imaging (MRI) of brain and spinal cord. Note the fine anatomic detail provided by T1 weighting. (From Marini JJ, Dries DJ. *Critical Care Medicine,* 5th ed. Philadelphia, PA: Wolters Kluwer; 2019; Fig. 11.15.)

Fig. 59.27 **A,** Time dependence of imaging ischemic stroke by unenhanced computed tomography (*CT*) in a patient presenting with new-onset neurologic deficit. The large ischemic zone was not evident on the earlier study. *Arrows* delineate compromised zone (*left*: upon admission; *right*: after 36 hours). **B,** Comparison of near-simultaneously obtained head CT *(top)* and diffusion-weighted magnetic resonance imaging (*MRI*) *(bottom)* of a patient with ischemic (right hemispheric) stroke. (From Marini JJ, Dries DJ. *Critical Care Medicine,* 5th ed. Philadelphia, PA: Wolters Kluwer; 2019: Fig. 11.16.)

Fig. 59.28 **Options for magnetic resonance imaging (MRI) display (normal brain, axial view).** T1-weighted brightness corresponds to fat content and details the anatomy particularly well. T2 weighting tends to highlight pathology associated with higher water content, such as cerebral edema or inflammation. The fluid-attenuated inversion recovery (FLAIR) image attenuates the cerebrospinal fluid (CSF) brightness of the T2 image and therefore is particularly helpful in distinguishing details of pathology. Diffusion-weighted images (DWI, not shown) are the best option for distinguishing well-perfused from ischemic tissues, as in early stroke. (From Marini JJ, Dries DJ. *Critical Care Medicine,* 5th ed. Philadelphia, PA: Wolters Kluwer; 2019: Fig. 11.17.)

mediastinal pathology (especially in the presence of parenchymal infiltrate), (5) searching for PEs, and (6) evaluating distribution and characteristics of opacities in greater detail than a CXR.

ABDOMINAL RADIOGRAPHY

Abdominal CT and Screening Films

Plain abdominal x-rays have largely been replaced by the abdominal CT scan, so it is important to become familiar with its essential elements (Fig. 59.29). The use of abdominal US and CT scanning is discussed in detail, as it relates to specific disease entities in Chapter 25. The standard examination of the abdomen, consisting of supine kidney-ureter-bladder (KUB) or "flat plate" and upright views, can still be useful and does not require a trip outside the ICU. If an upright film cannot be taken, a lateral decubitus view may be substituted.

KUBs still retain great functionality in the ICU, and like the CXR as compared with the chest CT, have the advantage of bedside mobility and lower cost. Line and tube placements can be verified via KUB. General bowel gas patterns can be examined and evidence of obstruction can be found. Systematic review of the KUB may furnish important information, especially after trauma. Fractures of the lower ribs on the left suggest the possibility of a ruptured spleen or lacerated kidney, as does medial displacement of the gastric bubble. Breaks in lower ribs on the right suggest the possibility of renal or hepatic damage. Fractures of the lumbar spine, pelvis, and hips may be seen as incidental findings on plain abdominal radiographs in trauma patients. A ground-glass appearance, displacement of the retroperitoneal fat stripe, or centralization of gas shadows suggests ascites or hemoperitoneum. Free air usually indicates a ruptured, viscus, gas-producing infection; barotrauma-induced pneumoperitoneum; or postoperative change. Free air is much more commonly seen as the result of upper gastrointestinal (GI) (stomach or duodenum) perforation rather than from colonic perforation (diverticulitis, appendicitis, colon cancer).

The KUB view is a poor indicator of liver size, and when in question, should not supplant careful physical examination or CT evaluation. The gallbladder is inadequately defined on the KUB view unless it is very distended or calcified. Less than 15% of gallbladder calculi are visible. Gas appearing in the biliary ducts is highly suggestive of infectious cholangitis but can occur after endoscopic retrograde cholangiopancreatography. The ingestion of massive amounts of carbonated beverages or intake of compounds that can generate gas when mixed with gastric acid (e.g., sodium bicarbonate) can also cause bile duct gas. Hepatic calcifications, although rare, may occur because of healed infection, hemangioma, or metastatic carcinoma. Films taken in different positions may help determine the location of right upper quadrant calcifications. Calcifications within the kidney or liver maintain a relatively fixed position, whereas stones within the gallbladder are usually mobile. Use of the KUB view in the diagnosis of the acute abdomen is discussed in Chapter 25.

Fig. 59.29 Normal anatomic structures visualized on an axial abdominal computed tomography (CT). (From Marini JJ, Dries DJ. *Critical Care Medicine,* 5th ed. Philadelphia, PA: Wolters Kluwer: 2019: Fig. 11.18.)

Findings Relevant to Specific Organs

Kidneys and Ureters

The visibility of the kidney on the KUB view depends on the amount of perinephric fat and overlying bowel gas. The combination of kidney enlargement and calcification suggests urinary tract obstruction or polycystic kidney disease. Bedside or dedicated renal US should be performed to rule out these conditions if still suspected. If nephrolithiasis is suspected, the renal outlines and course of both ureters should be carefully inspected for calculi (visible in up to 85% of cases). However, a noncontrast CT remains the optimal examination for this condition. Identifying gas in the renal pelvis is uncommon but may indicate emphysematous pyelonephritis, a condition seen most often in poorly controlled diabetics. Gas-producing infections of the bladder are also visualized occasionally.

Pancreas and Retroperitoneum

Asymmetric obliteration of the psoas shadows or retroperitoneal fat lines suggests a retroperitoneal process (most commonly pancreatitis or hemorrhage from a leaking aorta). Similar changes can accompany spontaneous hemorrhage or traumatic disruption. Although the pancreas is not normally seen on the plain radiograph, calcifications may occur in chronic pancreatitis. Localized areas of ileus over the pancreas, such as the "colon cut-off sign" and the "sentinel loop," may also help in the diagnosis of pancreatic inflammation.

Stomach and Bowel

The stomach normally contains some fluid and air. However, massive gastric dilation suggests gastric outlet obstruction, gastroparesis, or esophageal intubation. By contrast, because the small bowel normally contains little air, its gaseous distention indicates ileus or small bowel obstruction. Air-fluid levels of different heights within the same loop of small bowel on an upright film usually indicate mechanical small bowel obstruction and imply residual peristaltic activity. Fluid levels at the same height in a loop of bowel do not necessarily indicate mechanical obstruction. Absence of colonic or rectal gas in patients with small bowel air-fluid levels strongly suggests complete obstruction of the small bowel with distal clearing of gas. Conversely, the presence of gas in the colon (except for small amounts of rectal gas) all but excludes the diagnosis of complete small bowel obstruction. (Ileus or incomplete obstruction may be present, however.)

Colonic obstruction because of a sigmoid volvulus may be diagnosed via a KUB view that shows massive sigmoid dilation; the sigmoid forms an inverted "U" whose limbs rise out of the pelvis. Apposition of the medial walls of these bowel segments produces a midline soft tissue density whose inferior extent approximates the site of torsion. This produces a radiologic finding known as the *coffee bean sign.* A sigmoid volvulus has the bowel loop pointing to the right upper quadrant, whereas a cecal volvulus has the bowel loop pointing to the left upper quadrant. A variety of conditions leading to ICU admission may produce colonic pseudo-obstruction (Ogilvie syndrome) in which massive

colonic dilation occurs because of diminished parasympathetic activity. Radiographically, a CT will demonstrate the absence of a distinct transition point, and unlike the frequently encountered adynamic ileus, affects the small bowel to a lesser degree. Although usually managed conservatively, cecal dilatation to greater than 12 cm suggests the possibility of impending perforation and prompts decompressive interventions.

The frequently observed "thumbprinting" is a useful, highly significant but nonspecific sign of large bowel wall thickening that is most closely associated with ischemia. These nodular indentations appear at regular intervals along the bowel wall and may originate from bowel inflammation from other causes such as Crohn disease, ischemic colitis, *Clostridium difficile,* pseudomembranous colitis, or diverticulitis. Thumbprinting can be seen more chronically in such noninflammatory conditions as lymphoma and amyloid. When seen in conjunction with massive colonic dilation and supportive abnormalities of vital signs, toxic megacolon is highly likely.

Peritoneal Cavity

On the supine abdominal radiograph, ascites is demonstrated by diffuse haze, indistinctness of the iliopsoas stripes, centralization of small bowel segments, and abnormal separation of bowel loops. Increased pelvic density characterizes ascites on the upright film.

Abnormal gas collections are recognized by their nonanatomic location. Therefore all gas densities on supine and erect films require explanation. Each must be assigned to an anatomic segment of bowel. Gas may collect under the diaphragm or overlie the liver on erect or lateral decubitus films, respectively. Free air also allows visualization of both sides of the walls of gas-filled bowel. "Bubbly," curvilinear, or triangular gas collections between segments of bowel suggest abdominal abscess. Bowel ischemia may produce a characteristic pattern known as *pneumatosis cystoides* that represents gas within the bowel wall. Rarely, pneumatosis may rupture to produce free intraperitoneal air, simulating a perforated viscus. Bowel ischemia is more confidently diagnosed when thumbprinting is observed.

ULTRASOUND

Few areas of critical care practice have been adopted as quickly or affected care as profoundly as the bedside application of US imaging. Bedside US has major benefits over other modes of diagnostic imaging, including portability; lack of radiation hazard; speed of data acquisition; low cost; serial repeatability; and the ability to interrogate dynamic properties of the lungs and heart, which helps avoid costly tests, unnecessary delays, and transporting a critically ill patient.

US use in the ICU can be divided into (1) the traditional consultative approach where image acquisition and interpretation are done by providers not involved in bedside patient care and evaluate the organ studied in detail and (2) focused, goal-targeted POCUS, which is usually performed and interpreted by the provider caring for the patient. POCUS use in critical care is becoming more widely adopted because it eliminates clinical and time dissociation in patient care.[15]

Using POCUS for procedural guidance is considered standard of care for many of the procedures performed in an ICU. POCUS can be used as static guidance, such as during thoracentesis or paracentesis where the fluid is identified using POCUS, the skin entry point is marked, and the needle is inserted using the skin mark, or dynamic guidance, such as placement of venous or arterial catheters where the needle is visualized entering the vessel. More recently, POCUS has been used more commonly in the management of patients in shock, respiratory failure, trauma, or cardiac arrest or, less often, for assisting ventilator liberation.

The use of US comes with its own limitations. An adequate ultrasonic window may be obscured or degraded by fat, bone, dressings, or hyperinflated lung. In addition, ultrasonography is a user-dependent technology, and ensuring competence in image acquisition and interpretation is essential to applying POCUS successfully for patient care.[16] Although these skills cannot be acquired without successful hands-on training and practical clinical experience, the range of clinical potential and technical background for US are important to understand.

Organ-Targeted POCUS

Cardiac POCUS

Detailed ultrasonic examination of the stable patient with heart disease continues to be best assigned to consulting cardiologists who formally evaluate detailed echocardiograms acquired with high-capability equipment (Fig. 59.30). In emergency settings and for targeted critical care purposes, however, goal-targeted POCUS can be of high value to direct further steps in management.

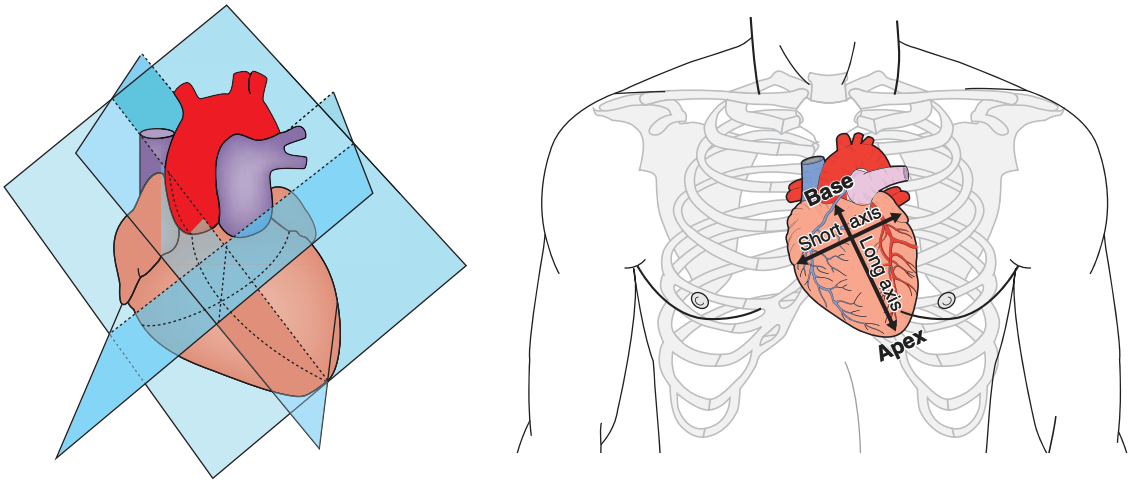


Fig. 59.30 Long and short axes of the heart used in cardiac ultrasound (echocardiography). Knowledge of acoustic windows and structural imaging correlations is quickly becoming an essential skill for the intensivist. (*Left,* from Allen HD. *Moss & Adams' Heart Disease in Infants, Children, and Adolescents, Including the Fetus and Young Adult,* 9th ed. Philadelphia, PA: Wolters Kluwer; 2016; *right,* from Penny SM. *Introduction to Sonography and Patient Care.* Baltimore, MD: Wolters Kluwer; 2015.)

Cardiac POCUS in its most basic form uses five views. Each provides certain information that complements the other views. These views are:

1. Parasternal long-axis view (Fig. 59.31) allows assessment of LV function by assessing myocardial thickening, endocardial excursion, and septal motion of the anterior leaflet of the mitral valve (EPSS) and evaluation of the presence of a pericardial vs. pleural effusion. A posterior pericardial effusion tracks anterior to the descending aorta. It is important to note that epicardial fat pads are hypoechoic and can mimic pericardial effusion. If the hypoechoic area does not move with the heart, it is likely an effusion, whereas if it moves with the heart, it is likely an epicardial fat pad. This view also allows assessment of the left atrial size in comparison with the aortic root and RV outflow tract. Less commonly, large vegetations can be seen clearly on the mitral or aortic valve using this view.
2. Parasternal short-axis view allows assessment of LV function and can visualize the presence of pericardial fluid. This view shows the anterior, lateral, posterior, and septal walls in one plane, which allows identification of wall motion abnormalities in the LV. The presence of the RV in this view allows comparison of right to left ventricular sizes and the assessment of the shape of the septum (flattening of the septum, which gives the LV a D shape, indicates increased RV pressure).
3. Apical four-chamber view is more challenging to obtain in critically ill patients and easier to obtain with the patient in the left lateral decubitus position. In addition to providing much of the same data provided by other views, this view allows measurements of the velocity time integral (VTI) when the aortic outflow tract is in plane. VTI measurement allows the calculation of cardiac output, and repeat measurements help confirm fluid responsiveness. Both are helpful in the management of patients in circulatory shock.
4. Subcostal view visualizes all four chambers and is the easiest way to visualize the heart while resuscitating a patient in cardiac arrest.
5. Inferior vena cava (IVC) view allows IVC measurements and allows the interpreting physician to calculate dynamic changes in IVC size with respiration, which helps identify fluid status and determine fluid responsiveness. When performing this examination, it is essential to ensure the visualized vessel is the IVC and not the aorta.

Experienced POCUS providers can apply advanced echocardiography for assessment of valvulopathy and assessment of diastolic heart disease. As the technical details for performing such studies are readily available in review articles and educational videos, we will not duplicate that work here.

Lung POCUS

Until quite recently, the artifacts on 2D images caused by sonic interactions of tissue and air were disregarded despite their high diagnostic value. Assuming the use of an appropriate probe, depth, and ultrasonic frequency range, normal lung; pneumothorax; and edematous, consolidated, and liquid-filled spaces return characteristic sonograms that vary during tidal breathing (Fig. 59.32). Sliding of the visceral pleura at its interface with the fixed parietal counterpart, in addition to

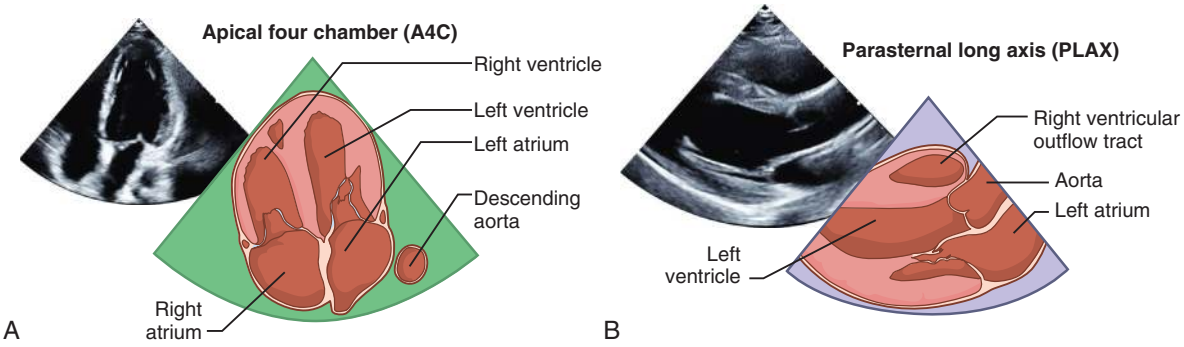


Fig. 59.31 Apical four-chamber **(A)** and parasternal long-axis views **(B)** of the heart with cardiac echo. (Modified from Barnett CF, Sweeney DA, Huddleston LL. Ultrasonography: Advanced applications and procedures. In VC Broaddus, JD Ernst, TE King Jr, et al, eds. *Murray & Nadel's Textbook of Respiratory Medicine,* 7th ed. Philadelphia, PA: Elsevier; 2022: Fig. 24.1.)

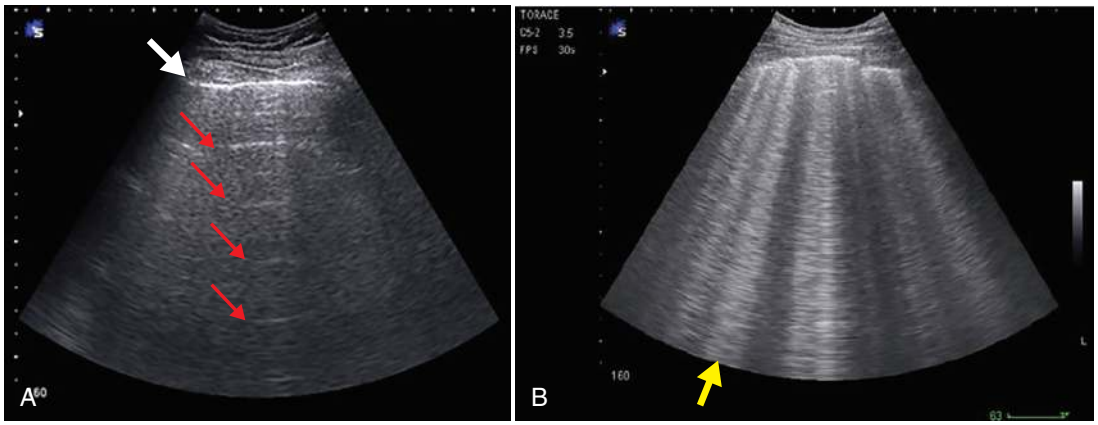


Fig. 59.32 **A,** A-lines *(red arrows)* are the diminishing ultrasonic reverberations of the pleural stripe *(white arrow)* through normal lung tissue. **B,** B-lines are linear streaks *(yellow arrow)* emanating from the pleural boundary. These indicate increased tissue water, such as caused by edema. (From Marini JJ, Dries DJ. *Critical Care Medicine,* 5th ed. Philadelphia, PA: Wolters Kluwer; 2019: Fig. 11.21.)

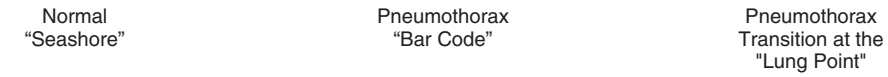


Fig. 59.33 Ultrasonic profiles in M-mode (focal, time based). The stationary transducer in **(A)** and **(B)** paints patterns that indicate blurring caused by lung motion beneath it **(A)** or monotonous reverberation in response to the air barrier caused by pneumothorax **(B)**. When the transducer is positioned at the interface between noncollapsed lung and pleural air, there is an abrupt transition between these ultrasonic M-mode patterns during the phases of the breathing cycle **(C)**. (From Marini JJ, Dries DJ. *Critical Care Medicine,* 5th ed. Philadelphia, PA: Wolters Kluwer; 2019: Fig. 11.23.)

repetitive curvilinear lines that fan out parallel to the pleural surface (A-lines), is characteristic of normal lung. A limited number of hyperechoic, self-erasing lines orthogonal to the pleural plane (B-lines or "lung rockets") are produced by interstitial lung edema. When B-lines are profuse, evenly distributed, and bilateral, alveolar edema likely is present. The homogeneous, sharply demarcated, and distinctly opaque sonographic shadow separating the parietal from the visceral pleura indicates an uncomplicated pleural effusion. Although there is no definite depth to determine safety when sampling pleural fluid, measuring a pleural liquid depth of greater than 1 cm indicates that needle thoracentesis can be safely performed at that site. US is essential to safely perform needle insertion when the patient is receiving mechanical ventilation or when the effusion is loculated.

A pneumothorax is characterized by an echo-free separation between the lung and chest wall. Confirmation is made when a motionless probe detects phasic (tidal) transitions during tidal breathing between echo-free and lung signatures. This "lung point" is confirmed by a "seashore-like" appearance on continuous M-mode tracing (Fig. 59.33).

Use of these characteristics in conjunction with limited cardiovascular ultrasonography directed toward leg clotting and right ventricular dilation is made in systematic protocols designed to rapidly determine the cause of acute dyspnea (e.g., the bedside lung ultrasound in emergency [BLUE] protocol). Thoracic interrogation is performed sequentially at three sites (anterior, lateral, and posterolateral) in the semirecumbent patient as evidence is sought for pneumothorax, lung edema, and consolidation or lung collapse. US of the cardiac and femoral zones completes the appraisal.

Vascular POCUS

As mentioned earlier, POCUS is considered a standard of care for placing vascular catheters. In addition to using the US during the procedure itself, POCUS can evaluate for evidence of a pneumothorax after internal jugular or subclavian central line placement. To do this, first confirm lung sliding in the upper anterior chest before placement. Then repeat the US after the procedure to evaluate the presence or absence of lung sliding. If it was present before and became absent, it suggests a pneumothorax occurred.

Evaluating the presence of DVT using compression ultrasonography is quick and almost as accurate as a radiology-performed full DVT examination in the ICU.[17] It is important to realize that although DVTs can be visualized within the vessel, fresh clots tend to be hypoechoic and cannot be seen. Hence, it is important to perform full vein compression, as lack of vein compressibility indicates the presence of a clot. To perform a lower extremity DVT compression examination, the leg is placed in a frog-leg position (external rotation at the hip with some flexion at the knee), and three to five compression examinations are done over the course of the femoral vein and one to three compression points over the popliteal vein behind the knee. Presence of a DVT could save the patient a trip through the CT scanner if venous thromboembolism (VTE) were suspected.

POCUS can also be used to confirm the presence of flow in the extremities' arteries, which can be helpful when a Doppler signal is not easily obtained. The US can be used to visualize the vessel and can apply color and/or Doppler signal to confirm flow.

Abdominopelvic POCUS

The kidneys are easily accessible with US, and a kidney POCUS examination mainly focuses on the presence or absence of hydronephrosis as an etiology of sepsis or acute renal failure. It is common to see other pathology in the kidneys, including renal cysts during POCUS examinations, and although it is important to be able to differentiate them from hydronephrosis, a detailed examination of the kidneys is still best performed by consultative US examination by a radiography specialist. A renal POCUS examination can be performed on the patient in the supine position by applying the transducer to the flanks, but the left

kidney tends to reside more posteriorly and therefore is more difficult to visualize in a supine patient.

Ultrasound excels in visualizing fluid, which makes it an essential tool to diagnose and treat ascites. Unfortunately, POCUS will not be able to differentiate the type of fluid. Hemoperitoneum and simple ascitic fluid have a similar appearance on US, and if bleeding is suspected, other diagnostic methods may be needed for confirmation. Using a high-frequency linear probe allows visualization of vasculature in the abdominal wall at the needle insertion point. Using this before paracentesis decreases the risk of bleeding complications.

The gallbladder and the biliary ducts can be visualized during POCUS examination either with the patient in the left lateral decubitus (preferred) or supine position. This allows measurement of gallbladder thickness, presence of stones, presence of pericholecystic fluid, and sonographic "Murphy sign." In the right clinical scenario, all can be signs of acute cholecystitis. Obtaining adequate biliary images requires a higher level of skill and expertise to identify pathology correctly. It is often prudent to request consultative US radiology examination to confirm POCUS findings.

Disease-Targeted POCUS

One of the major advantages of POCUS is the ability to evaluate multiple organs rapidly at the bedside with the goal of answering a specific clinical question. Protocols have been published to simplify this concept, combining different organs' ultrasonography to target the treatment of a specific patient presentation.

Trauma FAST Examination

Emergency abdominal US in adults with abdominal trauma (focused assessment with sonography for trauma [FAST] examination) is a widely used management-directing US survey whose results are more reliable after presentations for blunt rather than penetrating trauma (Fig. 59.34). The main goal is to detect newly developed pericardial, intrathoracic, or intraperitoneal free fluid. Acknowledged limitations are that FAST is less sensitive for pelvic bleeding, does not interrogate the retroperitoneum, and cannot reliably differentiate the nature of what caused the pathologic fluid collection (e.g., blood, urine, ascites). Points of sonographic access (windows) are used to evaluate the pericardial, peritoneal, and pleural cavities. Unless a pointed indication interrupts the order, the examination sequence reflects the severity of potential life-threatening risks. The heart is assessed for the presence of cardiac tamponade, global wall motion abnormalities and other evidence of injury, and the adequacy of right ventricular filling.

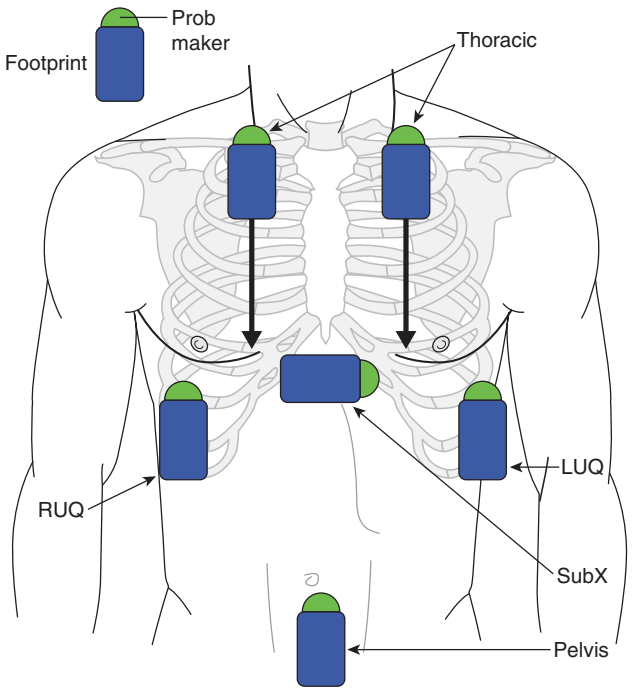


Fig. 59.34 The acoustic ultrasonic windows used in the FAST algorithm. *FAST*, Focused assessment with sonography for trauma. (From Marini JJ, Dries DJ. *Critical Care Medicine,* 5th ed. Philadelphia, PA: Wolters Kluwer; 2019: Fig. 11.24.)

After the heart and pericardium, the right flank (hepatorenal view or "Morison pouch"), left flank (perisplenic view), pelvis, and thorax (pneumothorax and hemothorax) are evaluated. The liver, spleen, and partially filled bladder provide the necessary sonographic windows. The abdominal sequence leads with the right flank and gutter before the left flank and gutter examinations because blood originating from both splenic and hepatic trauma must first pass through the Morison pouch before collecting in the more dependent pelvic cavity.

As in other applications of POCUS, the FAST protocol should be considered to provide very useful, but often not sufficiently definitive, information to preclude radiologic studies or even exploratory surgery. Some serious injuries are seldom visualized confidently by US (e.g., aortic and diaphragm tears, pancreatic lesions, bowel perforations, mesenteric trauma, and injuries that do not produce free fluid in amounts >250 mL). Fluid acutely collected in the pelvis may be either urine or blood. Although important penetrating injuries may go unsuspected with the initial evaluation, overall sensitivity of FAST in these and for all abdominal injuries may improve by performing serial US examinations.[18]

Circulatory Shock RUSH Examination

Using POCUS in a systematic way helps to rule out the major etiologies of shock in an accurate and rapid way. The rapid ultrasound for shock and hypotension (RUSH) examination includes assessment of three cardiac views (parasternal long axis, apical four-chamber, and IVC views) to quickly assess the presence of pericardial fluid/tamponade, evaluate the LV and RV size and function, and determine IVC status.[19] A hyperdynamic LV with small IVC should raise concern for hypovolemic/hemorrhagic shock, but if that hyperdynamic LV was detected in a fluid-resuscitated patient having a large IVC with no respiratory variations, then septic shock should be strongly considered. If an obvious etiology is not identified during the cardiac examination, assessment of both flanks (similar to a FAST examination) allows visualization of any free fluid in hepatorenal and perisplenic views. Typically, the pleural space is evaluated during this time to rule out hemothorax. Unlike a FAST examination, evaluating the kidneys for hydronephrosis is essential to rule out the renal system as an etiology or uncontrolled source of sepsis. Although not commonly encountered in a medical ICU, evaluating the aorta in the epigastric area allows detection of aortic aneurysm, dissection, and even rupture. Lastly, examination of the upper anterior part of the chest to evaluate for lung sliding excludes pneumothorax as an etiology of obstructive shock.

Depending on the clinical circumstances, a RUSH examination also should include a search for ectopic pregnancy and a DVT compression examination.

Acute Respiratory Failure BLUE Protocol

The bedside lung ultrasound in emergency (BLUE) protocol is commonly used for assessment of patients in acute respiratory failure.[20] It uses lung US to categorize the lung signals into different profiles, each associated with a specific diagnosis (Fig. 59.35).

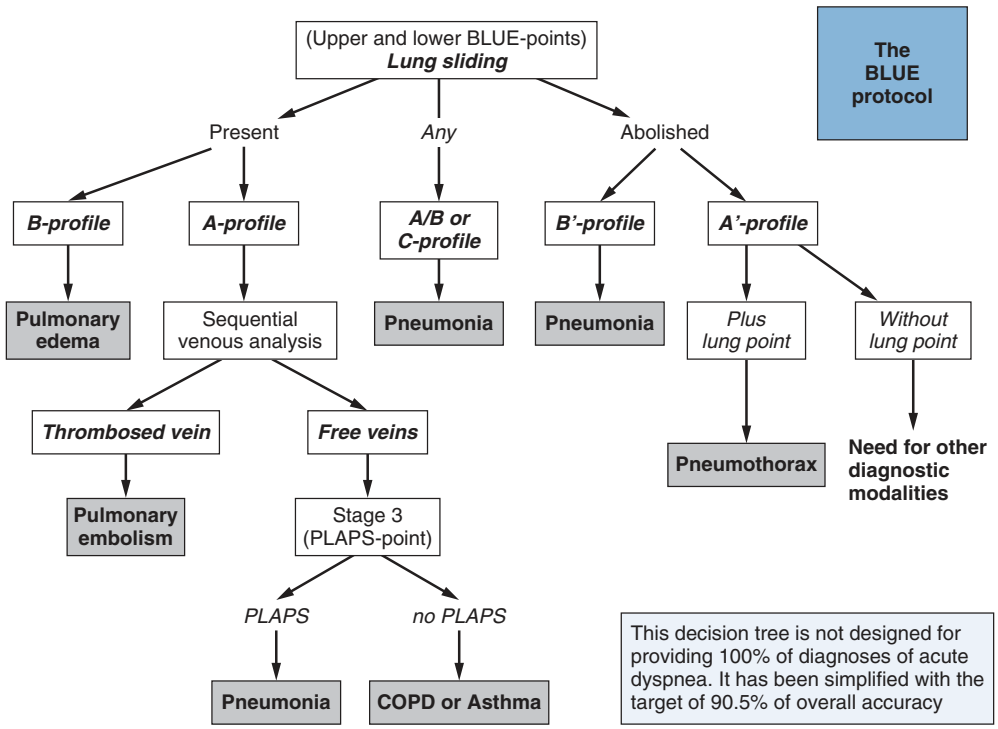


Fig. 59.35 The BLUE protocol. An algorithm using lung ultrasonography to guide diagnosis of severe dyspnea. *BLUE,* Bedside lung ultrasound in emergency; *COPD,* chronic obstructive pulmonary disease. (Modified from Lichtenstein DA, Mezière GA. Relevance of lung ultrasound in the diagnosis of acute respiratory failure: The BLUE protocol [published correction appears in *Chest.* 2013;144(2):721]. *Chest.* 2008;134:117–125, Fig. 7.)

INTERVENTIONAL RADIOLOGY FOR CRITICAL CARE

Interventional radiology (IR) became an indispensable service for critically ill patients in the early 21st century. The ability to perform a wide range of procedures percutaneously enables an ICU physician to pursue therapeutic paths that would have been deemed too risky in many critically ill patients. Dynamic imaging capabilities such as C-arm fluoroscopy and angiography, combined with elegant 3D reconstructions, precise localization, and an ever-expanding arsenal of catheter-based devices and stents, enable physicians to perform high-value, low-morbidity procedures. These include otherwise routine cannulation procedures that cannot be attempted successfully at the bedside, in addition to many sophisticated therapeutic procedures that stabilize hemorrhage and relieve ischemia.

Broadly speaking, the purposes of IR procedures can be classified as vascular and nonvascular in nature. The vascular indications include arterial embolization in patients with uncontrolled bleeding, extraction of thrombi, the placement or manipulation of intravascular catheters, and endovascular stent placements. The latter of these may be lifesaving (e.g., aortic dissection and transjugular intrahepatic portosystemic shunt [TIPS] procedures for portal decompression [Fig. 59.36]). Nonvascular indications for IR generally include drainage of an infected pocket and the placement of stents, feeding tubes, and suprapubic catheters. As noted earlier, these procedures are often performed in lieu of more traditional, invasive surgical procedures. Most IR services perform these procedures, provide consultation, and will assist in the decision-making process. The IR service should be engaged early in this process, particularly when surgical intervention is a contemplated alternative option. Although the range of problems and potential solutions is already vast and continually expanding, several of the more common procedures are highlighted next.

Vascular Interventions

Hemorrhage and Ischemia

A wide variety of life-threatening hemorrhagic events can be effectively addressed by angiography followed by embolization of the culprit vessel (Fig. 59.37). The sources of bleeding commonly involve the bronchial (e.g., submassive or massive hemoptysis), GI/mesenteric (e.g., upper or lower GI bleeding or retroperitoneal bleeding), or solid organ distributions (e.g., splenic rupture or postpartum hemorrhage). Control is routinely achieved, and infarction of the embolized tissue occurs only very rarely. It is important to discuss the findings of an embolization procedure with the interventional radiologist, as often they can provide insight as to whether additional procedures may be necessary to achieve hemostasis.

Type B aortic dissections requiring urgent or emergent correction can frequently be addressed by IR-directed stent placement (Fig. 59.38). End-organ ischemia of cerebral, extremity, mesenteric, or renal systems may often be effectively relieved by thrombus extraction (e.g., stroke) or by stenting, as may symptoms that persist despite optimal medical management. In advanced centers, quite sophisticated manipulations, such as aortic stent graft reconstruction, realignment of true lumen flow, and fenestration, can be successfully accomplished. Traumatic aortic injuries (e.g., pseudoaneurysm, minimal intimal tear, flow-limiting lesions) are evaluated and perhaps better addressed with less morbidity than open surgical repairs. The same principle of endovascular stent graft repair often (but not invariably) is feasible for ruptured thoracic or abdominal aortic aneurysm. These IR procedures carry lower morbidity than invasive surgery and are usually possible, assuming that the anatomy is favorable and the procedure is undertaken emergently. Symptomatically, ischemic smaller vessels of the brain, extremities, and mesentery can also be stented effectively, assuming such preconditions are met.

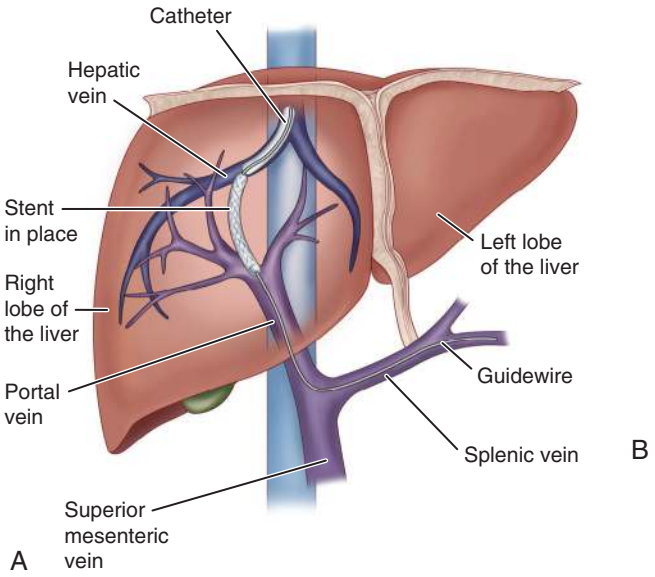


Fig. 59.36 **A,** Schematic depiction of catheter-mediated transjugular intrahepatic portosystemic shunt (TIPS) stenting procedure for portal venous decompression. **B,** TIPS stent inserted via catheter (subtraction fluoroscopic image with contrast). (From Marini JJ, Dries DJ. *Critical Care Medicine,* 5th ed. Philadelphia, PA: Wolters Kluwer; 2019: Fig. 11.25.)

Fig. 59.37 Colonic bleeding and prehemostatic **(A)** and posthemostatic (**B**) coiling of culprit vessel. (From Marini JJ, Dries DJ. *Critical Care Medicine,* 5th ed. Philadelphia, PA: Wolters Kluwer; 2019: Fig. 11.26.)

Venous Thrombosis

IR has been rapidly developing a useful role for both submassive and massive venothrombosis. Although the role of lytic therapy for hemodynamically stable submassive PE remains controversial, IR should be engaged early for consultation regarding catheter-based lytic infusions into the pulmonary artery or thrombectomy when standard medical management fails and systemic fibrinolysis is relatively or absolutely contraindicated.

IVC filter placement can readily be performed by IR. However, the indications for filter placement remain controversial. Generally, failure or a contraindication for systemic anticoagulation in the setting of known VTE remains a widely accepted indication for this procedure. However, there are some limited observational mortality data that call into question the benefit of this procedure even for this indication. Prophylactic IVC filters, especially in the setting of trauma, are recommended by some, but not all, societies, and their recommendation for use has not been entirely resolved (see later).

Perioperative patients with VTE or long bone and pelvic fractures are often candidates, as are those post-endovascular thrombolysis/thrombectomy with residual DVT. Patients who are immobilized with precarious cardiopulmonary compensation who would not be expected to withstand recurrent embolism are often considered, though

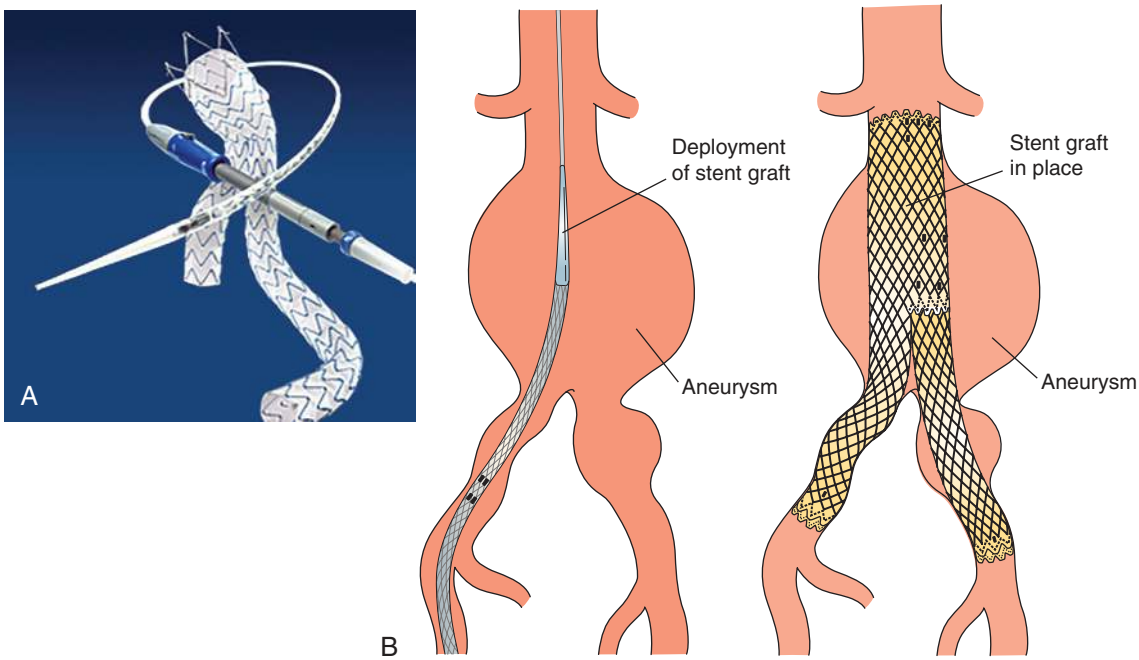


Fig. 59.38 A, Furled and unfurled dimensions of endovascular stent for large vessel. **B,** Insertion and deployment of endovascular stent repair of aortic aneurysm. (From Marini JJ, Dries DJ. *Critical Care Medicine,* 5th ed. Philadelphia, PA: Wolters Kluwer; 2019: Fig. 11.27.)

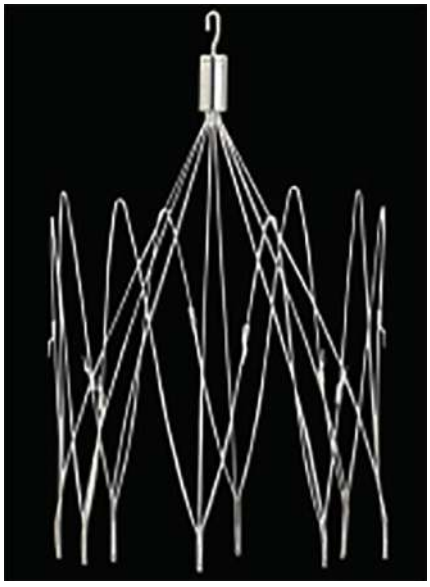


Fig. 59.39 One of many types of IVC filters (VenaTech). After the high-risk period for embolism has passed, the core can be snared by its hook and removed. This allows the cage to remain permanently in place, acting as a stent rather than an occlusive obstruction. *IVC,* Inferior vena cava. (From Marini JJ, Dries DJ. *Critical Care Medicine,* 5th ed. Philadelphia, PA: Wolters Kluwer; 2019: Fig. 11.28.)

again, use of filters in this patient population remains controversial. Overall, the rate of IVC filter placement in the United States has been decreasing since the Food and Drug Administration (FDA) issued a warning for their use in 2010 that was updated in 2014.

Both permanent and retrievable filters (Fig. 59.39) are currently available. Most, if not all, of present-day filters are MRI compatible. Filters can also be convertible over the short term from filtering to nonfiltering functions (see Fig. 59.39).

IR has become a critical part of early stroke management. Endovascular thrombectomy can provide critical restoration of cerebral blood flow in early stroke and carotid artery angioplasty, and stenting can decrease the risk for subsequent events. Likewise, intracerebral vascular stents may be considered to improve jeopardized perfusion of zones with critically compromised blood flow (Fig. 59.40). Cerebral aneurysms can be coiled, as can arteriovenous malformations.

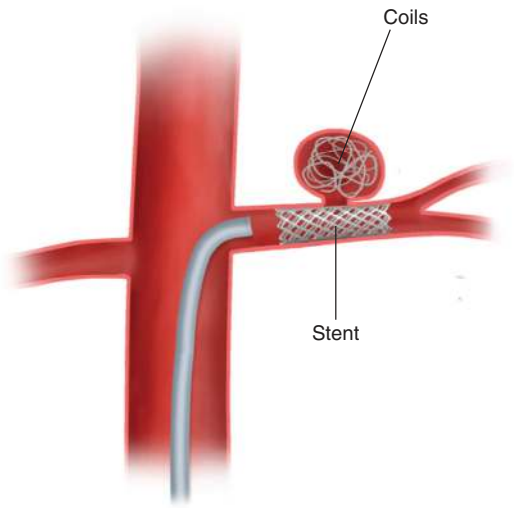


Fig. 59.40 Two useful endovascular interventions for cerebral aneurysm repair: stenting and aneurysm obliteration by coils and clot. (From Marini JJ, Dries DJ. *Critical Care Medicine,* 5th ed. Philadelphia, PA: Wolters Kluwer; 2019: Fig. 11.29.)

Catheter-directed thrombolysis and/or percutaneous thrombectomy has gained increasing traction but remains controversial for certain indications. Full-intensity treatment can be directed to the point of interest, with lower total anticoagulant doses carrying the potential of a full therapeutic effect with less risk of bleeding. However, well-designed multiarm trials have yet to be performed to demonstrate this efficacy in common conditions such as life-threatening pulmonary embolism (i.e., massive or high-risk submassive PE). Given this, the costs and risk of cannulation should be weighed against the theoretical benefit of lytic dose reduction. It should be remembered that patients should not simultaneously receive a thrombolytic infusion and full-dose anticoagulation. There are no clear guidelines as to when full-dose anticoagulation should start after cessation of catheter-directed lytics, and discussion with IR regarding the timing of this transition is recommended. Catheter-directed infusion therapy remains a strong consideration for iliofemoral and caval venous clots. The same strategy can be successfully applied to arterial occlusions occurring in circumstances of peripheral vascular disease or embolic, traumatic, and iatrogenic compromise of extremities, mesentery, or brain.

Percutaneous thrombectomy devices are diversifying and proliferating as their indications for use expand at a very rapid rate. Most devices rely on a suction removal mechanism with or without maceration. Such percutaneous procedures carry less morbidity risk than the more complex surgical interventions with which they compete. However, the efficacy of these devices in treating PE as compared with medical management remains uncertain at this time. Consequently, percutaneous thrombectomy of PE should be considered for patients who fail medical management and who have absolute or significant relative contraindications to thrombolysis.

Vascular Access

Bedside ultrasonography of critically ill patients has both improved the rate of successful placement and reduced the complication rate of vascular access. Nevertheless, many critically ill patients continue to present challenges to achieving bedside vascular access because of factors such as massive obesity, vasculopathy, and/or recurrent instances of ICU care. IR can provide valuable expertise in the placement of US-guided central lines, cooling catheters, hemodialysis catheters, ports, and tunneled central venous lines. Misplaced catheters can also be repositioned with relative ease (Fig. 59.41) and, likewise, arterial line access can usually be attained readily.

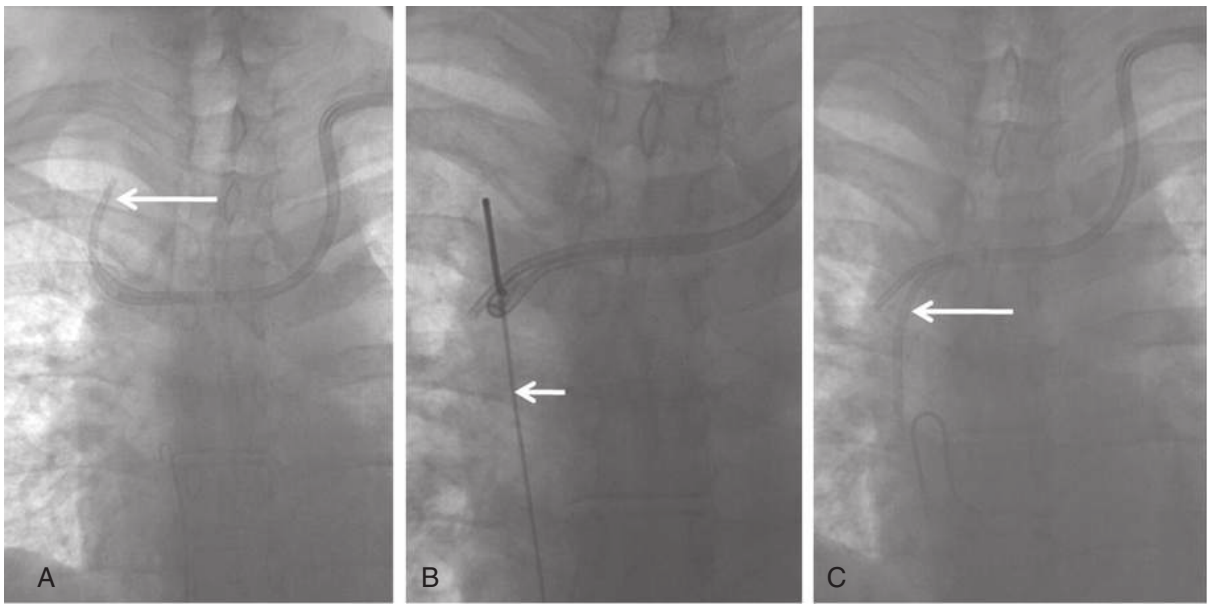


Fig. 59.41 Secondary malposition into the contralateral brachiocephalic vein in a 38-year-old man on hemodialysis. Chest radiograph **(A)** demonstrated the tips *(arrow)* of the left dialysis lines had spontaneously migrated into the right brachiocephalic vein. Fluoroscopy image **(B)** showed the use of a Sidewinder catheter *(arrow)* to pull the lines down into the superior vena cava (SVC). Postintervention image **(C)** showed satisfactory repositioning of the lines *(arrow)*. (From Nayeemuddin M, Pherwani AD, Asquith JR. Imaging and management of complications of central venous catheters. *Clin Radiol.* 2013;68[5]:529–544.)

Management of Pseudoaneurysms

Pseudoaneurysms may form as a result of trauma, infection, penetrating ulcer, or iatrogenesis. Treatment of these depends on location, etiology, and morphology. Infectious (mycotic) lesions generally require vascular surgery. However, IR is particularly well suited to address arterial site access anomalies at the groin, where US-guided thrombin injection may be a good option. Large vessels may be appropriate for stent, graft, or embolization. Traumatic aortic injuries or transections may often be addressed by thoracic stent grafting. Worrisome vascular injuries and tangles in branch vessels of solid organs are generally approached by embolization. Larger feeding vessels are often stented.

Nonvascular Indications for IR

Nephrostomy tubes may be required to address renal obstruction, pyonephrosis, and/or urosepsis if urologic placement of a retrograde stent is not possible or desirable. Abdominal or pelvic drains may best be inserted and positioned radiographically under CT or US guidance. Follow-up imaging is very frequently indicated (e.g., abscessograms and fistula assessment). Complicated abscesses of the lung can be externally drained, but this commonly results in bronchopleural fistula and/or seeding of the pleura with infectious material. Both complications may require later surgical intervention. Given this, thoracic surgical consultation should be pursued before addressing complicated pulmonary abscesses so as to choose the best treatment option. Similarly, though chest tubes are deftly placed into empyema pockets by IR, an open surgical approach is sometimes a better option for complicated spaces. Early surgical consultation is again advised.

Tubes to drain pneumothorax tend to be better positioned, smaller, and more flexible when placed in IR using fluoroscopic or CT guidance, promoting patient tolerance (Fig. 59.42). Poorly functioning drainage tubes that serve any purpose (air/fluid/pus) can be replaced, upsized, or repositioned in IR to optimize performance. After placement, decisions and management of drainage systems can be assigned to the interventional radiologist or to the bedside provider. This decision, if not already assigned by hospital policy, should be made at the time of tube insertion and followed through.

Fig. 59.42 Pigtail catheter inserted by IR into a loculated right apical space *(yellow arrow).* A necrotic abscess is evident on this fluoroscopic image *(red arrow). IR,* Interventional radiology. (From Marini JJ, Dries DJ. *Critical Care Medicine,* 5th ed. Philadelphia, PA: Wolters Kluwer; 2019; Fig. 11.31.)

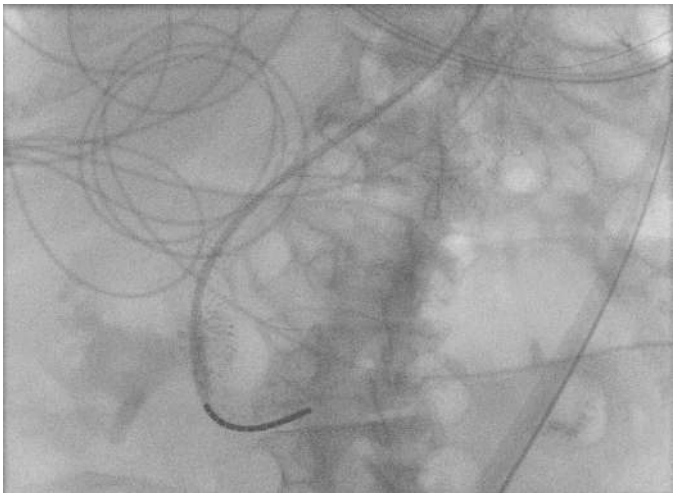


Fig. 59.43 Fluoroscopic placement of a small-bore nasojejunal (NJ) feeding tube transiting the third portion of the duodenum. This placement was performed in the same patient who experienced a previous failed attempt in Figure 59.5.

A variety of indications for IR involvement with tube placement relate to the GI tract. Cholecystostomy tube placement in IR is commonly a first-line intervention for the critically ill at prohibitively high risk for immediate cholecystectomy.

Patients with acalculous cholecystitis may undergo initial drainage, with tube removal occurring 4–6 weeks later, without the need for surgery at all, provided that the cystic and bile ducts are patent. Around two-thirds of patients avoid progressing to cholecystectomy in this way. Drains are also commonly placed when an obstruction cannot be effectively managed by endoscopy.

Feeding tubes, both percutaneous and nasally inserted, are also often placed by IR (Fig. 59.43). Percutaneous feeding tubes include both gastrostomy (G tube) and gastrojejunostomy (GJ tube) variants. The former are placed to vent and drain the stomach and can be used for feeding. The latter may be more appropriate for patients predisposed to reflux and/or inclined to aspirate by gastric dysmotility or outlet obstruction. Insertion of nasal G and GJ tubes is often relegated to IR when this cannot be accomplished at the bedside, for those at unusually high risk for procedural problems or tissue trauma, and for those in whom appropriate tube placement must be unequivocally assured.

Other useful applications of IR services include pain management and suprapubic catheter placement to address bladder outlet obstruction that cannot otherwise be resolved by transurethral insertion. Because challenging anatomy can be addressed, failed attempts at lumbar puncture may sometimes prove successful under IR imaging guidance. Precise site localization before local anesthetic injection may be the only reasonable approach to such intractable pain problems as radiculopathy and abdominal pain addressable by celiac plexus block or ablation (e.g., secondary to pancreatic carcinoma). Finally, intercostal blocks are effectively and safely performed by IR specialists.

KEY POINTS

- The value of a portable CXR usually depends on obtaining an appropriately penetrated, upright exposure in full inspiration. Consistency of technique from day to day is essential to optimize the value of serial films.
- Parenchymal infiltrates have many common potential etiologies, including atelectasis, embolism, edema, and hemorrhage. A minority of infiltrates represents infection; the diagnosis of nosocomial pneumonia requires clinical correlation and microbiologic confirmation.
- Although certain signs may be highly suggestive, the CXR does not reliably distinguish the high-permeability edema of ARDS from the hydrostatic pulmonary edema of volume overload or left heart failure.
- US has burgeoned as an imaging modality for applications by the intensivist, as it poses no risk of contrast or radiation exposure and can provide definitive, dynamic, and high-value information. With its near-immediate availability, US can facilitate an expanding variety of percutaneous bedside procedures and answer emergent questions relating to effusion, lung edema, and pneumothorax.
- Chest CT is quickly completed and often reveals conditions that were not suspected by plain radiographs. Reconstructed images sharply and convincingly define pathoanatomy, especially when contrast agents can be safely given.
- CT is the single best imaging modality for evaluating the abdomen unless the primary working diagnosis is cholelithiasis, ureteral obstruction, or ectopic pregnancy. US may be equally informative in such cases and is often the better choice when contrast exposure for CT is contraindicated.
- MRI is a modality that provides superb soft tissue imaging without ionizing radiation exposure but is time consuming and has relatively few ICU applications that do not relate to neurocritical care.
- IR provides a wide variety of interventions for the critically ill patient that are often of lower risk than traditional surgical interventions.
- Early interactive consultation with the diagnostic or interventional radiologist usually assures the best selection of procedure, optimal patient preparation, and efficient, bundled sequencing of tests and interventions.

References for this chapter can be found at expertconsult.com.

ACKNOWLEDGMENT

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60

Acute Respiratory Distress Syndrome

Julie A. Bastarache, Lorraine B. Ware, and Gordon R. Bernard

Acute respiratory distress syndrome (ARDS) is a common problem in the intensive care unit (ICU) that can complicate a wide spectrum of critical illnesses. First described by Ashbaugh and colleagues in 1967,[1] the syndrome was initially termed *adult respiratory distress syndrome* to distinguish it from the respiratory distress syndrome of neonates. However, with the recognition that ARDS can affect children, the term *acute* has replaced *adult* in the nomenclature in recognition of the typical acute onset that defines the syndrome. Although specific treatments for ARDS have been slow to emerge, new strategies of mechanical ventilation that improve mortality, targeted treatments for severe ARDS that include prone positioning, and fluid management strategies that reduce the duration of mechanical ventilation emphasize the importance of carefully personalized treatment of this condition. Although this point would seem to be straightforward, in practice, ARDS remains underdiagnosed,[2–5] and expert practitioners may disagree on the diagnosis[6–8] and treatment.

EPIDEMIOLOGY

The exact incidence of ARDS has been difficult to determine for a variety of reasons, with estimates ranging from 7 to 85 cases per 100,000 people. In the past, variable definitions of the syndrome were used.[9] The wide variety of causes and coexisting disease processes has also made identification of cases difficult both at the clinical and administrative coding levels.[10] The National Institutes of Health (NIH) first estimated the incidence at 75 per 100,000 population in 1977,[11] whereas a number of studies since then have reported lower incidences.[12] Two prospective studies confirmed the higher original NIH estimate. The first used enrollment logs from the National Heart, Lung, and Blood Institute, which sponsored an ARDS network of 20 hospitals and estimated that the incidence could be as high as 64 cases per 100,000 population. The second was a large, prospective study of residents of King County, Washington. In that study, the crude incidence of ARDS in adults was 78.9 per 100,000 patient years.[10] Several studies in the 1990s and 2000s suggest a decline in the incidence of ARDS over time,[13] including a prospective cohort study of trauma patients at risk for ARDS collected from 1997 to 2004 that showed that the incidence of ARDS decreased from 43% in 1997 to 12% in 2004.[14] A study of almost 3 million patients from the National Trauma Data Bank from 2011 to 2014 showed a further decline in ARDS incidence, with only 1% of all trauma patients developing this condition.[15] Another National Trauma Data Bank study found that among trauma patients who were mechanically ventilated, ARDS incidence decreased from 21.5% to 8.5% from 2007 to 2012.[16] In a population-based study in Olmstead County, Minnesota, the incidence of ARDS declined from 82.4 to 38.9 per 100,000 person-years from 2001 to 2008, despite concurrent increases in severity of acute illness and comorbidities in addition to a higher prevalence of major predisposing conditions.[17] Recent studies suggest that for some risk factors, ARDS incidence may actually be increasing. A large national study of 69 million hospital discharges in the United States from the National Inpatient Sample (NIS) showed that of the almost 1.2 million ARDS discharges, incidence rates increased from 180.7 cases/100,000 US population (2006) to 193.4 cases/100,000 US population (2014).[18] These increased rates were not uniformly distributed, however, with incidence of ARDS in pneumonia, shock, and sepsis increasing steadily over time, whereas rates of trauma- or transfusion-associated ARDS decreased. The global health burden attributed to ARDS is also substantial. A worldwide observational study of 459 ICUs from 50 countries across six continents (the LUNG SAFE study) included high-income European countries, high-income countries from the rest of the world, and middle-income countries. That survey showed wide variation in ARDS cases in the ICU, ranging from 6% to 48% of ICU patients during the 4-week study period.[5] Twenty-five percent of patients met criteria for severe ARDS in the European and middle-income countries, whereas only 18% had severe ARDS in high-income countries elsewhere. Another prospective multinational study of 119 ICUs from 16 countries (the PRoVENT study) found that among ICU patients at risk for ARDS, only 7% of patients developed ARDS.[19] Regardless of the exact incidence, it is clear that ARDS is a major global public health problem that will be encountered frequently by all physicians who care for critically ill patients.

RISK FACTORS

ARDS almost always occurs in the setting of a predisposing factor (Table 60.1), and the likelihood increases with multiple risk factors.[20,21] The commonly associated clinical disorders can be separated into those that directly injure the lung and those that indirectly injure the lung. Although it is not always feasible to determine the exact cause of ARDS in a given patient, direct causes appear to account for approximately one-half of all cases.[22] Regardless of the underlying cause, most patients with ARDS have a systemic illness with inflammation and organ dysfunction that are not confined to the lung.[23] Although the Berlin definition of ARDS requires designation of a risk factor, there is a small group of patients (2.2% of ARDS patients enrolled in ARDS network trials) who clinically have ARDS but do not have an identifiable risk factor.[24] These patients tend to be younger, have lower baseline severity of illness, and experience more ventilator- and ICU-free days.

Sepsis is the most common cause of indirect lung injury, with an overall risk of progression to ARDS of approximately 30%–40% among patients with sepsis requiring ICU admission.[18,20,25–27] In addition to sepsis itself being a risk factor for ARDS, the site of infection may influence the risk of lung injury. Among patients admitted to an ICU with sepsis, patients who had pneumonia as the source of sepsis

TABLE 60.1 Risk Factors Associated With the Development of Acute Respiratory Distress Syndrome

Direct Lung Injury	Indirect Lung Injury
Pneumonia	Sepsis
Aspiration of gastric contents	Multiple trauma
Pulmonary contusion	Cardiopulmonary bypass
Fat, amniotic fluid, or air emboli	Drug overdose
Near-drowning	Acute pancreatitis
Inhalational injury	Transfusion of blood products
Reperfusion pulmonary edema	
Vaping	

had an increased risk of ARDS compared with those with infections at other sites (abdomen, skin, soft tissue, etc.).[28] There is undoubtedly some geographic variation in risk of ARDS by site of infection. In developing countries or those in the tropics, risk factors for ARDS may be very different from those encountered in other parts of the world. For example, a study from India found that the four most common risk factors for ARDS were leptospirosis (18.7%), bronchopneumonia (17.3%), scrub typhus (12%), and dengue (12%).[29] Severe trauma with shock and multiple transfusions also can cause damage indirectly. Although the other causes of indirect lung injury are less common, many, such as transfusion,[30] are common interventions in the ICU setting. The most common cause of direct lung injury, pneumonia, may be of bacterial, viral, or fungal origin. In recent years, new risk factors for direct lung injury have emerged, including novel respiratory viruses such as severe acute respiratory syndrome (SARS),[31] Middle Eastern respiratory syndrome (MERS)[32] and other coronaviruses,[33] and inhaled exposures such as inhalation of vapors from electronic (e) cigarettes or other delivery vehicles.[34,35] Emerging in the summer of 2019, e-cigarette (vaping)–associated lung injury (EVALI) was first described among mostly young adults who presented with a clinical syndrome identical to ARDS.[36,37] Although the chemical composition of vaping liquid is complex, many cases seem to occur in patients using tetrahydrocannabinol (THC)-containing e-cigarettes.[36,38–41] Secondary conditions may also increase the risk. Such factors include chronic lung disease,[27] chronic or acute alcohol abuse,[42,43] cigarette smoking,[30,44,45] air pollution,[46–48] lung resection,[49] and obesity.[50] Interestingly, several studies have shown that patients with diabetes are less likely to develop ARDS.[51–53]

ARDS risk may be modified by the underlying genetic makeup of the individual. A genome-wide association study (GWAS) of African American patients with ARDS showed an association with a single nucleotide polymorphism (SNP) in the P-selectin glycoprotein ligand-1 gene.[54] A larger study of patients of European ancestry with sepsis as the risk factor for ARDS identified associations between variants in fms-related tyrosine kinase (FLT1), which encodes the vascular endothelial growth factor receptor 1 (VEGFR-1) protein, and the risk of ARDS.[55] Blood type, which is genetically regulated, may also be a risk factor for ARDS; blood type A is associated with increased risk of ARDS after sepsis or trauma.[56] Another study identified a variant of the hemoglobin scavenging protein haptoglobin (haptoglobin 2 allele) that is associated with increased ARDS among ICU subjects at risk.[57] Whether genetic risk factors for ARDS will eventually lead to more targeted clinical care for these patients is not yet clear.

Age may also be a risk factor, with some studies indicating higher ARDS risk with increasing age.[50] However, there may in fact be a nonlinear distribution of ARDS risk by age, as demonstrated by a multicenter cohort study of 5584 at-risk patients showing that adults >80 years old had a lower rate of ARDS (3.5%) versus those <80 years old (7.2%).[58] Another somewhat surprising finding is that prehospital vulnerability as measured by the Vulnerable Elders Survey (VES) was not associated with increased risk of ARDS.[59] Although transfusion of blood products is a well-known risk factor for ARDS,[60–63] the risk may differ by indication for transfusion. In the perioperative period, transfusion of blood products is associated with an increased risk of ARDS, particularly among those ventilated with high tidal volumes and driving pressures.[63] However, in an analysis of severely injured trauma patients who were treated with different transfusion regimens (the PROPPR study), infusion of crystalloid, but not blood products, was associated with an increased risk of ARDS, with each 500 mL of crystalloid infused increasing the ARDS rate by 9%.[64] To some extent, almost every patient in the ICU is at risk for developing ARDS, and vigilance is required to recognize the diagnosis and treat appropriately.

PATHOPHYSIOLOGY

The complex pathophysiology of ARDS remains incompletely understood.[65] Microscopically, lungs from afflicted individuals in the early stages typically show diffuse alveolar damage, with alveolar flooding by proteinaceous fluid, neutrophil influx into the alveolar space, loss of alveolar epithelial cells, deposition of hyaline membranes on the denuded epithelial basement membrane, and formation of microthrombi (Fig. 60.1).[66] The alveolar flooding occurs as a result of injury to the alveolar-capillary barrier and is a major determinant of the hypoxemia and altered lung mechanics that characterize early ARDS. The alveolar-capillary barrier is formed of two separate cell layers—the microvascular endothelium and the alveolar epithelium. Injury to the alveolar epithelium is a prominent feature histologically, with loss of alveolar epithelial barrier integrity and sloughing of alveolar epithelial type I cells. Alveolar epithelial apoptosis is widespread and likely contributes to the loss of epithelium seen ultrastructurally.[67,68] Although endothelial injury is less obvious at the microscopic level, ultrastructural studies reveal that it is widespread[69,70] and is accompanied by increased permeability.[65] Endothelial injury allows leakage of plasma from the capillaries into the interstitium and air spaces. The alveolar flooding in ARDS is characterized by protein-rich edema fluid resulting from the increased permeability of the alveolar-capillary barrier, in contrast to the low-protein pulmonary edema that results from hydrostatic causes such as congestive heart failure or acute myocardial infarction.[71–74] Over time, the pathologic changes of ARDS evolve, such that acute inflammation and pulmonary edema become less prominent and fibrosing alveolitis may appear. Recent autopsy studies show that fibroproliferative changes can be seen even early in ARDS and may coexist with exudative changes.[75] These may progress or resolve with time.

Neutrophils play an important role in the initial inflammatory response of ARDS.[76] Early ARDS is characterized by migration of neutrophils into the alveolar compartment.[69,70] Neutrophils can release a variety of injurious substances, including proteases such as neutrophil elastase, collagenase, and gelatinases A and B and reactive nitrogen and oxygen species. In addition, they can elaborate proinflammatory cytokines and chemokines that amplify the inflammatory response in the lung. Recent evidence suggests that neutrophil extracellular traps (NETs) that contain DNA, histones, and other intracellular proteins may act as damage-associated molecular patterns in amplifying the immune response in ARDS.[77,78] Resident alveolar macrophages are also involved in initiating and sustaining a proinflammatory cytokine cascade that leads to recruitment of neutrophils into the lung.[79] Age may be a factor in regulation of the pulmonary host response in ARDS.

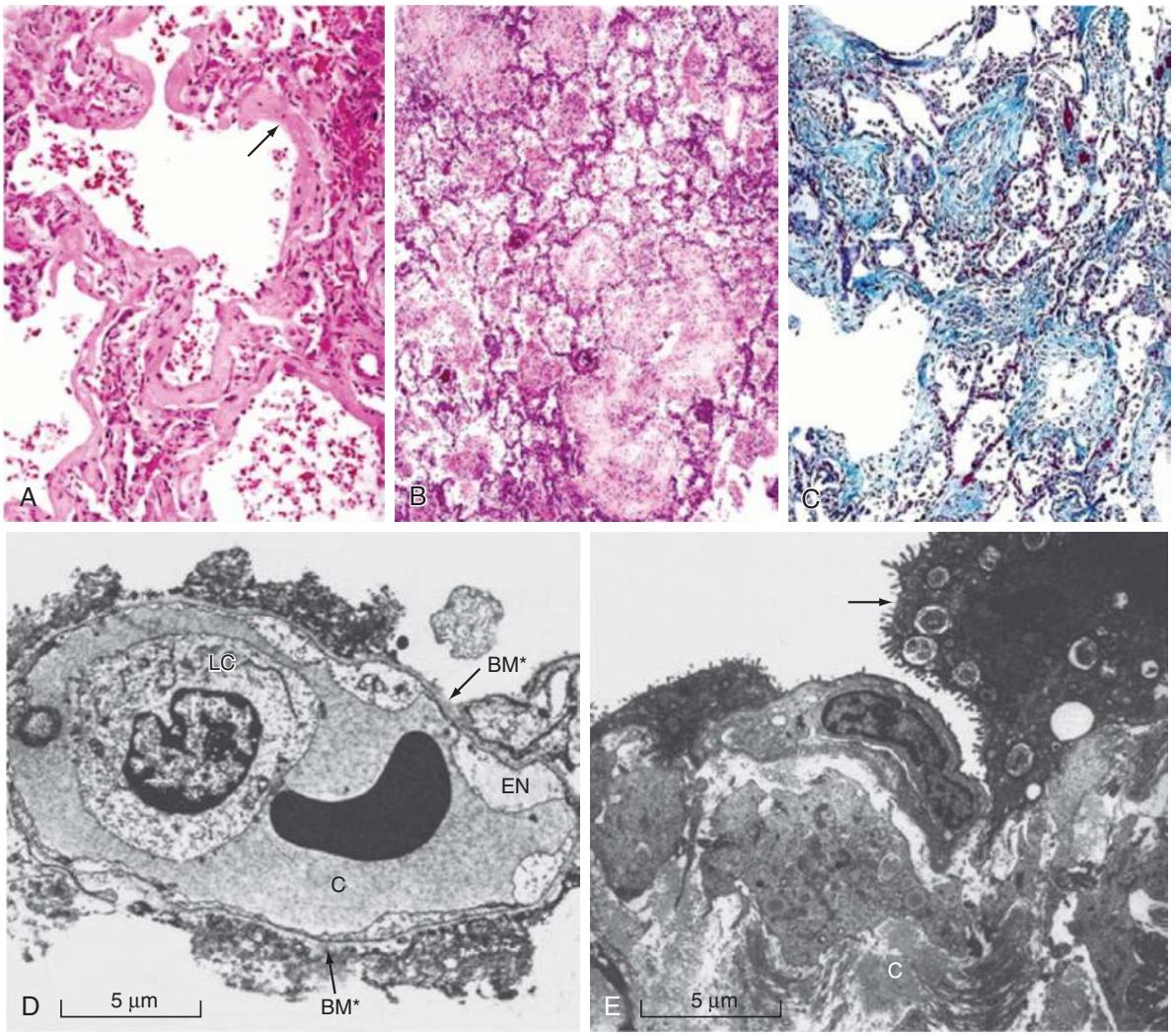

Fig. 60.1 Histologic Findings in Acute Respiratory Distress Syndrome (ARDS). **A,** A lung biopsy specimen obtained from a patient 2 days after the onset of the syndrome as a result of the aspiration of gastric contents. Characteristic hyaline membranes are evident *(arrow)*, with associated intraalveolar red cells and neutrophils, findings consistent with the pathologic diagnosis of diffuse alveolar damage (hematoxylin and eosin, ×90). **B** and **C,** Lung biopsy specimens obtained 14 days after the onset of sepsis-associated ARDS. **(B)** shows granulation tissue in the distal air spaces with a chronic inflammatory-cell infiltrate (hematoxylin and eosin, ×60). Trichrome staining in **(C)** reveals collagen deposition *(dark blue areas)* in the granulation tissue, a finding consistent with the deposition of extracellular matrix in the alveolar compartment (×60). **D,** A specimen of lung tissue from a patient who died 4 days after the onset of ARDS; there is injury to both the capillary endothelium and the alveolar epithelium. An intravascular neutrophil *(LC)* can be seen in the capillary *(C)*. Vacuolization and swelling of the endothelium *(EN)* are apparent. Loss of alveolar epithelial cells is also apparent, with the formation of hyaline membranes on the epithelial side of the basement membrane *(BM*)*. **E,** A specimen of lung tissue obtained from a patient during the fibrosing-alveolitis phase in which there is evidence of reepithelialization of the epithelial barrier with alveolar epithelial type II cells. The *arrow* indicates a typical type II cell with microvilli and lamellar bodies containing surfactant. The epithelial cell immediately adjacent to this cell is in the process of changing to a type I cell, with flattening, loss of lamellar bodies, and microvilli. The interstitium is thickened, with deposition of collagen **(C)**. (Permission from Ware LB, Matthay MA. Medical progress: the acute respiratory distress syndrome. *N Engl J Med.* 2000;342:1334–1349.)

Older adults have more exuberant inflammation in the lung compared with children and younger adults.[80]

In addition to acute neutrophilic inflammation and elaboration of a proinflammatory cytokine cascade, a variety of other abnormalities contribute to the pathogenesis of ARDS. Surfactant dysfunction is characteristic, with abnormalities in both the protein and lipid components.[81–84] This dysfunction likely results from disruption of normal surfactant activity by the influx of plasma proteins into the air spaces, intraalveolar proteolysis, and injury to the alveolar epithelial type II cells. Surfactant dysfunction may have important implications, both for lung mechanics and for host defense.[85] Activation of the coagulation cascade and impaired fibrinolysis are also apparent in patients with ARDS,[86,87] both in the lung[88–90] and systemically.[91] The airspace in ARDS is also characterized by increased oxidative stress with an alteration in the balance of endogenous oxidants and antioxidants with a fall in endogenous antioxidants[92] despite increased oxidant production.[93]

The contribution of ventilator-associated lung injury to the pathogenesis of ARDS has been increasingly recognized. There are several mechanisms by which mechanical ventilation can injure the lung. Ventilation at very high volumes and pressures can injure even the normal lung, leading to increased-permeability pulmonary edema caused by capillary stress failure[94] in conjunction with sustained elevations of circulating plasma cytokines.[95] In the injured lung, even tidal volumes that are normally well tolerated can lead to alveolar overdistention in relatively uninjured areas because the lung available for distribution of the administered tidal volume is greatly reduced and the distribution of inspired gas and stresses is uneven.[96,97] In addition to alveolar overdistention, cyclic opening and closing of atelectatic alveoli can cause lung injury even in the absence of alveolar overdistention. The combination of alveolar overdistention with cyclic opening and closing of alveoli is particularly harmful and can initiate a proinflammatory cytokine cascade.[98] A ventilatory strategy that was designed to minimize alveolar overdistention and maximize alveolar recruitment ameliorated this proinflammatory cytokine release.[99] This fundamental insight into the pathogenesis of clinical ARDS has led to multiple clinical trials of novel ventilatory strategies for patients with ARDS, including the landmark ARDS Network trial of 6 mL/kg versus 12 mL/kg tidal volume ventilation[100] and several trials of higher levels of positive end-expiratory pressure (PEEP) with or without maneuvers intended to maximize alveolar recruitment (see "Treatment" section later).

Although current treatment for all patients with ARDS is similar regardless of cause, emerging evidence indicates that there may be biologically and clinically distinct subphenotypes within ARDS that may respond differently to treatment.[101] One such distinction is between patients who develop ARDS as a result of direct injury to the lung (secondary to pneumonia or aspiration) and those who have primarily indirect injury to the lung because of a systemic insult (secondary to nonpulmonary sepsis or pancreatitis). Whether the distinction between direct and indirect lung injury is clinically useful is unclear,[102,103] but there are biologic differences between direct and indirect lung injury that inform pathogenesis. Patients with direct lung injury have higher circulating markers of lung epithelial injury, whereas those with indirect lung injury have higher levels of markers of endothelial injury.[104] Some investigators have demonstrated reduced respiratory system compliance in patients with ARDS caused by direct pulmonary injury as compared with that of indirect causes,[105] although total respiratory system compliance (including the chest wall) is similar.[106] Improved lung mechanics may be more likely in patients with direct lung injury with the application of PEEP and alveolar recruitment maneuvers.[107,108] However, in the largest cohort of patients studied to date, there was no difference in mortality between those with direct (pulmonary) and indirect (extrapulmonary) causes of lung injury.[22]

A potentially more clinically useful distinction is between ARDS subphenotypes derived using statistical approaches. Calfee and colleagues used latent class analysis to discover two distinct ARDS subphenotypes among patients enrolled in two large clinical trials based on clinical, laboratory, and biomarker measurements.[109] One group was characterized by high levels of proinflammatory cytokines, higher use of vasopressors, a higher prevalence of sepsis, and lower serum bicarbonate (hyperinflammatory endotype). This group had higher mortality and fewer ventilator-free and organ failure–free days compared with the group that had a more hypoinflammatory endotype. Most interestingly, the same two classes with similar defining features were independently derived from five large, heterogeneous patient cohorts.[110–112] Although these initial studies used a multitude of clinical, physiologic, and laboratory measures to identify endotypes, the model has subsequently been refined and simplified, such that excellent classification can be achieved with three variables: interleukin (IL)-8, protein C, and bicarbonate.[113] Although identification of biologically and clinically meaningful subphenotypes has the potential to alter therapeutic approaches to ARDS, it also may lead to significant breakthroughs in our mechanistic understanding of ARDS. For example, the two previously described ARDS subphenotypes have been shown to have distinct gene expression profiles in circulating leukocytes.[114]

DIAGNOSIS

Clinical Criteria

Several clinical definitions have been used for the diagnosis of ARDS since it was first described in 1967. Before 1994, a variety of definitions were used, including the Murray Lung Injury Score.[115] In 1994 the American–European Consensus Conference (AECC) published new clinical definitions for acute lung injury (ALI) and ARDS.[9] A modified version of the AECC definition, the Berlin definition,[116] is currently the primary diagnostic tool for ARDS for both clinical diagnosis and research purposes (Fig. 60.2). To meet the definition, the onset of ARDS, including bilateral infiltrates on chest radiograph, must occur within 1 week of a known precipitant. Patients must be receiving ≥5 cm H_2O of continuous positive airway pressure (CPAP); for mild ARDS, this airway pressure can be delivered by noninvasive positive-pressure ventilation. Severity is classified based on the degree of hypoxemia as mild, moderate, or severe. Mechanical properties of the respiratory system, such as compliance, are not used to grade disease severity. In all patients with suspected ARDS, an underlying cause of ALI (see Table 60.1) should be sought. In the absence of an identifiable underlying cause, particular attention should be given to other causes of pulmonary infiltrates and hypoxemia, such as hydrostatic (cardiogenic) pulmonary edema. Finally, the Berlin definition recognizes that elevated vascular

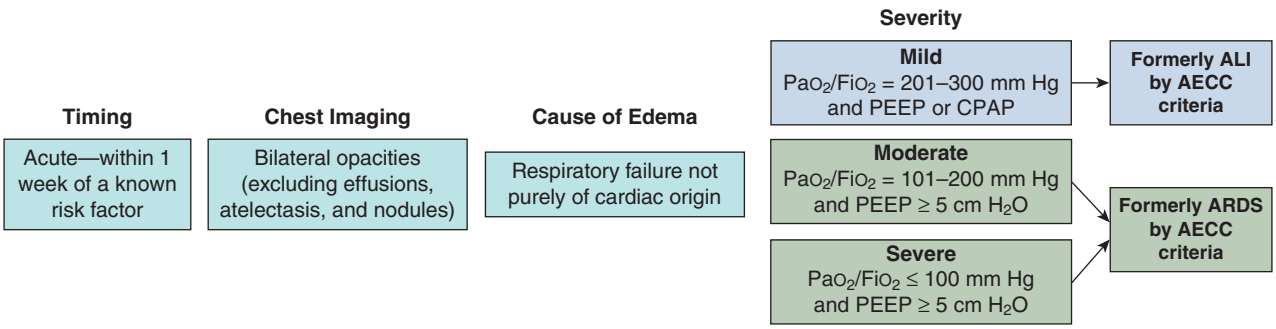

Fig. 60.2 The Berlin definition of ARDS. *AECC*, American–European Consensus Conference; *ALI*, acute lung injury; *ARDS*, acute respiratory distress syndrome; *CPAP*, continuous positive airway pressure; *FiO_2*, fraction of inspired oxygen; *PaO_2*, partial pressure of oxygen *PEEP*, positive end-expiratory pressure.

filling pressures and ARDS can coexist; there is no absolute requirement in the Berlin definition to rule out a cardiac cause of pulmonary edema unless a patient's respiratory failure cannot be explained fully by an ARDS risk factor. In such instances, objective cardiac testing such as echocardiography or pulmonary artery catheterization can be used.

One potential limitation of the Berlin definition is the need for arterial blood gas sampling to calculate a PaO_2/FiO_2 ratio. Recent work has shown good correlation between the SpO_2/FiO_2 ratio (measured by pulse oximetry) and the PaO_2/FiO_2 ratio,[117,118] with an SpO_2/FiO_2 ratio of 235 corresponding to a PaO_2/FiO_2 ratio of 200 and an SpO_2/FiO_2 ratio of 315 correlating to a PaO_2/FiO_2 ratio of 300. These correlations are valid only when the SpO_2 is less than 98% because the oxyhemoglobin dissociation curve is flat above this level. As measurement of oxygen saturation is noninvasive, continuous measurements and the use of the SpO_2/FiO_2 ratio in addition to the PaO_2/FiO_2 ratio may improve the ability of clinicians to diagnose ARDS and monitor its progression.[119]

Differentiation between ARDS and hydrostatic edema can be difficult, and there may be significant overlap in these conditions (Fig. 60.3).[120] A multicenter trial of intravenous catheter–directed fluid management strategies in patients with ARDS showed that 29% of those with clinically defined ARDS had a pulmonary artery occlusion pressure (PAOP) >18 mm Hg at the time of pulmonary artery catheter insertion but that 97% had a normal or elevated cardiac index, suggesting that they did not have clinical heart failure.[121] Other studies have shown similar rates of elevated PAOP in patients with ARDS.[122] There are no specific clinical or laboratory studies that can reliably distinguish between ARDS and hydrostatic edema. A study examining the diagnostic utility of serum levels of B-type natriuretic peptide (BNP) showed that BNP measured at admission could not reliably differentiate between hydrostatic edema and ARDS. Furthermore, BNP levels in these patients did not correlate with invasive hemodynamic measurements.[123] N-terminal BNP levels are also elevated in ARDS[124] but do not necessarily correlate with PAOP.

ARDS is a syndrome, not a specific disease. Therefore although the standardization of ARDS definitions has been of value for both clinical diagnosis and clinical research, the nature of ARDS is such that any definition will have shortcomings. First, the Berlin definition is based solely on clinical criteria because currently there is no laboratory test that allows clinical assessment of the presence or absence of ARDS. Second, the presence or absence of multiorgan dysfunction, an important determinant of outcome, is not specified. Finally, although the presence of bilateral infiltrates has major prognostic significance and is clearly a hallmark of the syndrome, the radiographic findings are not specific for ARDS,[6,125] and a variety of other conditions can produce them (Table 60.2).[126] For these reasons, diagnostic uncertainty in ARDS is common,[127] is a major barrier to initiation of appropriate therapy, and is one of the main reasons why clinicians fail to initiate lung-protective ventilation in clinically appropriate patients.[128]

Invasive Methods

In the majority of patients, the initial diagnosis of ARDS is made clinically. Invasive procedures for the diagnosis of ARDS are of limited clinical utility, and the benefits often do not outweigh the risks.[129] Among the potential invasive diagnostic methods available, bronchoscopy is the one most frequently used. Bronchoscopy may be indicated in the early phases of ARDS in patients for whom there is no identifiable predisposing risk factor and in the immunosuppressed. Bronchoalveolar lavage for cultures and cytologic examination can identify the cause of pneumonia and is particularly useful in the diagnosis of opportunistic infections. Lavage fluid usually has a predominance of

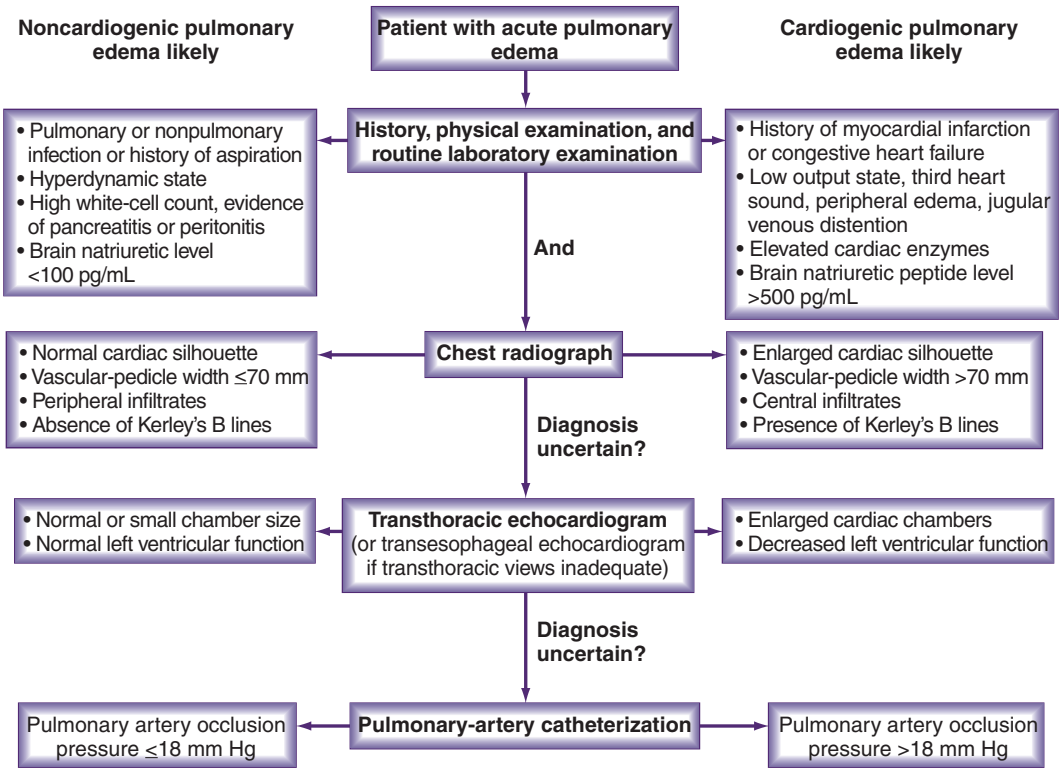

Fig. 60.3 Algorithm for Differentiating Between Cardiogenic and Noncardiogenic Pulmonary Edema. (With permission from Ware LB, Matthay MA. Clinical practice. Acute pulmonary edema. *N Engl J Med.* 2005;353[26]:2788–2796.)

TABLE 60.2 Conditions That Mimic ARDS

	Findings on Chest Imaging	Potential Diagnostic Tests
Diffuse alveolar hemorrhage	Bilateral alveolar and ground-glass infiltrates	Bronchoscopy with bronchoalveolar lavage
Pulmonary alveolar proteinosis	Central and lower lung zone alveolar infiltrates, "bat wing" appearance, "crazy paving" on CT	High-resolution CT, bronchoscopy with bronchoalveolar lavage and PAS staining
Acute interstitial pneumonia	Bilateral alveolar and ground-glass infiltrates, septal thickening, traction bronchiectasis	No alternative cause of ARDS identified, open or thoracoscopic lung biopsy
Cryptogenic organizing pneumonia	Peripheral distribution of alveolar infiltrates, migratory infiltrates	Bronchoscopy with transbronchial lung biopsy
Acute exacerbation of idiopathic pulmonary fibrosis	Ground-glass opacities superimposed on peripheral, basilar fibrotic changes	CT demonstrating characteristic fibrotic changes

ARDS, Acute respiratory distress syndrome; *CT,* computed tomography; *PAS,* periodic acid–Schiff.

Adapted from Janz DR, Ware LB. Approach to the patient with the acute respiratory distress syndrome. *Clin Chest Med.* 2014;35(4):685–696.

neutrophils, and there may be evidence of diffuse alveolar hemorrhage. Cytologic examination can be used to confirm the presence of diffuse alveolar damage.[130] Rarely, an alternative and directly treatable diagnosis is found, such as acute eosinophilic pneumonia, pulmonary alveolar proteinosis, diffuse alveolar hemorrhage, or unsuspected infection.

In the past, open lung biopsy was obtained more frequently for diagnosis. The degree of histologic abnormality on lung biopsy does not correlate with ultimate outcome as measured by pulmonary function,[131] but is associated with increased mortality.[132] Predictors of diffuse alveolar damage, the pathologic hallmark of ARDS, include duration of ARDS, more severe hypoxemia, increased tidal driving pressure, and more severe radiographic abnormalities.[133] Histologic appearance of the lung is widely varied, even in clinical ARDS, with one retrospective study finding diffuse alveolar damage (48%), lung fibrosis (39%), and organizing pneumonia (24%) on biopsies.[134] Open or thoracoscopic lung biopsy may still be useful in some cases for which the diagnosis remains uncertain and the underlying cause is not apparent. Although open lung biopsy can provide findings that lead to a change in treatment, postoperative complications occurred in 22%–35% of patients.[134,135] Several pathologic studies have shown that biopsy or autopsy can identify unsuspected diagnoses requiring specific therapy such as miliary tuberculosis, pulmonary blastomycosis, aspergillosis, or bronchiolitis obliterans organizing pneumonia in 40%–60% of cases[136–138]; however, the general applicability of these studies may be limited by the fact that they were retrospective case series. In a meta-analysis of published studies, open lung biopsy for well-selected patients altered their management in 73% of cases[135]; biopsy findings that alter management may be associated with better survival.[139]

In addition to familiarity with the Berlin definition of ARDS, the critical care clinician should be aware that ARDS has been called by a variety of other terms, some of which are seen mainly in older literature, but some remain in clinical use. Some of the more common of these terms include adult hyaline membrane disease, postperfusion lung or pump lung, shock lung, and adult respiratory insufficiency syndrome. The terms *reperfusion pulmonary edema, primary graft dysfunction, primary graft failure,* and *transplant lung* have been used to describe ARDS occurring immediately after lung transplantation. In addition, newly defined syndromes such as SARS,[31] MERS,[32] and EVALI[34,39,41] may be used to describe ARDS from specific causes. Regardless of the name applied, ARDS is a clinical syndrome that has prognostic and therapeutic implications above and apart from the underlying cause (i.e., infections, aspiration, trauma). This fact does not diminish the imperative to identify these underlying causes, if present, and treat them appropriately.

CLINICAL COURSE

Early ARDS

The Berlin definition aims to identify ARDS patients early in their course, in the acute or exudative phase. Clinically, the acute phase is manifested by the acute onset of radiographic infiltrates consistent with pulmonary edema, hypoxemia, and increased work of breathing. Radiographic infiltrates are bilateral (by definition) but may be patchy or diffuse, fluffy or dense (Fig. 60.4), and pleural effusions may occur.[140] The chest radiograph can be used to quantify the degree of pulmonary edema by calculating the Radiographic Assessment of Lung Edema (RALE) score, which takes into account both the density of the infiltrate and the distribution in each quadrant of the chest.[141] Furthermore, the RALE score may have predictive or prognostic utility.[141,142] Chest computed tomographic (CT) imaging, though rarely used clinically, has been employed extensively as an investigative tool to better define the nature of the radiographic infiltrates in patients with ARDS. The distribution of infiltrates by CT is surprisingly variable. Although some patients have evidence of diffuse alveolar edema on CT, many patients have more focal infiltrates, with areas of alveolar filling and consolidation occurring predominantly in dependent zones, whereas nondependent regions are relatively spared.[143–145] Studies have attempted to use CT to differentiate ARDS from hydrostatic edema but

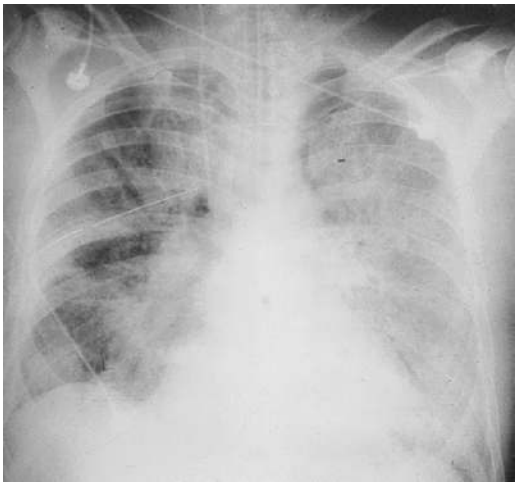

Fig. 60.4 Representative Chest Radiograph from a Patient with Acute Respiratory Distress Syndrome.

have not found useful indicators to differentiate the two.[146] However, even areas that appear spared in conventional radiographic images may have substantial inflammation when sampled using bronchoalveolar lavage[147] or imaged using fluorodeoxyglucose–positron emission tomography (FDG-PET).[148] Patients with more diffuse infiltrates may be more likely to respond to recruitment maneuvers[149]; whether CT imaging could be helpful for guiding ventilator treatment is not yet known, although one recent study attempted to guide ventilator treatment based on CT distribution of infiltrates.[208]

The hypoxemia that characterizes early ARDS usually is relatively refractory to supplemental oxygen. The increased work of breathing in the acute phase of ARDS is caused by decreased lung compliance as a result of fewer available alveolar units, tissue edema, greater airflow resistance,[150] and increased respiratory drive.[151] The combination of hypoxemia and increased work of breathing usually necessitates endotracheal intubation and mechanical ventilation, although occasionally patients can be managed with noninvasive ventilation or very high-flow nasal cannula oxygen (see "Treatment" section later).

In addition to hypoxemia and increased work of breathing, many patients with ARDS develop increased pulmonary vascular resistance, leading to pulmonary hypertension and acute right ventricular (RV) failure. The prevalence of pulmonary hypertension in patients presenting to the hospital with ARDS may be as high as 92%.[152] Even in the era of low tidal volume ventilation, one study used transesophageal echocardiography to show evidence of acute RV failure in 22% of 226 consecutive patients with moderate or severe ARDS.[153] Such findings were associated with an almost twofold increase in 28-day mortality. Attempts to reverse pulmonary hypertension and RV failure with pulmonary vasodilators such as sildenafil have decreased pulmonary artery pressure but produced concomitant increases in shunt fraction and decreases in oxygenation.[154] These findings suggest that although patients with ARDS have evidence of pulmonary hypertension, it may, in some cases, be a compensatory physiologic response that reduces blood flow to areas of severely compromised lung.

Late Fibroproliferative ARDS

In most patients, ARDS will substantially resolve after the acute phase. However, in others, the syndrome progresses to a fibrosing alveolitis. Fibrosing alveolitis usually becomes clinically apparent after 7–10 days, although evidence of deposition of extracellular matrix constituents has been identified in alveolar lining fluid from patients as early as the first day after intubation,[155] and autopsy studies show early fibrotic changes in some patients.[75] Radiographically, linear opacities develop, consistent with the evolving fibrosis. Histologically, pulmonary edema and neutrophilic inflammation are less prominent. A severe fibroproliferative process fills the air spaces with granulation tissue that contains collagen and fibrin in addition to new blood vessels and proliferating mesenchymal cells.[156,157]

Clinically, the late fibroproliferative phase of ARDS is characterized by continued need for mechanical ventilation, often with persistently high levels of PEEP and FiO_2. The lung compliance may fall even further, and pulmonary dead space elevates. If it has not developed in the acute phase, pulmonary hypertension may now emerge as a result of obliteration of the pulmonary capillary bed, and RV failure may occur.[158] This phase of the illness can be prolonged, lasting weeks, and can be very frustrating for the clinician, patient, and family, as small gains in pulmonary function are frequently offset by new problems, such as hospital-acquired infections and nonpulmonary organ dysfunction. Progressive deconditioning can make eventual weaning from mechanical ventilation difficult if the fibrosing alveolitis stage is prolonged. Perhaps in part because the use of lower tidal volumes lessens injury and improves the number of ventilator-free days, the incidence of fibrosing alveolitis seems to be falling. However, a recent autopsy study found more fibrotic changes in patients treated in the low tidal volume era than in patients treated with higher tidal volumes.[75] One possible explanation is that better supportive care has prolonged survival of some patients with more severe lung injury, allowing more time for fibrotic changes to develop and be detected at autopsy.

Resolution of ARDS

After sufficient time has elapsed, lung biopsies from ARDS survivors typically show normal or near-normal lung histology. For such histologically complete resolution of ARDS to occur, a variety of processes must be reversed. Alveolar edema is actively reabsorbed by the vectorial transport of sodium and chloride from the distal airway and alveolar spaces into the lung interstitium, where it can be cleared by the lymphatics or reabsorbed into the vasculature.[159] Water is passively absorbed along the osmotic gradient, probably through water channels, the aquaporins.[160] The majority of patients with early ARDS have impaired alveolar fluid transport; in those with intact alveolar fluid transport, faster rates of alveolar epithelial fluid transport are associated with better outcomes.[71] Soluble and insoluble protein must also be cleared from the air spaces. Soluble protein probably diffuses by a paracellular route into the interstitium, where it is cleared by lymphatics. Insoluble protein probably is removed by macrophage phagocytosis or alveolar epithelial cell endocytosis and transcytosis.[161]

The denuded alveolar epithelium must be repaired. The alveolar epithelial type II cell serves as the progenitor cell for repopulating the alveolar epithelium. Type II cells proliferate, migrate, and differentiate to reconstitute a tight alveolar epithelial type I cell barrier.[162] The inflammatory cell infiltrate must also resolve, but here the mechanisms are less clear. Resolution of neutrophilic inflammation may be predominantly via neutrophil apoptosis and phagocytosis by macrophages. However, one report suggests that neutrophil apoptosis is impaired in the lungs of patients with ARDS.[163] The resolution of fibrotic changes is also not well understood. Clearly, substantial remodeling is necessary to restore a near-normal alveolar architecture. In patients with advanced fibrosis, this process likely takes place over many months; pulmonary function abnormalities continue to improve, sometimes remarkably so, out to the first year and beyond in survivors of ARDS (see later).[164,165]

TREATMENT

Standard Supportive Therapy

Several societies have published comprehensive guidelines to assist clinicians in treating patients with ARDS.[166–171] Encouragingly, there has been a gradual decline in mortality attributable to ARDS over time,[172,173] likely reflecting improvements in standard supportive therapy and adherence to evidence-based guidelines for ventilator and fluid management and supporting care. Although detailed discussion of all aspects of supportive therapy is beyond the scope of this chapter, a few aspects will be considered.

Treatment of Predisposing Factors

First and foremost, a search for the underlying cause of ARDS should be undertaken. Appropriate treatment for any precipitating infection such as pneumonia or sepsis is critical to improving the probability of survival. In the immunocompromised host, invasive diagnostic evaluation, including bronchoscopy, may be warranted to uncover evidence of opportunistic infections. In a patient with sepsis and ARDS of unknown source, an intraabdominal process should be considered. Timely surgical management of intraabdominal sepsis is associated with better outcomes.[174] In some patients, the cause of lung injury will

not be specifically treatable (such as aspiration of gastric contents) or will not be readily identified.[24]

Fluid and Hemodynamic Management

Historically, patients with critical illness and ARDS received a pulmonary artery catheter (PAC) to manage fluid and hemodynamic status. A large, randomized European trial of PAC use (compared with no PAC use) in all patients admitted with ARDS[175] showed no difference in clinical outcomes on either group, suggesting that routine PAC use in ARDS without specified PAC-guided interventions is not beneficial. The ARDS Clinical Trials Network tested the value of pulmonary artery catheterization in the context of specific fluid management protocols and was unable to demonstrate the superiority of PAC over the central venous catheter in directing specific fluid management protocols in ARDS patients, and PAC use did not improve outcomes in these patients.[121] Some investigators have proposed that clinical outcomes in ARDS can be improved by delivery of supranormal levels of oxygen using vigorous volume resuscitation and positive inotropes. However, no benefit to supranormal levels of oxygen delivery has been demonstrated in patients with ARDS.[176,177]

For decades there was disagreement as to the best fluid management strategy in patients with ARDS. Proponents of a liberal fluid strategy reasoned that increased circulating volume would preserve end-organ perfusion and protect patients from the development of nonpulmonary organ failures. Reductions in intravascular volume can have adverse effects on cardiac output and tissue perfusion, factors that could contribute to multisystem organ failure. This concern is legitimate, because mortality in ARDS is usually from nonpulmonary causes, including other organ failures. Others supported a conservative fluid strategy in an attempt to reduce circulating volume, thereby reducing the driving force for pulmonary edema formation. In experimental lung injury, lower left atrial pressures are associated with less formation of pulmonary edema.[178,179] Some limited clinical evidence supported this latter approach.[180–183] Because of conflicting rationales and uncertainty, the ARDS Network conducted a large, multicenter, randomized controlled trial of catheter-driven fluid management in patients with ARDS (central venous catheter vs. PAC).[121] Once patients were out of shock, they were randomized to a liberal fluid treatment strategy that resulted in an average of 1L of fluid accumulation per day or to a conservative fluid treatment strategy with aggressive use of diuretics to achieve a goal central venous pressure (CVP) <4 mm Hg or a goal PAOP <8 mm Hg, resulting in an average of zero net fluid accumulation by day 7. Although there was no difference in mortality at 60 days (the primary outcome of the study), patients in the conservative group experienced improved oxygenation and significantly more ventilator-free days without the development of additional organ failures. In this study it did not matter whether treatment was guided by CVP measurements (derived from a central venous line) or from PAOP measurements (derived from a PAC).[184] These important findings have been confirmed in subsequent studies.[185]

Despite the findings in support of a conservative fluid management strategy in patients with ARDS, there continues to be a great deal of uncertainty about the appropriate goals for hemodynamic therapy in ARDS. Currently, the recommended strategy is to aim to achieve the lowest intravascular volume that maintains adequate tissue perfusion as measured by urine output, perfusion of other vital organs, and metabolic acid-base status using CVP monitoring to direct therapy. In fact, cumulative fluid balance has been shown to predict increased time on mechanical ventilation and mortality in patients with ARDS.[186] If organ perfusion cannot be maintained in the setting of adequate intravascular volume, then vasopressors and/or inotropes should be used to restore end-organ perfusion.[158] Available evidence does not support the use of one particular vasopressor or combination of vasopressors. Once shock has resolved, patients should be managed with a conservative fluid strategy, with the goal of driving the CVP <4 mm Hg when possible so as to keep fluid balance net zero during the ICU stay.

Nutrition

Standard supportive care for the patient with ARDS includes the provision of adequate nutrition. The enteral route is preferred to the parenteral route and is associated with fewer infectious complications.[187] Enteral feeding may also confer other beneficial effects. Experimentally, lack of enteral feeding promoted translocation of bacteria from the intestine.[188] In normal volunteers, administration of parenteral nutrition with bowel rest increased circulating levels of tumor necrosis factor-alpha (TNF-α), glucagon, and epinephrine and increased febrile responses compared with volunteers who received enteral nutrition.[189]

The goals of nutritional support in any critically ill patient include the provision of adequate nutrients for the patient's level of metabolism and the treatment and prevention of any deficiencies in micronutrients or macronutrients.[190] Whether a particular dietary composition could benefit patients with ARDS is unclear. Immunomodulation via dietary manipulation has been attempted by a number of investigators in critically ill patients using various combinations of omega-3 fatty acids, ribonucleotides, arginine, and glutamine. A meta-analysis of these trials suggested a beneficial effect on infection rate but not on overall mortality.[191] However, a large, multicenter, randomized placebo-controlled study of omega-3 fatty acid and antioxidant supplementation in patients with ARDS was stopped early by the data safety monitoring board for a trend towards excess mortality in patients receiving the omega-3 fatty acid supplement.[192] Using a different approach, a high-fat, low-carbohydrate diet reduced the duration of mechanical ventilation in patients with acute respiratory failure.[193] Although the mechanism of this beneficial effect was postulated to be caused by a reduction of the respiratory quotient and a resultant fall in carbon dioxide production, the most common cause of a high respiratory quotient in critically ill patients is not dietary composition but simply overfeeding.[190] A study of clinical outcomes in 1000 ARDS patients randomized to full calorie versus trophic (10 cc/hr) enteral feeds did not show any difference in mortality or other clinical outcomes.[194] Overall, there is still no compelling evidence to support the use of anything other than standard (enteral) nutritional support, with avoidance of overfeeding, in patients with ARDS.[195] How early to attempt institution of feeding remains an unanswered question.

Mechanical Ventilation

Lung-Protective Ventilation

Although historically a tidal volume of 12–15 mL per kg was often used in patients with ARDS, it is now clear that a low–tidal volume, end-inspiratory plateau pressure–limited ventilatory strategy reduces mortality. In 2000 the NIH ARDS Network published the findings of their first randomized, controlled, multicenter clinical trial in 861 patients.[100] The trial compared a lower tidal volume ventilatory strategy (6 mL/kg predicted body weight, plateau pressure <30 cm H_2O) with a higher tidal volume (12 mL/kg predicted body weight, plateau pressure <50 cm H_2O). In this trial, the in-hospital mortality rate was 40% in the 12-mL/kg group and 31% in the 6-mL/kg group, a 22% reduction. Ventilator-free days and organ failure–free days were also significantly improved in the low tidal volume group. Although the twofold separation between the tidal volumes used in the tested cohorts was unusually wide, these findings were truly remarkable, because no prior large randomized clinical trial of any specific therapy for ARDS had ever demonstrated a mortality benefit.

The currently recommended treatment strategy for patients with ARDS is summarized in Table 60.3. Predicted body weight is calculated

TABLE 60.3 Ventilator Management of Patients With ARDS

Calculate Predicted Body Weight (PBW)

- Males: PBW (kg) = 50 + 2.3 [(height in inches) − 60] or
  50 + 0.91 [(height in cm) − 152.4]
- Females: PBW (kg) = 45.5 + 2.3 [(height in inches) − 60] or
  45.5 + 0.91 [(height in cm) − 152.4]

Ventilator Mode

Volume assist/control until weaning

Tidal Volume (Vt)

- Initial Vt: 6 mL/kg predicted body weight
- Measure inspiratory plateau pressure (Pplat, 0.5 sec inspiratory pause) every 4 hours AND after each change in PEEP or Vt.
- If Pplat >30 cm H_2O, decrease Vt to 5 or to 4 mL/kg.
- If Pplat <25 cm H_2O and Vt <6 mL/kg PBW, increase Vt by 1 mL/kg PBW.

Respiratory Rate (RR)

- With initial change in Vt, adjust RR to maintain minute ventilation.
- Make subsequent adjustments to RR to maintain pH 7.30–7.45, but do not exceed RR = 35/min, and do not increase set rate if $PaCO_2$ <25 mm Hg.

I:E Ratio

- Acceptable range, 1:1–1:3 (no inverse ratio)

FiO_2, PEEP, and Arterial Oxygenation

Maintain PaO_2 = 55–80 mm Hg or SpO_2 = 88%–95% using the following PEEP/FiO_2 combinations:

FiO_2	0.3–0.4	0.4	0.5	0.6	0.7	0.8	0.9	1
PEEP	5–8	8–14	8–16	10–20	10–20	14–22	16–22	18–25

Acidosis Management

- If pH <7.30, increase RR until pH ≥7.30 or RR = 35/min.
- If pH remains <7.30 with RR = 35, consider bicarbonate infusion.
- If pH <7.15, Vt may be increased (Pplat may exceed 30 cm H_2O).

Alkalosis Management

If pH >7.45 and patient is not triggering ventilator, decrease set RR but not below 6/min.

Fluid Management

- Once patients are out of shock, adopt a conservative fluid management strategy.
- Use diuretics or fluids to target a central venous pressure (CVP) of <4 mm Hg or a pulmonary artery occlusion pressure (PAOP) of <8 mm Hg.

Liberation From Mechanical Ventilation

- Daily interruption of sedation
- Daily screen for spontaneous breathing trial (SBT)
- SBT when all of the following criteria are present:
  (a) FiO_2 <0.40 and PEEP <8 cm H_2O
  (b) Not receiving neuromuscular blocking agents
  (c) Patient is awake and following commands
  (d) Systolic arterial pressure >90 mm Hg without vasopressor support
  (e) Tracheal secretions are minimal, and the patient has a good cough and gag reflex

Spontaneous Breathing Trial

- Place patient on 5 mm Hg pressure support with 5 mm Hg PEEP *or* T-piece.
- Monitor HR, RR, and oxygen saturation for 30–90 minutes.
- Extubate if there are no signs of distress (tachycardia, tachypnea, agitation, hypoxia, diaphoresis).

based on measured height using the equations provided. This is a key point that is often overlooked by clinicians; use of actual rather than predicted body weight can result in the use of erroneously high and potentially injurious tidal volumes, particularly in female patients who are often treated with tidal volumes that are too high.[196] The tidal volume should initially be set at 6 mL/kg predicted body weight, similar to normal tidal volumes in spontaneously breathing adults at rest. However, if the end-inspiratory plateau pressure (measured during a 0.5-second pause) is still >30 cm H_2O, then the tidal volume must be reduced in a stepwise fashion by 1 mL/kg to a minimum of 4 mL/kg. Ventilation with this tidal volume is generally well tolerated. Some patients may experience breath stacking or dyssynchrony with the ventilator. Increasing the inspiratory flow rate and, if necessary, the level of sedation is usually sufficient to manage these problems. On average, patients receiving lower tidal volume ventilation do not require increases in dose or duration of sedatives compared with patients receiving higher tidal volume ventilation.[197,198] Respiratory acidosis may develop but usually is not symptomatic. Raising the respiratory

rate is usually sufficient to compensate; a rate as high as 35 was used in the aforementioned clinical trial. As with any mode of ventilation in ARDS, patients occasionally will require neuromuscular blockade to alleviate severe dyssynchrony. Although one randomized clinical trial showed a 28-day mortality benefit with use of neuromuscular paralysis with cisatracurium besylate for the first 48 hours in severe ARDS (PaO_2/FiO_2 <150),[199] a subsequent study of early neuromuscular blockade in ARDS (the ROSE trial) was stopped early for futility.[200] Given these recent findings, neuromuscular blockade should be reserved for patients with severe ARDS and refractory hypoxemia.

In the ARDS Network protocol, the level of PEEP and FiO_2 is titrated according to a set of predetermined values (see Table 60.3). The optimal level of PEEP in ARDS has been controversial. Higher levels of PEEP may be beneficial in preventing alveolar collapse and minimizing injurious repeated opening and closing of alveoli. On the other hand, unnecessarily high PEEP may overdistend and injure more compliant areas of the lung and adversely influence RV loading. Several studies have investigated the effects of different levels of PEEP in patients with ARDS.[201] One large multicenter trial conducted by the ARDS Network randomized patients with ARDS ventilated with low tidal volume ventilation to receive lower (mean PEEP levels on days 1–4 were 8.3 ± 3.2) versus higher levels of PEEP (mean PEEP levels on days 1–4 were 13.2 ± 3.5).[202] There were no differences between the groups in clinical outcomes, including ventilator-free days and mortality. Two other studies of the effects of PEEP in ARDS had similar results,[203,204] although one study did show an increase in the number of ventilator-free days and organ failure–free days with application of higher PEEP.[204] None of these trials reported increases in barotrauma related to higher PEEP levels. Although these three large studies have not shown beneficial effects of higher PEEP in ARDS, even in a large meta-analysis,[205] there may be a subset of patients who would benefit from higher PEEP. In a small trial, a ventilator strategy that incorporated low tidal volume and titration of the PEEP level to above the lower inflection point on each individual patient's pressure–volume curve improved mortality in ARDS.[206] However, measurement of the pressure–volume curve in any given patient is not always feasible in practice. Under certain circumstances, higher PEEP may even be harmful. A large, multicenter, randomized trial in 120 ICUs from nine countries found that PEEP titration and aggressive recruitment maneuvers increased mortality in patients with severe ARDS as compared with a low PEEP strategy.[207] Another study of personalized mechanical ventilation based on whether ARDS was focal (tidal volume of 8 mL/kg, low PEEP, and prone position) or diffuse (tidal volume of 6 mL/kg, along with recruitment maneuvers and high PEEP) on imaging did not show a difference in mortality between groups, but significant misclassification could have affected the results.[208] Although imprecise, current recommendations are to adjust the PEEP within an acceptable range (see Table 60.3) to achieve adequate oxygenation at a given FiO_2.

Some patient populations present specific challenges to ventilator management in ARDS. Pregnant or obese patients may be difficult to manage with the standard lung-protective strategy. One study showed that a specially trained team, which they termed a "lung rescue team," improved survival in the obese patient with ARDS.[209] In this study, morbidly obese adults were randomized to usual care (ARDSNet protocol) versus personalized mechanical ventilation with lung recruitment maneuvers, esophageal manometry, and hemodynamic monitoring. Mortality was cut almost in half in the intervention group (16% versus 31%).[209] Pregnant women with ARDS may require a higher driving pressure to achieve the same tidal volume and oxygenation.[210] In addition, studies have examined the use of lung-protective ventilation in at-risk subjects without ARDS with varying results.[211,212] Although most patients with ARDS, and possibly those at risk for ARDS, benefit from a standardized approach using the ARDS Network low tidal volume protocol, it is important to keep individual patient factors in mind when selecting ventilator settings.

Prone positioning was initially studied in several small[213–215] and three large trials[216–218] and was associated with improvements in oxygenation but no reduction in mortality. Subgroup analysis suggested potential benefit in severe ARDS, leading to a multicenter prospective randomized trial of prolonged prone positioning (>16 h/day) in patients with severe ARDS (PaO_2/FiO_2 <150). The impressive results indicated substantial reduction in 28-day mortality in the prone group.[219] Given the results of this trial, prone positioning should be considered in all patients with severe ARDS who do not have contraindications to that position change, such as elevated intracranial pressure, severe hemoptysis, recent sternal surgery, pregnancy, new deep venous thrombosis, or unstable fractures. Despite the evidence supporting prone positioning in patients with ARDS, this therapy has been adopted only reluctantly. A worldwide prospective observational study of 141 ICUs from 20 countries found that the minority of ARDS patients are prone, even in those with severe ARDS (32.9% received prone positioning). The most common reason for not using prone positioning was the impression that hypoxemia was not considered severe enough to require proning.[220]

Noninvasive Ventilation and High-Flow Nasal Cannula

Noninvasive positive-pressure ventilation (NIV) delivered by nasal or full face mask has been highly successful in avoidance of intubation in patients with acute exacerbations of chronic obstructive pulmonary disease (COPD).[221] NIV is commonly used in pediatric patients with ARDS,[222] although there is only one small randomized trial of 50 patients showing that NIV improved oxygenation and prevented the need for endotracheal intubation in children admitted with acute respiratory failure. The role for NIV in adults with ARDS is still unclear. A growing number of small studies suggest that bilevel NIV with pressure support ventilation and PEEP may reduce the need for intubation and improve outcomes in selected patients with ARDS.[223] However, data from large randomized controlled trials is still lacking. Furthermore, it seems likely that the majority of patients with ARDS will still require invasive mechanical ventilation. In one large multicenter study of 354 of 2770 patients with acute hypoxemic respiratory failure *who were not already intubated,* NIV failed in 30% of patients but failed in 51% of patients with ARDS.[224,225] Another multicenter study of early NIV in mild ARDS caused by pneumonia did not reduce the need for mechanical ventilation despite improvement in oxygenation with NIV.[226] Applied broadly to all patients with ARDS, NIV may actually be harmful. In a retrospective analysis of the LUNG SAFE study, NIV was used in 15.5% of ARDS patients and was associated with both a high failure rate (47.1% in severe ARDS) and increased ICU mortality.[227] One group of patients in whom NIV is particularly appealing includes those who are immunosuppressed for various reasons and are at highest risk for nosocomial infections. Encouraging results have now been reported in a variety of patients with acute respiratory failure and immunosuppression.[228–231] With the advent of newer methods for NIV, such as helmet NIV—an interface option that has been reported to reduce intubation rates and mortality[232]—indications and applications of NIV may increase.

More recently, very high-flow nasal cannula oxygen delivery has been tested in patients with acute hypoxemic respiratory failure as an alternative to immediate intubation. In a study of 310 patients with acute respiratory failure, including some patients with ARDS, treatment with high-flow nasal cannula increased ventilator-free days and reduced mortality compared with noninvasive or invasive mechanical ventilation.[233] One benefit of high-flow nasal cannula is that it can provide a small level of PEEP noninvasively. Pending data from larger randomized clinical studies, a trial of noninvasive mechanical ventilation or high-flow nasal cannula oxygen could be considered in a patient with ARDS who does

not have a severe oxygenation defect, hemodynamic instability, or altered mental status, as long as the patient can be closely observed and readily intubated if needed.

Pharmacologic Therapy

There is no specific pharmacologic therapy for ARDS. A variety of treatment strategies have been investigated in large randomized trials, including antiinflammatory strategies, surfactant replacement, vasodilation, novel anticoagulants, antioxidants, and strategies to enhance the resolution of pulmonary edema. Agents that appeared promising in experimental and early clinical studies but failed in large randomized trials include early glucocorticoids,[234–236] anti-TNF antibody fragments,[237] alprostadil,[238,239] surfactant,[240–242] ketoconazole,[243] *N*-acetylcysteine,[244] procysteine,[244] lisofylline,[245] statins,[246,247] albuterol,[248] recombinant activated protein C,[249] site-inactivated recombinant factor VIIa,[250] aspirin,[251] and possibly vitamin C.[252]

Some investigators have suggested that glucocorticoid therapy, although not helpful for the acute phase of ARDS, might hasten the resolution of late fibroproliferative ARDS. One very small randomized study (plagued by crossovers such that only four patients remained in the placebo arm) suggested that glucocorticoid therapy might be beneficial in late ARDS.[253] This question was addressed in a randomized, multicenter study conducted by the ARDS Network of 14 days of methylprednisolone in patients who had persistent ARDS for 7 days.[254] Compared with patients treated with placebo, those treated with methylprednisolone had an increase in the number of shock-free days and ventilator-free days by day 28 and improvements in oxygenation, but did not have improved long-term survival and had higher rates of reintubation after steroids were discontinued, perhaps in part because of neuromuscular weakness. Although there is a large body of evidence suggesting lack of benefit, or even harm, from routinely using glucocorticoids in all etiologies of ARDS, the story is still evolving. A recent open-label, randomized controlled study of early dexamethasone use in ARDS (139 patients) versus placebo (138 patients) resulted in a substantial increase in ventilator-free days (4.8 days) and a 15% reduction in mortality.[255] These provocative findings will need validation and must be considered cautiously, given the serious concern about the safety of high-dose glucocorticoids in critically ill patients, including the possibility of increasing the risk of nosocomial infections or critical illness polyneuropathy/myopathy and the lack of improvement in mortality, with routine use of glucocorticoids.

Despite the dismal findings of the numerous studies of pharmacologic therapy for ARDS to date, new therapeutic strategies are under investigation and may yet prove beneficial. Macrolides hold some promise for ARDS. In an unplanned secondary analysis of patients with ARDS enrolled in two large observational studies in the Netherlands, macrolide therapy was associated with reduced mortality.[256] A recently reported novel approach to sedation in patients with ARDS using inhaled sevoflurane[257] showed a reduction in circulating markers of lung epithelial injury and inflammation and improved oxygenation compared with intravenous sedation, suggesting that there may be some lung-protective effects of inhaled sedation. Currently, three large randomized clinical trials are planned to test the effects of sevoflurane for sedation in ARDS. Because of the failure of pharmacologic therapies in established ARDS, attention has turned to the prevention and early treatment of ARDS, and several trials are in the planning stages or ongoing. For established ARDS, cell-based therapy with intravenous mesenchymal stromal (stem) cells (MSCs) was found to be safe in a phase II clinical trial.[258] In preclinical studies, MSCs have pleiotropic protective and reparative effects in the lung, including secretion of antiinflammatory and antibacterial factors, secretion of epithelial and endothelial growth factors, and direct transfer of mitochondria to restore energy balance in the injured lung epithelium.[259] Another area under active investigation includes strategies to hasten or facilitate the resolution of ARDS. Such therapies might be targeted at increasing the rate of alveolar fluid clearance, encouraging alveolar epithelial repair, or modulating immune regulation of the resolution of inflammation.

One important consideration for future clinical trials is to use predictive and/or prognostic enrichment to tailor therapies to patients who are most likely to benefit.[260] In fact, a prognostic enrichment strategy was used in the recent dexamethasone study,[255] which may be one reason that the benefits of dexamethasone were measurable in this study. Another consideration is the patient with rapidly improving ARDS who may not remain in a study long enough to benefit from a therapy. In clinical trials of ARDS, 10.5%–13.9% of patients were extubated or had P/F ratios >300 on the day after study enrollment.[261] Rates of rapid resolution were even higher (24%) in the multicenter observational LUNG SAFE study.[262] In the future, carefully designed clinical trials using enrichment strategies or platform/adaptive designs may lead to therapeutic breakthroughs.

Rescue Therapies

Despite appropriate treatment, a fraction of patients with ARDS will have profound and refractory hypoxemia. The initial management of these patients includes increased sedation and neuromuscular paralysis to maintain adequate oxygenation, but there is wide variation in practice in the management of refractory hypoxemia.[263] In patients who do not respond to conventional treatment with low tidal volume ventilation and remain persistently hypoxemic, several nonproven rescue therapies can be tried to improve oxygenation in the acute setting (summarized in Table 60.4). Although previously viewed primarily as a rescue therapy, prone positioning improved mortality in moderately severe ARDS in one study[219] and is now being used more frequently in routine care of patients with moderately severe ARDS (PaO_2/FiO_2 <150) in addition to its utility in improving oxygenation in the setting of refractory hypoxemia. Extracorporeal membrane oxygenation (ECMO) has been used in patients with ARDS and severe hypoxemia. In specialized centers ECMO has been used successfully to treat patients with severe ARDS.[264–266] One large trial randomizing 180 patients with severe ARDS to ECMO versus conventional management reported improved survival without disability at 6 months in patients treated with ECMO.[267] In this study, patients randomized to ECMO were transferred to a specialty center to receive therapy. Upon arrival, only 75% of patients in the ECMO group were actually treated with ECMO. The study design makes it difficult to determine whether the transfer to a specialty center for care or the ECMO itself conferred benefit. Although the results of this study are encouraging, the need for transfer to a specialty center and the dropout rate of 25% upon transfer limit the generalizability of this study. The recently completed international EOLIA study randomized 124 patients with very severe ARDS to immediate ECMO or continued conventional treatment and found a trend towards improved 60-day survival in patients randomized to ECMO, with 44 of 124 patients (35%) in the ECMO group and 57 of 125 (46%) in the control group dying (relative risk, 0.76; 95% confidence interval [CI], 0.55–1.04; $P = .09$).[268] More contemporary studies combining ECMO or extracorporeal CO_2 removal with ultra-protective mechanical ventilation[269–271] have some encouraging findings, including improved long-term outcomes.[272–274] High-frequency oscillatory ventilation (HFOV) appeared to be promising in several small randomized trials in patients with ARDS,[275–279] with improvements in oxygenation in patients with severe hypoxemia. However, two large randomized clinical trials in severe ARDS failed to show a benefit,[280,281] and in one of the trials, mortality was higher in the HFOV group.[280] For this reason, HFOV should only be used as a rescue therapy and only by experienced operators. Other rescue therapies include the use of a pulmonary vasodilator, such as inhaled nitric oxide (NO) or inhaled prostacyclin. There have been several small randomized clinical trials of inhaled NO in ARDS; although none has shown improved mortality, its use has been

TABLE 60.4 Summary of Rescue Therapies for Acute Lung Injury and Acute Respiratory Distress Syndrome

Rescue Therapy	Year	How Studied	Number of Patients	Comments	References
ECMO	1979	Phase III	90	In this multicenter trial there was no benefit with the use of ECMO.	284
	2009	Phase III	180	This large randomized trial showed benefit to treatment with ECMO; however, 25% of patients assigned to ECMO did not receive this therapy, and the need for urgent transfer to specialized treatment centers limits general applicability of this trial.	267
	2018	Phase III	124	In this international trial, patients with severe ARDS were randomized to immediate ECMO or continued conventional treatment. There was a nonsignificant trend towards improved 60-day survival in patients treated with ECMO.	268
ECCOR	1994	Phase III	40	This newer form of extracorporeal therapy did not improve mortality.	285
	2019	Phase II	95	Use of ECCOR and ultraprotective ventilation was safe and feasible.	269
Prone positioning	2001	Phase III	304	Although prone positioning improved oxygenation, there was no mortality benefit.	217
	2009	Phase III	342	Patients were randomized according to severity of hypoxemia to receive 20 hours of prone positioning vs. usual care and had no reduction in mortality at 28 days or 6 months.	218
	2013	Phase III	466	Patients with more severe ARDS (PaO_2/FiO_2 <150 mm Hg) were randomized to supine or prone position (>16 h/day). Patients in the prone group had improved 28-day mortality.	219
HFOV	2002	Phase III	148	HFOV group had improved oxygenation but no difference in mortality.	275
	2005	Phase III	61	No significant differences in any outcome between the groups.	279
	2013	Phase III	548	HFOV had higher mortality and more hemodynamic instability.	280
	2013	Phase III	795	No difference in mortality.	281
Inhaled nitric oxide	1998	Phase II	177	Although some patients will have improvement in oxygenation with inhaled nitric oxide, there was no mortality benefit in any of these large studies.	286
	1999	Phase III	203		287
	2004	Phase III	385		288

ARDS, Acute respiratory distress syndrome; *ECMO,* extracorporeal membrane oxygenation; *ECCOR,* extracorporeal CO_2 removal; *FiO_2,* fraction of inspired oxygen; *HFOV,* high-frequency oscillatory ventilation; *PaO_2,* partial pressure of oxygen.

associated with improved oxygenation.[282] Inhaled prostacyclin is another pulmonary vasodilator that may be used as a rescue therapy in severe, refractory ARDS, although there are no randomized trials showing a mortality benefit.[283]

COMPLICATIONS

Complications are common in any critically ill patient population. Supportive care for all critically ill patients must include vigilance in both preventing and diagnosing common complications such as pulmonary embolus, acute myocardial infarction, gastrointestinal bleeding, and nosocomial infection. Certain complications are more common in ARDS patients and deserve special mention. Although not specifically a complication, some patients do suffer from prolonged mechanical ventilation and require prolonged critical care. For those patients who require prolonged ventilation, a tracheostomy is often required. Use and timing of tracheostomy vary widely throughout the world, with patients from high-income European countries being the most likely to get a tracheostomy, with median timing of insertion of 14 days.[289]

Barotrauma

Barotrauma occurs when air dissects out of the airways or alveolar space into surrounding tissues, leading to pneumothorax, pneumomediastinum, pneumatocele, or subcutaneous emphysema (Fig. 60.5). The exact incidence

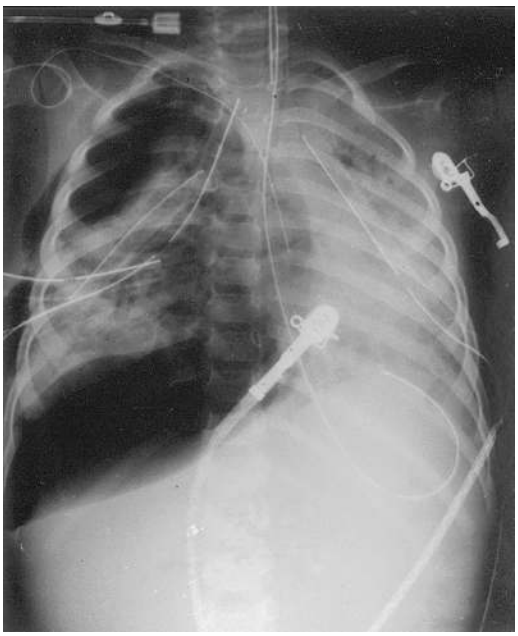

Fig. 60.5 Chest Radiograph Showing Tension Pneumothorax in a Patient with Acute Respiratory Distress Syndrome.

of pulmonary barotrauma in ARDS is unclear but appears to be declining. Data from two large randomized trials of protective ventilatory strategies suggest an incidence of early pneumothorax of 12%–13%.[100] In 861 patients enrolled in the NIH ARDS Network trial, approximately 10% developed some form of barotrauma, regardless of whether they were in the 6- or 12-mL/kg tidal volume arm. Furthermore, PEEP level was the only factor that predicted the development of barotrauma in a multivariate analysis.[290]

Treatment of barotrauma depends on the location of the extravasated air. Pneumothorax can be life threatening, particularly if it is under tension; immediate diagnosis and tube thoracostomy are essential. Pneumothorax should be considered in any mechanically ventilated patient with ARDS who develops sudden, unexplained worsening of hypoxemia, respiratory distress, or hemodynamic instability. A chest radiograph (preferably upright) or bedside lung ultrasound is usually sufficient to make the diagnosis, but in many cases the situation may be too urgent to complete diagnostic imaging (see Fig. 60.5). Pneumomediastinum and subcutaneous emphysema can be painful but do not require specific therapy other than analgesia. Air embolus is a potentially fatal complication of positive-pressure mechanical ventilation that has been reported occasionally in patients with ARDS[285,291,292] and usually occurs in conjunction with other evidence of pulmonary barotrauma, often simultaneously.

Nosocomial Pneumonia

The incidence of nosocomial pneumonia in patients with ARDS is difficult to quantify. Depending on the diagnostic definition and/or strategy employed, estimates range from 15% to 60%.[293,294] There is no consensus regarding the appropriate way to diagnose nosocomial pneumonia in the mechanically ventilated patient. Because patients with ARDS frequently die from uncontrolled infection, recognition and treatment of nosocomial pneumonia is an important component of caring for the ARDS patient. Clinical criteria commonly used in the diagnosis of nosocomial pneumonia include fever, elevated white blood cell (WBC) count, purulent airway secretions, and pulmonary infiltrates. However, these signs are often present in patients with ARDS, even in the absence of nosocomial pneumonia.[295] Autopsy studies of patients who died with ARDS show a high incidence of unsuspected pneumonia.[296–298] An in-depth discussion of diagnostic strategies is presented elsewhere in this text. Regardless of the methods used for diagnosis, early, appropriate, and empiric therapy is the mainstay of treatment for nosocomial pneumonia. The adequacy and timeliness of initial empiric therapy are important determinants of outcome. Knowledge of local resistance patterns is crucial, and a high index of suspicion is required.

Multiorgan System Dysfunction

Although ARDS is often thought of as a primary pulmonary disorder, it is often a systemic disorder with many similarities to sepsis or systemic inflammatory response syndrome (SIRS). Multiorgan system dysfunction is a common complication in ARDS. Organ dysfunction may result from the underlying cause of ARDS, such as sepsis, or occur independently. The exact incidence of multiorgan system dysfunction in ARDS is difficult to quantify. In the ARDS Network trial of low tidal volume ventilation, the mean number of nonpulmonary organ system failures per patient was 1.8.[100] Given the simultaneous occurrence of multiple organ failures, it is often difficult to determine the exact cause of death in ARDS patients, and survival ultimately depends on successful support of the failing organs.

Neuromuscular Weakness

Patients with ARDS are at high risk for developing prolonged muscle weakness that persists after resolution of pulmonary infiltrates is well underway and can complicate weaning from mechanical ventilation and rehabilitation. This clinical syndrome is commonly called *critical illness polyneuropathy* but has components of neuropathy and myopathy that can coexist or occur separately.[299] Although little prospective data are available, several studies suggest that neuromuscular abnormalities persist in many survivors of critical illness, even when studied up to 5 years after ICU discharge.[165,300] Prolonged muscle weakness is most common in critically ill patients who are treated with glucocorticoids. In other studies, neuromuscular blockade has also been implicated. In one study, the sustained use of corticosteroids was shown to be the best independent predictor of ICU-acquired paresis (odds ratio, 14.9; 95% CI, 3.2–69.8).[301] In the absence of a compelling clinical indication such as underlying connective tissue disease or another entity shown to respond, the use of glucocorticoids should not be routine practice. New clinical evidence in support of their clinical utility in certain forms of ARDS may become available.

CLINICAL OUTCOMES AND PROGNOSIS

Once a patient develops ARDS, several prognostic factors can help clinicians predict the outcome. Although the dead space fraction,[302,303] the ventilatory ratio, high driving pressure, and oxygen saturation index may predict mortality,[304–308] none are universally measured or monitored in ICU practice. For this reason, predictive models that use more readily available clinical variables have been developed.[309] In addition to dead space fraction, severe hypercapnia (CO_2 >50 mm Hg)[310] and a positive cumulative fluid balance at day 4 in patients with ARDS predict increased mortality,[311] further supporting the use of a conservative fluid strategy in patients with ARDS.[184] Conversely, body mass index was studied in a post hoc analysis of the OSCILLATE trial and found to have no association with mortality in patients with ARDS.[312]

The reported mortality from ARDS appears to be gradually declining,[172] although this finding has not been consistent between retrospective studies.[313] Before the 1990s, mortality in clinical trials was approximately 40%–60%.[314] Several recent single-center studies suggest that mortality rates measured in the same centers has declined over time.[315–318] In an ARDS Network study that enrolled 861 ARDS patients in the late 1990s, aggregate mortality to hospital discharge was 31% in the 6-mL/kg tidal volume arm and 40% in the 12-mL/kg tidal volume arm. However, mortality data from this study may significantly underestimate overall ARDS mortality because many severely ill patients were excluded, including those with advanced liver disease, bone marrow transplantation, severe chronic respiratory disease, burns greater than 30% body surface area, or any other underlying condition with a likelihood of death greater than 50% within 6 months. As has been observed in other studies, the risk of in-hospital mortality in this study was highest in those with sepsis (43%), intermediate in those with pneumonia (36%) or aspiration (37%), and lowest in those with multiple trauma (11%).[22] Interestingly, developing ARDS in the hospital is associated with a significantly higher mortality compared with at-risk controls (35% versus 5%).[319] The low tidal volume strategy was effective at reducing mortality across all causes of ARDS.[22] Another study has shown that implementation of the ARDS Network low tidal volume ventilator strategy is associated with lower hospital mortality compared with historical controls.[320] In a more recent ARDS Network study published in 2012, the overall 60-day mortality was 23%.[194]

Several recent multicenter studies in France,[321] Sweden,[322] Australia,[323] and Argentina[324] attempted to define mortality and prognostic variables in observational, population-based studies rather than from clinical trial participants. In these studies, mortality was variable, ranging from 32% for mild ARDS to 58%–60% for moderate to severe ARDS. Factors independently associated with mortality from ARDS varied from study to study and included age, Acute Physiology Score, PaO_2/FiO_2 ratio, organ failure or septic shock, immunosuppression,

cardiovascular failure, and chronic liver disease.[197,321,322,324] The large, multinational LUNG SAFE study has significantly informed our understanding of ARDS prognosis and outcomes in more recent years. Analyses from the LUNG SAFE study found that hospital mortality is higher in immunocompromised patients compared with immunocompetent patients[231] and in women with severe ARDS compared with men.[196] Further, analysis of data from LUNG SAFE identified several modifiable (lower PEEP; higher peak inspiratory plateau and driving pressures; and increased respiratory rate) and nonmodifiable (older age, active neoplasm, hematologic neoplasm, and chronic liver failure) risk factors for hospital mortality.[325] Not surprisingly, outcomes in developing countries are worse, with typical mortality rates of 45%.[29] Although most studies have reported short-term mortality from ARDS, a recent study examined 1-year mortality.[326] In a heterogeneous group of 641 patients with ARDS, 1-year mortality was substantially higher than hospital mortality (41% vs. 24%; $P < .0001$). In summary, these studies suggest that although some improvements in ARDS mortality have been made, mortality remains quite high in population-based studies, and improvements in short-term outcomes may not be reflected in better long-term outcomes.

ARDS survivors frequently have long-term functional disability, cognitive dysfunction, and psychosocial problems[327]; are more likely to be discharged to rehabilitation or long-term care facilities compared with controls[319]; and are high users of health care.[328] Many such problems persist even 5 years after the ARDS hospitalization,[329,330]and many patients are never able to return to prior functional status or work.[331,332] There may be distinct subtypes of ARDS survivors that benefit from a more tailored rehabilitation approach.[333] Interestingly, pulmonary function frequently returns to normal or near-normal in survivors. In a report of 1-year follow-up in 109 survivors of ARDS,[164] lung volumes and spirometry had returned to normal by 6 months. However, carbon monoxide diffusing capacity was persistently low throughout the year. Six-minute walk distances were persistently less than predicted at 12 months, largely because of muscle wasting and weakness rather than pulmonary function abnormalities.[164] Treatment with any systemic corticosteroid, the presence of illness acquired during the ICU stay, and the rate of resolution of the lung injury and multiorgan dysfunction during the ICU stay were the most important determinants of the 6-minute walk distance during the first year of follow-up. Other studies report that patients who survive ARDS have reduced health-related quality of life[334] and pulmonary disease–specific health-related quality of life.[335–337] Functional impairment often persists 2 years after ICU discharge.[338] In addition to physical and social difficulties after ARDS, survivors have high rates of depression and anxiety.[339]

KEY POINTS

- ARDS epidemiology, risk factors, and outcomes continue to change over time as new risks and modifiers emerge.
- ARDS is a syndrome with distinct clinical subphenotypes that may have differential responses to treatment.
- Treatment of the underlying cause, lung-protective ventilator management, a conservative fluid strategy, prone ventilation for patients with severe ARDS, and avoidance of complications remain the mainstays of therapy.
- Although survival rates have improved over time, survivors of ARDS experience long-term physical, psychological, and functional impairment.

References for this chapter can be found at expertconsult.com.

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This was a multicenter trial of 6-mL/kg compared with 12-mL/kg tidal volume in 861 mechanically ventilated patients with ALI or ARDS. The major finding was a reduction in hospital mortality in the 6-mL/kg group from 40% to 31%.

Bellani G, Laffey JG, Pham T, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA*, 2016;315:788–800.
The LUNG SAFE study was a large observational study to understand the global impact of ARDS. It prospectively enrolled 29,144 patients from 459 ICUs in 50 countries. The LUNG SAFE study has provided a wealth of information regarding diagnosis, risk factors, treatment, practice patterns, and outcomes of patients with ARDS.

Calfee CS, Delucchi K, Parsons PE, et al. Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomised controlled trials. *Lancet Respir Med.* 2014;2:611–620.
In this study, unbiased statistical methods applied to data sets from two large clinical trials revealed two distinct subphenotypes among patients with ARDS. Subsequently, these subphenotypes have been identified in multiple large data sets and may have a differential response to ARDS therapy.

Herridge MS, Cheung AM, Tansey CM, et al. One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med.* 2003;348:683–693.
In this multicenter study, the authors evaluated 109 survivors of ARDS at 3, 6, and 12 months after discharge from the hospital. Notably, functional disability was very common even at 12 months and was largely caused by muscle wasting and weakness. By contrast, pulmonary function was normalized, with the exception of persistent decrements in the diffusing capacity for carbon monoxide.

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These companion papers present the main findings from the ARDS Network Fluid and Catheter Treatment Trial (FACTT). The major findings from these two reports are that patients with ARDS who are not in shock should have CVP-directed management of a conservative fluid strategy with a goal CVP of < 4 mm Hg; such patients had more ventilator-free days compared with patients treated with a liberal fluid strategy.

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This case-based review article highlights the pathophysiologic and clinical differences between hydrostatic pulmonary edema and ARDS and provides a clinical algorithm for differentiating between the two.

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61

Drowning

Justin Sempsrott, Joost Bierens, and David Szpilman

DEFINITION

Drowning is the process of experiencing respiratory impairment from submersion or immersion in liquid. This process can be fatal, nonfatal with complications, or nonfatal without complications. This definition is increasingly used in the medical, professional, and research literature to allow consistent and correct data collection and comparison. Terms such as "near," "dry," "wet," "secondary," "active," or "passive" drowning, and "delayed onset of respiratory distress" should not be used, as they lack uniformity, imply spurious understanding of the drowning process, and detract attention from the final common pathway of cerebral anoxia.[1,2]

EPIDEMIOLOGY

Drowning is recognized by the World Health Organization (WHO) as a neglected public health priority. The 2017 WHO Global Burden of Disease reports approximately 300,000 unintentional drowning deaths, of which over 90% occur in low- and middle-income countries (LMICs), with 50% from China, India, Pakistan, and Bangladesh. Globally, drowning accounts for 7% of all fatal injuries and has the fourth highest overall injury mortality rate after road injuries, falls, and interpersonal violence.[3,4] However, exposure-adjusted, person-time death estimates for drowning are 200 times higher than for road injuries.[5]

In 48 out of 85 countries with reliable death registries, drowning is in the top five causes of death for children 1–14 years old, of which those aged 1–4 years old are disproportionately affected.[6] In Eastern European countries, the incidence of fatal unintentional drowning in children <19 years of age is between 5 and 7 per 100,000 compared with 0–1 per 100,000 in most other European countries.[7] Low-income and minority groups carry a higher burden from drowning. American Indians, Alaskan Natives, and African Americans; First Nation people in Canada; indigenous Fijian and Maori in the Pacific region; non-Western immigrants in the Netherlands; and foreign tourists in Spain all have higher risk for drowning mortality compared with their national counterparts.[8–10]

Although dramatic on their own, these national and international estimates vastly underrepresent the true burden of drowning. In addition to varied methodologies for reporting drowning deaths, the standard definition of drowning derives from a public health perspective and excludes drowning as a result of water and land transportation, intentional drowning, and those that occur as a result of floods. These other causes of drowning have a significant magnitude, and their numbers of victims may even be larger than the numbers resulting from unintentional drowning. Over 50% of the fatalities that occur during floods are caused by drowning. In some countries, suicide by drowning occurs more often than unintentional drowning, whereas in other countries the majority of the drowning burden is foreign tourists while snorkeling or scuba diving.

Data on nonfatal drowning are limited and, where reported, subject to diverse inclusion criteria. A study of Brazilian lifeguarded beaches showed a fatal:nonfatal ratio of 1:36,[11] whereas a national Australian data set shows an overall ratio of 1:2.7 with highest ratios in children 0–4 years (1:7.6) and drowning in pools (1:4.4).[12] In the Netherlands, the ratio for hospital admissions is approximately 1:3 for all drowning, but 1:2 for unintentional drowning and 1:0.25 for intentional drowning.[13]

Local context must be considered when treating drowning patients, which helps inform comorbidities or the inciting etiology of the drowning. In Australia, most drownings occur in the ocean and in private pools among children or those engaged in recreation.[14] In Brazil, more than 75% occur in rivers because of incidental and occupational exposures.[15] In Japan, a significant number of drownings occur in elderly patients in traditional hot-water tubs in their homes.[16–18] Water transportation accounts for 38% of all passenger transport in Bangladesh, greatly increasing the burden of incidental and occupational drowning risk.[19] The important common factor is that most drowning occurs in at-risk, economically disadvantaged communities, in the uninformed, and in the unprepared. As such, most drownings are preventable.

PATHOPHYSIOLOGY

The drowning process is a continuum, beginning with respiratory impairment as the person's airway goes below the surface of the liquid (submersion) or when high volumes of water impair the airway by splashing over the face (immersion). If rescued at any time, the process of drowning is interrupted, and this is called *nonfatal drowning*. If they die at any time, this is a *fatal drowning*. Submersion or immersion without evidence of respiratory impairment is a water rescue and not a drowning.[1]

When water is aspirated into the airways, coughing occurs as an initial reflex response. For this reason, prolonged coughing may be considered as a criterion that distinguishes drowning from other stress situations in the water. It is speculative if a brief laryngospasm may occur when the person starts to inhale water, but this is of indeterminate clinical significance. As submersion or immersion continues, with or without aspiration of water, hypoxemia leads to loss of consciousness, apnea, and pulmonary damage. Prolonged apnea and hypoxia precipitate cardiac arrest. Hypoxic cardiac arrest generally occurs after a period of tachycardia, then bradycardia, and ultimately pulseless electrical activity (PEA); only rarely does arrest manifest as ventricular fibrillation.[17] The process from submersion to cardiac arrest occurs in seconds to minutes. The only validated factor that predicts outcome at the scene is duration of submersion.[20] However, the factors that predict who will progress to cardiac arrest within seconds instead of minutes are poorly understood and should be the target of future research. In

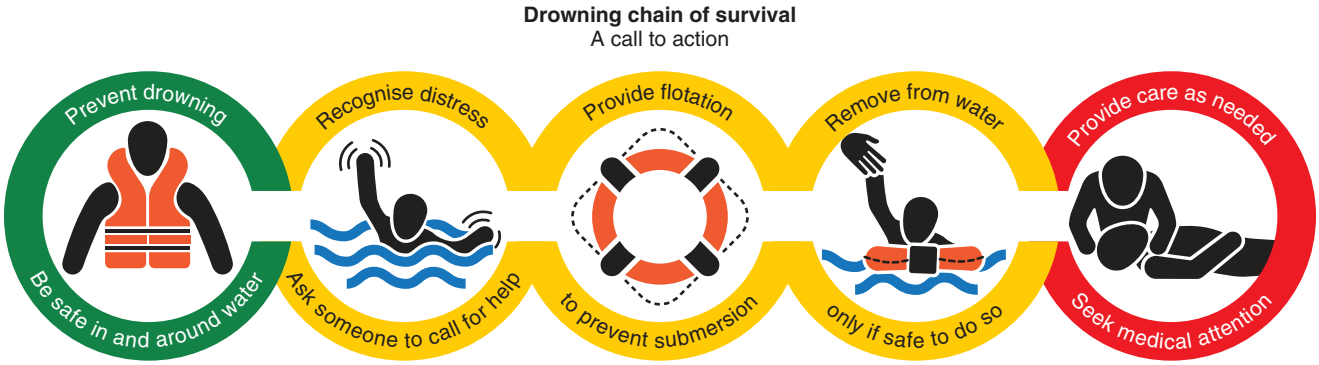

Fig. 61.1 Drowning Chain of Survival. (From Szpilman D, Webber J, Quan L, et al. Creating a drowning chain of survival. *Resuscitation*. 2014;85[9]:1149–1152.)

extraordinarily rare situations, such as when rapid external cooling triggers a mammalian diving reflex, or hypoxia is preceded by hypothermia during submersion in ice-cold water, this process can last for up to an hour. Under typical circumstances, irreversible cerebral damage occurs after 5–10 minutes of submersion.

If the person is rescued in time and the drowning process is interrupted, the clinical picture is determined by the duration of submersion, reactivity of the airways, and the amount of water that has been aspirated. Water in the alveoli causes surfactant destruction and washout. In humans, as little as 1 mL/kg may produce profound alterations in pulmonary gas exchange. Salt and freshwater aspiration cause similar clinical pathology—the symptoms and clinical treatments are identical for both. In either situation, the osmotic gradient can disrupt the integrity of the alveolar-capillary membrane; increase permeability; and exacerbate fluid, plasma, and electrolyte shifts. Regional or generalized pulmonary edema (depending on the amount of water aspirated and airway reactivity) reduces the exchange of O_2 and CO_2.[21–23] Based on the most recent animal and clinical studies from 1960 to 1980, aspiration of 2.2 mL/kg body weight leads to severe disturbance of oxygen exchange and decrease of arterial oxygen pressure (PaO_2) to approximately 60 mm Hg within 3 minutes. The combined effects of fluid in the lungs, loss of surfactant, and increased capillary-alveolar permeability can result in a 10%–40% decrease of lung compliance, increased right-to-left shunting in the lungs, atelectasis, and alveolitis.[24–27]

DROWNING CHAIN OF SURVIVAL

The drowning chain of survival is a visual representation of the relevant factors in the drowning process and shows the five steps to reduce drowning risk and severity (Fig. 61.1).[28]

Prevention

Prevention is unequivocally the most effective way to reduce the burden of fatal and nonfatal drowning. The WHO and other national prevention organizations estimate that 80%–90% of all drownings can be prevented when the appropriate measures are taken. Despite its profound importance, the multifactorial approach to drowning prevention and the layers of protection to prevent drowning are beyond the scope of this chapter. A wide range of reports, publications, and websites, however, are available on the issue.[3,4,29–31]

Recognize Distress and Call for Help

The second element in the drowning chain of survival is to recognize a person in distress and know how to activate help. Sending someone to call for help upon recognizing a person in distress is a key element that ensures early activation of professional rescue and emergency medical services (EMS).

For several decades, it has been assumed that persons exhibiting a surface struggle are generally recognized by the instinctive drowning response (IDR).[32] The IDR is a near-vertical body position, ineffective downward arm movements, ineffective pedaling or kicking leg actions, and little or no forward progress in the water. Video footage of drownings in pools has identified more diverse presentations of visible drowning behavior. All persons in this pilot study submerged completely within 2 minutes without subsequent resurfacing. This limited study and the anecdotal experience of the authors has identified numerous other surface struggle behaviors. Further study is needed to characterize these other movements and inform lifeguard and lay responder training programs.[33]

Provide Flotation to Stop the Process of Drowning

The next priority is to provide flotation as an interim measure to reduce submersion risk. This buys valuable time for those on scene to initiate rescue efforts and for emergency services to arrive. Devices such as ring buoys are purposely designed to provide flotation and can be made available at public locations where they can be deployed by bystanders. Improvised buoyancy aids such as empty plastic bottles or other containers, all kinds of sport balls filled with air, empty ice chests, or driftwood can also be used.

It is critical that laypersons take precautions not to become another drowning victim when attempting to engage in rescue responses. Many drowning persons cling to their would-be rescuer; therefore it is better to approach a struggling person with an intermediary object. When feasible, reaching out, throwing, or dropping the buoyancy aid without entering the water is the preferred method of providing flotation to someone in need of rescue.[11,34–36]

In-Water Ventilation

The drowning process leads first to unconsciousness and apnea, followed by cardiac arrest within several minutes. Between apnea and cardiac arrest, immediate in-water ventilations may provide benefit if provided safely and effectively. For the unconscious person, in-water ventilation can increase the rates of neurologically intact survival to hospital discharge by more than threefold. Effective in-water ventilation is only possible if the rescuer is highly trained. Drowned persons who are only in respiratory arrest may regain consciousness after a few rescue breaths. If there is no response, they should be assumed to be in cardiac arrest and be moved as quickly as possible to a boat or dry land where effective chest compressions can be performed. Chest compressions are

futile while the rescuer and person are in the water, so assessment for a pulse there does not serve any useful purpose.[37,38]

Remove From Water: Rescue Only If Safe to Do So

The attempt to perform a rescue typically involves three phases: approach, contact, and stabilization. Establishing adequate oxygenation is essential to interrupt the drowning process. Professional rescuers may use in-water ventilation as described earlier; otherwise, removing the person from the water as quickly as possible is critical to assist oxygenation and ventilation. Several strategies for removal can be used for bystander rescuers. The person can be helped by directing them to the closest and safest place to exit the water. If this fails, the lay rescuer may consider rescue by throwing a rope, life jacket, or something else that is able to float or reaching with a stick, branch, oar, or wading to them. Entering the water is a personal decision and may depend on the personal relationship with the person in water trouble (e.g., parents and children); distance to swim; swimming skills; and the depth, temperature, and velocity of the water. If available, it is strongly recommended that the rescuer wears a lifejacket or uses some type of flotation. However, sometimes these devices can also increase the risk that well-intentioned rescuers drown by a false sense of invulnerability that results in a rescue for which they are not prepared. If unconscious, the transport to shore should be as rapid as possible to minimize the hypoxic period. The airways should be kept open at all times, if possible.[39] Professional lifeguards can use several types of equipment that may facilitate the rescue[40]

Only a few studies have examined the prevalence of in-water cervical spine injury (CSI).[41,42] A retrospective study of 46,060 water rescues on sand beaches demonstrated an incidence of just 0.009%.[43] In another retrospective review of more than 2400 drowning cases, less than 0.5% had a CSI, and all of these had a history of obvious traumatic mechanism from diving, falling from height, or a motor vehicle collision.[44] Considering the low incidence of CSI and the detriment in delaying oxygenation in order to assure cervical spinal motion restriction, no attempt to immobilize the spine should be made while in the water without a compelling indication. In all cases where the person is unconscious, the priority should be oxygenation, ventilation, and rapid extrication, not cervical spine immobilization. In addition to delaying oxygenation, there is extensive literature showing the potential harms of cervical spine immobilization.

Provide Care as Needed (Resuscitation)

Once on land, the patient should be placed supine with the trunk and head at the same level. On sloped beaches or banks, this is parallel to the shoreline. The standard checks for responsiveness and breathing are carried out. If the patient is unconscious but breathing normally, the recovery position should be used.[45] Cardiopulmonary or isolated respiratory arrest comprises only ~0.5% of all lifeguard rescues. If the patient is not breathing, early oxygenation and ventilation are essential. The drowning process will continue, even out of the water, until the patient receives oxygen. If the patient is in cardiac arrest from drowning, this is primarily because of lack of oxygen. For this reason, cardiopulmonary resuscitation (CPR) by professional rescuers should follow the airway–breathing–circulation (ABC) sequence.[17,39] Because cardiac arrest in drowned persons is caused by asphyxia, cardiac compression only is much less effective and should only occur when there is no other option left.[46–49] For lay persons, the emphasis during training should be to perform breaths AND compressions instead of compression-only CPR.

Early basic life support contributes to better outcomes from drowning and should be initiated as soon as possible. Ventilation should be started with 5 effective initial breaths followed by 30 chest compressions and then continued with 2 breaths to 30 compressions until signs of life reappear, rescuer exhaustion occurs, or Advanced Life Support (ALS) or EMS assistance arrives. The presence of noncardiogenic pulmonary edema fluid (foam), caused by surfactant disruption and alveolar injury, makes initial ventilation often difficult because of decreased pulmonary compliance.[21–23,50] Another frequent complication of drowning resuscitation is regurgitation of stomach contents.[51] The presence of vomitus in the airway can result in further aspiration injury and impaired oxygenation.[52] Active efforts to expel water from the airway (abdominal thrusts or placing the person head down) should be avoided, as they only delay the initiation of ventilation, increase the risk of vomiting by more than fivefold, and lead to a significant increase in mortality.[28,53]

During the COVID-19 pandemic, international CPR guidelines and operational opinions emphasized the role of compression-only CPR for cardiac arrest of presumed cardiac etiology.[54,55] For the same reasons mentioned earlier, the ventilation-first approach for drowning victims has become rather difficult to accept and to apply without further considerations. Ventilation of a person with an active contact or respiratory pathogen in the airways will most certainly infect a person performing mouth-to-mouth ventilation, but this is less likely to occur during chest compressions and use of an automated external defibrillator (AED).[56] Additionally, the use of pocket masks and bag-mask ventilation with or without a HEPA filter are aerosol-generating procedures and will carry some degree of risk of infection to the rescuers. On the other hand, taking into account the young and healthy status of most members of aquatic rescue organizations, it is unlikely that the rescuer will die from participating in a drowning resuscitation that included ventilation. Guidelines have been developed for aquatic rescue organizations that address which elements have to be considered to stratify the risk of COVID-19 to the rescuer during drowning resuscitation.[57,58] These guidelines most of all address how to mitigate the risk to rescuers and relevant public health and ethical aspects (Fig. 61.2).

According to most studies, less than 10% of all drowned persons are in ventricular fibrillation.[38] Given this, the effectiveness of an AED in a drowning resuscitation scenario is low. Oxygenation, ventilation, and cardiac compressions should be optimized during drowning resuscitation before initiation of the AED. If the scenario suggests a sudden cardiac arrest in the water because of presumed ventricular fibrillation (VF) or ventricular tachycardia (VT), the AED should be applied immediately.

PREHOSPITAL ADVANCED LIFE SUPPORT

To save time, medical equipment of the EMS system should be brought to the patient instead of delaying care to transport them to the ambulance. Recommendations for when to start and stop resuscitation differ from cardiac arrest of presumed cardiac etiology (Table 61.1).

In cardiopulmonary arrest for the drowned person, the first priority should be to establish adequate oxygenation and ventilation using the highest concentration available, typically bag-mask ventilations with at least 15 liters per minute of oxygen until an orotracheal tube or a supraglottic airway can be inserted. Effective, high-quality chest compressions should be continued throughout the resuscitation. Once intubated, most patients can be oxygenated and ventilated effectively even in situations where copious noncardiogenic pulmonary edema fluid fills the endotracheal tube. Suctioning can disturb oxygenation and should be balanced against the presence of fluid that makes effective ventilation impossible. Once intubated, positive end-expiratory pressure (PEEP) should be used to optimize oxygenation, either via the ventilator or using a PEEP valve if using a bag-valve mask (BVM).

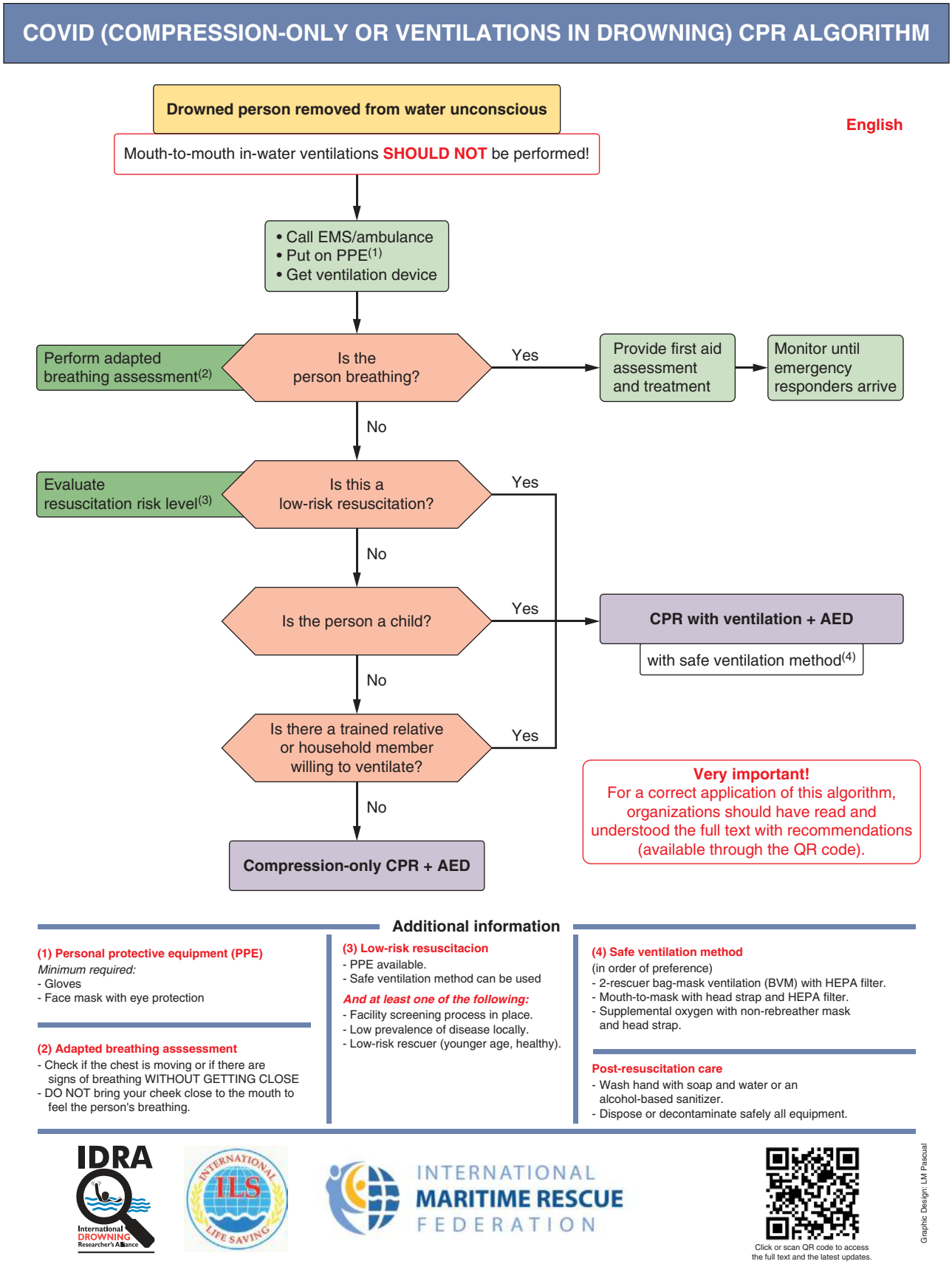

Fig. 61.2 Algorithm for the Resuscitation of Drowned Victims During COVID. *AED*, Automated external defibrillator; *CPR*, cardiopulmonary resuscitation; *EMS*, emergency medical services. (© International Drowning Researchers' Alliance [IDRA], International Life Saving Federation – Medical Committee [ILS-MC] and International Maritime Rescue Federation [IMRF]. https://www.international-maritime-rescue.org/Handlers/Download.ashx?IDMF=64744d12-5fa1-418f-ab78-dfdaabfde4b0.)

TABLE 61.1 Drowning: When to Initiate CPR and When to Discontinue

Question	Recommendations
In whom to begin?	Give ventilatory support for respiratory distress/arrest to avoid cardiac arrest. Start CPR in all submersions <60 minutes who do not present with obvious physical evidence of death.
When to discontinue?	Basic life support should continue unless signs of life reappear, rescuers are exhausted, or advanced life support can take over. Advanced life support should be ongoing until the patient has been rewarmed (if hypothermic) and asystole persists for more than 20 minutes.

CPR, Cardiopulmonary resuscitation.

BOX 61.1 Who Needs Further Medical Help After Rescue From the Water

(a) A patient who has experienced or required any of the following should be sent to a hospital:
- Loss of consciousness, even for a brief period
- Foam at the mouth or nose, cough, or dyspnea that persists more than a few minutes after removal from the water
- Rescue breathing was needed
- Cardiopulmonary resuscitation was needed
- A concomitant medical condition such as heart attack, spinal injury, other injury, asthma, epilepsy, intoxication, or delirium
- Any indication of neurologic impairment (e.g., altered mental status, confusion, lethargy)

(b) The following persons may be considered for release from care at the scene if, after 10–15 minutes of careful observation while being warmed with blankets or other coverings as required, the patient has ALL of the following:
- No cough
- Normal rate of breathing
- Normal circulation as measured by pulse in strength and rate and blood pressure (if available)
- Normal color and skin perfusion
- No shivering
- Is fully conscious, awake, and alert

In such cases, it is unwise for the patient to drive a vehicle, and the patient should be so advised. If any of these conditions does not apply or if the lifesaver has any doubt, then the patient should be advised to seek early medical attention.

(c) A small percentage of patients may have minimal symptoms that go unrecognized and become worse over the next several hours. Patients should be advised to seek care if they develop cough, shortness of breath, or any neurologic or respiratory symptoms over the next 6–8 hours.

The presenting rhythm in a drowning resuscitation setting is usually asystole or PEA. VF may occur if there is a history of coronary artery disease, use of epinephrine, or in the presence of severe hypothermia. If VF is present, defibrillation should be attempted. Peripheral venous or intraosseous access is the preferred route for drug administration. Intravenous (IV) administration of medication should follow the algorithms for asystole or PEA. Endotracheal administration of drugs is not recommended during CPR and certainly not for drowning. An orogastric tube can be placed to relieve gastric distention and prevent further aspiration, and this intervention can improve ventilation and circulation.[59,60] If initial resuscitation efforts are not successful, the person should be transported to a hospital where advanced neuroprotective therapies and rewarming can be accomplished while resuscitation is continued during transport. There are emerging data on the benefit of extracorporeal membrane oxygenation (ECMO) in drowning resuscitation, and patients can be transferred to ECMO-capable hospitals where available.[38]

If adequate oxygenation and ventilation have been provided at the scene by bystanders or lifeguards, an isolated respiratory arrest is frequently reversed before EMS arrives. Oxygen administration at the highest concentration available should continue until spontaneous breathing is restored. Once spontaneous ventilation occurs, oxygen should still be administered at the highest concentration available to maintain a saturation above 92%. Some patients may be able to maintain adequate oxygenation despite an elevated respiratory rate. In low- and middle-income or resource-deficit settings, the highest concentration of oxygen available may just be expired air ventilations. This approach is preferable to withholding ventilations until more advanced equipment arrives and may be lifesaving.

Early intubation and mechanical ventilation in spontaneously breathing patients is indicated when saturation remains below 92% or when respiratory fatigue occurs despite adequate oxygenation. Once intubated and sedated, most patients can be oxygenated and ventilated effectively. Mechanical ventilation should provide a tidal volume of 6–8 mL/kg of predicted body weight. Fraction of inspired oxygen (FiO_2) can initially be 1.0 but should be reduced when both indicated and feasible. Ventilation strategies follow the same guidelines and lung-protective principles of the Acute Respiratory Distress Syndrome (ARDS) Network.[61] If hypotension is initially present and not corrected by oxygen or caused by pneumothorax, a rapid crystalloid infusion should be used.[62]

The majority of conscious drowned persons have only mild distress with little or no aspiration. Treatment is to provide supportive care and oxygen at the highest concentration available. These patients can present a disposition dilemma for rescuers who must determine whether or not additional care is needed at a hospital or higher level of care. Simply put, all persons who cough or have other symptoms that do not resolve within a few minutes of rescue should be transported to a hospital (Box 61.1).

Out-of-hospital cardiac arrest (OHCA) caused by presumed cardiac etiologies is far more common than that caused by drowning. Improved training and high-performance CPR programs have led to improved survival. Conversely, drowning resuscitations present many practical challenges for prehospital providers that must be taken into consideration when developing training and response programs. In essence, the difficulties encountered in drowning resuscitation must be anticipated through realistic, high-fidelity training and feedback. Drowning patients frequently vomit, are pediatric, and are found in outdoor settings with sloped surfaces, uneven footing, and varied lighting. Prehospital training scenarios for drowning patients should take these factors into consideration. Many prehospital drowning resuscitations are attended by lifeguards, police, or other nonmedical first responders. Professional response agencies should be aware of the level of training and capabilities of other responders who may attend a drowning resuscitation in their jurisdiction. Improving survival from drowning requires intentional, targeted, realistic training and optimized system performance.[63]

In-Hospital Treatment. Prehospital treatment should continue or be initiated once the patient is admitted to the emergency department (ED). During initial assessment, it is important to recognize that drowning is sometimes precipitated by a trauma, seizure, stroke,

hypoglycemia, or cardiac dysrhythmia. Additional diagnosis and therapies can be required. In some patients a toxicologic screen for suspected alcohol, recreational drug use, or drug overdose maybe justified and may complement other features of the history of the incident, such as depression, suicide, or parental/elder neglect.

Respiratory Concerns. Many drowning patients present with a clinical picture very similar ARDS. Respiratory management should follow updated ARDS guidelines, including efforts to minimize volume trauma and barotrauma.[64,65] Some 10% of ventilated drowning patients develop a pneumothorax secondary to positive-pressure ventilation and local areas of hyperinflation.[66] Any sudden deterioration in hemodynamic stability after the start of mechanical ventilation should be considered to be the result of pneumothorax or other barotrauma until proven otherwise. Ventilation involving permissive hypocapnia or hypercapnia is not suitable for the drowned person and may worsen hypoxic-ischemic brain injury.[62]

In selected conscious, cooperative, and less symptomatic patients, noninvasive ventilation is effective and may prevent endotracheal intubation.[38,67–69]

Vigilance for infectious complications is important.[70] Pneumonia is often initially missed because of the early radiographic appearance of water in the lungs. Pools, rivers, and beaches generally have insufficient bacteria colonization to induce pneumonia in the immediate post-drowning period. Prophylactic antibiotics tend to only select out more resistant and more aggressive organisms and are not indicated. Daily monitoring of tracheal aspirates for Gram stain, culture, and sensitivity is advised. The first sign of pulmonary infection usually occurs in the third or fourth day of hospitalization, when pulmonary edema is expected to be resolving. Unlike the edema, the infection is diagnosed by fever, sustained leukocytosis, persistent or new pulmonary infiltrates, and increased leukocyte numbers in tracheal aspirates. If the patient needs mechanical respiratory assistance, the incidence of ventilator-associated pneumonia increases. Effective antibiotic therapy sometimes needs to be based on information about the predominant organisms in the water where the drowning occurred. If there are reasons to suspect ventilator-associated pneumonia, antibiotics should be directed to the sensitivity of the predominant microorganisms in the intensive care unit (ICU) or by cultures, if available. Early fiberoptic bronchoscopy may be useful for evaluating infection and for occasions when therapeutic clearing of sand, gravel, or other solids is indicated. Corticosteroids for pulmonary injury should not be used except for bronchospasm.[13,71–73]

Circulatory Issues. Cardiac dysfunction with low cardiac output is common immediately after severe drowning. Low cardiac output is associated with high pulmonary capillary occlusion pressure, high central venous pressure, and high pulmonary vascular resistance and can persist for days after correction of oxygenation and perfusion abnormalities. This may add a cardiogenic component to drowning-associated noncardiogenic pulmonary edema. Low blood pressure, if present, can be corrected with better oxygenation, rapid crystalloid infusion, and restoration of normothermia. Vasopressor infusion should be used only in refractory hypotension to improve cardiac output when replacement with crystalloid is inadequate to restore blood pressure. Electrocardiogram (ECG), echocardiography, pulmonary artery catheterization, or noninvasive alternatives may be needed to assess cardiac function, and ejection fraction can help to guide the clinician in titrating inotropic agents, vasopressors, or both if volume crystalloid replacement has failed. Whether pulmonary edema occurs after salt or freshwater drowning, there is no evidence to support the use of any specific IV fluid therapy, diuretics, or water restriction.[70,74–76]

Mixed respiratory and metabolic acidosis occurs in most drowning patients. Acidosis should be corrected when pH is lower than 7.2 or bicarbonate is less than 12 mEq/L despite adequate ventilatory support. Significant depletion of bicarbonate is rarely present in the first 10–15 minutes of CPR, and IV sodium bicarbonate is not indicated during the initial resuscitation. In hypothermic patients, arterial blood gases do not need to be temperature corrected (the alpha-stat or pH-stat concept).[77]

Recently, more data have become available about periods of renal insufficiency and coagulopathies in drowning persons that are secondary to anoxia, shock, or hemoglobinuria. Measurements of electrolytes, blood urea nitrogen, creatinine, and hemoglobin should be considered, but there are no pathognomonic or unique findings in the drowned person.[78–82]

Neurologic System. The most important complication in severe drowning that requires CPR, beyond reversible pulmonary injury, is anoxic-ischemic cerebral insult. Most late deaths and long-term sequelae of drowning are neurologic in origin.[70,83–86] Although the highest priority in resuscitation after drowning is restoration of spontaneous circulation, every effort in the early stages after rescue should be directed at preventing further neurologic damage. These steps include providing adequate oxygenation (High FiO2) to maintain SatO2 > 92% and establishing effective cerebral perfusion (mean arterial pressure around 100 mm Hg). Any patient who remains comatose and unresponsive after successful CPR or deteriorates neurologically should undergo careful and frequent neurologic function assessment. Consensus guidelines on the brain-oriented treatment of comatose drowning victims include head elevation by 15%–30% in hemodynamic stable patients, establishing normal oxygenation and saturation (to prevent hypoxia and hyperoxia), normocapnia, normal body temperature (to prevent hypothermia and treat hyperthermia; however, a temperature between 32°C and 34°C can be considered during the first 12–72 hours). Guidelines also target normal blood pressure (diagnose and treat hypotension and hypertension) and optimized volume, osmotic, and glycemic status. Comatose drowning victims should be transferred to centers with adult or pediatric intensive care expertise. Frequent neurophysiologic and neuroimaging monitoring (ECG, somatosensory evoked potential [SSEP], N_2O, intracranial pressure [ICP], computed tomography [CT], or magnetic resonance imaging [MRI]) and follow-up of serum biomarkers may be needed. The effects of prolonged induced hypothermia after drowning are inconclusive. There is not yet evidence for any pharmacologic therapy that may influence neurologic prognosis.[62]

Ice-Water Drowning. In some drowned patients, a low body temperature is the reflection of slow cooling because of prolonged submersion in water below body temperature and portends a poor prognosis. In others, hypothermia may be the result of rapid cooling in ice-cold (<7°C) water, which presents a diagnostic and prognostic dilemma. Rapidly developed deep hypothermia caused by drowning in ice-cold water can provide a protective mechanism that allows survival despite prolonged submersion episodes. The cold water triggers the mammalian diving reflex and, likely more importantly, decreases the rate of cerebral oxygen consumption by approximately 5% per each °C decrease in temperature within the range of 37°C to 20°C. However, other mechanisms may have an added role, such as the maintenance of intracellular processes. Although the rare cases of survival in cold water receive significant attention both in peer-reviewed and lay media, they represent rare outliers, and the primary determinant of survival is duration of submersion.[20,87–94]

The paradox in drowning resuscitation is that the hypothermic patient must be warmed in order to be effectively resuscitated, but may benefit from induced therapeutic hypothermia after successful

resuscitation. An important dictum that has been developed from experience with ice-water drowning and accidental hypothermia is that patients who appear dead after exposure to very cold temperatures should not be pronounced dead until they are at near-normal core temperature and remain in asystole. Good outcomes have been reported in scattered case reports and in small case studies of postresuscitation drowned patients who were kept hypothermic or treated with therapeutic hypothermia despite predicted poor outcome.[95,96] More recent studies demonstrate, however, that the beneficial effect of low body temperature on neurologic survival is limited.[83,84] Emerging data show benefit from ECMO in hypothermic drowned persons and will likely inform future research.[38]

DECISION TO ADMIT TO THE ICU, GENERAL WARD, OR DISCHARGE

The decision to observe the nonintubated patient in the ED, the ward, or the ICU should be based on a detailed history, trends in monitoring, diagnostic imaging, and laboratory studies. Patients with minimal symptoms after aspiration of small amounts of liquid typically either get better or worse within the first few hours. Patients who have normal respiration, no coughing, normal room air oxygen saturation, and normal mentation during the first 6–8 hours after the event can be safely discharged.

Although the lay media describes drowning persons who develop respiratory complications up to 72 hours after being initially asymptomatic, there are no well-documented published cases of completely asymptomatic patients who later decompensate after early release. Patients presenting more than 8 hours after an aquatic accident with new respiratory or other symptoms should be evaluated for other medical or traumatic etiologies such as spontaneous pneumothorax, viral myocarditis, pneumonia, respiratory syncytial virus, urinary tract infection, or cholecystitis.

Drowning Severity Classification

A classification scheme based on over 85,000 lifeguard rescues was developed to stratify mortality rates and risks among drowned persons based on their presenting symptoms. The six grades of severity can be easily assessed by an on-scene rescuer, EMT, or physician (Fig. 61.3).[97] The algorithm supports and guides prehospital treatment and transport decisions and provides general mortality estimates.[98–100]

OUTCOME

With advances in ICU therapeutics, the clinical outcome of drowning patients has become primarily related to the neurologic outcome after resuscitation.[76,94,99,101]

Patients who have been resuscitated, are comatose, or show other neurologic deficits should undergo intensive assessment and care. Questions such as "How can we know if the effort to resuscitate will be meaningful?" "How long should we continue to resuscitate?" and "What should we expect as life quality after successful resuscitation?" need to be answered. Both at the rescue site and in the hospital, no single indicator appears to be an absolutely reliable predictor of outcome.[76,93,94] Prolonged submersion with successful resuscitation is not only possible in cold or icy water but also (in rare cases) from prolonged warm water drowning.[28,102] A recent systematic review concluded that the outcome of drowning is almost solely determined by one single factor—duration of submersion.[93] Basic and advanced life support enable drowning patients to achieve their best outcome possible when the duration of cardiopulmonary arrest (submersion time included) is minimized. Most patients who show improvement and are alert (or are stuporous or obtunded but respond to stimuli 2–6 hours after the incident) have normal or near-normal neurologic outcomes.

To inform future research and better understand the prognosis of drowned persons, prehospital agencies are advised to use the formal definition of drowning and the Utstein template for reporting data from drowning resuscitation.[1,2]

Treatment in Resource-Deficit Settings

The lack of adequate resources in LMICs or in disaster, remote, wilderness, or resource-deficit settings has significant implications for drowning survival and treatment. At the site of initial resuscitation and rescue, oxygen should still be provided at the highest concentration available, which may just be by mouth-to-mouth or mouth-to-mask. Chest compressions should be initiated in addition to ventilation if the person is pulseless. Understanding the prognosis becomes even more critical if the crucial downstream elements of the chain of survival, especially a functioning EMS system or access to an advanced healthcare facility, are not present. Careful consideration should be given to only starting resuscitation if submersion time is known to be less than 25 minutes and to terminating resuscitation if unsuccessful after 30 minutes of chest compressions and ventilations. Conversely, if consciousness or return of spontaneous circulation is achieved, priority should be given to immediate transport to a hospital, even if it takes several hours or even days. Once in the hospital, the same priorities for oxygenation apply.[4,103]

KEY POINTS

- Drowning is a serious and neglected public health threat, claiming the lives of more than 300,000 people per year worldwide. Exposure-adjusted, person-time estimates for drowning deaths are 200 times higher than traffic accidents. Over 85% of drowning deaths are preventable.
- Prevention is the best treatment for drowning, which is beyond the scope of this chapter.
- The "drowning chain of survival" refers to a series of water-safety interventions that, when put into action, reduce the morbidity and mortality associated with drowning.
- When resuscitation is needed, the first priority is the immediate provision of optimal ventilation and oxygenation.
- Patients not requiring intubation typically improve within 48 hours and do not have long-term sequelae.
- Although intubated patients should be managed according to the most current ARDS protocols, hypercapnia and hypocapnia should be avoided, as this may exacerbate neurologic damage.
- Survival is most dependent on duration of submersion. Patients who arrive at the ED alert typically have a favorable course. Prognosis for patients arriving obtunded is more difficult to predict.

References for this chapter can be found at expertconsult.com.

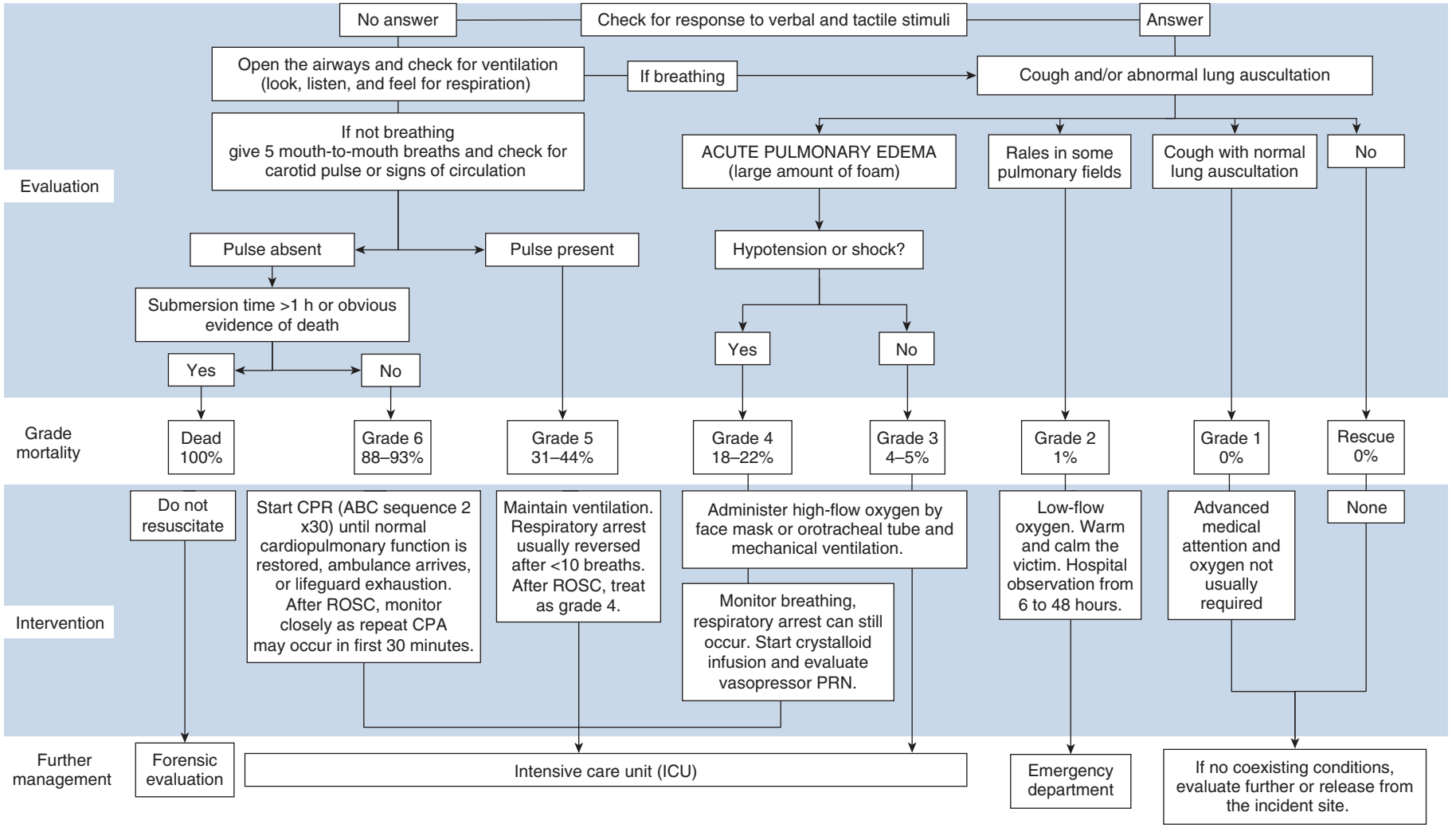

Fig. 61.3 Drowning Severity Classification and flow Chart Strategy Decision Based on Evaluation of 87,339 Rescues. *CPA,* Cardiopulmonary arrest; *ABC,* Airway–breathing–circulation; *CPA,* cardiopulmonary arrest; *PRN,* as needed; *ROSC,* return of spontaneous circulation.

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Aspiration Pneumonitis and Pneumonia

Paul E. Marik

Aspiration is defined as the misdirection of oropharyngeal or gastric contents into the larynx and lower respiratory tract.[1] The consequent pulmonary syndromes that follow depend on the quantity and nature of the aspirated material, frequency and chronicity of aspiration, and nature of the host's defense mechanisms. The most important acute syndromes include *aspiration pneumonitis,* characterized in its most severe form and in a predisposing setting as Mendelson syndrome, a chemical pneumonitis caused by the aspiration of gastric contents, and *aspiration pneumonia,* an infectious process caused by the aspiration of oropharyngeal secretions that have been colonized by pathogenic bacteria.[1,2] Although some overlap exists between these two syndromes, they are distinct clinical entities. Consequences of chronic aspiration include bronchiectasis, chronic bronchitis, lipoid pneumonia, interstitial lung disease, organizing pneumonia, bronchiolitis obliterans, diffuse aspiration bronchiolitis, and *Mycobacterium fortuitum* pneumonia.[3] This chapter focuses on acute aspiration, namely, aspiration pneumonitis and aspiration pneumonia. It is critically important to distinguish between these two syndromes, as their management differs considerably. Aspiration pneumonia is a bacterial pneumonia caused by the aspiration of colonized oropharyngeal secretions. It most commonly develops in elderly patients and those with neurologic disorders. By contrast, aspiration pneumonitis is caused by the inhalation of regurgitated gastric contents, causing a chemical pneumonitis.[1] The administration of antibiotics is central to the management of aspiration pneumonia, whereas the treatment of aspiration pneumonitis is largely supportive.[1] The distinction between these two syndromes is based largely on clinical criteria (Table 62.1). Although gastric biomarkers for aspiration are increasingly available (pepsin, amylase, lipid-laden macrophages), none have been clinically validated.[2–4] Serum procalcitonin and other inflammatory markers are unable to distinguish aspiration pneumonitis from aspiration pneumonia.[5] This imprecision is not surprising, considering that proinflammatory mediators play a central role in the pathophysiology of both syndromes and are responsible for the transcription of procalcitonin.[6]

ASPIRATION PNEUMONITIS

Aspiration pneumonitis is best defined as acute lung injury after the aspiration of regurgitated gastric contents.[1] This problem occurs in patients with marked disturbances of consciousness, such as drug overdose, seizures, coma resulting from acute neurologic insults, massive cerebrovascular accident, head trauma, and general anesthesia. Adnet and Baud demonstrated an association between the degree of altered mental status as measured by Glasgow Coma Scale and aspiration, supporting the pathophysiologic link between these entities.[7] In clinical practice, drug overdose is the most common cause of aspiration pneumonitis, occurring in approximately 10% of patients hospitalized after massive drug ingestion. Aspiration pneumonitis also occurs commonly with acute alcohol intoxication and after a generalized seizure.[8] Historically the syndrome most commonly associated with aspiration pneumonitis is Mendelson syndrome, reported in 1946 in obstetric patients who aspirated while receiving general anesthesia.[9]

Although aspiration is a widely feared complication of general anesthesia, clinically apparent aspiration in nonemergent situations is exceptionally rare in modern anesthesia practice, and in healthy patients the overall morbidity and mortality are low. Nevertheless, aspiration pneumonitis is an important perioperative complication and remains the most common cause of anesthesia-associated fatality, accounting for between 10% and 30% of all anesthetic deaths. The risk of aspiration with modern anesthesia is reported to be between 2.9 and 4.7 per 10,000 general anesthetics (about 1 in 3000 anesthetics), with a mortality incidence of approximately 1:125,000.[10,11] Emergency surgery (particularly trauma and abdominal surgery with delayed gastric emptying), procedures performed at night, inadequate anesthesia, obesity, obstetric patients, elderly immobilized patients, and patients with obstructive sleep apnea are considered to be at a higher risk of such aspiration.[11,12]

Pathophysiology

Mendelson emphasized the importance of acid when he showed that un-neutralized gastric contents introduced into the lungs of rabbits caused severe pneumonitis indistinguishable from that caused by an equal amount of 0.1 N hydrochloric acid.[9,13,14] However, if the pH of the vomitus was neutralized before aspiration, the pulmonary injury was minimal. Experimental studies have demonstrated that the severity of lung injury increases significantly with the volume of the aspirate and less directly with its pH; a pH of less than 2.5 is typically required to cause severe aspiration pneumonitis. In experimental models, a two-phase injury results when acid is instilled into the lungs. The initial injury phase (within 1 hour of acid exposure) is primarily because of the acid's direct caustic effects on pulmonary tissue, whereas the second injury phase (beginning at 3–4 hours and peaking at 4–6 hours postexposure) results from the products released by recruited neutrophils.[15,16] The intensity of the alveolar neutrophil infiltration correlates with the severity of the acute lung injury. Once localized to the lung, neutrophils play a key role in the development of lung injury through the release of reactive oxygen species (ROS) and proteases that are injurious to the lung. Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase is the major source of ROS in activated polymorhpho nuclear leukocytes, (PMNs;). Other sources of ROS after gastric aspiration include superoxide anions generated by xanthine oxidase.[17] ROS exacerbate acute lung injury through several mechanisms, including direct cellular injury, nuclear factor-κB (NF-κB) activation, and activation of other proinflammatory mediators such as tumor necrosis factor-alpha (TNF-α) and interleukin-8 (IL-8). The activation of NADPH oxidase in neutrophils is linked to the generation of neutrophil extracellular traps

TABLE 62.1 Contrasting Features of Aspiration Pneumonitis and Aspiration Pneumonia

Feature	Aspiration Pneumonitis	Aspiration Pneumonia
Mechanism	Aspiration of sterile gastric contents	Aspiration of colonized oropharyngeal material
Pathophysiologic process	Acute lung injury from acidic and particulate matter	Acute pulmonary inflammatory response to bacteria and bacteria products
Bacteriologic findings	Initially sterile, with subsequent bacterial infection possible	Gram-negative rods, gram-positive cocci, and rarely, anaerobic bacteria
Major predisposing factors	Depressed level of consciousness	Dysphagia and gastric dysmotility
Age group affected	Any age group, but usually young persons	Usually elderly persons
Aspiration event	May be witnessed	Usually not witnessed
Typical presentation	Patient with a history of depressed level of consciousness in whom a pulmonary infiltrate and respiratory symptoms develop	Institutionalized patient who presents with features of a "community-acquired pneumonia" with an infiltrate in a dependent bronchopulmonary segment
Clinical features	No symptoms, or symptoms ranging from a nonproductive cough to tachypnea, bronchospasm, bloody or frothy sputum, and respiratory distress	Tachypnea, cough, fever, and signs of pneumonia

(NETs). NETs are extracellular strands of decondensed (unwound) DNA in complex with histones and neutrophil granule proteins. NETs contain serine proteases and other antimicrobial products that damage the lung.

The stomach contains a variety of substances in addition to acid. Several experimental studies have demonstrated that aspiration of small, particulate food matter from the stomach may cause severe pulmonary damage, even if the pH of the aspirate exceeds 2.5.[18,19] These studies suggest that cell recruitment and expression of inflammatory mediators are most pronounced after injury with combined acid and small food particles. These data are supported by findings in patients in whom the most severe lung injury was observed after aspiration of gastric fluids with particulate food matter.[20,21] In healthy subjects, gastric acid prevents the growth of bacteria, and the contents of the stomach are normally sterile. Bacterial infection therefore does not play a significant role in the early stages of acute lung injury after aspiration of gastric contents.

Clinical Presentation

Aspiration of gastric contents can present dramatically, with a full-blown picture that includes gastric contents in the oropharynx, wheezing, coughing, shortness of breath, cyanosis, pulmonary edema, hypotension, and hypoxemia, which may progress rapidly to severe acute respiratory distress syndrome (ARDS) and death (Fig. 62.1). However, many patients may not express impressive signs or symptoms associated with aspiration, whereas others may simply develop a new cough or wheeze. In some patients, aspiration may be clinically silent, manifesting only as arterial desaturation with radiologic evidence of aspiration. Warner and colleagues studied 67 patients who aspirated while undergoing anesthesia.[14] Forty-two (63%) of these patients were totally asymptomatic, 13 required mechanical ventilatory support for more than 6 hours, and 4 died.

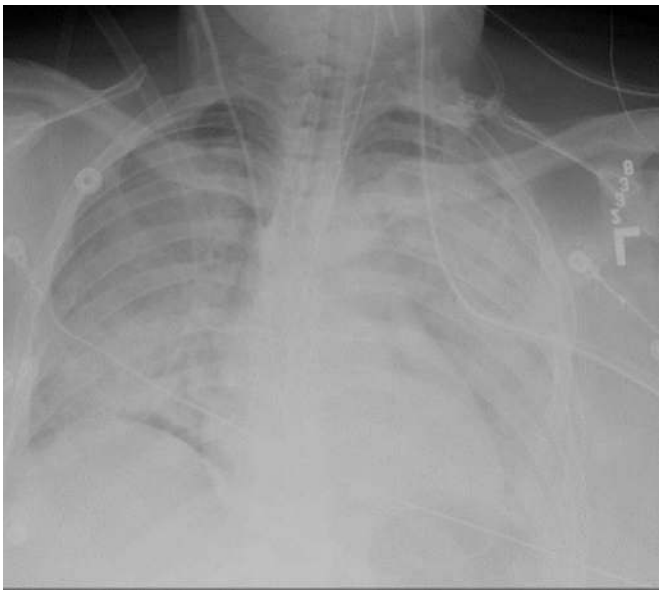

Fig. 62.1 Chest radiograph demonstrating severe bilateral air space disease (ARDS) in a patient who aspirated after anesthesia.

Management of Aspiration Pneumonitis

The upper airway should be suctioned after a witnessed aspiration. Endotracheal intubation should be strongly considered in patients who are unable to protect the airway. Although common practice, the prophylactic use of antibiotics in patients with strongly suspected or witnessed aspiration is not recommended.[1,22] Similarly, the use of antibiotics shortly after an aspiration episode is discouraged in most patients who develop a fever, leukocytosis, and a pulmonary infiltrate, as their use may simply encourage overgrowth of resistant organisms in an otherwise uncomplicated chemical pneumonitis. However, empiric antimicrobial therapy is appropriate in patients who aspirate gastric contents in the setting of small bowel obstruction or in other circumstances associated with colonization of gastric contents. Antimicrobial therapy should be considered in patients with an aspiration pneumonitis that fails to resolve within 48 hours. Empiric therapy with broad-spectrum agents is recommended. Antimicrobials with anaerobic activity are not routinely required.

Corticosteroids are potent antiinflammatory agents that act largely by repression of the transcriptional activity of NF-κB. Glucocorticoids have been used in the management of aspiration pneumonitis since 1955[23–25]; however, their role as monotherapy appears restricted, possibly because of their limited effects on neutrophils and ROS. Vitamin C, acting synergistically with low-dose corticosteroids and thiamine,

has emerged as an important strategy in treating various conditions characterized by widespread and profound inflammation.[26] Vitamin C is a potent antioxidant and inhibitor of NAPDH oxidase and would likely reduce the severity of acute lung injury after acid aspiration.[27] In addition, vitamin C inhibits NETosis.[28] We have previously described two patients with "anesthesia-related" aspiration pneumonitis and severe ARDS who were treated with hydrocortisone, ascorbic acid, and thiamine (HAT therapy) who appeared to respond dramatically to this intervention.[29] Mixed results have been reported from prospective randomized controlled trials that explored the potential benefits of this treatment strategy in the management of sepsis and ARDS. We suggest, however, that this simple, safe, readily available, and cheap intervention be strongly considered in patients with acid aspiration–induced acute lung injury.

Prevention of Aspiration During Anesthesia

In recent years, more liberal preoperative fasting guidelines have been promoted. In heathy adults without an increased risk of regurgitation or aspiration, solids should be avoided after midnight; however, a light meal such as dry toast may be considered up to 6 hours before anesthesia, and clear liquids such as water, coffee without milk, or fruit juice can be ingested up to 2 hours before induction.[30,31] Meta-analyses of randomized controlled trials comparing fasting times of 2–4 hours with more than 4 hours report smaller gastric volumes and higher gastric pH values in adult patients given clear liquids 2–4 hours before a procedure, and this approach is currently endorsed by the American Society of Anesthesiology (ASA).[32]

Preoperative antacids, histamine-2 (H2) receptor blockers, proton pump inhibitors (PPIs), and prokinetic agents have been used to reduce the volume and/or acidity of the gastric contents and hence the risk of aspiration and its consequences. There is, however, a lack of data indicating that any of these drugs reduce the risk of aspiration pneumonia.[33] The routine use of these drugs is not recommended by the ASA guidelines.[32] Standard teaching suggests that rapid-sequence induction with cricoid pressure should be performed when intubating patients at increased risk of aspiration. Although not proven to reduce the risk of aspiration during emergent intubations, cricoid pressure is currently considered the standard of care in this situation.

ASPIRATION PNEUMONIA

Aspiration pneumonia refers to the development of a radiographic infiltrate in the setting of risk factors for increased oropharyngeal aspiration. Approximately half of all healthy adults aspirate small amounts of oropharyngeal secretions during sleep. Presumably the low burden of nonvirulent bacteria in normal pharyngeal secretions, together with forceful coughing, active ciliary transport, and normal humoral and cellular immune mechanisms clear the inoculum without sequelae.[1] However, if normal mechanical, humoral, or cellular mechanisms are impaired or if the aspirated inoculum is large enough, pneumonia may follow. Any condition that increases the volume and/or bacterial burden of oropharyngeal secretions in the setting of impaired host defense mechanisms may lead to aspiration pneumonia. Indeed, the volume of the aspirate correlates strongly with the development of pneumonia in stroke patients undergoing swallow evaluation.[34] Factors that increase oropharyngeal colonization with potentially pathogenic organisms and increase the bacterial load augment the risk of aspiration pneumonia. The clinical setting in which pneumonia develops largely distinguishes aspiration pneumonia from other forms of pneumonia. However, there is considerable overlap. This is illustrated by the fact that otherwise healthy elderly patients with "community-acquired pneumonia" (CAP) have a significantly higher incidence of silent aspiration when compared with age-matched controls.[35]

Epidemiology

The lack of specific and sensitive markers makes the epidemiologic study of aspiration syndromes difficult. Furthermore, most studies do not distinguish between aspiration pneumonitis and aspiration pneumonia. Nevertheless, several studies list "aspiration pneumonia" as the cause of CAP in 5%–15% of cases.[36,37] CAP is a major cause of morbidity and mortality in the elderly, and it is likely that aspiration is the major cause of pneumonia in this advanced age group. Epidemiologic studies have demonstrated that the incidence of pneumonia increases with aging, the risk being almost six times higher in those over the age of 75, compared with those less than 60 years of age.[38,39] The attack rate for pneumonia is highest among those in nursing homes.[40]

Dysphagia in Patients With Aspiration Pneumonia

Impaired swallowing is the major risk factor leading to aspiration pneumonia. In addition, dysphagia contributes significantly to predisposing protein-energy malnutrition and dehydration. Impairment in any component of the swallow mechanism, including anatomic abnormities of the upper airway or esophagus, can lead to dysphagia.[41] Dysphagia has traditionally been associated with brainstem and bilateral cerebral infarction, though it has more recently been shown to occur in isolated cerebral infarctions as well. Furthermore, dysphagia is commonly associated with silent cerebral infarctions.

Dysphagia is remarkably common in Westernized nations and is a major cause of morbidity and mortality. Indeed, aspiration pneumonia is probably the final common pathway by which most chronically ill patients die. It has been estimated that over 16 million senior citizens in the United States suffer from dysphagia.[42] Furthermore, in the United States an additional 300,000–600,000 patients develop swallowing dysfunction each year from neurologic disorders.[43] Dysphagia affects more than 30% of patients who have had a cerebrovascular accident, 52%–82% of patients with Parkinson disease, 84% of patients with Alzheimer disease, up to 40% adults aged 65 years and older, and more than 60% of elderly institutionalized patients.[44] The efficiency of the swallowing mechanism decreases with aging, predisposing to aspiration. Kikuchi and colleagues evaluated the occurrence of silent aspiration in otherwise "healthy elderly patients" with CAP and age-matched control subjects using indium chloride scanning.[35] Silent aspiration was demonstrated in 71% of patients with CAP compared with 10% of control subjects. The impaired swallowing mechanism of the elderly can be attributed to diminished sensation, silent cerebral infarction, cerebral atrophy, a delay in the synapse conduction of the afferent inputs to the central nervous system, and lingual weakness (sarcopenia) caused by aging.[45,46]

Risk Factors for Dysphagia

The major risk factors for dysphagia are listed in Table 62.2. In patients with an acute stroke, the incidence of dysphagia ranges from 40% to 70%.[47] Dysphagic stroke patients who aspirate are at an increased risk of developing pneumonia.[48,49] Although dysphagia gradually improves in most patients after a stroke, in many the swallowing difficulties follow a fluctuating course, with 10%–30% continuing to have dysphagia with aspiration.[50,51]

Factors That Increase the Risk of Pneumonia in Patients Who Aspirate

Although the presence of dysphagia and the volume of the aspirate are key factors that predispose patients to aspiration pneumonia, a number of other influences play an important role.[34] Colonization of the

TABLE 62.2 Risk Factors for Dysphagia and Aspiration Pneumonia

Cerebrovascular disease
Ischemic stroke
Hemorrhagic stroke
Subarachnoid hemorrhage
Degenerative neurologic disease
Alzheimer dementia
Multi-infarct dementia
Parkinson disease
Amyotrophic lateral sclerosis (motor neuron disease)
Multiple sclerosis
Head and neck cancer
Oropharyngeal malignancy
Oral cavity malignancy
Esophageal malignancy
Other
Scleroderma
Diabetic gastroparesis
Reflux esophagitis
Presbyesophagus
Achalasia

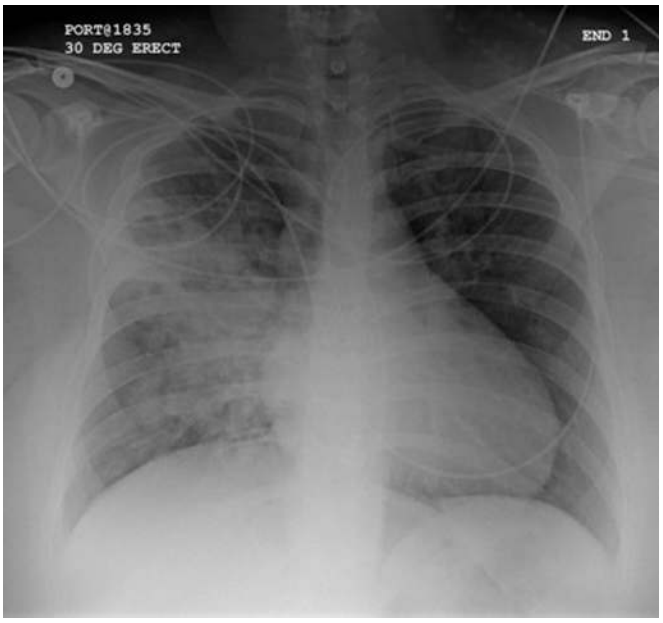

Fig. 62.2 Opacification of the right perihilar region and superior segment of the right lower and upper lobes consistent with aspiration pneumonia in a 75-year-old patient who suffered a stroke.[52]

oropharynx is an important step in the pathogenesis of aspiration pneumonia. The elderly have increased oropharyngeal colonization with pathogens such as *Staphylococcus aureus* and aerobic gram-negative bacilli (e.g., *Klebsiella pneumoniae* and *Escherichia coli*).[52] Although this increased colonization may be transient, it underlies their increased risk of pneumonia with these pathogens. Furthermore, colonization of dental plaque may be an important risk factor for aspiration pneumonia.[53] The defects in host defenses that predispose to enhanced colonization with these organisms are uncertain; however, dysphagia with a decrease in salivary clearance and poor oral hygiene may be major predispositions.[54] Residents of long-term care facilities are prone to poor oral health because of a lack of hygiene in addition to conditions of periodontal and/or dental disease. Frequent use of PPIs increases gastric and oropharyngeal colonization with potentially pathogenic organisms. Gulmez and colleagues reported that the concurrent use of PPI in patients over the age of 60 increased the risk for community-acquired (aspiration) pneumonia.[55]

Diagnosis and Management of Aspiration Pneumonia

There is no "gold standard" test to diagnose aspiration. Furthermore, in patients with aspiration pneumonia, unlike the case of aspiration pneumonitis, the critical episode of aspiration is generally not witnessed. The diagnosis is therefore inferred when a patient with known risk factors for aspiration has an infiltrate involving a characteristic bronchopulmonary segment.[52] In patients who aspirate in the recumbent position, the most common sites of involvement are the posterior segments of the upper lobes and the apical segments of the lower lobes (Fig. 62.2).[1,8,52] By contrast, the basilar segments of the lower lobes are favored in patients who aspirate in the upright or semi-recumbent position. The usual picture is that of an acute pneumonic process, which runs a course similar to that of a typical CAP. Untreated, however, these patients appear to have a higher incidence of cavitation and lung abscess formation.[56]

Antimicrobial therapy is indicated in patients with aspiration pneumonia. The choice of antibiotics should depend on the setting in which the aspiration occurred and the patient's premorbid condition. Evaluation includes such considerations as whether the aspiration occurred in the community or in a health care facility and such patient characteristics as alcoholism, oral hygiene, intravenous drug abuse, and recent use of antibiotics or acid suppressive therapy.[57]

Aspiration pneumonia most commonly occurs in a health care facility (health care–acquired pneumonia [HCAP]) or in an acute care hospital (hospital-acquired pneumonia [HAP]). HCAP refers to pneumonia that develops in the growing population of individuals receiving health care in venues outside the hospital, including dialysis clinics, nursing homes, and long-term acute care (LTAC) facilities. Patients with HCAP and risk factors for infection with a drug-resistant pathogen should be treated with broad-spectrum agents. Although commonly prescribed (and often considered the standard of care), antimicrobials with specific anaerobic activity are not routinely warranted.[1,8] In one of the most rigorous studies to date, El-Sohl and colleagues performed protected quantitative bronchial sampling in 95 patients with severe aspiration pneumonia.[58] Out of the 67 pathogens identified, gram-negative enteric bacteria were the predominant organisms isolated (49%), followed by anaerobic bacteria (16%) and *S. aureus* (12%). A single anaerobic bacterium was isolated from 11 patients, usually in association with a gram-negative pathogen. Although seven cases with anaerobic isolates received initially inadequate antimicrobial coverage to address those organisms, six had effective clinical responses. Antimicrobials with specific anaerobic activity may only be indicated in patients with periodontal disease, patients expectorating putrid sputum, and patients with a necrotizing pneumonia or lung abscess on chest radiograph.[1,57,59,60] Prophylactic antibiotics are not recommended for preventing pneumonia in patients with dysphagia who have suffered a stroke.[61]

Assessment and Management of Dysphagia

All elderly patients with CAP and chronic idiopathic lung disease (ILD) in addition to patients with a recent cerebrovascular accident and those with degenerative neurologic diseases should be referred to a speech and language pathologist (SLP) for a formal swallowing evaluation.[49,62] Those patients with dysphagia require the formulation

and implementation of an individualized management strategy. A clinician's bedside assessment of the cough and gag reflex is unreliable in screening for patients at risk of aspiration. Because objective swallowing evaluation can be performed with a nasogastric (NG) tube (or feeding tube) in place, it is not necessary to remove such tubes (and interrupt enteral feedings) to evaluate dysphagia. Similarly, there is no contraindication to leaving an NG tube in place to supplement oral alimentation.[63]

The management of patients with dysphagia requires the coordinated expertise of a number of health care professionals, including the patient's primary care physician, pulmonologist, SLP, clinical dietician, occupational therapist, physiotherapist, nurse, oral hygienist, dentist, and the patient's primary caregivers. The goal is to optimize the safety, efficiency, and effectiveness of the oropharyngeal swallow; to maintain adequate nutrition and hydration; and to improve oral hygiene. Enhanced quality of life, wherever possible, should direct management. Whenever appropriate, emphasis should be placed on encouraging oral versus nonoral nutritional intake and hydration.

A fundamental principle of rehabilitation is that the best therapy for any activity is the activity itself. Therefore because swallowing is logically considered the best therapy for swallowing disorders, rehabilitation should be aimed at identifying ways of ensuring safe and effective swallowing in individual patients. Current treatment for dysphagia includes prevention of aspiration in the form of dietary and fluid modifications, compensatory maneuvers, position changes, and rehabilitation exercises.[64] Diet modification is a common treatment for dysphagia. Modifications in food consistency are individually determined by means of the clinical swallow and/or videofluoroscopic swallow evaluation. Reduction in bolus volume and enhancement of bolus viscosity significantly improve the safety of swallowing and reduce the risk of aspiration.[45] In addition to changes in diet, maintenance of oral feeding often requires compensatory techniques to reduce aspiration risk or to improve pharyngeal clearance. A variety of behavioral techniques are used, including modifications in posture, head position, and breathing efforts, in addition to specific swallowing maneuvers.

Tube Feeding

Tube feeding is not an essential intervention for all patients who aspirate. Short-term tube feeding, however, may be indicated in elderly patients with severe dysphagia and aspiration in whom improvement of swallowing is likely to occur. Nakajoh and colleagues demonstrated that the incidence of pneumonia was significantly higher in stroke patients with dysphagia who were fed orally compared with those who received tube feeding (54.3 vs. 13.2%, $P < 0.001$), despite the fact that the orally fed patients had a higher functional status (higher Barthel index).[65] The FOOD trials consisted of two large randomized studies that enrolled dysphagic stroke patients.[66] In the first trial, patients enrolled within 7 days of admission were randomly allocated to early tube feeding or to no tube feeding. Early tube feeding was associated with an absolute reduction in risk of death of 5.8%. The second trial allocated patients to early NG feeding or early feeding via a percutaneous endoscopic gastrostomy (PEG) tube. PEG feeding was associated with an absolute increase in the risk of death of 1% and an increased risk of death or poor outcome of 7.8%. Patients with a PEG were less likely to be transitioned to oral feeding than the NG group and were more likely to be living in an institution. This may in part explain the higher mortality of the PEG-fed patients. It is interesting to note that PEG-fed patients were more likely to develop pressure sores, suggesting that these patients may have received different (perhaps less attentive) nursing care. The results of the FOOD trials suggest that dysphagic stroke patients should be fed early via an NG or feeding tube and transitioned to oral feeding as their dysphagia resolves. Those patients whose dysphagia does not resolve may be candidates for placement of a PEG tube.

Oral Hygiene

Dental plaque and the "tongue coating" serve as a reservoir of potentially pathogenic organisms.[53] Occupants of residential homes tend to have poor oral hygiene and rarely receive treatment from dentists and oral hygienists.[67] An aggressive protocol of oral care will reduce colonization with potentially pathogenic organisms and decrease the bacterial load, measures that have been demonstrated to reduce the risk of aspiration pneumonia.[68–71] Oral care should not be overlooked in edentulous patients, as "tongue cleaning" is associated with a decreased oropharyngeal bacterial load.[72,73]

Pharmacologic Management

The neurotransmitter substance P is believed to play a major role in both the cough and swallow sensory pathways. Angiotensin-converting enzyme (ACE) inhibitors prevent the breakdown of substance P and may theoretically be useful in the management of patients with aspiration pneumonia. A number of studies have demonstrated a lower risk of aspiration pneumonia in stroke patients treated with an ACE inhibitor compared with other antihypertensive agents.[74,75] This observation was initially noted in Japanese patients, and it has been suggested that this benefit was restricted to Asian populations.[76] Furthermore, it has been postulated that lipophilic ACE inhibitors may be more beneficial than hydrophilic ACE inhibitors.[77] However, a population-based case-control study from the UK demonstrated that the ACE inhibitor currently received was associated with a reduction of the risk of pneumonia in the general population (odds ration [OR] 0.75, 95% confidence interval [CI] 0.65–0.86).[78]

CONCLUSION

Aspiration pneumonia and pneumonitis are common clinical syndromes. Aspiration pneumonitis follows the aspiration of gastric contents, usually in patients with a markedly decreased level of consciousness. Treatment of aspiration pneumonitis is essentially supportive. Aspiration pneumonia occurs in patients with dysphagia and usually presents as a CAP or HCAP with a focal infiltrate in a gravitationally dependent bronchopulmonary segment. Patients with aspiration pneumonia require treatment with antibiotics selected on the basis of the risk of infection with a drug-resistant pathogen in addition to management of the underlying dysphagia.

KEY POINTS

- Aspiration pneumonitis is a chemical pneumonitis that occurs after the aspiration of gastric contents.
- Aspiration pneumonitis occurs in the setting of a marked alteration of the level of consciousness.
- The treatment of aspiration pneumonitis is largely supportive.
- Aspiration pneumonia is a bacterial pneumonia that occurs in patients with dysphagia.
- Aspiration pneumonia is treated with antibiotics, with the choice of antibiotics depending on the setting in which the aspiration occurred.
- Patients with aspiration pneumonia require a comprehensive dysphagia evaluation and a multidisciplinary management strategy.

References for this chapter can be found at expertconsult.com.

ANNOTATED REFERENCES

El-Sohl AA, Pietrantoni C, Bhat A, et al. Microbiology of severe aspiration pneumonia in institutionalized elderly. *Am J Respir Crit Care Med.* 2003;167:1650–1654.
This important publication evaluated the pathogens associated with aspiration pneumonia and clearly demonstrated that anaerobic bacteria play a minor role in this syndrome.

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63

Severe Asthma Exacerbation in Adults

Thomas Corbridge and James Walter

MAGNITUDE OF THE PROBLEM AND RISK FACTORS

Each year in the United States, acute asthma accounts for approximately 1.8 million emergency department (ED) visits, 190,000 hospitalizations, and 3500 deaths.[1] Although death rates have decreased slightly over the last 20 years, African Americans, women, and older patients continue to be at increased risk.[1] For the subgroup of patients requiring hospital admission, in-hospital mortality is very low in patients not requiring ventilatory support. Mortality in intubated and mechanically ventilated patients is often associated with out-of-hospital cardiopulmonary arrest.[2,3]

Inadequate outpatient asthma control increases the risk of poor outcomes, including death.[4] Risk factors for an exacerbation-prone phenotype include cigarette smoking, medication nonadherence, psychosocial factors, poverty, obesity, severe sinus disease, frequent infections, and alterations in host cytokine response to viral infections.[5–7] However, even patients with mild asthma are at risk for serious exacerbations.[6] Risk factors for fatal or near-fatal asthma are listed in Table 63.1.

PATHOPHYSIOLOGY OF ACUTE AIRFLOW OBSTRUCTION

Rapid-onset exacerbations are a rare but distinct form of acute asthma. These exacerbations are predominantly bronchospastic events that evolve over minutes to hours and follow exposure to allergens or irritants, stress, illicit drugs, or the use of nonsteroidal antiinflammatory agents or beta-blockers in susceptible patients. They are generally not triggered by infection.[8] More commonly, asthma attacks evolve over 24 hours or longer and are associated with increased airway wall inflammation, bronchospasm, and mucous plugs. These exacerbations take longer to resolve and may be triggered by viral infections or *Mycoplasma pneumoniae.*[8]

Regardless of trigger or tempo, the common endpoints of a severe exacerbation include critical expiratory airflow obstruction, inadequate expiratory time, dynamic hyperinflation (DHI), increased work of breathing, and decreased diaphragm force generation. A patient with a respiratory rate (RR) in the high twenties or thirties has less than 2 seconds to exhale the tidal breath. If this time is insufficient to fully exhale, lung volumes increase and tidal breathing occurs at higher lung volumes, where respiratory system compliance is low and the respiratory muscles that drive inflation are less efficient. DHI is self-limiting if hyperinflation increases lung elastic recoil pressure and airway diameter to enhance expiratory flow. At the end of exhalation, incomplete gas emptying elevates alveolar volume and pressure, a state referred to as *auto–positive end-expiratory pressure (auto-PEEP).*[9] Overcoming the effects of auto-PEEP requires increased inspiratory work to drop pleural pressures enough to generate inspiratory flow. Concurrent with increases in resistive and elastic loads is decreased diaphragm force generation from the mechanical effects of DHI, fatigue, and acidemia, increasing the risk of respiratory arrest and death.[10]

Hypoxemia results from a decrease in ventilation ($\dot{V}_A$) relative to perfusion ($\dot{Q}$) in alveolar-capillary units. Hypoxemia severity generally tracks the severity of airflow obstruction, but in recovering patients, spirometry and peak flow may improve faster than partial pressure of oxygen (Pao_2) and $\dot{V}_A/\dot{Q}$ inequality, indicating that larger airways recover faster than smaller airways. Acutely ill asthmatics may also have small areas of high $\dot{V}_A$ relative to $\dot{Q}$ and increased physiologic dead space when blood flow decreases to hyperinflated units. Although elevated physiologic dead space can contribute to hypercapnia, alveolar hypoventilation is the more likely cause in acute asthma.

Large swings in intrathoracic pressure accentuate the normal inspiratory fall in systolic blood pressure, a phenomenon called *pulsus paradoxus* (PP). During forceful inspiration, intrathoracic pressure falls, lowering right atrial and right ventricular (RV) pressures and augmenting RV filling. Enhanced right-sided filling shifts the intraventricular septum leftward. This results in decreased left ventricular (LV) compliance and incomplete LV filling. DHI further impedes LV filling by causing tamponade-like physiology, and it increases LV afterload.

Forced exhalation increases intrathoracic pressures and impedes right-sided filling. The net result of these cyclical changes in pleural pressure is increased PP. A decline in PP generally signals improvement, with the important exception that fatigue and inability to generate large pleural pressure swings also drop PP.[10]

CLINICAL FEATURES

The hallmarks of a moderate to moderately severe exacerbation are tachypnea and respiratory distress. Patients may have difficulty speaking in long sentences and present with wheezing and prolongation of the expiratory phase. Hypoxemia and respiratory alkalosis occur commonly. Severe exacerbations are signaled by upright positioning, diaphoresis, monosyllabic speech, RR over 30/min, accessory muscle use, tachycardia, and a PP greater than 25 mm Hg.[7,11] Hypoxemia with normocapnia or hypercapnia indicates a severe exacerbation. Decreased mental status, paradoxical breathing, bradycardia, absence of PP from fatigue, and a quiet chest signal impending arrest. Severe exacerbations may also be complicated by tachyarrhythmias, RV strain, and myocardial ischemia. Posture, speech, and mental status allow for quick appraisal of severity, response to therapy, and need for intubation. The emergence of wheezes in patients presenting initially with a quiet chest from poor air movement suggests improved airflow rates and clinical status. Additionally, it is worth considering that "all that wheezes is not asthma." Table 63.2 lists other diagnostic considerations.

PEAK FLOW MEASUREMENTS

Early measurement of the peak expiratory flow rate (PEFR) or forced expiratory volume in the first second of expiration (FEV_1) helps characterize exacerbation severity. Severe exacerbations are characterized by a PEFR or $FEV_1 \leq 50\%$ of predicted or personal best, and alternative diagnoses should be considered when lung function is preserved.[7] Failure of pharmacotherapy to improve expiratory flow significantly after the initial 30–60 minutes further predicts a refractory course requiring sustained treatment in the ED or hospitalization. Measurements of expiratory flow are not required in every patient. They are not likely to alter therapy in patients presenting with classic signs and symptoms of acute asthma, and obtaining peak expiratory flow measurements in a tenuous patient can worsen bronchospasm to the point of respiratory arrest.

ACID-BASE STATUS

Arterial blood gases are indicated in patients with severe asthma exacerbations that are not responding significantly to initial therapy. Serial blood gases are generally not required unless the patient is mechanically ventilated. Although a venous blood gas can provide a reasonable approximation of arterial pH and a quick screen for hypercapnia, the poor correlation between arterial and venous partial pressure of carbon dioxide (PCO_2) is a notable limitation of relying solely on venous blood gases in the critically ill patient with asthma.[12] Hypoxemia and respiratory alkalosis are common in mild to moderate exacerbations. Eucapnia and hypercapnia suggest a severe exacerbation, but not necessarily the need for intubation, as even hypercapnic patients may respond to pharmacotherapy and/or noninvasive ventilation.

Renal compensation in response to respiratory alkalosis of adequate duration manifests as a normal anion gap metabolic acidosis. Lactic acidosis can result from increased work of breathing and the use of either high-dose nebulized or parenteral beta-agonist therapy.[13,14]

TABLE 63.1 Risk Factors for Fatal or Near-Fatal Asthma

Frequent emergency department visits and hospitalizations
Intensive care unit admission
Intubation (prior or current)
Hypercapnia
Barotrauma
Psychiatric illness
Poor adherence to medical regimen
Illicit drug use
Poverty
Inadequate access to medical care
Overuse of short-acting inhaled beta-2 agonist
Current or recent use of oral corticosteroids
Not using inhaled corticosteroids
Poor perception of airflow obstruction
Comorbidities (e.g., coronary artery disease)
Food allergy

TABLE 63.2 Differential Diagnosis of Acute Asthma

Chronic obstructive pulmonary disease exacerbation
Vocal cord dysfunction
Intraluminal mass or foreign body
Aspiration
Tracheal stenosis
Infectious bronchitis or pneumonia
Heart failure ("cardiac asthma")

CHEST RADIOGRAPHY

Chest imaging rarely affects management in classic cases of asthma exacerbation. Indications for chest imaging include localizing signs on examination, concerns regarding barotrauma, questions regarding alternative diagnoses, and assessment of endotracheal tube position.

EMERGENCY DEPARTMENT DISPOSITION

Patients demonstrating an inadequate response to albuterol over the first 30–60 minutes of therapy in the ED invariably require hospital admission or prolonged treatment in the ED.[15] Approximately one-third of patients fall into this "nonresponder" category (Fig. 63.1).

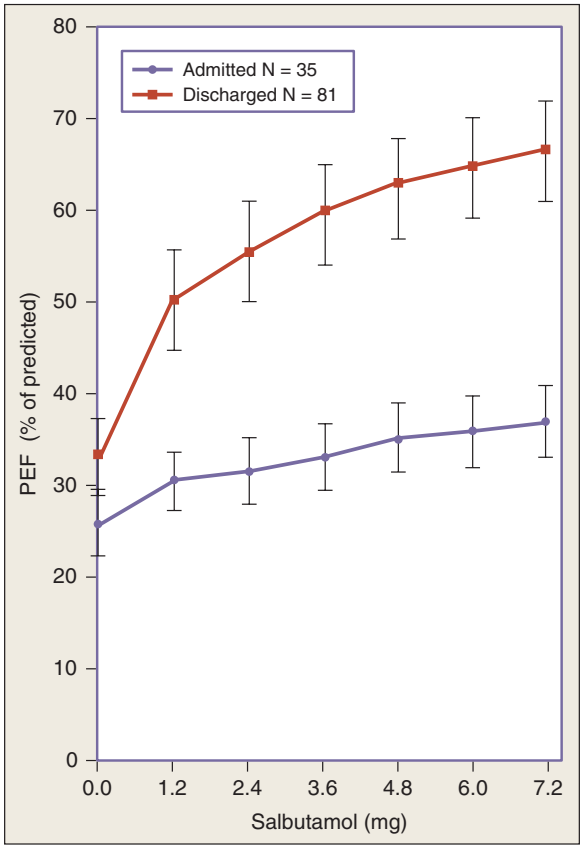

Fig. 63.1 Dose–response relationship to albuterol 4 puffs (400 μg) every 10 minutes in 116 acute asthmatics, of whom 67% obtained discharge criteria after administration of 2.4 mg of albuterol within 1 hour; half of the responders met discharge criteria after 12 puffs. Patients with a blunted cumulative dose–response relationship were hospitalized. (Reproduced with permission from Rodrigo C, Rodrigo G. Therapeutic response patterns to high and cumulative doses of salbutamol in acute severe asthma. *Chest.* 1998;113:593.)

Along these lines, the Global Initiative for Asthma (GINA) report recommends hospital admission for patients presenting with a PEFR less than 50% of predicted or 50% of the patient's personal best on presentation and <60% after initial treatment.[7] Intensive care unit (ICU) admission is required for respiratory failure, the need for frequent albuterol treatments, deterioration despite treatment, fatigue, altered mental status, and cardiac complications. Patients with a PEFR between 60% and 80% of predicted or personal best after treatment may be eligible for discharge from the ED on appropriate therapy, although clinical judgment may favor admission, especially when the outpatient setting is suboptimal or noncompliance favors directly observed therapy. Patients with a good response can be discharged with appropriate maintenance therapy and instructions for follow-up.

OXYGEN

Supplemental oxygen should be administered to maintain oxygen saturations above 90%. Doing so improves oxygen delivery to tissues, including the respiratory muscles, and reverses hypoxic pulmonary vasoconstriction. Oxygen further protects against desaturation consequent to beta-agonist-induced pulmonary vasodilation with increased blood flow to low $\dot{V}_A/\dot{Q}$ units.

PHARMACOLOGIC MANAGEMENT

Selected drugs used in the treatment of acute asthma are listed in Table 63.3.

Beta-2 Agonists

Inhaled short-acting beta-2 agonists (SABAs) treat the bronchospastic component of acute asthma. They can be delivered in a repetitive or continuous fashion, depending on clinical response and side effects, which include tremor, hypersensitivity/paradoxical reactions, cardiovascular effects, and hypokalemia. Recommended doses in acute asthma are higher than approved on the label and are based on clinical judgment, clinical trials, and guideline recommendations. Excessive SABA use has been associated with fatalities. The limits of intensive SABA use should be kept in mind; many asthmatics presenting to the hospital for rescue have done so because their outpatient inhaler was not effective.

A commonly used strategy is albuterol, 2.5 mg by nebulization, every 20 minutes during the first hour. In severe asthma exacerbations, continuous administrations delivering the same total dose may be slightly superior to repetitive doses. Albuterol can also be delivered effectively by metered-dose inhaler (MDI). MDIs with spacers are less expensive and faster; handheld nebulizers require less supervision and coordination. The most recent GINA report recommends albuterol 4–10 puffs by MDI with a spacer every 20 minutes for the first hour.[7] The treatment strategy after the first hour depends on the clinical response and side effects. An as-needed approach may be preferable to scheduled dosing to decrease total drug exposure.

Although albuterol is the most widely used SABA, other SABAs are available, including levalbuterol. A meta-analysis demonstrated that levalbuterol was not superior to albuterol in acute asthma.[16]

Subcutaneous epinephrine or terbutaline should be avoided in patients able to take inhaled therapy. If the patient is refractory to inhaled therapy, subcutaneous treatment may be beneficial, especially if there are concerns regarding anaphylaxis. Subcutaneous treatment is risky, however, particularly in older patients at risk for coronary artery disease, and it should only be used with caution by seasoned clinicians. Long-acting beta-2 agonists (LABAs) are not commonly used to treat severe asthma exacerbations, although they have been studied in this setting.[17] LABAs combined with an inhaled corticosteroid (ICS) are commonly prescribed on discharge to help achieve outpatient control and prevent future exacerbations.

Ipratropium Bromide

The modest bronchodilator properties of ipratropium bromide preclude its use as a single agent in acute asthma, and the addition of ipratropium to albuterol is of limited benefit in patients with mild or moderate attacks. However, in patients with severe attacks, ipratropium added to albuterol is more effective than albuterol alone,[18,19] even though it does not have Food and Drug Administration (FDA)–approved labeling for treatment of asthma. For nebulization in adults, 0.5 mg of ipratropium bromide can be added to 2.5 mg of albuterol; by MDI, 4–8 puffs of ipratropium bromide can be added to 4–10 puffs of albuterol. If a combination albuterol/ipratropium bromide inhaler is used, one recommended dose is 4–10 puffs every 20 minutes. In addition to the warnings and precautions for albuterol, patients receiving ipratropium bromide should be monitored for urinary tract and ocular side effects. Special care should be taken to avoid inadvertently spraying ipratropium into a patient's eyes, which can cause additional toxicity, including mydriasis. Albuterol and ipratropium can be continued for the first 1–3 hours as guided by clinical response and toxicity, after which albuterol can be continued as a single agent.

Corticosteroids

Systemic corticosteroids are invariably recommended for patients with severe asthma exacerbations. A rare exception might be the patient demonstrating an immediate and durable response to initial SABA therapy alone; these patients of course remain candidates for increasing or starting ICS therapy. Corticosteroids treat inflammation by promoting new protein synthesis, and their effects are typically delayed, underlining the importance of early initiation. Systemic steroids decrease hospitalization rates, speed the rate of recovery, and decrease the chance of relapse after discharge. Warnings and precautions pertinent

TABLE 63.3 Selected Drugs Used in the Treatment of Acute Asthma

Albuterol	2.5 mg in 2.5 mL normal saline by nebulization every 15–20 min × 3 in the first hour or 4–10 puffs by MDI with spacer every 10–20 min for 1 hour, then as required; for intubated patients, titrate to physiologic effect and side effects
Levalbuterol	1.25 mg by nebulization every 15–20 min ×3 in the first hour; then as required
Epinephrine	0.3 mL of a 1:1000 solution subcutaneously every 20 min × 3. Terbutaline is favored in pregnancy when parenteral therapy is indicated. Use with caution in patients older than age 40 and in patients with coronary artery disease
Corticosteroids	Methylprednisolone IV or prednisone PO 40–80 mg/day in 1 or 2 divided doses until PEFR reaches 70% of predicted or personal best
Anticholinergics	Ipratropium bromide 0.5 mg (with albuterol) by nebulization every 20 min, or 4–8 puffs by MDI with spacer (with albuterol) every 20 min
Magnesium sulfate	2 g IV over 20 minutes; repeat once as required (total dose 4 g, unless hypomagnesemic)

IV, Intravenous; *MDI,* metered-dose inhaler; *PEFR,* peak expiratory flow rate; *PO,* per os (oral).

to systemic steroids include hyperglycemia, hypertension, steroid myopathy, insomnia, psychosis, hypokalemia, fluid retention, and bone loss.

Oral steroids are as effective as parenteral steroids for patients able to tolerate oral medications. Single-dose formulations of an intramuscular preparation are reasonable in patients deemed unlikely to be compliant with oral steroids after discharge.

Various dosing regimens have been studied, and debate continues regarding the optimal dosing strategy. For hospitalized adults, the Expert Panel Report 3 recommends 40–80 mg/day of prednisone, methylprednisolone, or prednisolone in one or two divided doses until PEFR reaches 70% of predicted or the patient's personal best.[20] GINA recommends 1 mg prednisolone/kg/day or equivalent to a maximum of 50 mg/day. For outpatients, a common strategy is to use prednisone 40 mg/day for 5–10 days, with early follow-up to guide further administration.

There is no clear role for high-dose ICSs in acute asthma. However, as mentioned, ICSs play a pivotal role in achieving outpatient asthma control, and patients should be discharged from the ED or hospital on an ICS-based treatment strategy.

Other Therapies

Aminophylline does not usually provide additional bronchodilation in adults treated optimally with beta-2 agonists, and it increases the frequency of side effects, including tachyarrhythmias. It should not be used routinely in the management of patients with severe exacerbations.

The safety and efficacy of intravenous (IV) magnesium sulfate, $MgSO_4$, in adults treated for acute asthma in the ED has been studied by meta-analysis.[21] The results demonstrate that a single infusion of 1.2 g or 2 g IV $MgSO_4$ over 15–30 minutes reduces hospital admissions and improves lung function in adults with acute asthma who have not responded adequately to supplemental oxygen, SABAs, and IV corticosteroids. There is no established role for inhaled $MgSO_4$ in acute asthma.[22]

There are insufficient data to recommend leukotriene modifiers in acute asthma. The most compelling data come from the use of IV montelukast in adults, but the IV formulation is not available in the United States. There is no benefit to adding oral montelukast to conventional therapy in the management of severe asthma exacerbations.[23] Likewise, mucolytic agents, although usually well tolerated, have limited efficacy in exacerbated asthma and have been associated with a tendency to exacerbate bronchospasm.

Methodologic differences, small patient numbers, and failure to control for upper airway obstruction have plagued studies of heliox. Taken in sum, the data do not support its routine use in acute asthma, but it may be reasonable to try in severe cases in which a high fraction of inspired oxygen is not needed to maintain full oxygenation. Data further suggest that heliox as a driving gas for nebulized SABAs improves PEFRs and decreases hospital admissions in patients with severe exacerbations.[24]

Unlike select exacerbations of chronic obstructive pulmonary disease, antibiotics such as azithromycin do not improve outcomes and are not recommended in acute asthma unless there is clinical concern for bacterial pneumonia.[7,20]

NONINVASIVE VENTILATION

Despite the common and increasing use of noninvasive ventilation (NIV) in patients with acute asthma, limited data are available to define its role in this setting. Additional well-designed, controlled, prospective trials are needed. A systemic review of 13 studies meeting inclusion and exclusion criteria determined a trend towards better outcomes in patients receiving NIV, but the variability of the studies precluded conclusive recommendations.[25] A Cochrane systematic review that included five trials did not demonstrate a clear benefit to NIV for the outcomes of mortality or intubation.[26] A large retrospective cohort study capturing 13,390 US patients showed that NIV was the initial mode of ventilation for 556 patients (4.0%) and that invasive mechanical ventilation was the initial choice for 668 patients (5%).[27] Twenty-six patients (4.7% of NIV-treated patients) were intubated for NIV failure. In-hospital mortality was 0.2%, 2.3%, 14.5%, and 15.4%, respectively, for patients not ventilated, patients receiving NIV, patients requiring invasive mechanical ventilation, and patients intubated after NIV failure. The increased mortality rate seen in patients failing NIV emphasizes the need for close monitoring during NIV to avoid an undue delay in intubation.

NIV includes the use of low levels of nasal continuous positive airway pressure (CPAP) of 5–7.5 cm H_2O or, more commonly, bilevel positive airway pressure (BiPAP). One recommendation for BiPAP is to start 8 cm H_2O inspiratory pressure support and 3 cm H_2O of expiratory positive airway pressure. Pressures are adjusted as required to achieve an RR below 25/min and a tidal volume above 7 mL/kg.[28] NIV should be used only in alert, cooperative, and hemodynamically stable patients, and again, it is mandatory to monitor patients carefully for failure to avoid a delay in intubation.[29] High-flow nasal oxygen does not have a defined role in asthma exacerbations.

INTUBATION AND MECHANICAL VENTILATION

Respiratory arrest or impending arrest (e.g., exhaustion, progressive symptoms despite maximal therapy, a quiet chest, worsening hypercapnia, and altered mental status) are indications for intubation. After intubation, clinicians should be prepared for hypotension, which stems from sedation and paralysis, hypovolemia, positive pressure mechanical ventilation, lung hyperinflation, and potential tension pneumothorax.

Inappropriately fast RRs result in inadequate exhalation time and dangerous levels of DHI. Clues to this include excessive efforts required to deliver manual breathes during Ambu bag ventilation, high airway pressures during mechanical ventilation, hypotension, and tachycardia. When critical DHI is suspected, a trial of hypopnea (two to three breaths per minute) or apnea in a well-oxygenated patient for 30–60 seconds is both diagnostic and therapeutic. This deflation maneuver lowers airway pressures, increases cardiac preload, and helps restore cardiopulmonary stability. Tension pneumothorax is an important additional consideration, even in patients responding to a deflation maneuver.

Initial Ventilator Settings

Expiratory time (Te), tidal volume (Vt), and the severity of airway obstruction determine the level of DHI during mechanical ventilation.[30,31] Expiratory time is determined by minute ventilation and the inspiratory flow rate. Lowering RR and increasing the inspiratory flow rate prolong Te (Fig. 63.2). The magnitude of deflation achieved by these strategies may be small because expiratory flow rates are typically quite low in severe asthma, but even small changes in lung volume may be clinically relevant. Note that high inspiratory flow rates increase peak airway pressures and may worsen patient–machine synchrony and that high inspiratory flow rates may increase RR in spontaneously breathing patients and thereby actually decrease Te.[32]

An initial minute ventilation of 7–8 L/min in a 70-kg patient generally avoids dangerous levels of DHI.[33] This goal can be achieved by choosing volume-controlled ventilation (VCV) with an RR between 12

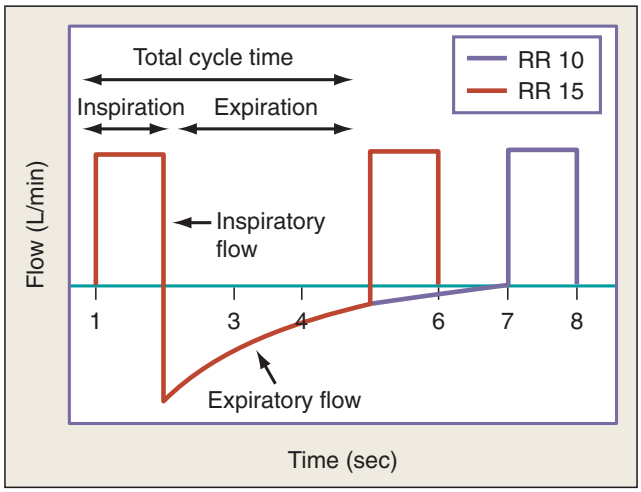

Fig. 63.2 Effects of changing respiratory rate (RR) on expiratory time (Te) with a tidal volume (VT) of 1000 mL and a constant inspiratory flow rate of 60 LPM (1 LPS). Note that with an RR of 15/min, total cycle time (amount of time allowed for one complete breath) is 4 seconds. Inspiratory time (Ti) is 1 second, and Te is 3 seconds, resulting in an I:E of 1:3. Note that the expiratory flow persists at the time of the next delivered breath (as demonstrated by failure of the exhalation flow tracing to return to baseline or zero flow), suggesting the presence of auto-PEEP. By lowering RR to 10/min, total cycle time increases to 6 seconds and Te is 5 seconds, resulting in an I:E of 1:5. Lower RR allows for greater exhalation of the delivered breath and lower end-expiratory plateau pressure (not shown), although effects are modest because of low end-expiratory flow rates.

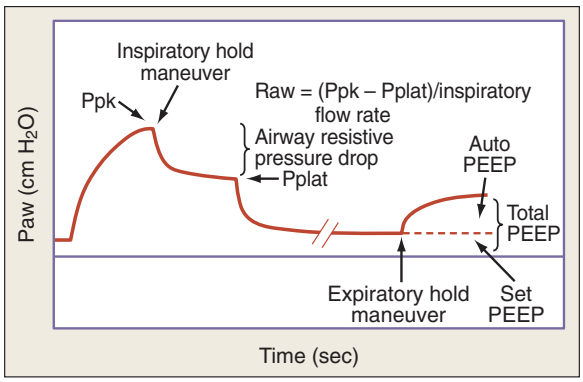

Fig. 63.3 Pressure–time tracing during mechanical ventilation demonstrating measurement of peak inspiratory pressure (Ppk), plateau pressure (Pplat), and auto-PEEP. While delivering a constant inspiratory flow (not shown), airway pressure (Paw) increases to Ppk, the sum of airway resistive pressure and Pplat. Airway resistive pressure and Pplat are determined by an inspiratory pause during which inspiratory flow is temporarily stopped to eliminate airway resistive pressure, allowing Paw to fall from Ppk to Pplat. If inspiratory flow is set at 60 L/min, the resistance pressure drop equals airway resistance (Raw) in units of cm H_2O/L/sec. An end-expiratory hold maneuver is performed to measure auto-PEEP. During this maneuver, Paw increases by the amount of auto-PEEP present. Note that end-inspiratory and end-expiratory hold maneuvers are performed on different breaths.

and 14/min and a VT between 7 and 8 mL/kg. In spontaneously breathing patients, a low level of set PEEP (e.g., 5 cm H_2O) usually reduces the inspiratory work of breathing by decreasing the pressure gradient required to overcome auto-PEEP, without aggravating lung inflation. A constant inspiratory flow rate of approximately 60 L/min or a decelerating flow strategy with an average flow of >40 L/min are reasonable starting points, but decelerating flows may be better tolerated in awake patients. Theoretically, pressure-controlled ventilation (PCV) may deliver more uniform distribution of ventilation than VCV, but the delivered VT is variable with PCV and affected by changes in the degree of bronchoconstriction and hyperinflation.[34] No data support assist control (AC) over synchronized intermittent mandatory ventilation with pressure support (PS) for major clinical outcomes in a broad range of patients.[35]

Assessing Lung Inflation

Avoiding critical DHI is central to ventilator adjustments, but measuring lung volumes is challenging in clinical practice.[3] The only validated method is to measure the volume of gas at end inspiration, termed *Vei*, by collecting expired gas from total lung capacity (TLC) to functional residual capacity (FRC) over 40–60 seconds of apnea. The utility of this measure is limited by the need for paralysis and expertise with monitoring. Although Vei may underestimate air trapping in the presence of slowly emptying lung units, a Vei greater than 20 mL/kg correlates with barotrauma.[33] Surrogate measures of lung inflation include the single-breath plateau pressure (Pplat) and auto-PEEP. Accurate measurements of both of these pressures require ventilator synchrony and absence of patient effort, and neither pressure has been validated to predict outcomes. Pplat is an estimate of maximal average alveolar pressure that is determined by briefly stopping flow at end inspiration (Fig. 63.3). Pplat is affected by the properties of the entire respiratory system, including lung, chest wall, and abdomen. Thus Pplat can vary significantly from patient to patient even for the same degree of DHI. For example, an obese patient will likely have a higher Pplat than a nonobese patient for the same extent of DHI. A common, but unvalidated, recommendation is to maintain a Pplat <30 cm H_2O.

Auto-PEEP is the lowest measurable alveolar pressure achieved during the respiratory cycle. It can be estimated by recording airway opening pressure during an end-expiratory hold maneuver (see Fig. 63.3) in the absence of interference from patient effort. Persistence of expiratory gas flow at the beginning of inspiration (which can be detected by auscultation or from flow tracings) also suggests auto-PEEP (see Fig. 63.2). Auto-PEEP of some units may be rather dramatically underestimated when there is poor communication between alveoli and the airway opening. For this reason, the plateau pressure yields a better estimate of gas trapping during VCV. Significant elevations of auto-PEEP (e.g., >15 cm H_2O) are a sign of severe exacerbation.

Ventilator Adjustments

Although not validated by controlled trials, one logical approach to adjusting the ventilator limits Pplat is a general principle of management (Fig. 63.4). If initial ventilator settings result in Pplat exceeding 30 cm H_2O, then RR should be decreased to drop it below that level. Dropping RR may result in hypercapnia, but doing so may be preferable to hazardous DHI and is generally well tolerated hemodynamically. Anoxic encephalopathy and myocardial dysfunction are relative contraindications to permissive hypercapnia, however, because of the potential for hypercapnia to dilate cerebral vessels, decrease myocardial contractility, and constrict the pulmonary vasculature. Lowering RR may not increase partial pressure of carbon dioxide in the arteries ($Paco_2$) as much as expected if decreasing DHI simultaneously reduces physiologic dead space. If hypercapnia results in a blood pH of less than 7.20 and RR cannot be increased because of the Pplat limit, starting an infusion of sodium bicarbonate is an option, although this has not been shown to improve outcomes. If Pplat is less than 30 cm H_2O

and pH continues less than 7.20, it is reasonable to increase RR until Pplat reaches the 30 cm H_2O limit; however, alveolar ventilation may not benefit in direct proportion to the increase in ventilation, especially if reducing expiratory time generates additional auto-PEEP. As patients improve and DHI diminishes, RR can be safely increased as needed to normalize pH and $Paco_2$.

Whether this strategy decreases the risk of barotrauma is unknown. One study of barotrauma in patients mechanically ventilated with limited V_T and airway pressures included 79 patients with asthma.[36] Five of these patients (6.3%) developed barotrauma. Tidal volumes and airway pressures did not differ between patients with and without barotrauma.

Sedation and Paralysis

Sedation improves comfort, safety, and patient–ventilator synchrony. In patients expected to be extubated quickly (e.g., patients with a more pure form of bronchospasm), propofol is recommended because it allows for rapid reversal of sedation after its discontinuation. Benzodiazepines are less expensive alternatives, but time to awakening is less predictable, particularly after prolonged use, and they may be more deliriogenic. Minimal data are available to inform the use of dexmedetomidine or dissociative-dose ketamine in this setting. For analgesia and to help suppress respiratory drive, an opioid should be strongly considered as an addition to propofol or benzodiazepine. Daily interruption of sedatives and analgesics helps avoid undue drug accumulation in addition to being an important component of best practice for all mechanically ventilated patients.[37]

Short-term paralysis is indicated when safe and effective mechanical ventilation cannot be achieved by sedation and analgesia alone. Cisatracurium is a common choice because it is essentially free of cardiovascular effects, does not release histamine, and does not rely on hepatic and renal function for clearance. Complications associated with paralysis include myopathy, venous thromboembolism, airway secretion retention, ventilator-associated pneumonia, and death from inadvertent machine disconnection.

Use of Bronchodilators During Mechanical Ventilation

Controlled trials are needed to inform the optimal use of bronchodilators in intubated patients and to provide evidence for or against common recommendations. Intubated patients generally require higher drug dosages to achieve a clinical effect. This likely stems from a combination of refractory airflow obstruction and challenges delivering an effective dose to the targeted receptors. Whether bronchodilators are administered by MDI or nebulizer, patient–ventilator synchrony helps to optimize delivery. MDIs require a spacing device on the inspiratory limb of the ventilator, and nebulizers should be administered close to the ventilator. Dropping the inspiratory flow rate during nebulization helps minimize turbulence, but this strategy may worsen DHI and should be time-limited. In-line humidifiers should be stopped during treatments.

At the same constant inspiratory flow and tidal volume, a fall in the peak-to-pause airway pressure gradient demonstrates decreased inspiratory airway resistance, and declines in Pplat and auto-PEEP suggest lung deflation. These favorable changes in mechanics indicate a therapeutic bronchodilator response (Fig. 63.5). Lack of a measurable response suggests that the patient is refractory to bronchodilators, that the delivery and/or dose of drug is suboptimal, or that there is another problem causing fixed airflow obstruction such as a kinked or plugged endotracheal tube.

Other Considerations

Rarely, the management strategies mentioned earlier fail to stabilize the patient. In these situations, general anesthetic bronchodilators may reduce peak pressures and $Paco_2$, but these agents are associated with hypotension and arrhythmias and their benefits are short lived.[38] Heliox delivered through the ventilator circuit may also decrease peak pressure and $Paco_2$, but its use requires significant institutional expertise, planning, expense, and modest fraction of inspired oxygen (FiO_2) requirement. Use of extracorporeal membrane oxygenation (ECMO) may be considered at experienced centers for patients with life-threatening DHI, progressive barotrauma, or respiratory acidosis that worsens despite optimal pharmacologic and ventilator management. In a review of registry data from the Extracorporeal Life Support Organization, survival to hospital discharge for patients with asthma placed on ECMO was 83.5%, suggesting ECMO may be a lifesaving intervention

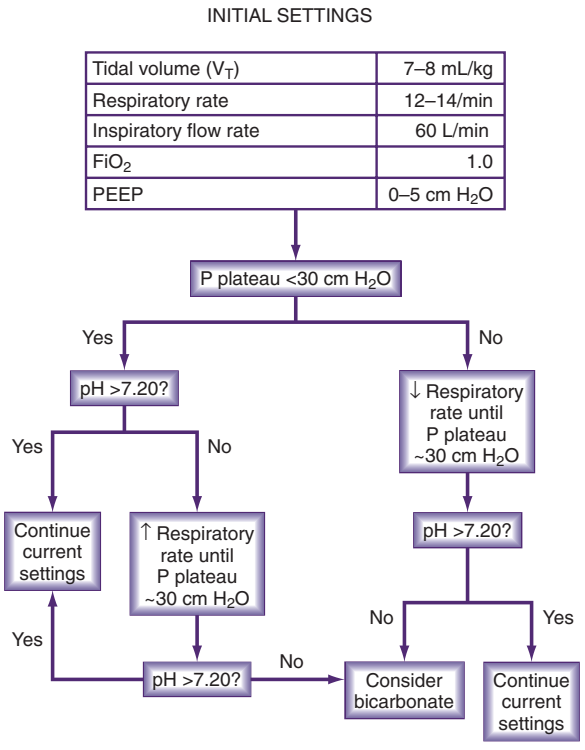

Fig. 63.4 Recommendations for initial ventilator settings and subsequent ventilator adjustments based on Pplat (end-inspiratory plateau pressure) and arterial pH in patients with severe asthma exacerbation.

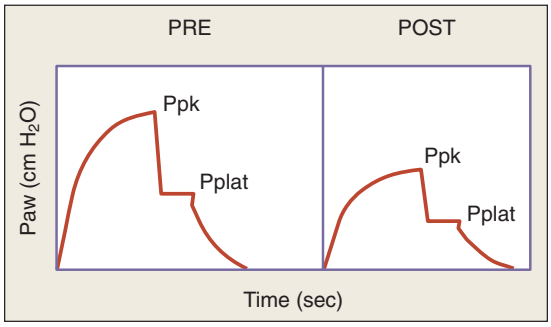

Fig. 63.5 Pressure–time tracings before and after successful administration of a bronchodilator. Note the drop in both airway resistive pressure and end-expiratory plateau pressure (*Pplat*), reflecting increased airway diameter and decreased lung inflation, respectively. *Paw*, Airway pressure; *Ppk*, peak inspiratory pressure.

for carefully selected patients.[39] The use of extracorporeal CO_2 removal ($ECCO_2$-R)—a low-flow extracorporeal support system that requires smaller-bore vascular access than ECMO—has also been described in case reports. Further research is needed to clarify the safety and efficacy of $ECCO_2$-R in the setting of life-threatening asthma.[40]

Extubation

Extubation criteria have not been validated for patients with acute asthma. One approach is to perform a spontaneous breathing trial once $Paco_2$ normalizes, DHI improves, airway resistance is <20 cm H_2O/L/sec, mental status is acceptable, oxygen requirements are minimal, PEEP is ≤ 5 cm H_2O, hemodynamics are stable, and secretions are not excessive. Patients with labile asthma may meet these criteria quickly after intubation; more commonly, 24–48 hours of mechanical ventilation are required. After extubation, observation in an ICU is recommended for an additional 12–24 hours.

POSTEXACERBATION MANAGEMENT

The importance of education, adherence to controller agents (e.g., corticosteroids and long-acting bronchodilators), environmental control measures, and close follow-up cannot be overstated. Patients who have experienced severe asthma exacerbations are at risk for subsequent attacks and asthma-related death. In this regard, a tri-society task force report and GINA have provided recommendations for treatment and follow-up after discharge.[41,42]

KEY POINTS

- Inadequate outpatient control of asthma is associated with poor outcomes.
- Severe exacerbations are characterized by diaphoresis, upright positioning, inability to speak in long sentences, use of accessory muscles, a widened PP, and normocapnia or hypercapnia. Altered mental status, paradoxical breathing, bradycardia, and a quiet chest indicate impending respiratory arrest.
- Acutely ill asthmatics respond variably to inhaled beta-agonists. Frequent (or continuous) administration of albuterol is required in refractory patients. Addition of ipratropium bromide to albuterol may confer additional benefit in patients with severe attacks.
- Systemic steroids are indicated for severe asthma exacerbations.
- Limited data support the use of NIV to decrease the inspiratory work of breathing in acute asthma.
- Postintubation hypotension suggests inadequate expiratory time, causing DHI and decreased cardiac preload. A trial of apnea or hypopnea is both diagnostic and therapeutic in this setting. Tension pneumothorax is an additional important diagnostic consideration for postintubation hypotension.
- During mechanical ventilation, prolong the expiratory phase by setting low minute ventilation and an adequate inspiratory flow rate. Assess DHI by measuring plateau pressure; if necessary, accept moderate hypercapnia to decrease DHI.
- Avoid prolonged paralysis and sedation during mechanical ventilation.
- ECMO should be considered at high-volume centers for patients with life-threatening DHI, progressive barotrauma, or refractory respiratory acidosis despite optimal pharmacologic and ventilator management. Further study is needed to clarify the role of extracorporeal CO_2 removal ($ECCO_2$-R) in the management of life-threatening asthma.
- Discharge planning should focus on asthma education and strategies to achieve and assess asthma control, optimizing controller medications, and ensuring timely follow-up to help prevent future exacerbations.

References for this chapter can be found at expertconsult.com.

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64

Chronic Obstructive Pulmonary Disease

Peter M.A. Calverley and Paul Phillip Walker

Chronic obstructive pulmonary disease (COPD), a major cause of death and disability worldwide, is one of the most common reasons for intensive care unit (ICU) admission. Several monographs review this complex disorder in some detail.[1,2] The intensivist's view of COPD is predominantly physiologic, focusing on the impact of disrupted function on the individual's normal homeostatic mechanisms. Although many important insights that have shaped our understanding of COPD have come from ICU studies, other aspects of this disorder must be considered if a rational approach to COPD management is to be developed.

Access to ICU care for sick COPD patients remains relatively inequitable among different healthcare systems. In North America and parts of Western Europe, most patients are offered ICU care, but in other relatively developed healthcare systems, such as in the United Kingdom, this is not the case. Even physicians in the same healthcare system differ significantly in their selection of patients for ICU referral.[3] These choices may be influenced by local resource availability, but they are also conditioned by the generally pessimistic view of the outcome achievable with this treatment intervention. However, poor response to treatment in the ICU is not universal, and extended periods of mechanical ventilation are not invariably required to successfully manage patients with COPD.[4] Nevertheless, intensivists often take a particularly bleak view of the prognosis of COPD patients compared with others entering their units. In one prospective study, intensivists estimated the survival of the sickest COPD patients to be 10% at 180 days post admission, when in fact it was 40%.[5] In one survivor population, 96% were happy to have received ventilator support after being mechanically ventilated, despite their continuing physical problems.[6] Survival appears to relate more to the severity of the acute illness, such as higher acute physiology scores, longer preceding hospital length of stay, level of consciousness, and cardiac dysrhythmia, rather than comorbidity factors such as age, forced expiratory volume in 1 second (FEV_1), and functional capacity.[7] Clearly, decisions about ventilator support should not be made in the emergency department without sufficient medical information or a proper discussion with the family; this was something that was seen in only a minority of cases in past England and Wales national audits of hospitalizations resulting from COPD.[8] The widespread adoption of noninvasive ventilatory support has increased the number of physiologically decompensated patients offered appropriate treatment (see later for further details), although many patients are managed outside of the conventional ICU setting.

DEFINITION AND NATURAL HISTORY

Although the most appropriate definition of COPD has been debated, it has less of an impact in the context of ICU care, where acute hospitalization is usual only in cases of severe and well-established disease. The currently favored definition, developed by the Global Initiative for Chronic Obstructive Lung Disease (GOLD), is:

> *Chronic obstructive pulmonary disease (COPD), a common preventable and treatable disease, is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases and influenced by host factors including abnormal lung development. Significant comorbidities may have an impact on mortality and morbidity.*[9]

The emphasis here is on incompletely reversible airflow obstruction that is persistent and often progressive. Comorbidities are very common in patients seen in the ICU and make patient management more difficult. Symptomatic exacerbations contribute significantly to morbidity at all stages of the natural history of COPD and are the usual reason for ICU admission.[9,10] Symptoms and disability usually parallel these processes, although some individuals can apparently cope with a severe degree of airflow limitation without seeking medical help. Such patients tend to present to the emergency room when they develop a severe exacerbation of COPD. In this situation, it is wisest to offer ventilatory support until the patient has at least had a chance to improve with conventional medical therapy. More commonly encountered is a patient whose progressive illness is accompanied by repeated exacerbations, events that identify an accelerated decline in both lung function and health status.[11,12] Such patients have often been hospitalized on previous episodes, and their response to treatment is usually clearly established. Once hospitalization has occurred, it is likely that subsequent exacerbations will lead to further hospital visits.[13]

The usual inhaled particles or gases that produce COPD are a complex mixture of hydrocarbons and particulates derived from tobacco smoke. These are the principal causes of COPD in the United States and Western Europe,[14] although other factors such as poor lung function during childhood and childhood respiratory illness, bronchial hyperresponsiveness, and low birth weight may also be important.[15] The associated inflammatory changes, which persist when smoking stops,[16,17] are thought to explain the airway and parenchymal destruction and fibrosis within the lung.

The natural history of COPD explains why the number of patients presenting for ICU care has not diminished in the last three decades as might be expected, given the overall reduction in tobacco consumption in Western countries. This is illustrated by the classic study of Fletcher and Peto, the results of which were confirmed by longitudinal data from the Framingham study.[18,19] Although the rate of decline of lung function is reduced in individuals who stop smoking, the lung function already lost is never regained, and even if the rate of decline of lung function returns to normal, these patients are still more likely

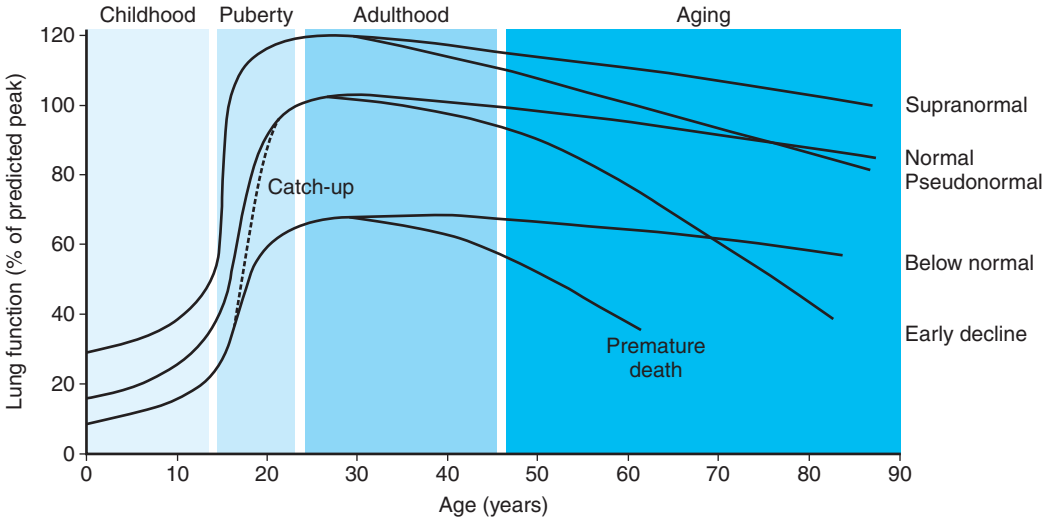

Fig. 64.1 Potential Trajectories of Lung Function, Showing the Effect of Smoking Cessation on Each Cohort. Both abnormal lung development and aging contribute to lung function and determine lung function, which can lead to chronic obstructive pulmonary disease (COPD) in adulthood. This explains the group of never-smokers who develop COPD and why older ex-smokers can present to the intensive care unit with severe disease despite years of abstinence. (Reproduced from Agustí A, Hogg JC. Update on the pathogenesis of chronic obstructive pulmonary disease. *N Engl J Med.* 2019;381:1248–1256.)

to experience disability as they age. Thus in an aging population that contains many former smokers, a significant number will still develop complications of COPD that require ICU care. It is now recognized that many COPD patients experienced inadequate lung growth in early life for a variety of reasons, and this contributes to their chances of developing COPD in later life even though they have little or no history of tobacco exposure (Fig. 64.1).[20] As noted already, comorbidities are common in COPD,[21,22] and most patients with significant symptoms resulting from COPD have at least one, if not multiple, comorbid diseases, especially cardiovascular problems.[23]

PATHOLOGY

The pathologic features of COPD depend on the stage of the illness and the part of the lung examined.[24] In patients likely to need ICU care, the central airways show mucous gland hypertrophy and goblet cell metaplasia, whereas more peripheral airways show variable combinations of smooth muscle hypertrophy, peribronchial fibrosis, luminal occlusion by mucus, and enlarged lymphoid follicles. Alveoli are often, but not invariably, enlarged by the loss of alveolar walls, with an attendant loss of support for the small noncartilaginous airways in this region of the lung. There is evidence of persistent inflammation, with neutrophils in the airway lumen and macrophages in the airway wall. $CD8^+$ T lymphocytes are more prominent in this response than in bronchial inflammation of an asthmatic type, although intermediate states appear to exist.[25] Inflammatory cells are also present adjacent to breaks in the alveolar wall.[26] Overall, as the clinical and spirometric severity of the disease increases, so do the numbers of each cell population involved in the inflammatory process.[27] In addition, extraluminal lymphoid follicles develop containing $CD4^+$ lymphocytes, possibly reflecting a response to repeated infective exacerbations.[27] Recent work has linked elements of this host immune response to the lung microbiome assessed using DNA sequencing.[28] It is now clear from ex vivo airway measurements[29,30] and in vivo observations of the total airway count using CT scanning[31] that there is a significant fall in the number of small airways early in the natural history of smoking-related COPD which precedes the development of emphysema in most cases. Thus irreversible lung damage is present when its functional impact is very limited in most COPD patients. Data obtained during exacerbations, though limited, support an increased role for neutrophils and, surprisingly, eosinophils,[32] which may explain why these events accelerate lung function decline.[33] The utility of blood eosinophil count as a biomarker of exacerbation risk remains contentious,[34] but that indicator does seem to predict the ability of inhaled corticosteroids to prevent COPD exacerbations.[35] Current ideas about the pathogenesis of COPD and its relationship to function have been authoritatively reviewed by Agustí and Hogg.[36]

PHYSIOLOGY

The pathologic changes just described combine to produce the characteristic diagnostic finding of reduced FEV_1 at a given lung volume, which is usually assessed on a time base as an FEV_1/forced vital capacity (FVC) ratio of less than 0.7. Technically, this should be 70% of the age-adjusted normal value for this ratio, because lung elastic recoil declines with age, even in healthy individuals. However, data from large population-based studies suggest that the fixed ratio is generally a better predictor of future mortality and morbidity.

COPD affects all aspects of lung function, but its primary impact is a change in lung mechanics. This is traditionally analyzed in terms of the static (no flow) and dynamic (flow) properties of the respiratory system.[37] Because chest wall mechanics are believed to be structurally, if not functionally, normal in COPD (they are seldom measured directly), changes in the pressure-volume characteristics of the respiratory system are determined by alterations in lung compliance, often attributed to the loss of elastic recoil caused by emphysema. How large a role this plays in changes in tissue compliance is not known. The resulting steeper slope, early-onset inspiratory plateau, and increase in end-expiratory lung volume are typical of the pressure-volume relationships observed in patients with COPD. Changes in end-expiratory lung volume and increases in residual volume change chest wall geometry in favor of a lower, flatter diaphragm and a more horizontally oriented rib cage; these changes, in turn, impair the inspiratory muscles' ability to develop pressure and increase the overall work of

breathing.[38] Expiratory muscle activation is common in severe COPD[39,40] even at rest and provides a useful clinical marker of respiratory distress. The dynamics of the respiratory system are influenced by its static properties but also differ significantly between inspiration and expiration. Maximum inspiratory flow is affected by inspiratory resistance and by the inspiratory muscles' ability to develop pressure (and thus indirectly by chest wall geometry). Maximum expiratory flow is influenced by expiratory pressure generation and, more importantly, by the onset of volume-related airflow limitation, best described by the maximum expiratory flow-volume loop. As lung volume falls during expiration, airways close or become flow limited; hence, the flow at a specific lung volume is reduced. Although an assessment of flow (FEV_1) relative to total volume change during expiration (FVC) is useful in defining COPD, an assessment of tidal flow limitation is more helpful in determining the degree of dyspnea experienced by the patient.[41] More attention is now being paid to the determination of expiratory flow limitation under tidal conditions. In the past, detection was difficult, involving invasive measurements or reliance on body plethysmography, which tended to overestimate the incidence of tidal expiratory flow limitation. The development of the negative expiratory pressure test and, more recently, within-breath variation in respiratory system reactance has changed this.[42] The within-breath method assesses more breaths, is less prone to observer error, and can be automated in the future for ICU application.[43] Abolishing tidal flow limitation detected in this way can be used to minimize intrinsic positive end-expiratory pressure (PEEP) in spontaneously breathing COPD patients.[44]

In general, the lower the FEV_1, the greater the likelihood that expiratory flow limitation is present. However, some COPD patients are not flow limited on every breath and regulate their end-expiratory lung volume to try to minimize this. When respiratory drive rises (e.g., during exercise), during disease exacerbations, or when minute ventilation has to increase to maintain gas exchange during ventilator weaning, this resting variation in expiratory lung volume is likely to decrease. If expiratory flow and hence tidal volume are to increase, end-expiratory lung volume must rise; this further increases the work of breathing and the sensation of respiratory distress. This process, described as *dynamic hyperinflation*, has been clearly demonstrated during exercise and can be lessened by bronchodilator treatment, which aids lung emptying.[45]

In the ICU, patients have a high respiratory drive during weaning and adopt a rapid, shallow breathing pattern. Total respiratory muscle work increases, in part because of the increased operating lung volumes, but also because of the presence of intrinsic positive end-expiratory pressure (PEEPi), also termed *auto-PEEP*. This represents the pressure that must be developed to overcome residual expiratory driving pressure before inspiratory flow can begin.[46] Thus the overall impairment of mechanical function in COPD is substantial, and both static and dynamic properties interact—a concept best captured by the time constant of the respiratory system, which is the product of the total respiratory system resistance and compliance. This parameter is greatly lengthened in COPD and helps explain why lung emptying is delayed and dynamic hyperinflation occurs. There is substantial evidence of regional inhomogeneity in more severe COPD. Differences in the regional time constants explain why COPD patients are prone to barotrauma during mechanical ventilation, despite seemingly acceptable peak inspiratory pressures, and why gas exchange can be quite disordered in this population.

Gas Exchange

Arterial hypoxemia is common in COPD but becomes clinically significant in stable patients only when the partial pressure of oxygen in arterial blood (PaO_2) falls below 60 mm Hg, a problem largely confined to patients with an FEV_1 below 35% of their predicted value. Hypoxemia in COPD is predominantly the result of ventilation-perfusion mismatching, often worsens during exercise, and is readily corrected by a small increase in the inspired oxygen concentration, unless the situation is made worse by secretion retention or severe pneumonia or pulmonary edema.[47] Arterial hypercapnia is seen in some, but not all, hypoxemic patients who are clinically stable, but it is more frequent, at least temporarily, in hospitalized individuals.[48] A combination of ventilation-perfusion mismatching caused by an increase in physiologic dead space and a degree of effective alveolar hypoventilation explains this phenomenon. Acute rises in the partial pressure of arterial carbon dioxide ($PaCO_2$) precipitate respiratory acidosis, a more reliable guide to prognosis and the need for ventilation than the $PaCO_2$ itself.[49,50]

Control of Breathing

Despite years of study, there is no conclusive evidence that ventilatory control is abnormal in COPD patients. However, the response to sustained mechanical loading appears to be variable in healthy subjects[51] and may explain why some individuals with COPD adopt the breathing patterns they do. Traditional techniques of studying respiratory control, which involve stimulation with exogenous CO_2 or nitrogen, suggested that respiratory drive was reduced. However, studies using mouth occlusion pressure techniques or recording the electrical activation of inspiratory muscles suggest that respiratory drive is generally high, even in those COPD patients who tolerate relatively high levels of CO_2.[52–54] Studies of breathing patterns have been more instructive. In general, the lower the tidal volume, the higher the $PaCO_2$.[55] This is because the ratio of the relatively fixed anatomic dead space volume to tidal volume increases as the latter is reduced. Small tidal volumes are accompanied by an increased respiratory frequency to maintain the somewhat higher-than-normal level of minute ventilation. The resulting shortening of inspiratory time is also associated with hypercapnia.[55] The system appears to be regulated to minimize peak inspiratory pressure generation, even at the cost of impaired gas exchange. There are theoretical reasons for believing that this is both energy efficient and likely to minimize the occurrence of inspiratory muscle fatigue.[56] This also explains the usefulness of rapid, shallow breathing as an index of failure of ventilator weaning when neuromechanical coupling in the respiratory system is under stress.[57]

Pulmonary Circulation

In the past, considerable attention was paid to the determination of pulmonary artery pressure in COPD patients, but this is now thought to be less important. Undoubtedly, pulmonary artery pressure increases[58] in hypoxemic COPD patients, reflecting a combination of hypoxic vasoconstriction and pulmonary vascular remodeling. How important this is in the daily limitation of exercise reported by these patients is not clear, but it is known that treatment with domiciliary oxygen retards disease progression[59] and may even reduce pulmonary artery pressure. More specific attempts at therapy, including treatment with vasodilators, phosphodiesterase enzyme type V (PDEV) inhibitors, and nitric oxide—studied inside and outside the ICU—have been unsuccessful, usually resulting in unacceptable worsening of ventilation-perfusion mismatching.[60] Further investigation and treatment are reserved for the small number of patients (<5%) who have severe pulmonary hypertension that is disproportionate to their COPD severity.[61] Assessment of pulmonary hypertension is not part of a routine evaluation in COPD patients, but its occurrence is important to note when interpreting changes in central venous pressure in instrumented patients.

SYSTEMIC EFFECTS

There is good evidence that systemic (extrapulmonary) factors are important in COPD. Patients with a reduced body mass index die sooner than better-nourished individuals with a similar degree of pulmonary function impairment, and those who can gain weight fare better.[62] There are data to show that peripheral muscle function is impaired,[63] fiber type is altered,[64] and exercise is associated with increased oxidative stress.[65] The earlier concept of a specific COPD myopathy has now largely been abandoned, as the major burden falls on the lower limb muscles, with preserved function in the upper limb muscle groups. This likely reflects inactivity, which is worse in those with exacerbated COPD.[66] Weakness of the quadriceps muscle is an independent guide to a poor prognosis,[67] and its occurrence appears to be independent of the presence of cardiovascular problems.[68] In contrast, although the wealth of circulating biomarkers in COPD appear to relate to mortality, their measurement has contributed little to practical management so far.[69]

EXACERBATIONS

An *exacerbation* of COPD is currently defined as sustained worsening of the patient's condition from the stable state (beyond normal day-to-day variation) that is both acute in onset and necessitates a change in regular medication.[9] The key feature is the sustained change from usual daily symptoms. The operational requirement for a change in treatment is more arbitrary but is almost always present in patients referred for ICU care. Disease exacerbation is the principal cause of ICU admission with COPD, and patients commonly have or are at risk of developing significant *respiratory failure,* defined as a PaO_2 below 60 mm Hg with or without an increase in $PaCO_2$.[70] The most common causes of exacerbation are listed in Table 64.1. Viral and bacterial infections are both relevant,[64] with rhinoviruses commonly reported in most series; *Haemophilus influenzae* and *Streptococcus pneumoniae* are the principal bacterial pathogens.[71,72] Some patients, particularly those with a regular cough and green sputum production, develop persistent lower respiratory tract colonization, making the interpretation of qualitative microbiology difficult.[73] Studies of the changing microbiome during acute exacerbations have shown significant reductions in species diversity and increases in the relative importance of *Haemophilus* and *Moraxella* species.[74]

Not all exacerbations of COPD have an infectious precipitant, and changes in the degree of atmospheric pollution can precipitate events in some patients.[75] The frequency of exacerbation rises as spirometric impairment worsens,[76] and although a history of a previous exacerbation can define subsets of patients more likely to exacerbate subsequently, the short-term predictive power of the exacerbation history is modest at best.[77]

The physiologic consequences of increased airflow obstruction secondary to increased inflammation within the bronchial tree are summarized in Fig. 64.2. Whatever the precipitant, the key event appears to be a change in lung mechanics. Previously, attention focused on alterations in respiratory system resistance, but more recent data emphasize that airway narrowing and closure may be more important, particularly by producing changes in operating lung volumes (see earlier discussion). Observations in patients recovering from hospitalized exacerbations have shown progressive improvements in respiratory system reactance (a measure of inspiratory resistance and flow limitation) together with reductions in end-expiratory lung volume that are most evident in patients reporting less dyspnea.[78]

Pneumonia is an important reason for hospitalization in COPD, is more frequently seen in these patients than in others, and is associated with worse outcomes.[79] Pneumonia is diagnosed more frequently in patients taking the inhaled corticosteroid fluticasone propionate,[80] especially older patients with worse airflow obstruction.[81] These pneumonias are not necessarily associated with poor outcome in terms of mortality or health status[80] and are not seen with all types of inhaled corticosteroids.[82,83] At present the benefit of inhaled corticosteroid treatment, especially combined with a long-acting inhaled bronchodilator, outweighs the apparent risk of increased pneumonia events.[84]

TABLE 64.1 Causes of Chronic Obstructive Pulmonary Disease Exacerbation

NEW INFECTION
Bacterial (*Haemophilus influenzae, Streptococcus pneumoniae, Moraxella catarrhalis*)
Change in an existing strain (e.g., *H. influenzae*)
Viral (influenza, rhinovirus, respiratory syncytial virus)
ATMOSPHERIC POLLUTION
Sulfur dioxide, oxides of nitrogen
TEMPERATURE CHANGE
Often related to pollution episodes
INTERCURRENT ILLNESS*
Pneumonia, pulmonary embolus, pneumothorax
POSTOPERATIVE
Especially after upper abdominal surgery

*Clinical presentation is dominated by the primary illness, but respiratory failure can occur.

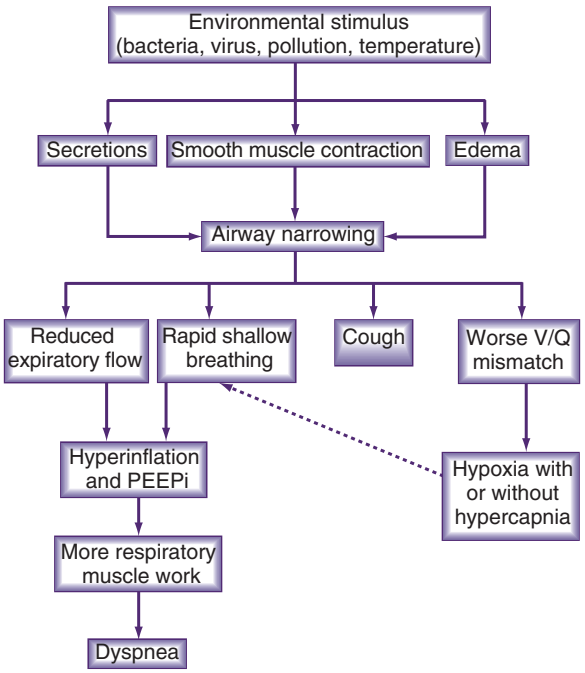

Fig. 64.2 Schematic of Principal Physiologic Changes that Accompany an Exacerbation of Chronic Obstructive Pulmonary Disease. Note that deterioration in one area tends to produce worsening in other areas and leads to a downward spiral in functional abnormality. *PEEPi,* Intrinsic positive end-expiratory pressure; *V/Q,* ventilation-perfusion.

INTENSIVE CARE UNIT REFERRAL

The need for ventilatory support is the primary reason for ICU referral of COPD patients. The various indications for mechanical ventilation (Table 64.2) vary in frequency from institution to institution. Before referring a patient for ICU care, and especially for any form of ventilatory support, it is important to determine what degree of intervention is appropriate.

PRINCIPLES OF TREATMENT

Four general principles guide the management of COPD patients presenting acutely to the ICU, and each should contribute to shortening the duration of illness and stabilizing the patient physiologically until either the natural course of the disease or the effects of therapy lead to its resolution.

Treat Precipitating Factors

Bacterial infection is the most common reason for ICU admission of COPD patients. There is now good evidence that antibiotics shorten the symptomatic period, even when patients are treated with corticosteroids.[85] If given early, antibiotics are associated with lower mortality, fewer episodes of intubation, and shorter hospital stays.[86] Radiographic evidence of pneumonia likely requires a broadening of the antibiotic spectrum, but whether the infection is confined to the airways or involves the alveoli, antibiotic therapy should follow locally established guidelines designed to minimize the development of resistance within the ICU and to address known patterns of drug resistance in the community and the hospital. Broad-spectrum penicillins or, more commonly, cephalosporins are usually recommended, often with an intravenous macrolide. Colonization with methicillin-resistant *Staphylococcus aureus* is a frequent problem and requires particular vigilance in the selection of antibiotics. Likewise, excessive use of broad-spectrum agents can produce superinfection, such as *Clostridium difficile* diarrhea.

The 2009–2010 H1N1 influenza A pandemic made the role of antiviral drugs clearer, and a meta-analysis showed that the early use of neuraminidase inhibitors (within 48 hours) was associated with a lower mortality, though this was not specific for acutely ill COPD patients.[87] In fact, during that pandemic the infection was not a particular problem for COPD patients, possibly reflecting prior partial immunity,[88] but if this virus is diagnosed, the use of antivirals such as oseltamivir is prudent. Similar considerations apply to other viral pneumonias. Whether the new outbreak of coronavirus infection will behave in a similar way is unclear at present.[89]

TABLE 64.2 Indications for Invasive Mechanical Ventilation

Severe dyspnea, with use of accessory muscles and paradoxical abdominal motion
Respiratory frequency >35 breaths/min
Life-threatening hypoxemia (PaO_2 <40 mm Hg or PaO_2/FiO_2 <200 mm Hg)
Severe acidosis (pH <7.25) and hypercapnia ($PaCO_2$ >60 mm Hg)
Respiratory arrest
Somnolence, impaired mental status
Cardiovascular complications (hypotension, shock, heart failure)
Other complications: metabolic abnormalities, sepsis, pneumonia, pulmonary embolism, barotrauma, massive pleural effusion
Noninvasive positive-pressure ventilation failure (or exclusion criteria)

FiO_2, Fraction of inspired oxygen; *$PaCO_2$*, partial pressure of carbon dioxide in arterial blood; *PaO_2*, partial pressure of oxygen in arterial blood.

Reduce Lung Volume and Increase Expiratory Flow

Agents that improve lung emptying, commonly by increasing airway caliber or preventing airway closure, interfere with the vicious circle of pulmonary hyperinflation. This has been demonstrated in stable patients using exercise as a model of hyperinflation,[45] but the data in spontaneously breathing COPD patients during exacerbations are much less satisfactory. Nonetheless, treatment with regular but high doses of short-acting nebulized beta-agonists such as albuterol or ipratropium (2.5–5 mg or 250–500 μg, respectively) is usually recommended. There is no clear evidence that one drug is better than the other,[90] and combination therapy is commonly used. Intravenous theophylline, or one of its derivatives, is often added to these regimens but is no more effective than a placebo infusion.[91,92]

Reduce Pulmonary Inflammation

Several randomized controlled trials have shown that oral corticosteroids shorten the duration of hospitalization and accelerate improvement of post-bronchodilator FEV_1 during an exacerbation of COPD.[93,94] Patients randomized to treatment with oral corticosteroids were less likely to relapse during the subsequent month and showed a number of other benefits, although these did not always reach statistical significance.[95] There is little detriment from giving a short (5-day) course of oral corticosteroids rather than a long (14-day) course. Steroid dose is dramatically reduced,[96,97] and inhaled corticosteroids do not need to be given if systemic therapy is used. In the ICU, corticosteroid treatment is often given to patients on mechanical ventilation. Two studies have given conflicting results. One study using 10 days of tapering-dose methylprednisolone reported a shorter period of ventilation and reduced noninvasive ventilation (NIV) failure,[98,99] whereas a larger study that used up to 10 days of higher-dose prednisolone showed no benefit but higher rates of hyperglycemia.[100] A retrospective review of the dose of systemic corticosteroids used within the first 48 hours of admission to an intensive therapy unit (ITU) showed better lower ITU and hospital length of stay, shorter period of ventilation, less use of insulin, and fewer fungal infections in COPD patients given less than 240 mg methylprednisolone per day.[101] Caution should be exercised because, in addition to the already noted effects, these individuals are often at risk for relatively acute-onset corticosteroid myopathy.[102] In the absence of a large randomized controlled trial and recognizing that 94% of patients in the retrospective review were prescribed systemic corticosteroids, it appears appropriate to use lower doses for shorter periods. It is possible that better targeting of specific endotypes of patients may be effective. A post hoc analysis of systemic corticosteroids used acutely for nonventilated COPD exacerbations found the rate of relapse was lower in patients with higher blood eosinophil counts.[103]

Manage Gas Exchange

It is relatively easy to improve oxygenation in an uncomplicated exacerbation of COPD.[104] Raising the inspired oxygen concentration to 28%–35% is usually sufficient to achieve a PaO_2 greater than 90 mm Hg. However, this can be accompanied by an undesirable increase in $PaCO_2$, with its accompanying respiratory acidosis. Such an increase in $PaCO_2$ impairs respiratory muscle function, at least during loaded breathing,[105] and often precedes more serious clinical deterioration, including impairment of consciousness. The reasons for this effect have been debated for many years, with some advocating a reduction in respiratory drive from the carotid chemoreceptors, and others citing

a worsening ventilation-perfusion match as the cause.[104] Each view has evidence to support it, but the actual cause is likely a combination of both problems, with ventilation-perfusion mismatching being particularly important in severely ill patients, and hypoventilation playing a larger role in those not yet sick enough to require intubation.[106]

Although the phenomenon of oxygen-induced hypercapnia has been recognized for decades, it remains a real problem. In one large center in the United Kingdom, 34% of individuals showed evidence of oxygen-induced hypercapnia.[50] The use of high-flow oxygen in the emergency room is widespread, as is the false sense of security provided by a high oxygen saturation. Many intensivists have legitimate concerns about the failure to adequately oxygenate COPD patients who have a compromised circulation, along with the attendant risk of unanticipated mortality. However, there is growing evidence that clinical outcomes are worse in the ICU when an oxygen saturation of 96% is exceeded. Patients whose problems are predominantly the result of COPD and who have a normal hemoglobin and preserved cardiac output can maintain adequate tissue oxygen delivery with an oxygen saturation as low as 85%, and they will do quite well if an arterial oxygen saturation (SaO_2) of 90%–93% is maintained. The modest increase in inspired oxygen needed to achieve this (often 24%–28%) is accompanied by less hypercapnia and may help avoid the need for ventilatory support. However, if cardiac output is impaired (reduced blood pressure, poor peripheral circulation) or tissue metabolic demands are increased (e.g., in sepsis secondary to pneumonia), a higher SaO_2 may be required to ensure sufficient oxygen delivery; in this case, the consequences of any resultant hypercapnia, including the need for ventilatory support, must be accepted. Oxygen delivery by high-flow nasal cannula provides a new approach that may be helpful in COPD management.[107] As yet, direct comparisons of this approach with either conventional oxygen therapy or NIV as a primary treatment in decompensated COPD patients are lacking.

NONINVASIVE VENTILATION

This topic is reviewed in detail in Chapter 55, but some key issues relevant to COPD are worth emphasizing. Much of the data supporting the use of NIV were obtained in patients with hypercapnic respiratory failure resulting from COPD exacerbations, and several excellent reviews have analyzed these data.[108–111] It is no surprise to see that the widespread use of NIV has led to a substantial increase in the number of COPD patients with decompensated respiratory failure being offered treatment without any increase in the treatment-related mortality.[112]

NIV offers potential benefit in COPD. Intuitively, it seems reasonable to expect that it would increase tidal volume, improve CO_2 elimination, and hence reduce respiratory drive. Studies of gas exchange using a multiple inert gas elimination methodology confirmed that CO_2 elimination is increased, but overall ventilation-perfusion mismatch is not changed during NIV.[113] A more important effect is the unloading of the respiratory muscles, which often approach fatigue conditions in severe episodes of respiratory failure. By assuming some of the additional workload required to overcome PEEPi, NIV directly reduces the drive to breathe, and the respiratory rate falls, a good prognostic feature for NIV success.[114] Data from randomized controlled trials suggest that there is a mean fall of 3.1 breaths per minute (95% confidence interval 4.3–1.9) with the institution of NIV in COPD patients.[115] This allows more effective emptying of the lungs and less dynamic hyperinflation. The resulting improvement in the intensity of breathlessness is usually a much earlier sign of successful NIV treatment in COPD than are changes in blood gas tensions, which often lag behind evidence of clinical improvement.

TABLE 64.3 Efficacy of Noninvasive Ventilation Compared With Usual Care

Outcome	Number of Patients Studied	Relative Risk (95% Confidence Interval)	NNT
Treatment failure	529	0.51 (0.38–0.67)	5
Death	523	0.41 (0.26–0.64)	8
Intubation	546	0.42 (0.31–0.59)	5
Complications	143	0.32 (0.18–0.56)	3

NNT, Number needed to treat—the number of patients who must be treated to prevent this outcome in one individual.

Evidence-based reviews provide a reasonable series of recommendations based on the relative effectiveness of NIV. Key points, including the number of patients needed to be treated to prevent one significant event or complication, are shown in Table 64.3.[108] NIV is associated with less treatment failure, lower mortality, fewer complications, and a lower intubation rate compared with conventional medical treatment. NIV reduces ICU or hospital stay by approximately 3 days and favorably influences gas exchange. With NIV, pH increases by a mean value of 0.03 units (0.02–0.04), $PaCO_2$ falls by 3 mm Hg (5.9–0.23 mm Hg), and PaO_2 rises by 2 mm Hg (−2 to +6 mm Hg). The lower rate of nosocomial pneumonia associated with NIV is a particular advantage. No benefit was seen from the use of a helium-oxygen mixture with NIV compared with oxygen alone.[116]

Treatment failure, which occurs in 10%–15% of cases in many US hospitals,[117,118] reflects an inability to adapt to NIV or progression of the underlying disease. Data suggest that patients likely to subsequently fail with NIV can be prospectively identified by a high blood sugar on admission (irrespective of having diabetes), a raised respiratory rate, or a high APACHE 2 score. All these variables are relatively effective predictors of risk, but combining them increases their discriminant power.[114] Another study confirmed the importance of acute physiology (APACHE 2 score) but also highlighted higher failure rate and mortality risk if the individual had cancer.[117] In addition to its role in the acute phase of respiratory failure, NIV can be valuable as a "bridge" in helping patients wean from intubated positive-pressure ventilation. In an important multicenter prospective trial, Nava and colleagues randomized people who had failed a T-piece weaning trial to either NIV or further mechanical ventilation.[119] NIV was associated with fewer days of ventilatory support (10.2 versus 16.6, respectively), shorter ICU stay (15.1 versus 24 days, respectively), less nosocomial pneumonia, and better 60-day survival (92% versus 72%, respectively). These results were achieved in a unit with experience in NIV. The generic use of weaning by NIV has proven less successful, particularly if patients have significant cardiac disease or established acute respiratory distress syndrome (ARDS).[120] However, further data from Spain have confirmed the value of this approach in hypercapnic patients limited primarily by COPD.[121,122] In a Cochrane review, outcomes were superior in all areas when early extubation followed by NIV was compared with continued mechanical ventilation. It is still unclear whether high-flow nasal oxygen is helpful in this setting. In a large randomized study in which 20% of patients had COPD, high-flow nasal therapy was equivalent to both NIV and conventional therapy as an aid to weaning from mechanical ventilation.[123]

MECHANICAL VENTILATION

Mechanical ventilation should be considered when NIV is not appropriate or has failed. Patients with a pH below 7.25 are more likely to

require this intervention, although in current practice most physicians first offer a trial of NIV unless the patient is hemodynamically unstable or the treatment is contraindicated. Persistent significant hypoxemia despite treatment with NIV, hypotension, and impaired mental state are all predictors of imminent respiratory arrest and the need for intubation and institution of mechanical ventilation.

Ventilation Strategies

A wide range of ventilation strategies have been advocated for use in COPD, each with its own proponents; none has shown a clear advantage over its competitors, however. Familiarity with the equipment used in the context of COPD is probably more important than the relatively minor differences between ventilator modes. The most commonly used approaches, together with their proposed advantages, are summarized in Table 64.4.

Assisted Ventilation and Weaning

As acidosis resolves and oxygen requirements fall, it is possible to reduce the degree of sedation and allow the patient to make some contribution to ventilation before weaning. Several modes of ventilatory support are available in these circumstances, and again, there is no specific advantage of one over another.[124,125] There is an impression, however, that reliance on spontaneous intermittent mandatory ventilation prolongs subsequent weaning. Although not universally accepted, there are good data supporting the use of spontaneous breathing trials in clinically stable COPD patients to determine when they are ready to wean.[126–128] The ability to sustain ventilation in the absence of increasing CO_2, worsening acidosis, or clinical distress (reflected by an increase in blood pressure, heart rate, or restlessness) is generally agreed to be a predictor of future weaning success. Although COPD patients are less likely to achieve these goals as early as other ICU patients, the reintubation rate in those who do meet these criteria is low.[126,127] Unfortunately, breathing through a ventilator circuit delivering continuous positive airway pressure (CPAP) may be associated with significant increases in inspiratory resistance arising largely from the endotracheal tube,[128] and it is sensible to use pressure support to offset some of this additional respiratory work. Evidence in favor of using pressure support instead of unassisted weaning (e.g., via T-piece) continues to accumulate.[129] For those patients who need more prolonged support, postextubation NIV is particularly helpful.

A variety of predictors of weaning success have been developed to try to identify when successful weaning will occur. Unfortunately, none has proved entirely reliable, and relatively few have been assessed prospectively. An empirical approach based on the criteria listed in Table 64.5 is widely used. An aggressive policy toward weaning is justified in COPD patients because failure to wean is invariably associated with a worse prognosis and prolonged ventilation.

TABLE 64.4 Modes of Ventilation

Mode	Method	Comment
Assist-control	Preset tidal volume, patient triggered with backup rate	Patient still performs substantial work of breathing; dynamic hyperinflation worsens this
Spontaneous intermittent mandatory ventilation	Preset number of breaths of a preset volume—patient does the rest	Patient still makes an effort during part of machine breath—involves more patient work, especially at low respiratory rates
Pressure support ventilation	Pressure set to augment each inspiration—tidal volume depends on patient effort, pulmonary mechanics, and pressure applied	Basis of noninvasive ventilation therapy; pressure titrated to a respiratory rate below 27 breaths/min; asynchrony with machine breaths a problem at high pressures
Proportional assist ventilation	Flow and volume generated proportional to patient effort	Experimental technique; requires accurate measurement of elastance and resistance + an intact drive to breathe; proven effective in COPD patients

TABLE 64.5 Criteria for Weaning Failure

Increasing hypercapnia or worsening hypoxemia (<55 mm Hg)
pH <7.32
Increased respiratory rate >35 breaths/min
Increase in heart rate or blood pressure by 20% of baseline
Agitation, sweating, or impaired consciousness

NONVENTILATORY ISSUES

Therapy employed in spontaneously breathing patients is still required in those undergoing mechanical ventilation. High-dose nebulized bronchodilators are commonly used, singly and in combination,[130,131] and it is important to pay attention to the details of drug delivery. If a metered-dose inhaler is used instead, it should always be given with some form of spacer device. Parenteral corticosteroids are commonly administered. This is not without hazard, particularly because of the real risk of myopathy, as reviewed earlier in this chapter.

Clearance of secretions is important in ventilated patients, and it is essential that the patient's hydration state be maintained to facilitate mobilization. Whether specific mucolytic drugs such as *N*-acetylcysteine are helpful is unclear, and no high-quality scientific studies are available to definitively support or reject their use. As with all ICU patients, the psychological impact of the illness and its treatment is considerable, and sensitive support during the recovery phase is needed. As noted, hospitalization with COPD is an important inflection point in the trajectory of this illness. Patience is required, as functional recovery is often slower than is appreciated by the physician or hoped for by the patient.

PROGNOSIS

The prognosis after an exacerbation of COPD is better than the gloomy outlook proposed by some physicians. Nonetheless, patients who experience exacerbations appear to have a more severe clinical course than those who do not, and they report a worse overall quality of life.[132] The associated mortality risk subsequent to ICU admission is significant. In one North American series, 7.4% of patients treated with NIV died, as did 16.1% of those treated with mechanical ventilation.[118] However, some groups do worse, and individuals with COPD treated with long-term oxygen therapy who failed NIV and received mechanical ventilation had 23% in-hospital mortality and 45% 1-year mortality. Twenty-seven percent were discharged to nursing care.[133] Patients with a low FEV_1, significant comorbidity, and a particularly poor performance status at home have the worst outlook.[134] These factors should be considered when decisions about the requirement for

ventilatory support are made. However, as noted already, the physician's view of the very sick COPD patient can be unduly pessimistic. Exacerbations leave patients relatively immobile.[56] The initial encouraging data concerning potential benefits from early rehabilitation have not been confirmed in a large randomized controlled trial of patients hospitalized because of an acute COPD exacerbation but not ventilated. The intervention was robust and included aerobic and resistance training, neuromuscular electrical stimulation, a written self-management plan, and education; however, no reduction in readmission was seen in the following year.[135] As result the European Respiratory Society/American Thoracic Society (ERS/ATS) guidelines for the management of COPD exacerbations made a conditional recommendation against the early use of pulmonary rehabilitation postexacerbation.[111]

Changes in clinical practice continue to improve the outlook for COPD patients. Better prevention, earlier diagnosis, and more specific evidence-based therapy contribute to this.[136] The impact of NIV on acute care has been enormous, as has closer adherence to evidence-based recommendations across the field of intensive care,[137] something about which both practitioners and their patients can feel proud. Despite the increasing age and complexity of the patients with COPD admitted to the ICU, their prognosis and future prospects continue to improve.

KEY POINTS

- The prognosis of patients with COPD admitted to the ICU is better than commonly believed.
- The burden of symptomatic COPD is likely to rise for several decades more, despite effective smoking cessation programs in many countries.
- Small changes in forced expiratory flow are associated with significant impairment in lung mechanics, particularly airway closure and dynamic hyperinflation, and worse gas exchange.
- Common upper respiratory tract pathogens and respiratory viruses precipitate most exacerbations of COPD. Treatment aimed at these agents is useful, but it is not as important as improving lung emptying and maintaining gas exchange until the acute insult resolves.
- Oral and intravenous corticosteroids shorten the duration of an exacerbation and reduce the risk of relapse. However, high-dose treatment beyond 2 weeks provides no advantage and actually poses a risk, especially in ventilated patients.
- Maintaining oxygenation is relatively easy, but there are risks of carbon dioxide retention and acidosis if high-flow oxygen is administered. Keeping oxygen saturation between 91% and 93% ensures adequate tissue oxygen delivery if the cardiac output is stable.
- Respiratory acidosis is a poor prognostic marker in COPD exacerbations and a strong indicator of the need for assisted ventilation.
- Unless contraindicated, NIV is the safest and most effective way of managing acute respiratory failure. More acidotic patients should be managed in an ICU with the option of endotracheal intubation and mechanical ventilation if NIV fails.
- COPD patients meet conventional weaning criteria less frequently than other ICU patients do, but they are more likely to wean successfully when they do meet the criteria.
- Seriously ill COPD patients should be encouraged to make advance directives, particularly after an ICU admission involving any form of ventilatory support.

References for this chapter can be found at expertconsult.com.

ANNOTATED REFERENCES

Bafadhel M, Peterson S, De Blas MA, et al. Predictors of exacerbation risk and response to budesonide in patients with chronic obstructive pulmonary disease: a post-hoc analysis of three randomised trials. *Lancet Respir Med.* 2018;*6*(2):117–126.
This study examined data from previous COPD trials where the impact upon exacerbations of a combination inhaled corticosteroid/long-acting beta-agonist inhaler was assessed. Only smoking and eosinophil count predicted the impact of the inhaled therapy, with people with higher baseline eosinophil counts likely to derive greater benefit from treatment. The importance of serum eosinophil count in predicting response by COPD patients to a wide variety of different treatments is becoming clearer.

Hernández G, Vaquero C, Colinas L, et al. Effect of postextubation high-flow nasal cannula vs noninvasive ventilation on reintubation and postextubation respiratory failure in high-risk patients: a randomized clinical trial. *JAMA.* 2016;316(15):1565–1574.
This randomized controlled trial examined 604 patients who were extubated and then randomized to either high-flow nasal oxygen or noninvasive ventilation for 24 hours. The primary outcome was reintubation or development of respiratory failure within 72 hours. High-flow nasal oxygen was found to be equivalent to NIV and felt to offer significant advantage to certain high-risk patients.

Lange P, Celli B, Agustí A, et al. Lung-function trajectories leading to chronic obstructive pulmonary disease. *N Engl J Med.* 2015;373(2):111–122.
This study is one of a number of recent publications examining traditional models of lung function decline leading to the development of COPD. Individuals with a low FEV_1 in early adulthood were more likely to develop a low FEV_1 by early middle age despite no accelerated decline in lung function. The study highlights the importance of early life events in the development of adult lung function and illustrates that accelerated decline in lung function is not necessarily present in people who develop COPD.

Mayhew D, Devos N, Lambert C, et al. Longitudinal profiling of the lung microbiome in the AERIS study demonstrates repeatability of bacterial and eosinophilic COPD exacerbations. *Thorax.* 2018;73(5):422–430.
The study involved lung microbiome assessment in people with COPD at a time of clinical stability and during exacerbations. Specific subgroups were seen, with some COPD patients prone to eosinophil-driven or bacterial-driven exacerbations, and these were often repeated for an individual. Common bacteria included Haemophilus *and* Moraxella. *Viral exacerbations were typically discrete and not repeated.*

Zannin E, Chakrabarti B, Govoni L, et al. Detection of expiratory flow limitation by forced oscillations during noninvasive ventilation. *Am J Respir Crit Care Med.* 2019;200(8):1063–1065.
This is a small study of 10 subjects with COPD who had previously suffered hypercapnic respiratory failure and were treated with bilevel noninvasive ventilation. When stable, the subjects received bilevel ventilation, and forced oscillation measurements were made to detect flow-limited breaths and thresholds for detection of flow limitation established based on expiratory reactance. It is hoped this technique may be useful in ventilator-dependent patients to tailor the level of PEEP, though this requires larger studies in patients who are ventilated acutely.

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65

Pulmonary Embolism

Paul S. Jansson and Christopher Kabrhel

INTRODUCTION

Venous thromboembolism (VTE) encompasses the continuum of disease that includes deep venous thrombosis (DVT; also sometimes referred to as *deep vein thrombosis*) and pulmonary embolism (PE). The prototypical VTE event occurs when a blood clot forms in the deep veins of the legs, detaches, and then embolizes through the vasculature and heart to lodge in the pulmonary arteries, where it is referred to as a PE. The presentation of VTE varies widely, based on the size of the clot and the pathophysiology of the individual. Manifestations range from an incidentally diagnosed PE in an otherwise asymptomatic patient to hemodynamic collapse and sudden death. The diagnosis and management of VTE in the intensive care unit (ICU) present diagnostic and therapeutic challenges that differ from the routine management of VTE in the emergency department or outpatient setting. Overall, the mainstay of treatment for VTE is pharmacologic anticoagulation. For more high-risk VTE, thrombolytic therapy (systemic or catheter-directed) or thromboembolectomy (open-surgical or percutaneous) may be indicated. Adjuvant therapies for the management of VTE may include placement of an inferior vena cava (IVC) filter or extracorporeal life support (ECLS).

EPIDEMIOLOGY

In North America, the incidence has been estimated at 38–112 cases per 100,000, with an estimated global disease burden of approximately 10 million cases per year.[1–3] VTE has a slightly higher incidence in males and increases with the age of the patient.[4–6]

Although the diagnosis of VTE has been increasing over time, primarily because of the use of more sensitive imaging techniques,[7] it may be underdiagnosed in subsets of hospitalized patients. Surveillance studies have found undiagnosed PEs in 24% of trauma patients[8] and 18.7% of patients undergoing mechanical ventilation unrelated to PE.[9] Between 3% and 16% of patients were noted to have undiagnosed PE on routine autopsy.[10–12]

VTE occurs commonly in the ICU, even in the face of routine measures to prevent it. A relatively small percentage (between 0.4% and 2.7%) of patients admitted to the ICU have undiagnosed VTE on arrival,[13,14] but surveillance studies estimate the incidence of DVT in the ICU between 1.0% and 9.6% and the incidence of PE between 0.5% and 2.3%, despite appropriate pharmacologic prophylaxis.[13–15] In critically ill patients without appropriate prophylaxis, VTE is very prevalent, with a 19% incidence of DVT found in one study.[16] PE is the third most common cause of cardiovascular death, with a higher mortality rate than that of myocardial infarction.[17] Overall, PE is responsible for approximately 100,000 deaths per year in the United States.[6,18]

Both the clinical presentation and the mortality risk associated with VTE vary widely, depending on the pathophysiology of the individual patient. Some PEs are asymptomatic and diagnosed incidentally, whereas some cause sudden cardiac arrest. In a large, modern cohort, the 30-day case fatality rate was 2.0% for VTE and 3.9% for PE. The 1-year mortality rate ranges from 12.9% to 30%, although a large proportion of such deaths are attributable to underlying comorbidities.[3,19,20] For patients with a normal blood pressure and no evidence of right ventricular dysfunction, attributable mortality incidence is below 5% and even less than 1% in some studies.[21,22] In contrast, for patients with shock or cardiac arrest, the fatality risk is higher: approximately 30%–53% in shock and up to 95% in cardiac arrest.[23–25] Of fatal events, the initial presentation may be that of sudden death, with approximately 34% of VTE-related deaths presenting as sudden death in one European cohort.[26] For untreated PE, the short-term mortality currently approximates 25%–30%, Historically, studies have reported associated mortality as high as 87%.[27] For obvious reasons, data describing the natural history of untreated VTE are limited.

For many patients, VTE is a chronic disease. Recurrence is common, with the highest risk during the first 6–12 months after diagnosis.[28] In one study cohort, recurrence after 5 years was 20%–25% for all patients and exceeded 25% in those patients with VTE without clear provoking factors.[29] The 10-year recurrence is approximately 30%.[30] The DASH score (e Table 65.1) can be used to predict VTE recurrence in patients without a clear provoking risk factor and uses the patient's age, sex, use of exogenous hormones, and residual D-dimer level to estimate an annual recurrence rate.[31,32]

Return to normal lung structure and function may be a prolonged process. In one study 28% and 15% of patients had residual PE on lung perfusion imaging or computed tomography (CT) imaging, respectively, after 9 months of anticoagulation.[33] Another study found >10% vascular obstruction in 10% of patients after a year of anticoagulation.[34] Although lung function does return to normal in most patients, a small but significant number of patients will develop chronic thromboembolic pulmonary hypertension (CTEPH), and up to 4% of patients have elevated pulmonary artery pressures 2 years after the initial PE diagnosis.[35]

RISK FACTORS

Risk factors for the development of VTE have classically been separated into inherited and acquired categories.[36] Table 65.1 presents a summary of risk factors.

Inherited risk factors typically center around disorders in clotting factor production or activity. The most common genetic risk factors are the factor V Leiden mutation (with a prevalence of 4%–5%) and the prothrombin gene mutation (20210A, seen in 2%–4% of patients).[37–39] Among the other inherited risk factors are antithrombin deficiency, deficiencies of proteins C and S, hyperhomocysteinemia, and a number of single-nucleotide polymorphisms.[40–43] Acquired risk

e TABLE 65.1 DASH Prediction Score for Recurrent VTE

Criterion	Points
D-dimer abnormal 1 month after stopping anticoagulation	+2
Age ≤50 years	+1
Male patient	+1
Hormone use at VTE onset (if female)	−2

Interpretation:

Cumulative Points	Annual Recurrence Risk
≤1	
Consider discontinuing anticoagulation	3.1%
≥2	
Consider continuing anticoagulation	9.3%

TABLE 65.1 Risk Factors for PE

Inherited Risk Factors
Factor V Leiden
Prothrombin mutation
Antithrombin deficiency
Protein C deficiency
Protein S deficiency
Acquired Risk Factors
Vascular Damage
Surgery
Trauma/burns
Previous VTE
Inflammatory or Procoagulant States
Active cancer
Antiphospholipid syndrome
Chronic inflammatory diseases
Pregnancy
Obesity
Nephrotic syndrome
Heparin-induced thrombocytopenia
Venous Stasis
Hospitalization or immobility
Paralysis
Prolonged travel
Factors Common in the ICU
Sepsis
Central venous catheter
Pharmacologic paralysis
Acute renal failure, dialysis
Mechanical ventilation
Blood products
Vasopressors

factors are those developed during a person's lifetime and include surgery, particularly orthopedic and oncologic surgeries, and the presence of trauma, burns, or fractures. VTE occurs after 1% of orthopedic surgeries, despite appropriate thromboprophylaxis.[44]

Active cancer is a major risk factor, with such patients having twice the VTE incidence of patients without cancer. VTE is the second leading cause of death in patients with cancer and cancer-related VTE, accounting for approximately 20% of all VTEs.[45–47] The risk is highest in the first few months after diagnosis, and is especially elevated in adenocarcinomas.[48,49] Cancer cells themselves may provoke inflammation and a procoagulant state,[50,51] and a number of chemotherapeutic drugs increase clotting risk.[52]

Chronic disease states also increase the risk for VTE.[53] Advanced age correlates with increased risk because of both innate factors, such as the relative decrease in the levels of proteins C and S, and the acquisition of other clot-provoking influences.[54–56] Morbid obesity conveys a risk of VTE up to six times that of individuals of normal weight.[57,58] Previous VTE is one of the strongest risk factors for recurrent disease,[59] likely a result of existing risk factors and damage to vessel walls or valves.[60] Poorly controlled inflammatory diseases such as inflammatory bowel disease increase the risk of VTE when compared with their well-controlled peers.[61,62] Lupus, in particular, elevates VTE risk, primarily through the lupus "anticoagulant" (actually a misnomer) and anti–beta-2-glyocoprotein antibodies.[63–65]

High estrogen states increase the risk for VTE.[66] Supplemental estrogen used for oral contraception or taken in the postmenopausal state may increase the risk of VTE by three to four times.[67,68] Pregnancy is another high-estrogen state, which is often coupled with mechanical compression of the gravid uterus on pelvic veins and/or cesarean section surgery. The highest risk of pregnancy-associated VTE occurs in the immediate postpartum period.[69]

Acquired risk factors are particularly common in the ICU population.[14] Immobility is a predisposition that is particularly relevant for ICU patients. Immobility may be intentional, such as in the long-haul traveler,[70] or iatrogenic, such as associated with joint fixation,[71] mechanical ventilation,[9] and pharmacologic paralysis.[72] Central venous catheters increase VTE risk, with femoral catheters being particularly implicated.[73–76] Heparin-induced thrombocytopenia has been associated with a high risk of VTE,[77] as have sepsis[78] and multisystem organ failure.[79]

PATHOPHYSIOLOGY

Normally, a physiologic equilibrium exists regarding hemostasis. Prothrombotic factors are balanced by such naturally occurring anticoagulants as antithrombin III and proteins C and S and by the body's own fibrinolytic system. Acting together, these mechanisms prevent pathologic thrombosis.[80] When disrupted, a procoagulant state can lead to inappropriate thrombosis and the development of VTE. The classical description of the conditions leading to pathologic thrombosis is termed *Virchow's triad*: the combination of endothelial damage, the presence of a hypercoagulable state, and stasis of normal blood flow.

Pathologic thrombosis typically begins around the valves of the veins,[81] regions with slower flow and relative hypoxemia, which in association with predisposing risk factors, can lead to small deposits of thrombus.[82,83] In most patients, skeletal muscle contractions "pump" to displace a nascent thrombus into the bloodstream, where it is degraded by the body's natural fibrinolytic system. However, in the presence of stasis, the thrombus expands, trapping alternating layers of fibrin and red blood cells between aggregated platelets.[84] As the clot expands, venous flow becomes turbulent and slows, further promoting stasis and thrombosis. Eventually, blood flow through the vein stops, and the thrombus propagates proximally until it reaches the next bifurcation of the vasculature. From there, the clot may continue to extend proximally, or it may embolize into the flowing venous bloodstream, which carries it through the right side of the heart to lodge in the tapering pulmonary arterial vasculature as a PE. Air, amniotic fluid, tumor, and foreign bodies can also embolize in a similar manner. Discussion of the pathophysiology and management of these conditions is beyond the scope of this chapter.

DVT occurs most frequently in the lower extremities, with over 90%–95% of DVTs occurring in the leg veins.[85] Most clinically significant DVTs involve the proximal veins of the leg, such as the iliac, femoral, and popliteal,[86] and the vast majority of PEs occur when such proximal DVTs embolize. More than 50% of patients diagnosed with proximal DVT will have evidence of concurrent PE, and up to 70% of patients diagnosed with PE will have a detectable DVT, which in both cases, may be asymptomatic.[87–91] Lower leg DVTs, such as those in the calf veins, rarely embolize, but may extend to the proximal veins if left untreated.[89,92–94]

The individual patient's response to the PE depends on the number of emboli (extent of the clot burden) and the patient's underling cardiopulmonary function and neurohormonal response. When an embolus lodges in the pulmonary vasculature, a complex set of

physiologic responses occur (Fig. 65.1). Acute vascular obstruction leads to increased pulmonary vascular resistance and increased pulmonary artery pressure. Significant increases in pulmonary artery pressure are seen when approximately 30%–50% of the arterial bed is occluded.[95] Shock and cardiopulmonary collapse may occur with large emboli; right ventricular failure may result if the mean pulmonary artery pressure exceeds 40 mm Hg.[96]

Inflammation occurs around the thrombus, with platelets secreting histamine, serotonin, and thromboxane A_2, which act to cause pulmonary vasoconstriction and bronchoconstriction, inducing alveolar hypoxemia.[97] This, in turn, results in a cycle of worsening hypoxic vasoconstriction, further raising pulmonary vascular resistance, pulmonary artery pressures, and right ventricular afterload. Surfactant production is reduced, leading to atelectasis and worsening this hypoxia-driven cycle.

Physiologic dead space increases and V/Q mismatch occurs as involved alveoli are ventilated but not perfused. Minute ventilation is increased, typically by a disproportionate increase in the respiratory rate, resulting in respiratory alkalosis. However, for those patients who are unable to increase their minute ventilation sufficiently, such as those who are mechanically ventilated undergoing pharmacologic paralysis, hypercapnia will result.[96]

The abrupt increase in pulmonary vascular resistance and consequent pulmonary artery pressure is felt most acutely by the right ventricle (RV). As the RV strains against the increase in pressure, its thin wall dilates outward, leading to an increase in wall stress and a decrease in coronary perfusion. RV work increases, predisposing to a mismatch between myocardial oxygen demand and supply. In turn, this can cause acute ischemia and further worsen the function of the RV, particularly with the tachycardia common in acute PE. A decrease in RV cardiac output, whether as a result of ischemia, dilation, or inability to pump against the elevated pulmonary artery pressures, worsens the cycle of hypoxic pulmonary vasoconstriction.

As RV pressure rises, the interventricular septum can bow into the left ventricle (LV). With a bowed septum, the LV encounters impaired relaxation, distensibility, and diastolic filling, reducing preload to the LV and potentially decreasing cardiac output. A decrease in the LV

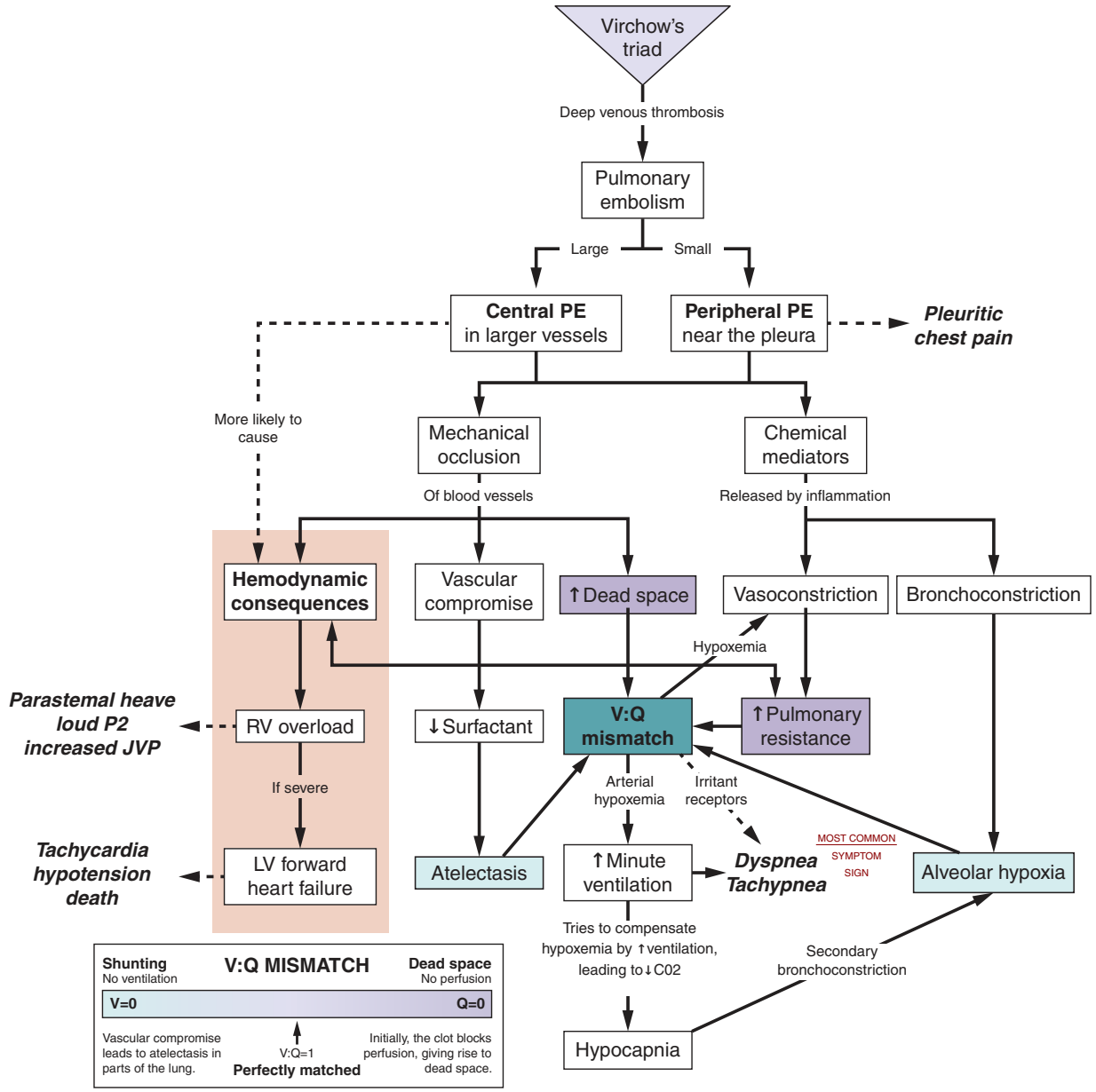

Fig. 65.1 Pathophysiology of Pulmonary Embolism. (From Wong E, Chaudry S. *Venous Thromboembolism. McMaster Pathophysiology Review*. available from: https://pathophys.org/vte). Hamilton, Ontario, Canada.)

cardiac output worsens the hypoxia-driven cycle and contributes to hemodynamic collapse. Increased right atrial pressures may open a patent foramen ovale and lead to intracardiac shunting and worsening hypoxemia.

Myocardial strain and elevated filling pressures may lead to the release of neurohormonal modulators such as the natriuretic peptides (brain natriuretic peptide [BNP] and N-terminal pro-BNP [NT-proBNP]). Ischemia and microinfarctions of the RV can occur, releasing cardiac troponins.[98–100]

DIAGNOSIS

Clinical Presentation

The range of clinical presentations of PE is among the widest of any condition. Symptoms of VTE are nonspecific, and therefore a high index of suspicion must be maintained.

The most common symptom in acute PE is dyspnea. (e Table 65.2 lists the prevalence of common signs and symptoms of PE.) Dyspnea is typically rapid in onset, within seconds in 46% of patients or minutes in another 26%.[101–103] More peripherally located PEs may result in lung infarction. Pleuritic chest pain accompanies these in up to 74% of cases.[104] A minority of these patients exhibit hemoptysis, commonly attributed to hemorrhage of the infarcted lung. Other findings include a cough, orthopnea, or wheezing. Given the common coexistence of DVT, many patients will also exhibit associated signs and symptoms, including calf or thigh pain and lower extremity swelling or edema. Although syncope has been traditionally described as a presenting symptom of PE, it is relatively rare—reported at less than 2% of instances.[105] PE is a relatively common cause of sudden cardiac arrest, however, and precipitates approximately 8% of all such events. Symptoms preceding cardiac arrest may include sudden dyspnea.[106,107]

Many patients are asymptomatic, even with large PE.[103,108] Therefore the first clinical clue may come from the physical examination. Tachypnea is the most common sign, seen in 54% of patients. Physical signs of DVT are detected in approximately 47%. Although traditionally taught as a common finding, tachycardia is only present in 24% of patients. Auscultation may reveal rales, wheezes, decreased breath sounds, or an accentuated second heart sound, but these findings are nonspecific and occur more commonly in alternative conditions.[103]

Differential Diagnosis

The differential diagnosis in patients with suspected PE includes cardiopulmonary disorders for each mode of presentation (see Clinical Presentation). For patients presenting with dyspnea, tachypnea, or hypoxemia, possible alternative diagnoses include atelectasis, pneumonia, pneumothorax, pleural effusion, aspiration, pulmonary edema, bronchial obstruction, alveolar hemorrhage, and other pulmonary disorders. For patients who present with pleuritic chest pain or hemoptysis, possible diagnoses include pneumonia, pneumothorax, pericarditis, aortic dissection, neoplasm, pleurisy, and musculoskeletal disorders. For patients who present with right-sided heart failure or cardiovascular collapse, possible diagnoses include myocardial infarction, acute massive hemorrhage, sepsis, cardiac tamponade, heart failure, hypovolemia, and tension pneumothorax. Other considerations related to PE include sepsis, fat, air, amniotic fluid, tumor emboli, and in situ thrombosis (e.g., sickle cell chest syndrome).

Diagnostic Testing

Because the common signs and symptoms lack specificity for VTE, diagnostic testing is required. DVT and PE are not separate and unrelated disorders, but rather represent a continuous syndrome of VTE in which the initial presentation may suggest DVT, PE, or both. Therefore strategies for diagnosis typically include testing for both PE and DVT. In addition, many patients will undergo simultaneous diagnostic testing for other potentially life-threatening disorders.

Assessment of Probability

The initial step in diagnosing PE involves the use of a probability assessment to calculate a pretest probability of disease. The two most commonly used clinical prediction rules are the Wells Score and the revised Geneva Score[109,110] (e Table 65.3). Other less commonly used scores include the Pisa Score, the Revised Pisa Score, and the Charlotte Score.[111–113] Experienced clinical gestalt performs similarly to clinical scoring symptoms, although scoring systems may have slightly higher specificity.[114,115] However, all of these decision rules were developed and validated primarily in the outpatient and emergency department settings. Although the scores generally perform well in the hospitalized patient, they may show poor performance in the ICU.[116,117]

Laboratory Testing

Laboratory testing plays either a supporting or exclusionary role in the diagnosis of PE, as there is no specific blood test for the disease. However, such testing can alter pretest probability, provide alternative diagnoses, and help with the risk stratification of PE once diagnosed.

Arterial Blood Gas Testing

Arterial blood gas testing, although commonly performed in the ICU, is no longer routinely used for the diagnosis of PE. In one study of patients with PE, 74% of patients had hypoxemia (defined as a partial pressure of oxygen [PaO_2] of <80 mm Hg) and 86% of patients had an abnormally elevated alveolar-arterial oxygen gradient.[101] These findings are neither sufficiently sensitive nor specific to rule in or rule out the presence of PE.[118–120]

Cardiac Markers

BNP and its precursor, NT-proBNP, are released from the myocardium in response to distention and theoretically could serve as markers for acute RV strain because of acute PE. However, they are neither sensitive nor specific for diagnosis and are better used to grade severity and prognosis.[121–123]

Similarly, cardiac troponins may be released from the RV from the pathologic dilation and microinfarction that occur in response to PE, particularly in larger or more hemodynamically significant PEs. Like BNP, however, troponin cannot be used to rule out the disease and is best deployed as a marker of severity and prognosis.[124–126]

Emerging Biomarkers

Early clinical studies may show evidence that circulating micro RNA (miRNA) may be used to detect pulmonary embolism, but this option has not yet entered clinical practice.[127]

D-Dimer

D-dimer is a fibrin degradation product produced by the plasmin-catalyzed lysis of cross-linked fibrin. Although it is highly sensitive for VTE, it is nonspecific, especially in ICU patients.[128] For low- and moderate-risk patients, as determined by a clinical decision rule or experienced clinician gestalt, a D-dimer below the assay's diagnostic cutoff (often <500 ng/mL) can be used to rule out VTE, although the negative predictive value drops as the pretest probability increases. Some authors advocate for a more liberal threshold of <1000 ng/mL in low-risk individuals,[129,130] whereas other studies advocate an "age-adjusted D-dimer," where a "negative" D-dimer corresponds to a value less than the patient's age × 10 (e.g., for a low-risk 65-year-old, a negative D-dimer would be

e TABLE 65.2 Prevalence of Signs and Symptoms in Acute PE

Symptom	Prevalence
Dyspnea	77%–79%
Pleuritic pain	39%–74%
Cough	4%–43%
Extremity swelling	24%–39%
Extremity pain	11%–42%
Sign	**Prevalence**
Tachypnea	26%–68%
Tachycardia	29%–57%
Rales	21%–48%
Hemoptysis	5%–16%
Fever	4%–10%

Adapted from Halevy J, Cushman M. Pulmonary embolism for the cardiologist: emphasis on diagnosis. *Curr Cardiol Rep*. 2018;20(11):120.

e TABLE 65.3 Common Prediction Scores

Wells Criteria for Pulmonary Embolism (PE)

Criterion	Points
Clinical signs or symptoms of deep venous thrombosis (DVT)	3
PE is the #1 diagnosis or equally likely	3
Heart rate >100	1.5
Immobilization for at least 3 days or surgery within the previous 4 weeks	1.5
Previous PE or DVT	1.5
Hemoptysis	1
Malignancy with treatment within 6 months or palliative treatment	1

Interpretation:

Three-Tier Group	Prevalence of PE
Low risk (<2 points)	1.3%
Moderate risk (2–6 points)	16.2%
High risk (>6 points)	37.5%
Two-Tier Group	
PE unlikely (0–4 points)	12.1%
PE likely (>4 points)	37.1%

Revised Geneva Score for Pulmonary Embolism

Criterion	Points
Age >65	1
Previous DVT or PE	3
Surgery (under general anesthesia) or lower limb fracture in the last month	2
Active malignancy	2
Unilateral lower limb pain	3
Hemoptysis	2
Heart rate:	
<75	0
75–94	3
≥95	5

e TABLE 65.3 Common Prediction Scores—cont'd

Pain on lower limb palpation and unilateral edema	4

Interpretation:

Point Summary	Prevalence of PE
Low risk (<3 points)	9%
Moderate risk (4–10 points)	27.5%
High risk (>10 points)	71.7%

<650 ng/mL).[131] These approaches have been validated in outpatients, but not yet in the ICU population.

Despite extensive validation and study of the D-dimer assay to rule out VTE in the outpatient setting, it does not have much utility in the ICU.[132,133] Because of the high prevalence of VTE in the ICU, the preponderance of factors that increase the risk of both VTE that generates a positive D-dimer on that basis, and the poor performance of the test in the relevant patient population, D-dimer is unlikely to prove useful in ruling out PE in many ICU patients.[134,135]

Electrocardiography

Electrocardiography (ECG) is routinely performed in the diagnostic evaluation of PE because the wide differential diagnosis includes many cardiopulmonary etiologies. Unfortunately, the ECG findings of PE are nonspecific. Sinus tachycardia is reported as the most common abnormality in acute PE, even though some studies report as few as 29% of patients display that finding.[128] RV dilation and strain may manifest on ECG as a new or incomplete right bundle branch block, right axis deviation, or RV hypertrophy. The classic triad of S1Q3T3 (that is, an S wave in 1, Q wave in III, and T-wave inversion in III) is another marker of RV strain that occurs only in a minority of PE patients.[136] A wide variety of additional ECG findings have been described in acute PE, but none are specific for the disease, and many patients with acute PE will have a normal ECG.[137,138]

Diagnostic Imaging

Given the poor sensitivity and specificity of the history, physical examination, laboratory, and ECG testing in acute PE, imaging is typically required to diagnose or exclude VTE in the ICU. The particular study chosen will depend on specific characteristics of the patient and the capabilities of the hospital. For example, a CT scan may be indicated, but to undergo this, a patient must be clinically stable enough to travel outside of the ICU to the radiology department and must be able to lie flat, take a deep breath, and receive IV contrast. Fig. 65.2 suggests a diagnostic algorithm for imaging in the ICU.

Chest Radiograph

Plain radiography of the chest is commonly performed in the ICU, but is typically not useful to confirm the diagnosis of PE. The chest radiograph may display nonspecific signs in acute PE, such as atelectasis, pleural effusion, or reduced pulmonary vascularization,[96] but normal studies are also common.[139] Classically described findings such as the Westermark sign (a sharp transition from an enlarged pulmonary artery to an area of oligemia) or Hampton hump (a pleural-based hyperdense area representing a pleural infarction) are rarely seen.[140] Chest radiography is therefore most useful to quickly establish an alternative diagnosis for the patient in whom PE is being considered. A normal chest x-ray in the presence of significant dyspnea, hypoxia, chest pain, or tachycardia should increase the suspicion for PE and may also help in assessing suitability for a ventilation/perfusion (V/Q) scan.

Chest Computed Tomography

CT scanning of the chest using a PE protocol (typically referred to as CT angiography [CTA], CT-PE, or CT-PA [pulmonary angiography]) is the most commonly used and important test in the modern diagnosis of PE.[141] CTA uses a multidetector CT scanner to acquire

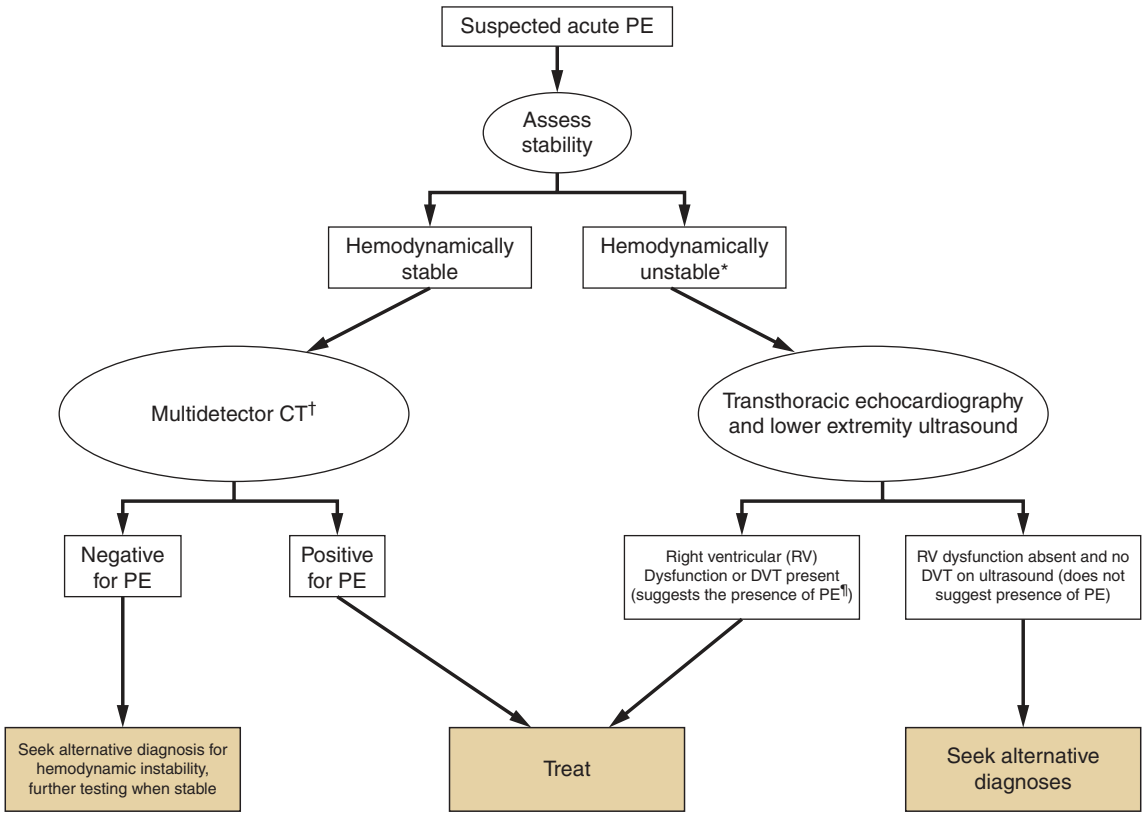

Fig. 65.2 Diagnosis of Pulmonary Embolism. *CT,* computed tomography; *DVT,* deep venous thrombosis; *ICU,* intensive care unit; *PE,* pulmonary embolism. *Search for alternative and concomitant diagnoses. †If contraindication to intravenous (IV) contrast exists, consider ventilation-perfusion scintigraphy, lower extremity venous compression ultrasound, or MR angiography. ¶Try to confirm the presence of PE with additional testing. Proximal lower extremity DVT serves as a surrogate to PE in the appropriate clinical setting.

thin sections of the chest, with the addition of a bolus of IV contrast dye to opacify the pulmonary arteries. Improper timing of the contrast bolus, patient motion, body habitus, artifact, or poor cardiac output may render the study nondiagnostic.

In 15%–20% of patients, CTA provides an alternative diagnosis, such as the presence of pneumonia, pneumothorax, lung tissue disease, or aortic dissection.[142,143] CT may also assist in the grading of PE severity by assessing for the presence of right heart strain (Fig. 65.3A and B).

In an early validation study, CTA had a sensitivity of 83% and a specificity of 96%, with 6% of studies labeled nondiagnostic.[144] With a high probability for PE (as assessed by the Wells criteria), the positive predictive value was 96%, and with a low probability, the negative predictive value was 96%. However, poor diagnostic accuracy accompanied discordance between the pretest probability and the imaging results. Refinements in technology have resulted in a sensitivity and specificity for PE that exceed 90%, even as radiation doses have decreased.[145] Although increasingly diagnosed by newer higher-resolution scanners,[146] the presence of small subsegmental PEs has substantial interrater variability and may lead to overdiagnosis.[147,148] Furthermore, the clinical significance of these small clots is debated.[149]

Radionuclide Lung Scanning

With the advances in CTA technology, the utilization of V/Q scanning has decreased. Nevertheless, given the numerous contraindications to CTA and the presence of nondiagnostic CT scans, there remains a role for V/Q imaging.[104] The perfusion (Q) aspect of the V/Q scan involves an IV injection of technetium (Tc)-99m–labeled macroaggregated albumin particles. The ventilation (V) aspect involves inhaled tracers (e.g., aerosolized Tc-99m–labeled agents or noble gases such as krypton-81 and xenon-133).[150] Gamma camera images of the patient's chest are then obtained.

The diagnostic ability of the V/Q scan stems from its ability to detect mismatches in ventilation and perfusion. Classically, a wedge-shaped perfusion defect may be seen in the perfusion images, corresponding to an area of the pulmonary vasculature that has been blocked by the presence of an embolus. Therefore normal perfusion imaging suggests the absence of an acute PE; if perfusion scanning is performed and normal, the ventilation aspect of the imaging may be omitted. However, the presence of a perfusion deficit can occur as a result of other diseases that cause the shunting of blood away from a diseased portion of lung. Therefore a decrease in perfusion should be correlated with the absence of a coexisting ventilation deficit (e.g., a "mismatch") to diagnose acute PE. V/Q imaging is correlated with a contemporaneous chest radiograph. "Normal" chest radiographs are typically required for certainty, as abnormal chest radiographs raise the probability of false-positive V/Q results. Because the diagnosis depends on secondary signs of a PE and not direct visualization of a thrombus, results are given as a probability.[151] Overall, the sensitivity of V/Q for the diagnosis of acute PE ranges from 85% to 93%, with a specificity of 80%–97%.[152,153] Unfortunately, only 23% of inpatients have normal perfusion imaging and the majority of hospitalized patients have nondiagnostic examinations.[104,154,155]

Compared with CTA, V/Q scanning exposes the patient to significantly less ionizing radiation, particularly to the breast.[156,157] For these reasons, V/Q scanning may be preferred in patients with contrast dye allergy, renal insufficiency, pregnancy, or for younger patients. However, many patients require additional imaging (e.g., CTA) after a nondiagnostic V/Q scan, and for these patients, the overall radiation dose will be greater than if CTA was performed as the first test. Given the low prevalence of normal chest radiography in the ICU patient population, the high rate of nondiagnostic scans, and the lack of ability to diagnose other disease processes, V/Q scanning remains a secondary study to CTA in the modern diagnosis of acute PE.

Magnetic Resonance Imaging

Magnetic resonance imaging using an angiography protocol (MRA) has limited utility in the diagnosis of acute PE. Unfortunately, images are technically inadequate in 25%–52% of studies.[158] MRA has excellent specificity for the diagnosis of PE, approaching 100% in most studies, but its sensitivity varies based on the location of the PE. Central and lobar PE are routinely diagnosed with sensitivities nearing 100%, but sensitivity for subsegmental PE may be as low as 40%.[159,160] In addition to directly showing the filling defect of a thrombus, MRA can provide information about the morphology of the RV.[96,161] The addition of MR perfusion imaging increases the sensitivity to 93% for subsegmental PEs and 100% for larger emboli.[162] The main advantage of MR imaging is the lack of ionizing radiation, but the longer study time, limited diagnostic ability for other thoracic pathologies, and traditional contraindications (such as the presence of a metallic implant) do not support its routine adoption for the diagnosis of PE.

Pulmonary Angiography

Traditional pulmonary angiography was once the gold standard for the diagnosis of acute PE but has largely been supplanted by multidetector CTA. The sensitivity of pulmonary angiography is similar to that of CT imaging,[163] and reliability significantly drops at the subsegmental level.[164,165] The risks are similar to those of other cardiac catheterizations,

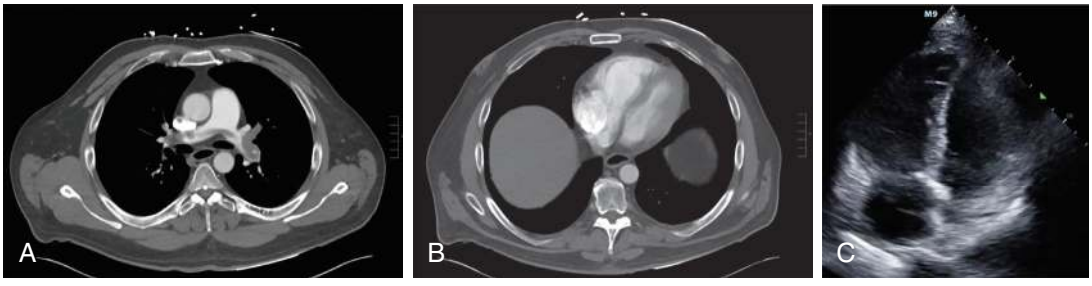

Fig. 65.3 Suggested Management of the Patient with Acute PE. **A,** Acute pulmonary embolism. Cross-sectional computed tomography angiography (CTA) using a pulmonary angiography protocol showing a large bilateral acute pulmonary embolism overlying the main pulmonary bifurcation ("saddle PE"). **B,** Acute right heart strain. Cross-sectional CTA using pulmonary angiography protocol reveals an enlarged right ventricle in the setting of acute pulmonary embolism, suggestive of acute right heart strain. **C,** Acute right heart strain on ultrasound. Ultrasonographic apical four-chamber view of the heart showing acute right heart strain. The right ventricle (left side of the image) is larger than the left ventricle, a pathologic finding. (Images A and B courtesy of Dr. Jeffrey Shyu, Brigham and Women's Hospital, Boston, MA. Image C courtesy of Dr. Heidi Kimberly, Brigham and Women's Hospital, Boston, MA.)

and the procedure has been reported to carry risks of 2% mortality and 5% morbidity.[166] Now typically only used during the performance of endovascular therapy such as catheter-directed thrombolysis, catheter angiography also allows hemodynamic measurements which may be useful in management.

Echocardiography

Echocardiography plays an important role in the workup of suspected and proven PE in the ICU and is most useful diagnostically for assessing secondary signs of PE. The most common findings that suggest acute PE include RV dilation and hypokinesis, an increase in the ratio between the RV and the LV (see Fig. 65.3C), tricuspid regurgitation, paradoxical septal motion (movement of the septum into the LV during systole), interventricular septal shift toward the LV, McConnell sign (hypokinesis of the free wall of the RV with normal motion of the apex), decreased tricuspid annulus plane systolic excursion (TAPSE), and pulmonary artery dilation.[167–169]

In acute PE, a sudden increase in right-sided pressures often occurs, leading to RV dilation and strain. Elevated RV pressures without commensurate RV hypertrophy suggest an acute event such as PE; conversely, RV hypertrophy suggests a preexisting condition.

Although a number of echocardiographic findings have been identified that correlate with the presence of acute PE, echocardiography is poorly sensitive for the diagnosis of PE, particularly in the hemodynamically stable patient. Therefore for a hemodynamically stable patient with suspected acute PE, echocardiography can neither rule in nor rule out the disease.[170–172] However, for the hypotensive patient, an echocardiogram that does not show signs of right heart dysfunction almost certainly excludes PE as the primary cause of the hemodynamic decompensation. Helpfully, echocardiography assists with evaluating alternative etiologies for hypotension (such as pericardial tamponade, valvular heart disease, LV dysfunction, aortic dissection, and hypovolemia) and can easily be performed at the bedside.[173–175] Therefore for an unstable patient in the ICU with contraindications to other diagnostic imaging studies, transthoracic echocardiography (TTE) may help support the presumptive diagnosis of acute PE. Transesophageal echocardiography (TEE) is highly specific for the diagnosis of PE, particularly when combined with the presence of RV overload on TTE.[176,177] Rarely, TEE may reveal a clot in the right side of the heart or thrombus in transit.[178–184] TEE requires specialized equipment and is operator dependent. Therefore it is not routinely used in the diagnosis of acute PE.

For the ICU patient diagnosed with PE via other imaging studies, echocardiography can provide valuable information about cardiopulmonary function and reserve. Particularly important to the diagnosis of PE is the ability of echocardiography to diagnose right heart strain, which is important in the risk stratification of PE.[185–187] Despite its value in prognostication and risk stratification, echocardiography is not recommended as a routine test in the hemodynamically stable and normotensive patient.[188,189]

Venous Compression Ultrasonography

Venous compression ultrasonography ("ultrasound") is the modern standard for diagnosis of ongoing DVT.[190,191] Ultrasound may directly visualize thrombus in the blood vessel or may show secondary signs of DVT such as incomplete compressibility of the vein, suggesting the presence of intraluminal thrombus. Additional ultrasound techniques include the use of Doppler imaging and flow augmentation with manual calf compression. The combination of these sonographic techniques leads to a sensitivity and specificity well over 95% for the presence of proximal DVT.[190] Several studies have confirmed excellent performance of point-of-care ultrasonography by trained intensivists, emergency physicians, and hospitalists, with sensitivity between 86% and 100% and specificity of 90%–96% compared with radiology-performed ultrasound.[192–194]

Although venous ultrasound cannot directly identify PE, and the absence of demonstrable DVT does not exclude the presence of PE, ultrasonography remains helpful in supporting the diagnosis of PE. Because most PE originates from lower extremity DVT and many patients with acute PE will have concomitant DVT,[195,196] a new DVT diagnosis in the setting of symptoms suggestive of acute PE is considered diagnostic.[197] Detection of proximal DVT provides an indication for treatment regardless of the presence or absence of PE and reduces the need for further diagnostic testing.[198,199] As such, ultrasound is particularly helpful in the presence of inconclusive CT results, nondiagnostic V/Q scan results, or in patients with contraindications to other diagnostic imaging.

Particularly important for ICU patients, DVT may occur in non–lower extremity sites such as the arms, head and neck, or trunk.[200,201] Major risks for the development of upper body DVT include the presence of central venous catheters and cancer.[79,85] Because DVT of the upper body is less common, research on diagnostic techniques and protocols is more limited.[202] Additionally, ultrasonography of the proximal upper extremity veins is technically limited because of the clavicle overlying the subclavian vein and superior vena cava.[203]

Venography

Although ultrasonography has become the primary diagnostic modality for DVT, a number of other methods of venography exist. CT venography (CTV) can be performed at the same time as CT pulmonary angiography. Like CTA, CTV can also provide an alternative diagnosis beyond vascular structures and can show larger venous structures (such as the iliac veins and inferior vena cava [IVC]) that ultrasonography may not be able to image.[204] The addition of CTV to CTA increases the sensitivity for VTE, and further improvements in sensitivity may be obtained by direct contrast injection to the affected limb.[205] However, the improvement in sensitivity comes at the expense of increased exposure to radiocontrast media and significant increases in radiation.[206] Given these risks, ultrasound is generally preferred over CTV.

MR venography (MRV) has excellent sensitivity and specificity, nearly 100% in some studies,[207] can give information about the age of thrombosis,[208] and can provide an alternative diagnosis. MRV imparts no radiation, and some protocols do not require contrast media.[210] Expense and duration preclude its use for most ICU patients, but MRV can be useful in specific scenarios, such as the pregnant patient with concern for pelvic or IVC thrombus.[211]

Catheter-based venography was previously regarded as the gold standard for the diagnosis of DVT but has been almost entirely replaced by ultrasound.[212] Direct venography is invasive, requiring catheterization of the venous system of the leg, exposure to contrast dye, and radiation.[213,214] Because of the technical problems with its use and the availability of safe and reliable alternatives, it is rarely used in contemporary practice, except in very limited circumstances, such as during placement of an IVC filter.

Diagnostic Summary

A diagnostic pathway for PE in the ICU is presented in Fig. 65.2. The specific approach used should depend on individual patient circumstances and available diagnostic modalities. Stable patients may undergo transport for testing outside of the ICU. For unstable patients or those at high risk of complications during transport, bedside testing is recommended. Unstable patients should also undergo testing to work through the differential diagnosis list of life-threatening illnesses and to allow for rapid intervention. Given the number of risk factors for PE and the high prevalence of the disease in the ICU population, imaging via CTA will typically be the first diagnostic test in the hemodynamically stable

patient. For hemodynamically unstable patients, TTE and ultrasonography should be performed first.

CLASSIFICATION, PROGNOSTIC ASSESSMENT, AND SEVERITY

Although there is an important distinction between acute and chronic PE, acute PE has the most relevance to the ICU and therefore will be discussed here. Acute PE severity is stratified based on physiologic, laboratory, and radiologic measurements. Hemodynamically stable patients without evidence of RV dysfunction are considered "low-risk" PE, and have low (about 1%) mortality. The presence of right heart strain places the acute PE into the "submassive" or "intermediate-risk" PE category. Right heart strain is defined by the radiologic presence of RV enlargement on CTA or by characteristic echocardiographic findings.[167,215,216] RV dysfunction on echocardiography has been associated with a 2.5-fold (95% confidence interval [CI] 1.2–5.5) increased risk of mortality,[217] and RV dysfunction on CT has been associated with a 1.8-fold (95% CI 1.3–2.6) increased risk of mortality.[218] The presence of right heart dysfunction can also be defined by the presence of laboratory biomarkers, such as the presence of an elevated troponin or NT-proBNP/BNP.[124] A recent meta-analysis found that an elevated troponin is associated with a 4.3-fold (95% CI 2.1–8.5) increase in mortality after PE.[126]

The most severe category of PE is defined as "massive" or "high-risk" PE. Massive PE is described as acute PE with either shock or persistent hypotension (where hypotension is defined as a systolic blood pressure <90 mmHg or a decrease of >40 mg Hg from baseline) not resulting from another etiology like sepsis or dysrhythmia.

The European Society of Cardiology (ESC) recently updated their recommendations for PE risk stratification (Table 65.2)[219] to include a risk score, either the Pulmonary Embolism Severity Index (PESI)[220,221] or the simplified Pulmonary Embolism Severity Index (sPESI).[222] The PESI and sPESI use a number of elements from the history (age, history of cancer, and history of cardiopulmonary disease) and physical examination (tachycardia, hypotension, and hypoxemia) to prognosticate all-cause 30-day mortality. However, because of their lack of association with PE-specific mortality, it is not clear whether these scores should be used to guide advanced treatments such as thrombolysis.

In the current ESC classification system, "low-risk" PE includes patients without any evidence of right heart strain (defined by radiologic criteria or laboratory biomarkers) and a low-risk PESI/sPESI. "Intermediate-risk" PE includes patients with "high-risk" classification on the PESI/sPESI and is further subdivided into "intermediate-high" if there is both radiographic and biomarker evidence of right heart strain or "intermediate-low" if either one or neither is positive. Finally, "high-risk" PE includes patients with evidence of shock or hypotension. Importantly, patients are classified as "high-risk" in the presence of shock or hypotension, regardless of the presence of an elevated risk score or laboratory biomarkers.

A number of additional prognostic scoring systems also exist, including the Geneva risk score,[223] Hestia criteria,[224] Shock Index,[225] Global Registry of Acute Coronary Events (GRACE) score,[226] PREP score,[227] PROTECT multimarker index,[228] Bova score,[229] and RIETE score.[230] Of note, none of these clinical prediction tools have been developed or validated specifically for patients in the ICU.

Although not included in most diagnostic scores or classification systems, thrombus burden and the presence of coexisting DVT are also associated with increased mortality in acute PE.[231–233] D-dimer levels, which reflect thrombus burden, are also correlated with morbidity and mortality.[234–239] However, there is only a loose relationship between the anatomic location of a PE and its physiologic consequences. For example, the term "saddle" PE has classically been used to describe a large PE overlying the bifurcation of the pulmonary artery trunk. Although "saddle" PE has colloquially been used to imply a large, potentially hemodynamically significant PE, patients with acute saddle PE are often asymptomatic and hemodynamically stable, so the term has little use in classifying the severity of PE.[8,240]

TREATMENT OF ACUTE PE

The management of acute PE depends on a number of factors, including the clinician's confidence in the diagnosis of PE, the hemodynamic status of the patient, the degree of RV dysfunction, bleeding risk, non PE-related prognosis, patient preferences, and patient-specific factors that could affect treatment safety and efficacy. The fundamentals of treatment for acute PE include initial resuscitation, prompt therapeutic anticoagulation with drug monitoring (if necessary), consideration of thrombolysis or thrombectomy, and avoidance of complications. Assuming there are no contraindications, patients for whom there is a high suspicion of acute PE should receive empiric anticoagulation before completion of diagnostic testing, especially if a delay in testing is expected. A management algorithm is shown in Fig. 65.4.

Initial Resuscitation

Volume Administration

For hypotensive patients, a cautious fluid challenge with administration of IV crystalloid in small-volume boluses (such as 250–500 mL) may improve cardiac output.[241,242] A volume status examination should occur before and after administration of fluid and should be tailored to the hemodynamics of the patient. Aggressive administration of IV fluids should be avoided, as this may result in RV overdistention, compression of the LV by the septum, decreased cardiac output, and myocardial ischemia.[243,244]

Vasopressors

If the administration of an initial bolus of IV fluids does not improve the patient's hypotension, vasopressors should be administered. There are limited experimental data on the appropriate initial vasopressor,[245] but expert consensus suggests that norepinephrine should be the initial agent in blood pressure support.[219] Dobutamine has been used in selected cases but may worsen hypotension via peripheral beta-2 agonism unless coadministered with norepinephrine.[246,247] Vasopressin may play an accessory role as a vasopressor that does not raise pulmonary vascular resistance.[248]

Vasodilator Therapies

Pulmonary arterial vasodilators may decrease pulmonary vascular resistance and pulmonary arterial pressure, thereby decreasing RV afterload.[249] The successful use of inhaled nitric oxide and epoprostenol have been reported in several case series.[250–254] However, a recent clinical trial failed to show benefit of inhaled nitric oxide in hemodynamically stable patients with PE and RV dysfunction.[255,256]

Supplemental Oxygen

Hypoxemia occurs commonly in hemodynamically significant acute PE, and hypoxemic vasoconstriction may worsen acute pulmonary hypertension. Expert consensus recommends the administration of supplemental oxygen to target a pulse oximetry saturation of 90% or greater.

Intubation and Mechanical Ventilation

Great caution should be exercised in the intubation and ventilation of a patient with acute PE, as these procedures may precipitate

TABLE 65.2 Risk Stratification

Early Mortality Risk		RISK PARAMETERS AND SCORES			
		Shock or Hypotension	PESI Class III–V or sPESI ≥ 1	RV Dysfunction on Imaging	Cardiac Biomarkers
High		+	(+)	+	(+)
Intermediate	Intermediate-high	−	+	Both positive	
	Intermediate-low	−	+	Either one or none positive	
Low		−	−	Assessment optional: if assessed, both negative	

- Any shock or hypotension is classified as high risk, regardless of PESI/sPESI class or biomarkers.
- RV dysfunction on imaging characterized by RV dilation or increased RV/LV ratio (usually greater than 1.0) on CT or echocardiography and hypokinesia of RV wall or increased tricuspid regurgitation jet on echocardiography.
- Cardiac biomarkers = elevated cardiac troponin or natriuretic peptide.

Adapted from Konstantinides S, Barco S, Lankeit M et al. Management of pulmonary embolism: an update. *J Am Coll Cardiol.* 2016;67(8):976–990.

Pulmonary Embolism Severity Index (PESI)

Criterion	Points
Age	Age in years
Male sex	10
History of cancer	30
History of heart failure	10
History of chronic lung disease	10
Heart rate ≥110	20
Systolic blood pressure <100 mm Hg	30
Respiratory rate ≥30	20
Temperature <36°C	20
Altered mental status	60
O_2 saturation <90%	20

Interpretation:

Total Points	Class	30-Day Mortality
0–65	I	0.0%–1.6%
66–85	II	1.7%–3.5%
86–105	III	3.2%–7.1%
106–125	IV	4.0%–11.4%
≥126	V	10%–24.5%

Simplified Pulmonary Embolism Severity Index (sPESI)

Criterion	Points
Age >80	1
History of cancer	1
History of chronic cardiopulmonary disease	1
Heart rate ≥110	1
Systolic blood pressure <100 mm Hg	1
O_2 saturation <90%	1

Interpretation:

Total Points	30-Day Mortality
Low risk (0 points)	1.1%
High risk (≥1 point)	8.9%

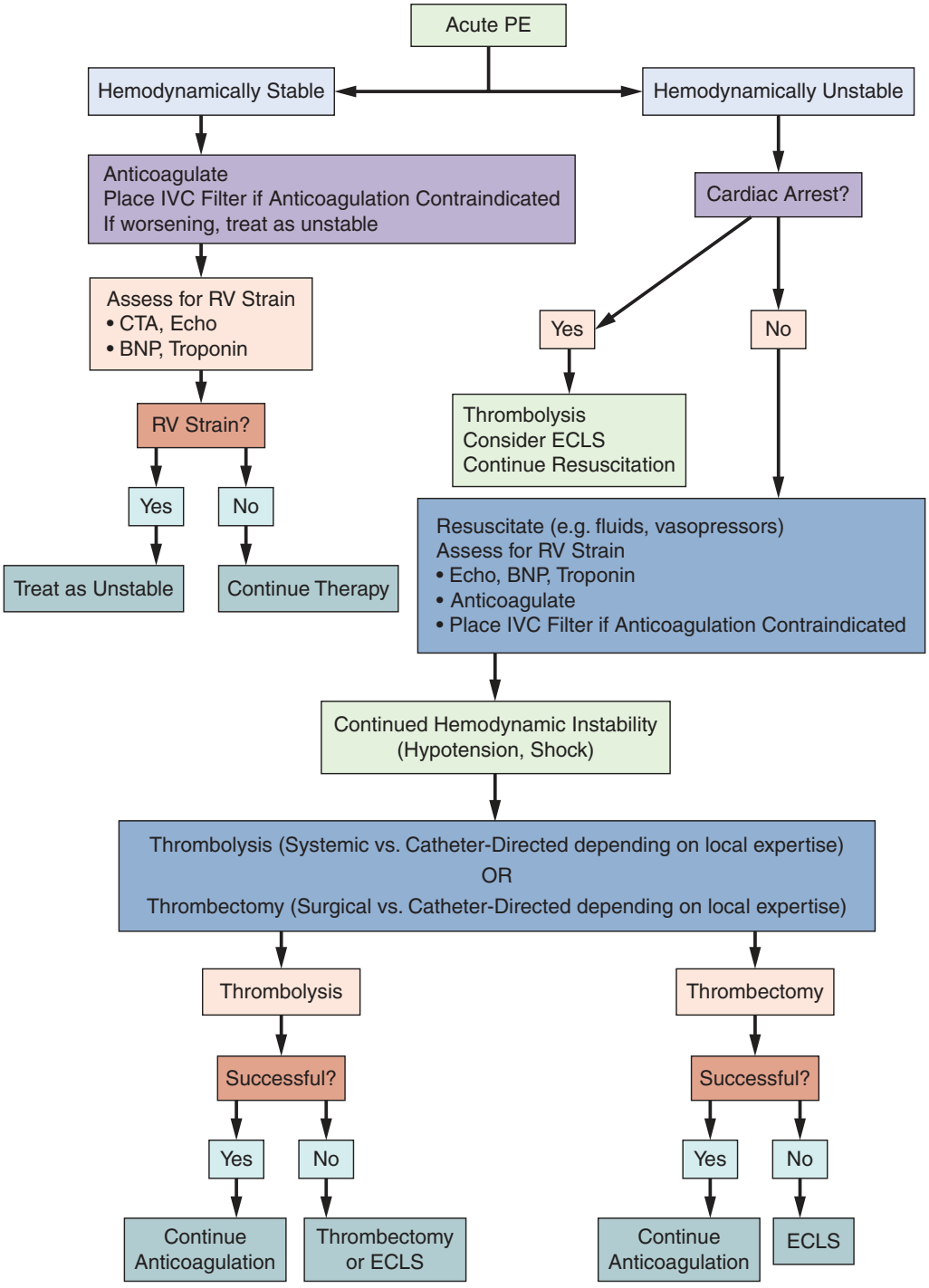

Fig. 65.4 *BNP,* Brain natriuretic peptide; *CTA,* computed tomography angiography; *ECLS,* extracorporeal life support; *IVC,* inferior vena cava; *PE,* pulmonary embolism; *RV,* right ventricle.

hemodynamic collapse and cardiac arrest. Because the increased intrathoracic pressure brought by mechanical ventilation can further lower preload and worsen RV failure, preintubation hemodynamics should be optimized and an infusion of vasopressors should be considered for those patients needing intubation.[257–259] Many induction and sedative agents cause hypotension and transient hypoxemia during the apneic period of an intubation, which can increase pulmonary vascular resistance and worsen RV failure. Therefore intubation should be rapidly accomplished by a skilled operator, using induction medications that preserve cardiovascular stability. Careful attention should also be paid to postintubation ventilator management to optimize RV function.[260]

Anticoagulation

Anticoagulation is the mainstay of treatment for acute PE. Anticoagulation prevents new clot formation and extension of clots and recurrence of disease. Selection of the appropriate anticoagulant medication depends on a number of individual factors, including availability and ease of administration, onset of action and time to peak, patient-specific

features such as metabolism and excretion, bleeding risk, drug interactions, and reversibility. Upcoming procedures or anticipated thrombolysis may favor a medication with a shorter half-life, whereas patients at high risk of bleeding may benefit from an anticoagulant with a readily available reversal agent. The choice of anticoagulant in the ICU should focus on short-term management, whereas long-term treatment choices can be deferred until after the patient leaves the ICU. (e Table 65.4 provides information on the dosing of commonly used anticoagulant medications.)

Patients with a high clinical suspicion for PE should undergo empiric parenteral anticoagulation while awaiting diagnostic imaging unless the bleeding risk is prohibitively high. Initial anticoagulation after the diagnosis of PE is usually accomplished with a parenteral agent in the immediate management period before transitioning to an oral agent. However, the development of direct-acting oral anticoagulants, which are both effective and safe for the treatment of VTE, are viable alternatives for initial treatment in most cases.

All patients should undergo a bleeding risk assessment and evaluation for contraindications before anticoagulant therapy is initiated. Risk factors for bleeding with anticoagulation are listed in Table 65.3. Major contraindications to anticoagulant treatment include intracranial bleeding, severe active bleeding, or recent neurologic or spinal surgery. Relative contraindications include recent major surgery, ischemic stroke, nonsevere active bleeding, thrombocytopenia, or bleeding diathesis. Nonsteroidal antiinflammatory drugs increase the risk of bleeding on anticoagulation, so their use should be minimized.[261] Although studies have identified risk factors for anticoagulant-associated bleeding in patients with VTE, for most patients admitted to an ICU with PE, the benefits of anticoagulation outweigh the risks.[262,263]

Unfractionated Heparin

Despite the development of new anticoagulant medications, unfractionated heparin (UFH) remains the initial parenteral medication of choice for many patients with acute PE in the ICU. Though endogenously produced, commercial UFH is isolated from porcine or bovine intestines as a mix of different-length polysaccharides.[264] These long chains bind to antithrombin III (AT), potentiating the inactivation of factors Xa and IIa (thrombin).[265]

After an initial bolus, the infusion rate of UFH is commonly titrated using a nomogram based on the activated partial thromboplastin time (aPTT) or the anti-Xa level and monitored every 6 hours until a steady state is reached.[266] Typically, the minimum therapeutic threshold of UFH corresponds to 1.5 times the mean control value or the upper limit of normal of the aPTT range, so many institutions will target 1.5–2.5 times the upper limit of the test's normal range. For anti-Xa, this corresponds to a range of 0.3–0.7 unit/mL. The actual aPTT range will vary between institutions based on the assay used. Each aPTT reagent should be correlated to an anti-Xa assay, particularly when switching manufacturers.[265]

The efficacy of UFH depends partly on achieving a therapeutic level of UFH within the first 24 hours of treatment.[96,267] Unfortunately, the anticoagulant response to a standard dose of UFH varies widely among patients, and numerous studies have demonstrated difficulties in clinical practice with reliably administering therapeutic doses of IV UFH, even despite the use of a dosing protocol and nomogram.[265,268–271] Because of its short half-life, utility with renal dysfunction, and availability of a reversal agent, UFH is often the first medication used for treatment of acute high-risk PE in the ICU. However, given its unreliability in anticoagulation, a different anticoagulant should be chosen for those patients for whom thrombolysis or interventional procedures are not immediately planned.

Heparin-induced thrombocytopenia (HIT) occurs within 5–10 days of the initiation of heparin in about 5% of patients. HIT type I (HIT-I), characterized by a transient decrease in platelet count, occurs within the first 2 days of therapy because of a direct effect of heparin that causes platelet aggregation. HIT-I is not clinically significant and does not require a change in therapy.[272] HIT type II (HIT-II) is much more concerning and is an immune-mediated disorder caused by antibodies targeting the platelet–heparin complex (specifically, platelet factor 4 [PF4]).[273] Recognition of the PF4–heparin complex by immunoglobulin G (IgG) leads to both thrombocytopenia and an activation of the clotting cascade, leading to arterial and venous thrombosis, which can be life-threatening. Patients with HIT-II have a 30-fold increased thrombotic risk.[274]

The diagnosis of HIT-II is made clinically using the 4T score while awaiting laboratory confirmation[275] (e Table 65.5). Laboratory diagnosis is typically accomplished using the highly sensitive immunoassay for the PF4–heparin complex and confirmed using the highly specific serotonin release functional assay.[274] For patients in whom there is a high suspicion for HIT-II, heparin therapy should be discontinued immediately and the patient transitioned to an alternative form of anticoagulation, typically a parenteral direct thrombin inhibitor.[276] Although fondaparinux and factor Xa inhibitors have increasingly been used for alternative anticoagulation in HIT-II, they have not yet entered guidelines as recommended therapy.[277–279]

Low-Molecular-Weight Heparin

Low-molecular-weight heparin (LMWH) is obtained by the chemical or enzymatic degradation of UFH from approximately 45 saccharides to 15 saccharides.[280] Similarly to UFH, LMWH binds to AT to inactivate factors Xa and II (thrombin). The decreased length of the LMWH chains decreases the ability of AT to bind thrombin compared with UFH, and therefore its major mechanism of action is from the inactivation of Xa.[281] Several different formulations of LMWH are commercially available with similar characteristics.[282]

LMWH is given subcutaneously and has excellent bioavailability (>90%) and a longer half-life when compared with UFH. LMWH is renally cleared and thus is contraindicated in renal failure. It is administered once or twice a day in weight-based dosing and does not require laboratory monitoring. Nonetheless, anti-Xa levels can be used to measure its efficacy, if needed. When compared with UFH, LMWH has a more predictable anticoagulant response.[280,282]

Overall, LMWH appears to have fewer serious complications, more reliable anticoagulation, lower rates of recurrent thrombus, a lower risk of bleeding, and requires less monitoring than UFH.[283] LMWH also appears to have a lower rate of heparin-induced thrombocytopenia.[284–287] Protamine can be used to reverse LMWH, but its efficacy in reversing Xa blockade is limited.[288,289] Therefore in the patient for whom an invasive intervention is not immediately planned and who can otherwise tolerate the medication, LMWH appears superior to UFH. Limitations include subcutaneous administration; among patients in the ICU receiving DVT prophylaxis with LMWH, patients receiving vasopressors had lower anti-Xa activity than those not on vasopressors[290,291] and anti-Xa activity is also variable in the setting of subcutaneous edema.[292,293] The appropriate dose of LMWH in morbid obesity is also unclear.[294]

Fondaparinux

Fondaparinux is a heparinoid that contains only the biochemically active pentasaccharide sequence of UFH. It binds to AT to inhibit factor Xa but has no activity against thrombin. Fondaparinux has nearly 100% bioavailability after subcutaneous injection and a relatively long half-life when compared with UFH and LMWH.[295] Renally cleared, it should not

e TABLE 65.4 Initial Anticoagulant Therapy for VTE

Medication	Route	Initial Dosing*	Monitoring	Maintenance Dosing
Unfractionated heparin	IV	80 units/kg bolus, then 18 units/kg/hr infusion	aPTT 1.5–2.5 normal *or* anti-Xa 0.3–0.7	–
Low-molecular-weight heparin	SQ	Enoxaparin 1 mg/kg BID Dalteparin 200 units/kg daily Tinzaparin 175 IU/kg daily	None	Same as initial
Fondaparinux	SQ	5–10 mg daily (based on patient weight)	None	Same as initial
Warfarin	PO	5 mg daily (generally) with heparin bridge	INR 2.0–3.0	Adjusted by INR
Apixaban	PO	10 mg BID × 1 week	None	5 mg BID
Rivaroxaban	PO	15 mg BID × 3 weeks	None	20 mg daily

*Initial dosing for patients with normal renal function. Dose adjustments or discontinuation may need to be made for patients with reduced renal function. *aPTT*, Activated partial thromboplastin time; *INR*, international normalized ratio; *VTE*, venous thromboembolism.

TABLE 65.3 Risk Factors for Bleeding With Initial Anticoagulant Therapy

RISK FACTORS	
Age >65 years	Diabetes
Age >75 years	Anemia
Previous bleeding	Antiplatelet therapy
Cancer	Poor anticoagulant control
Metastatic cancer	Comorbidity and reduced functional capacity
Renal failure	Recent surgery
Liver failure	Frequent falls
Thrombocytopenia	Alcohol abuse
Previous stroke	Nonsteroidal antiinflammatory drug

Interpretation:

ESTIMATED ABSOLUTE RISK OF MAJOR BLEEDING			
	Low Risk (0 Risk Factors)	**Moderate Risk (1 Risk Factor)**	**High Risk (≥2 Risk Factors)**
Anticoagulation (0–3 months)			
Baseline risk (%)	0.6	1.2	4.8
Increased risk (%)	1.0	2.0	8.0
Total risk (%)	1.6	3.2	12.8
Anticoagulation (after 3 months)			
Baseline risk (%/year)	0.3	0.6	≥2.5
Increased risk (%/year)	0.5	1.0	≥4.0
Total risk (%/year)	0.8	1.6	≥6.5

Adapted from Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest*. 2016;149(2):315–352.

be used in renal dysfunction. Dosing is weight-based and does not require monitoring. Fondaparinux does not appear to cause HIT.[296,297] Its safety and efficacy appear to be similar to UFH in PE and LMWH for DVT.[298,299] Given its longer half-life and the lack of a reliable reversal agent,[300] fondaparinux is not typically the initial anticoagulant utilized in the ICU but may be a reasonable choice in selected patients.

Vitamin K Antagonists

The vitamin K agonists (VKAs or coumarins) block the function of vitamin K epoxide reductase, depleting the necessary cofactor for activation of the vitamin K–dependent coagulation factors II, VII, IX, and X (and the anticoagulant proteins C and S).[301] Because of the delay in onset of action caused by the presence of circulating coagulation factors and the potential for procoagulant activity at the initiation of therapy resulting from the initial depletion of the anticoagulant proteins, VKAs are typically given alongside a "bridge" of another anticoagulant medication, typically a heparinoid.[302] The VKAs are given orally, and therapeutic monitoring is required to achieve a targeted international normalized ratio (INR) range of 2.0–3.0. Because of a large number of medication interactions and patient-specific variability, there is significant lability in anticoagulation efficacy, and the dosing requires close laboratory monitoring.[303] Given the delay in anticoagulation, large number of interactions, and variable anticoagulation, in addition to the development of newer direct-acting anticoagulant medications with more favorable safety profiles, the use of VKAs in PE is more relevant to chronic anticoagulation.

Direct Oral Anticoagulants

The development of the direct oral anticoagulant (DOAC) medications has quickly changed the management of VTE. In contrast to the VKAs, the DOACs have a more rapid onset, shorter half-life, wider therapeutic window, and more predictable pharmacokinetics without the need for therapeutic monitoring.[304] The DOACs are categorized into two major categories, the direct factor Xa inhibitors and the direct thrombin inhibitors.

Orally administered, the factor Xa inhibitors directly bind factor Xa to prevent the cleavage of prothrombin to thrombin.[305] Unlike heparin, they do not require the presence of antithrombin. The two DOACs approved for the initial treatment of VTE, rivaroxaban and apixaban, both require a higher dosage in the first week(s) of therapy before decreasing to a maintenance dose (see e Table 65.4). Edoxaban, a third approved DOAC, requires at least 5 days of overlapping parenteral therapy before being used as monotherapy, whereas the fourth medication, betrixaban, is approved only for VTE prophylaxis.

When compared with LMWH and VKAs in large clinical trials, the factor Xa antagonists have shown equivalent efficacy for the treatment of VTE, while offering a more favorable safety profile.[306–309] Although these medications have become the first-line treatment for most patients in the outpatient setting because of their reliable anticoagulant effect without the need for routine monitoring, a number of factors limit their use in the ICU, including oral dosing, limitations of use in renal dysfunction, and until recently, limited options for anticoagulation reversal.[310]

The only oral direct thrombin inhibitor is dabigatran, which directly inhibits circulating and clot-bound thrombin.[311] In large clinical trials dabigatran has shown equivalent performance to warfarin with a favorable safety profile[312,313] and has the benefit of a reliable reversal agent, idarucizumab.[314] Dabigatran requires at least 5 days of parenteral therapy with another anticoagulant before its use in VTE, which limits its use in the ICU.

Parenteral direct thrombin inhibitors include bivalirudin, argatroban, and desirudin. They are not approved for the treatment of PE and are typically used off-label for anticoagulation in patients with HIT.[276]

Thrombolytic Therapy

In contrast to anticoagulant medications, which prevent clot propagation, thrombolytic (or fibrinolytic) drugs lead to rapid clot lysis by converting plasminogen to plasmin.[315] Earlier thrombolytic drugs such as streptokinase and urokinase have largely been replaced by more fibrin-specific agents modeled on the naturally occurring enzyme tissue plasminogen activator (tPA). Recombinant genetic engineering has led to the development of three major thrombolytic medications: alteplase (recombinant tissue-type plasminogen activator or r-tPA), reteplase (recombinant plasminogen activator, rPA), and tenecteplase (TNK-tPA). Alteplase is given as a 100-mg IV bolus over 2 hours, reteplase is given as 10 units IV over 2 minutes and then repeated 30 minutes later, and tenecteplase is given as a single weight-based bolus dose.[316]

Thrombolytic therapy provides more rapid lysis of PE than anticoagulation.[317] This clot resolution can restore pulmonary perfusion and promptly lower pulmonary artery pressure and resistance, thereby improving RV function.[318] Over 90% of patients will show a response with thrombolysis.[319] The benefit of thrombolysis appears to be highest when initiated within 48 hours of symptom onset but may remain for up to 2 weeks afterwards.[320] Meta-analyses of thrombolysis have shown lower rates of mortality[321–323] and lower rates of clinical deterioration and recurrent PE, though at the expense of higher rates of major and

e TABLE 65.5 4T Score for Heparin-Induced Thrombocytopenia

Criterion	Points
Thrombocytopenia	
Platelet count fall >50% AND platelet nadir ≥20	2
Platelet count fall 30%–50% OR platelet nadir 10–19	1
Platelet count fall <30% OR platelet nadir <10	0
Timing of platelet count fall:	
Clear onset between days 5 and 10 OR platelet fall ≤1 day) prior heparin exposure within 30 days)	2
Consistent with days 5–10 fall but not clear; onset after day 10 OR fall ≤1 day (prior heparin exposure 30–100 days ago)	1
Platelet count fall <4 days without recent exposure	0
Thrombosis or Other Sequelae	
New thrombosis OR skin necrosis; acute systemic reaction post-intravenous heparin bolus	2
Progressive OR recurrent thrombosis: non-necrotizing skin lesions; suspected thrombosis (not proven)	1
None	0
Other Causes for Thrombocytopenia	
None apparent	2
Possible	1
Definite	0

Interpretation:

Point Summary	Probability
Low probability (≤3 points)	≤5%
Intermediate probability (4–5 points)	~14%
High probability (6–8 points)	~64%

intracranial bleeding.[324] The benefit-to-risk ratio of thrombolysis therefore seems to be highest in those patients with hemodynamic instability in the setting of acute PE (e.g., high-risk or "massive" PE) and intermediate- and high-risk patients who are showing signs of hemodynamic worsening despite appropriate anticoagulation.[325] Younger patients also seem to benefit more than older patients. The long-term benefit of thrombolysis is uncertain, as studies have yet to demonstrate clear improvement in long-term mortality, dyspnea, or RV function.[326] Lower-dose systemic thrombolysis has shown promise in early trials for intermediate-risk PE and for some patients with relative contraindications to thrombolysis. Because these studies have not been replicated in well-designed, large-scale trials, such use is still experimental.[327–329]

The primary risk of thrombolytic therapy is major bleeding. Studies have suggested rates of major bleeding as high as 22%, with a 3% risk of intracranial hemorrhage, although a more recent meta-analysis showed rates of 9.2% and 1.5%, respectively.[23,321] Bleeding associated with thrombolytic treatment can be catastrophic and lead to death; therefore careful patient selection is crucial. Contraindications to thrombolytic therapy are given in Table 65.4.

Expert consensus recommends that UFH be stopped during the administration of r-tPA and TNK-tPA, though it can be continued if rPA is used. Anticoagulation is generally resumed after thrombolysis, typically with UFH in case urgent reversal is needed.[219]

Although no mortality benefit has been demonstrated with empiric thrombolysis in undifferentiated cardiac arrest, fibrinolysis is generally recommended in cardiac arrest resulting from presumed or known PE.[330,331] Alteplase may be given as a 50-mg bolus,[332] and tenecteplase, although technically weight-based, is typically given as a 50-mg bolus for ease of administration.[333] When fibrinolytics are given in cardiac arrest, consensus recommendations suggest cardiopulmonary resuscitation (CPR) should be continued for at least 60–90 minutes before terminating resuscitation attempts.[334]

Interventional Techniques

Inferior Vena Cava Filter

Insertion of an IVC filter is indicated for patients with acute PE with an absolute contraindication to anticoagulant therapy or for patients with recurrent PE despite adequate anticoagulation.[219] Many clinicians also favor insertion of an IVC filter for patients with large PE and residual iliofemoral DVT that could result in sudden cardiac arrest if it were to embolize. IVC filters prevent the embolization of thrombus to the heart and pulmonary vasculature but do not aid in resolution of the thrombus; therefore the patient should receive anticoagulation if the contraindication to anticoagulation resolves. The routine placement of IVC filters for patients with proximal DVT without PE is not supported,[335] as it does not reduce mortality[336] and increases the risk of subsequent DVT.[337]

Permanent IVC filter insertion has largely been replaced by the development of retrievable filters, which have a high rate of successful placement and removal.[338,339] Removal should take place within several weeks of insertion, although most "retrievable" IVC filters are never retrieved.[340] Coordination with specialists who can remove an IVC filter after discharge from the ICU is very important. The most common complications of IVC filter placement are IVC penetration and occlusion; other complications include filter movement or migration and fracture.[341] Because the complication rate increases with time[340] and the success of retrieval decreases with time,[342] IVC filters should be removed as soon as clinically appropriate.[339]

Catheter-Directed Treatment

Catheter-directed treatment includes a variety of endovascular treatments for acute PE, including thrombolysis and thrombectomy.[343] Catheter-directed thrombolysis involves the insertion of a catheter into affected pulmonary arteries to directly deliver fibrinolytic into the thrombus, theoretically avoiding the shunting of blood away from the occluded artery and into nonoccluded vessels.[344] Some catheters include ultrasound to facilitate the entry of thrombolytics into the thrombus, though the clinical benefit of this functionality is unknown.[345] Catheter-based techniques allow the delivery of much lower doses of thrombolytic medications over a longer period, theoretically reducing the risk of major bleeding.[344,346] Catheter-directed thrombolysis appears to be as effective as systemic thrombolysis in high-risk PE with a lower risk of bleeding[347–349] and may be superior to anticoagulation alone in intermediate- and high-risk PE, though large clinical trials comparing catheter-directed thrombolysis with either anticoagulation alone or with systemic thrombolysis have not yet been performed.[350] Other percutaneous catheter-based techniques include fragmentation, aspiration thrombectomy, and mechanical thrombectomy. These procedures are only available at specialized centers, and data supporting these techniques are limited to case series.[351–353]

Surgical Embolectomy

Surgical embolectomy (thrombectomy) has a role for patients who have high-risk PE and a contraindication to thrombolytic therapy or

TABLE 65.4 Contraindications to Fibrinolytic Therapy

Major Contraindications
Structural intracranial disease
Previous intracranial hemorrhage
Recent ischemic stroke (3 months)
Active bleeding
Recent brain or spinal surgery
Recent head trauma with fracture or brain injury
Bleeding diathesis
Relative Contraindications*
Systolic blood pressure >180 mm Hg
Diastolic blood pressure >110 mm Hg
Recent (nonintracranial) bleeding
Recent surgery
Recent invasive procedure
Noncompressible vascular puncture
Remote ischemic stroke (>3 months)
Therapeutic anticoagulation
Traumatic cardiopulmonary resuscitation
Pericarditis or pericardial fluid
Diabetic retinopathy
Pregnancy
Age >75 years
Low body weight (<60 kg)
Female
Black race

*Relative contraindications are those that have been associated with increased bleeding risk in retrospective studies of thrombolysis. Severity of condition and clinical judgment should determine importance of relative contraindications.

Adapted from Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest*. 2016;149(2):315–352.

failed thrombolytic therapy.[219] Additionally, embolectomy should be considered for thrombus-in-transit through the right heart or crossing a patent foramen ovale.[354] Surgical embolectomy requires general anesthesia, cardiopulmonary bypass, and available personnel and equipment. Because standard technique involves a median sternotomy and pulmonary artery incision, embolectomy is technically most feasible for large, central PEs. Intraoperative TEE should be performed because of the high prevalence of extrapulmonary thromboembolism in this patient population.[355]

Traditionally, surgical embolectomy has had a prohibitively high mortality rate, over 50% in early trials[356] and 59% when performed after cardiac arrest.[357] However, this was most likely the result of selection bias and the use of surgical embolectomy only after cardiac arrest and other efforts, such as thrombolysis, had failed.[358] With improved patient selection and surgical technique, a more recent, large meta-analysis found in-hospital all-cause mortality of 26.3%,[359] and some centers have reported mortality rates lower than 11%.[360,361]

For patients with massive, high-risk PE, surgical embolectomy leads to more rapid decreases in pulmonary artery pressure and RV diameter with a lower complication rate than systemic thrombolysis.[362–364] Surgical embolectomy appears to have similar mortality to catheter-based therapies with a lower failure rate in the treatment of massive, high-risk PE, but available data are subject to selection bias, as surgical techniques have been traditionally reserved for the most critically ill.[365] The decision to proceed with either surgical embolectomy or catheter-directed techniques will depend on the available personnel, equipment, and specific conditions of the patient.

Extracorporeal Life Support

ECLS (also called *extracorporeal membrane oxygenation* or *ECMO*) can be used in acute high-risk PE to unload the RV, increase cardiac output, and provide oxygenation.[358] ECLS can be used either as a bridge to surgical embolectomy or as definitive (destination) therapy with anticoagulation alone.[354] Most data on ECLS are from published case series, but a systematic review showed an overall survival rate of 70.1% with similar mortality for catheter-directed thrombolysis, surgical embolectomy, and systemic thrombolysis in patients with massive, high-risk PE.[366] ECLS requires significant institutional infrastructure, including equipment, physician specialists, perfusionists, and well-established protocols. These requirements limit its utility to specialized centers.[344]

Team-Based PE Therapy

Similar to the management of acute coronary syndromes, stroke, and trauma, pulmonary embolism response teams (PERTs) have been developed to coordinate care for patients with higher-risk acute PE.[367,368] PERTs can assist with the early management, triage, and coordination of advanced interventional techniques such as catheter-directed thrombolysis, surgical embolectomy, or ECLS, in addition to facilitating follow-up. As the management of intermediate- and high-risk PE is complex, PERT may rapidly coordinate expertise from diverse disciplines to develop a plan of care.[369–371]

KEY POINTS

- VTE includes both DVT and PE, which occurs when a DVT embolizes and travels through the heart to lodge in the pulmonary arterial vasculature.
- The critically ill patient is at high risk for the development of PE because many risk factors for thrombus formation are common in the ICU.
- History, physical examination, and traditional scoring systems are unreliable in the ICU patient; therefore diagnostic imaging is the test of choice for the diagnosis of acute PE in the ICU.
- Patients suspected of acute PE should promptly undergo CT using an angiography protocol (CTA) as the initial diagnostic study of choice; a subset of patients with contraindication to CTA may undergo V/Q scanning. The hemodynamically unstable patient should be expediently examined by echocardiography and compressive venous ultrasonography.
- Anticoagulation is the mainstay of treatment for acute PE. For patients diagnosed with acute PE or with high pretest probability, anticoagulation should be promptly administered, often using a parenteral heparinoid.
- Unstable patients with high-risk PE should be assessed for definitive therapy by thrombolysis (either systemic or catheter-directed) or surgical embolectomy. A PERT may help coordinate advanced therapies.

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66

Pneumothorax

Sharad Chandrika and David Feller-Kopman

INTRODUCTION

The term *pneumothorax* was first coined by Itard in 1803.[1] Pneumothorax is defined as the presence of air in the pleural space. Traditionally, pneumothorax has been categorized into primary, secondary, traumatic, and iatrogenic. Spontaneous pneumothorax is considered "primary" when there is no obvious underlying lung disease and "secondary" when there is a known underlying lung disease such as emphysema or cystic lung disease. As thoracic imaging has evolved, subtle cystic/fibrotic disease is more easily visualized, and the categorization of primary vs. secondary has been called into question.[2] Traumatic pneumothorax is secondary to penetrating or blunt thoracic trauma, which is further categorized as iatrogenic or noniatrogenic. The clinical implications of pneumothorax are dependent on the degree of lung collapse of the lung on the affected side and the patient's underlying cardiopulmonary reserve. A simple pneumothorax may rapidly progress to a life-threatening "tension pneumothorax" with resultant hypoxia and/or hypotension or cardiogenic shock, especially if the patient is receiving positive-pressure ventilation. Therefore it is imperative that healthcare workers in the intensive care unit (ICU) be able to rapidly diagnose and treat a patient with pneumothorax.

PATHOPHYSIOLOGY

Pleural membranes line the surface of the lung and the lining of the chest wall. Under normal physiologic conditions, the lungs are inflated secondary to airway pressure being higher than the pleural pressure.[3] Pneumothorax most commonly results from a breach in the visceral pleura, but air may also enter the pleural space from the atmosphere (trauma/iatrogenic) or via gas-producing organisms in the setting of empyema.[4] Primary spontaneous pneumothorax (PSP) typically occurs in tall, thin males with an "ectomorph" body habitus, and is thought to be the result of increasing pleural porosity or rupture of previously unseen subpleural blebs.[5] Although height and male sex are risk factors for primary spontaneous pneumothorax, smoking has been identified as the most important risk factor contributing to the development of the disease.[6] The relative risk of pneumothorax increases from 7 to 100 times higher in light to heavy smokers.[6] Smoking cessation is associated with a significant reduction in the risk of recurrence[7] (Table 66.1). Several inherited disorders such as Marfan syndrome, Birt-Hogg-Dubé syndrome, other mutations of the folliculin gene (FLCN), alpha-1-antitrypsin deficiency,[1] and homocystinuria also predispose to pneumothorax. Traumatic pneumothorax is the second most common clinical finding after chest trauma, following broken ribs. Iatrogenic pneumothorax in the ICU most often occurs after central venous access, thoracentesis, transbronchial lung biopsy, and positive-pressure ventilation.[8]

The progression from a simple pneumothorax to tension pneumothorax relies on the continued escape of gas into a closed pleural space. This leads to increasing pleural pressure, with resultant atelectasis and hypoxemia. As the pleural pressure continues to elevate, venous return is limited, resulting in a fall in cardiac output and shock. Animal studies have investigated the pathophysiology of tension pneumothorax.[9–12] Proposed mechanisms contributing to tension physiology include hypoxia caused by shunting of blood through the atelectatic lung, hypoventilation resulting from increased transpleural pressure causing reduced diaphragmatic excursion, and decreased preload from increases in intrathoracic pressure. The traditionally taught mechanism of vena cava mechanical obstruction likely plays less of a role.[9] Major clinical findings may differ depending on whether the patient is spontaneously breathing or on positive-pressure ventilation. Hypoxia is usually the main finding in spontaneously breathing patients. Patients with impaired respiratory drive (needed to decrease intrathoracic pressure and increase venous return) or hypovolemia, however, may have reductions in cardiac output.

Patients on mechanical ventilation pose the highest risk for hemodynamic instability. The rate of increase in volume in the pleural space depends on the volume and pressure being delivered and degree of pleural injury. With an increasing volume of gas entering the pleural space, a critical point is reached, resulting in decreased venous return and eventual equalization of pressure within the cardiac chambers, in turn leading to a decrease in cardiac output and, ultimately, cardiac arrest.[13]

DIAGNOSIS AND EVALUATION

The diagnosis of pneumothorax in critically ill patients can sometimes be made with information from the history and physical examination, noting acute onset of dyspnea or chest pain, tachycardia, hypotension, decreased breath sounds, pulsus paradoxus, and contralateral tracheal deviation. Tension pneumothorax should be suspected if severe tachycardia, hypotension, hypoxia, or cyanosis have developed. Although clinical features can be used to diagnose the presence of a pneumothorax, it should be noted that many of these findings are nonspecific and have not been a reliable indicator of pneumothorax size, especially in the case of secondary spontaneous pneumothorax (SSP) where severe symptoms of dyspnea can be out of proportion to the size of the pneumothorax, and underlying emphysema can cause diminished breath sounds. Acute changes in ventilatory parameters, such as a reduction in tidal volume or increase in airway pressures resulting from reduced respiratory system compliance, may be associated with pneumothorax but can also be found in other disease states and therefore have the potential to be misinterpreted under different clinical scenarios.

TABLE 66.1 A Possible Alternative Classification System to Categorize Pneumothorax

	Management Issues
Iatrogenic pneumothorax	Likely benign course in which conservative management may be appropriate
Traumatic pneumothorax	Management of coincident trauma or parenchymal injury
Pneumothorax associated with endometriosis	Potential role for hormone treatment; high risk of recurrence
Pneumothorax with a genetic predisposition (e.g., Marfan syndrome, Birt-Hogg-Dubé syndrome)	Related multisystem pathology; familial screening
Idiopathic pneumothorax	Likely low risk of recurrence; conservative or ambulatory management may be appropriate
Pneumothorax with previously unrecognized abnormal parenchyma (e.g., respiratory bronchiolitis or bullous disease)	Smoking cessation; consideration of early surgical intervention in selected cases
Pneumothorax associated with infection or immunocompromise	Identification of underlying immunocompromise; targeted antimicrobial treatment
Pneumothorax with abnormal parenchyma in context of known lung disease (e.g., COPD, cystic fibrosis, lung cancer, interstitial lung disease)	High risk of ongoing air leak and recurrence; suitability for surgical intervention; optimizing management of existing lung disease

COPD, Chronic obstructive pulmonary disease.

From Bintcliffe OJ, Hallifax RJ, Edey A, et al. Spontaneous pneumothorax: time to rethink management? *Lancet Respir Med.* 2015;3(7):578.

Because of the lack of specificity of the clinical examination, radiologic imaging remains the gold standard for the diagnosis of pneumothorax.[14] It should be understood, however, that therapeutic intervention (i.e., needle decompression or chest tube placement) may be required in unstable patients based on a clinical diagnosis before radiographic confirmation[15] (Fig. 66.1).

Portable chest radiographs traditionally have been the initial diagnostic test in the ICU to diagnose a pneumothorax. Most of these radiographs have the patient in the supine or semirecumbent position rather than an erect position.[16] However, caution should be exercised when interpreting supine radiographs, as the most nondependent part of the chest (where air will collect) is in the costophrenic recess, known as the *deep sulcus sign*.[17] A skin fold on chest radiograph may resemble a pneumothorax by mimicking a sharp lung edge but, in fact, represents a normal finding.[18] Skin folds may be seen in elderly or obese patients and can be confirmed by a repeat radiograph in a different position.

Because of the limitations of chest radiography, it is important to treat the patient and not the radiograph. In the right clinical situation with concern for tension pneumothorax, clinicians should proceed with immediate pleural evacuation to avoid further clinical decompensation. If there is doubt in regard to the findings on a chest radiograph and the patient is stable, it is advised to seek the expert opinion of the radiologist and/or further imaging with ultrasound or chest computed tomography (CT).[19]

CT is the gold standard test for confirming the diagnosis and size of the pneumothorax. CT also allows for assessment of underlying lung parenchyma and pleural-based lesions and can differentiate bullous disease from pneumothorax, potentially avoiding inappropriate drainage and creation of a parenchymal-pleural fistula.[20] With the widespread use of CT scanning, the diagnosis of occult pneumothoraces has become more common. The occult pneumothorax is defined as a pneumothorax detected via CT that was not clinically suspected or recognized on standard chest radiography.[21] This may be more common with the increased availability of CT scans. The overall incidence of occult pneumothorax in trauma patients ranges from 2% to 15% and can be as high as 64% in multitrauma patients.[22] There is controversy on how to treat patients with an occult pneumothorax on mechanical ventilation because of the potential escalation to tension pneumothorax. A multicenter randomized study in a trauma population on mechanical ventilation did not show a difference in respiratory distress between observation vs. prophylactic chest tube insertion (relative risk: 0.71; 95% confidence interval: 0.40–1.27).[23] Ultimately, 31% of the observed patients had subsequent chest tube placement nonurgently for worsening pneumothorax on imaging without an increase in morbidity. Although this single study lends support for the observation of occult pneumothoraces in mechanically ventilated trauma patients, further studies are needed to guide management in different populations and situations. Expert consensus remains that clinical judgment is used to determine if drainage is needed.[24]

Thoracic ultrasound has become an increasingly accessible tool in the ICU for the diagnosis of pneumothorax. There are several advantages of ultrasound over chest radiograph and CT, including availability at the bedside, absence of radiation, real-time imaging, and the ability to easily perform dynamic and repeat evaluations. A recent meta-analysis has shown that ultrasound is more sensitive and specific than a standard chest radiograph for detecting pneumothorax and can be used to assess lung re-expansion after tube thoracostomy.[25] The major pitfall in ultrasound is in acquiring the skills of image acquisition and interpretation for the nonradiologist.[26] Another limitation is that severe subcutaneous emphysema will limit ultrasound waves penetrating into the thoracic cavity and also create an "E-line" artifact. A study comparing ultrasound with CT/chest radiographs for the diagnosis of occult pneumothorax showed that the use of ultrasound detected 92% of occult pneumothoraces diagnosed with CT.[27] Ultrasound is extremely useful in ruling out pneumothorax after pleural procedures and central line placement, negating the need and time delay for a portable radiograph.[28,29]

Normal movement of the underlying lung with respiration produces a "sliding" or "gliding" sign, and this dynamic movement identifies the visceral pleura and lung parenchyma. Examination of the lung with ultrasound commonly shows A-lines and B-lines. A-lines are horizontal, hyperechoic lines that represent reverberation artifacts of the visceral-parietal pleural interface. B-lines, also known as *comet tail artifacts,* are caused by echo reverberations of the air-filled lung and appear as narrow, hyperechoic, raylike opacities extending from the pleural line to the edge of the ultrasound screen without the fading that moves with lung sliding. As pleural air would block the visualization of the underlying lung, the presence of B-lines and lung sliding rule out a pneumothorax, with a negative predictive value of 100% in the location of the chest probe.[30] It is important to examine several locations on the thorax, especially the superior anterior and lateral

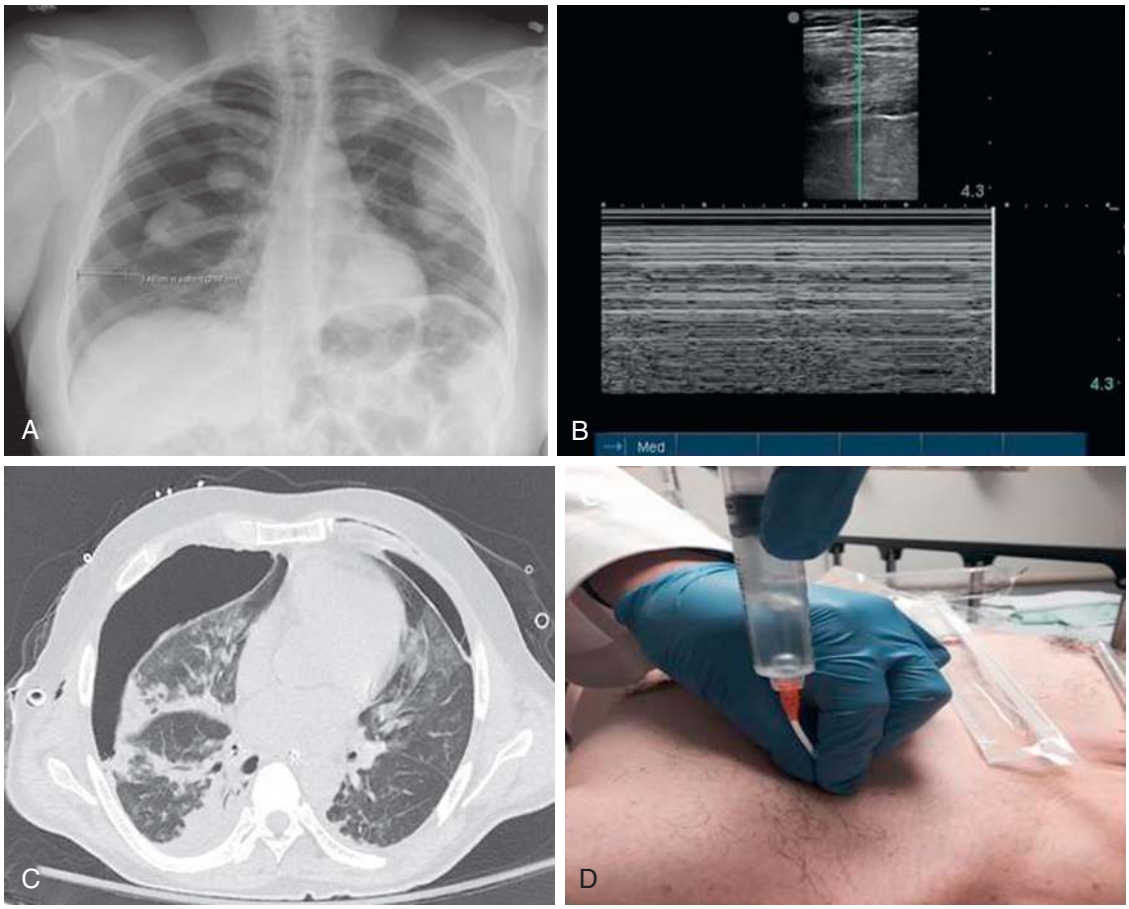

Fig. 66.1 Different Modalities for Diagnosing Pneumothorax. **A,** Chest x-ray. **B,** US M-mode. **C,** CT scan. **D,** Needle aspiration. *CT,* Computed tomography; *US,* ultrasound.

chest wall, where air would normally accumulate. One can also fail to see lung sliding when there is contralateral mainstem intubation, pleural-parenchymal adhesions, endobronchial obstruction, or diaphragmatic paralysis. Therefore the main utility of ultrasound for the assessment of pneumothorax lies in its ability to rule out a pneumothorax. Lung ultrasound, however, can also be used to rule in pneumothorax by identifying the point where the lung separates from the chest wall. This is seen as an area where normal lung sliding meets an area where no lung sliding is seen and has been termed the *lung point*. The lung point can be visualized with both B-mode and M-mode ultrasound and, when seen, has 100% specificity for pneumothorax.[31] The sensitivity of the lung point for pneumothorax is inversely proportional to the size of the pneumothorax, as a large pneumothorax would prevent the parenchyma from opposing the chest wall. Ultrasound has recently been used to serially follow the lung point and determine if the pneumothorax is enlarging.

MANAGEMENT

Appropriate treatment of pneumothorax is dictated by the clinical assessment of symptoms, pneumothorax size, and etiology. The primary goal of the management of a pneumothorax is to restore normoxia and hemodynamic stability and evacuate air from the pleural space, allowing visceral and parietal pleural apposition.

There is no universal consensus regarding the management of PSP. The British Thoracic Society (BTS) and American College of Chest Physicians (ACCP)[32,33] recommend that select patients with small (defined as <2 cm at the hilum on standard chest x-ray [CXR] by the BTS and <3 cm at the apex by the ACCP) PSP without symptoms be managed with observation. In patients with PSP >2 cm and/or symptoms, BTS recommends simple aspiration, whereas the ACCP recommends chest tube drainage. Both BTS and ACCP recommend pneumothorax prevention in patients with recurrent pneumothorax. Pleurodesis as an alternative strategy is recommended by both BTS and ACCP guidelines where the patient may not be a surgical candidate or be unwilling to undergo surgery. Operative intervention is reserved for patients with recurrent pneumothorax or individuals who plan to engage in high-risk activities (such as flying or diving).

As patients with SSP have underlying lung disease with less cardiopulmonary reserve, they typically present more acutely than those with PSP and require more urgent drainage, and hospitalization is recommended.[34] The BTS and ACCP recommend the use of high-flow oxygen and observation in a hospitalized setting for patients with small/asymptomatic SSP and chest drainage for symptomatic or large SSP.

The majority of patients in the ICU with a pneumothorax require evacuation of pleural space.[35] Pneumothorax secondary to barotrauma, tension pneumothorax, and concurrent sepsis has been significantly and independently associated with an increased risk of death in the ICU.[36] The BTS recommends intercostal drainage for all pneumothoraces in patients on a mechanical ventilator and those exhibiting signs or suspicion of tension physiology, traumatic pneumothorax, or hemothorax and postsurgical pneumothoraces.[32] The role of needle decompression has not been well elucidated for patients on mechanical ventilation, and

there are data to suggest that the therapeutic effect of this intervention may be insufficient despite proper placement and positioning.[37,38] If needle decompression is performed, standard tube thoracostomy is usually subsequently required for definitive management.

The standard treatment for a mechanically ventilated patient with a pneumothorax or tension pneumothorax is tube thoracostomy.[39,40] Several studies have reported excellent success rates using small-bore catheters.[41] These tubes are associated with less pain and likely have reduced complications in patients with thrombocytopenia or coagulopathy. The risk of serious complications associated with small-bore catheters is small, with a frequency of organ injury of 0.2% and a malposition rate of 0.6%. The largest risk is drain blockage, with a rate of 8.1%, and it is easily preventable with scheduled sterile flushing to maintain patency.[42]

The use of ultrasound has decreased the rate of complications and should be routinely used, especially in the nonemergent placement of chest tubes.[15] If there is a high clinical suspicion of tension pneumothorax, chest tube insertion should not be delayed while awaiting radiographic confirmation; however, in this case, it may be prudent to perform open (surgical) thoracostomy as opposed to the modified Seldinger technique to avoid injury to the lung, heart, or other organs should pneumothorax not be present.[43]

PERSISTENT AIR LEAK

A persistent air leak (PAL) is defined as an air leak present for >5–7 days and may represent a more complex problem requiring additional treatment beyond chest tube insertion. Factors such as poor nutrition, the size of the pleural injury, mechanical ventilation, and medications (i.e., steroids) may hinder the resolution of pneumothorax. For most patients with PAL, conservative measures such as continued chest tube drainage are recommended. Many of these leaks will resolve spontaneously. Additionally, if the patient can clinically tolerate a water seal (even if the pneumothorax enlarges), the lack of an increased transpleural pressure gradient created by chest tube suction can expedite healing of the visceral pleura. Other supportive strategies include the optimization of nutrition and therapy for comorbidities. For select patients who fail conservative therapy, bronchoscopic therapy with endobronchial valve placement can be attempted. Bronchoscopic treatment implanting a unidirectional endobronchial valve to isolate and close the fistula has been described to be safe and effective and is approved for a humanitarian device exemption in the United States.[44] The valves are currently indicated for the treatment of prolonged air leaks or leaks that are likely to be prolonged (defined as >7 days) after lobectomy, segmentectomy, or surgical lung volume reduction. The procedure is performed by first identifying the "culprit" airway via sequential bronchoscopic balloon occlusion. When the airway leading to the alveolar-pleural fistula is occluded, the amount of air leak in the chest drainage system will stop or be significantly reduced. The valve is then sized and inserted through the working channel of the flexible bronchoscope. The visceral pleura defect is then allowed to heal, and the valve is removed 6 weeks later.

For patients who fail or are not candidates for bronchoscopic or surgical approaches, ambulatory drainage devices and nonsurgical pleural procedures are options (e.g., blood patch or chemical pleurodesis) that can be offered. Although no randomized studies have compared different chemical agents for pleurodesis, a recent large European prospective series showed that European-graded talc used for pleurodesis is effective and safe.[8,9] Nonsurgical pleural procedures are also considered complementary when surgical or bronchoscopic methods achieve a partial response only. Choosing among them should be individualized and depends on fistula size, local expertise, and patient preference. Except for patients with persistent air leaks, procedures to prevent the recurrence of a PSP should be reserved for the second pneumothorax occurrence, yet be considered after the first SSP.

KEY POINTS

- Pneumothorax is common in the ICU and may have various clinical presentations.
- Treatment of a highly suspected tension pneumothorax should not be delayed for radiographic confirmation.
- Occult pneumothorax on mechanical ventilation should be closely monitored if chest tube insertion is readily available.

References for this chapter can be found at expertconsult.com.

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Community-Acquired Pneumonia

Girish B. Nair and Michael S. Niederman

INTRODUCTION

Pneumonia is an infection of the gas-exchanging units of the lung and has a wide spectrum of clinical severity, ranging from mild outpatient illness to severe respiratory failure and sepsis. Pneumonia and influenza together are the eighth leading cause of death in the United States and the number-one cause of death from infectious diseases.[1,2] Pneumococcal pneumonia–related hospitalization has been projected to increase 96% by 2040 in the United States alone, with an estimated increase of $2.5 billion annually in healthcare expenditure.[3] Pneumonia in the community setting or occurring within 48 hours after hospital admission is termed *community-acquired pneumonia* (CAP). In an effort to streamline the use of appropriate antibiotics, the guidelines for managing CAP were recently updated by American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA), with significant departure from the 2007 recommendations.[4] Healthcare–associated pneumonia (HCAP) is no longer recognized as a separate entity, and caution is advised to use biomarkers such as procalcitonin (PCT) as a diagnostic test to identify bacterial pneumonia.[4] The pneumonia-related mortality rate increases to more than 10% in hospitalized patients and can exceed 30% in those requiring intensive care unit (ICU) level of care.[5–7] Pneumonia patients requiring mechanical ventilation (MV) or invasive vasopressor support (IVS) and those with pneumonia-related hypotension that is unresponsive to fluids alone are generally considered as having severe CAP (SCAP). However, there is no uniform definition for SCAP, and it often proves challenging to define severe pneumonia and the need for ICU care. Severity assessment scores may identify high-risk patients and help with decision on site of care. Delay in providing ICU level of care for patients with life-threatening pneumonia is associated with worse outcomes. Implementing a large, publicly funded pneumococcal vaccination strategy for infants and young children has led to a significant improvement in herd immunity and a decrease in age-adjusted pneumonia rates.[8]

INCIDENCE

The annual incidence of pneumonia ranges from 5 to 11 per 1000 population, and the majority of patients are treated out of the hospital.[1,9] However, the major portion of the total cost of treating patients with pneumonia is concentrated in hospitalized patients—particularly those admitted to critical care units. In addition, those with comorbid illness and those of advanced age make up a large proportion of the hospitalized, critically ill CAP patients. Although CAP can vary from being a relatively mild ailment to a severe illness, very few hospitalized patients are severely ill enough to require ICU admission.[10,11]

Time to ICU admission may have an impact on subsequent prognosis. Woodhead and colleagues found that earlier ICU admission (within 2 days of hospitalization) was associated with a lower mortality rate (46.3%) than later admission (>7 days in the hospital, 50.4% mortality rate).[12] Restrepo and colleagues also noted a higher mortality rate among CAP patients admitted to ICU after 48 hours as compared with direct admission or within 24 hours, even after adjustment for severity of illness (47.4% vs. 23.2%, $P = .02$).[13] Other studies have shown higher odds of short-term mortality (odds ratio [OR] = 2.6) for patients who were initially triaged to the general ward but later admitted to the ICU.[14,15]

The economic liability associated with CAP remains significant at >$17 billion annually in the United States.[16] Kaplan and colleagues evaluated the cost of care for 623,718 elderly patients with CAP in the United States and found two-thirds of the population had one or more underlying illnesses, with congestive heart failure, the most common comorbidity, present in 32%.[11] The overall mortality rate was 10.6%, but rose higher with advancing age, nursing home residence, and comorbid illness. The mean length of stay (LOS) was 7.6 days, with cost generally paralleling LOS and being disproportionately high for those needing MV. Kozma and colleagues, in a study of approximately 1.5 million CAP admissions, showed a potential economic benefit of $2300 per 1 less day per patient spent in the hospital.[17] Other studies of CAP have reported that costs are higher for patients with comorbid illness than those without, as might be expected. However, in those without comorbid illness, the cost for those who died was less than for those who survived, whereas the opposite was true when the entire CAP population was considered.[18]

RISK FACTORS FOR DEVELOPING SCAP

In all studies of CAP, patients who are admitted to the hospital or ICU commonly have a number of coexisting illnesses, suggesting that individuals who are chronically ill have an increased risk of developing severe illness (Table 67.1).[19] In studies of SCAP, serious coexisting illness is present in 46%–66% of all patients.[11,19,20] The common chronic illnesses in these patients are respiratory disease, cardiovascular disease, and diabetes mellitus.[1,6,21] The most common respiratory illness in CAP patients is chronic obstructive pulmonary disease (COPD), a finding that applies to those with either mild or severe forms of CAP.[6,10]

Cigarette smoking has been identified as a risk factor for bacteremic pneumococcal infection, especially in younger patients with fewer comorbid conditions, and "current smoking" status is associated with a higher mortality in CAP patients compared with nonsmokers or ex-smokers.[10,22,23] Other common illnesses associated with CAP include malignancy, neurologic illness (including seizures), and AIDS.[1,20] One study identified alcohol abuse as a risk factor, along with the failure to receive antibiotic therapy before hospital admission, a finding suggesting that a delay in therapy may convert milder forms of pneumonia into a more severe illness.[20] Genetic differences in the immune

response may predispose certain individuals to more severe forms of infection and adverse outcomes.[24] Also, use of inhaled corticosteroids is related to increased risk of developing serious pneumonia.[25]

PROGNOSTIC FACTORS

In recent years there has been a trend towards increased hospitalizations in patients with a diagnosis of CAP, especially in the elderly and those with comorbid diseases, who may also have higher mortality.[26,27] Various studies have pointed out a high inpatient mortality among CAP patients, ranging from 12.1% to 24.4%, but even higher in patients admitted to the ICU.[5–7] Investigators from the Community-Acquired Pneumonia Organization (CAPO) international cohort study reported mortality differences between patients hospitalized for CAP. A higher frequency of deaths occurred in Latin America (13.3%) compared with Europe (9.1%) and the United States (7.3%).[28] In a meta-analysis of 33,148 patients with CAP, the overall mortality rate (OR) was 13.7%, but in those admitted to the ICU, the mortality rate was 36.5% (Box 67.1).[7]

Metersky and colleagues evaluated factors predicting in-hospital versus postdischarge mortality in 21,223 Medicare patients, 65 years old or older, admitted with a diagnosis of pneumonia.[5] The authors noted a mortality rate of 12.1% within 30 days of admission (52.4% of the deaths occurred during the hospital stay), and the in-hospital rate of mortality was higher in patients requiring MV on admission, who had bacteremia, who had hypotension (systemic blood pressure <90 systolic), who had a respiratory rate >30 per minute, who had a pH <7.35, or who had renal failure. Of note, the timing of death (early versus late) was unrelated to baseline patient demographic factors or comorbidities, but in-hospital mortality related to the severity of illness.

In other studies, the clinical features that have predicted a poor outcome (Table 67.2) include advanced age (>65 years), preexisting chronic illness of any type, absence of fever on admission, respiratory rate exceeding 30 breaths/min, diastolic or systolic hypotension, elevated blood urea nitrogen (BUN >19.6 mg/dL), profound leukopenia or leukocytosis, inadequate antibiotic therapy, need for MV, hypoalbuminemia, and the presence of certain "high-risk" organisms (type III pneumococcus, *Staphylococcus aureus,* gram-negative bacilli, aspiration organisms, or postobstructive pneumonia).[1] One study of 3233 patients in Spain found that risk factors for all-cause mortality were a higher severity of illness on admission, need for ICU care, and the presence of multilobar infiltrates. However, late mortality rate (after at least 3 days)

TABLE 67.1 Risk Factors for Developing Severe Community-Acquired Pneumonia

Advanced age
Comorbid illness (e.g., chronic respiratory illness, cardiovascular disease, diabetes mellitus, neurologic illness, renal insufficiency, malignancy)
Cigarette smoking
Alcohol abuse
Absence of antibiotic therapy before hospitalization
Failure to contain infection to its initial site of entry
Immune suppression
Genetic polymorphisms in the immune response

BOX 67.1 Factors Related to Increased Mortality in Hospitalized CAP Patients[7]

1. Male sex (OR = 1.3)
2. Pleuritic chest pain (OR = 0.5)
3. Hypothermia (OR = 5.0)
4. Systolic hypotension (OR = 4.8)
5. Tachypnea (OR = 2.9)
6. Diabetes mellitus (OR = 1.3)
7. Neoplastic disease (OR = 2.8)
8. Neurologic disease (OR = 4.6)
9. Bacteremia (OR = 2.8)
10. Leukopenia (OR = 2.5)
11. Multilobar infiltrates (OR = 3.1)

OR, Odds ratio.

TABLE 67.2 Risk Factors for a Poor Outcome From Community-Acquired Pneumonia

Patient-Related Factors
Male sex
Absence of pleuritic chest pain
Nonclassic clinical presentation
Neoplastic illness
Neurologic illness
Age ≥65 years
Family history of severe pneumonia or death from sepsis
Abnormal Physical Findings
Respiratory rate ≥30 breaths/min on admission
Systolic (<90 mm Hg) or diastolic (≤60 mm Hg) hypotension
Tachycardia (>125 beats/min)
High fever (>40°C) or afebrile
Confusion
Laboratory Abnormalities
Blood urea nitrogen ≥19.6 mg/dL
Leukocytosis or leucopenia (<4000/mm^3)
Multilobar radiographic abnormalities
Rapidly progressive radiographic abnormalities during therapy
Bacteremia
Hyponatremia (<130 mmol/L)
Multiple organ failure
Respiratory failure
Hypoalbuminemia
Thrombocytopenia (<100,000/mm^3) or thrombocytosis (>400,000/mm^3)
Arterial pH <7.35
Pleural effusion
Pathogen-Related Factors
High-risk organisms: type III pneumococcus, *Staphylococcus aureus,* gram-negative bacilli (including *Pseudomonas aeruginosa*), aspiration organisms, severe acute respiratory syndrome (SARS)
Possibly high levels of penicillin resistance (minimal inhibitory concentration of at least 4 mg/L) in pneumococcus
Therapy-Related Factors
Delay in initial antibiotic therapy (more than 4 hours)
Initial therapy with inappropriate antibiotic therapy
Failure to have a clinical response to empiric therapy within 72 hours

was reduced if blood cultures were negative, antibiotic therapy was consistent with guidelines, and an etiologic agent was identified.[29]

In another prospective study of 1166 SCAP patients from 17 different countries, factors related to mortality at 28 days and at 6-month follow-up were higher Acute Physiology and Chronic Health Evaluation (APACHE) II scores, lower hematocrit, and need for MV. Lower pH on arterial blood gas analysis predicted early mortality.[6] Other studies have noted that an elevated red blood cell distribution width, either alone or in combination with elevated BUN ≥30 gm/dL, was related to increased 90-day mortality and a complicated hospital course in CAP patients, likely reflecting the inflammatory suppression of erythropoiesis in severe infection.[30,31] In general, severity of illness on admission most affected early mortality, whereas therapy-related, modifiable risk factors affected late mortality.

Prina and colleagues noted a biphasic relationship between platelet count and mortality in hospitalized CAP patients, with mortality rate increasing for values outside the range of 100,000 to 400,000/mm^3.[3,32] The authors noted more respiratory complications, such as empyema and pleural effusion, in patients with thrombocytosis (platelet count $\geq 4 \times 10^5$/mm^3) than in those without. On the other hand, those with thrombocytopenia (platelet count $\leq 10^5$/mm^3) had higher rates of severe sepsis, septic shock, invasive MV, and ICU admission than the remainder of the studied population. In another study, Laserna and associates observed a biphasic relationship when relating CAP mortality to arterial partial pressure of carbon dioxide ($PaCO_2$) on admission. Both hypocapnia ($PaCO_2$ <35 mm Hg) and hypercapnia ($PaCO_2$ >45 mm Hg) were risk factors for higher 30-day mortality and a greater need for ICU admission, compared with patients with a normal $PaCO_2$, even after excluding those patients with COPD.[33]

As with other acute severe infections, any delay in treatment or admission to the ICU in patients with SCAP can lead to higher rates of complications and increased risk of mortality.[13] Several studies have noted an increased mortality rate when CAP patients experience a delay in the initiation of appropriate antibiotic therapy, with most studies using an average of 6 hours elapsed since being first evaluated in the emergency room as the cutoff value.[1,10,20,34,35] Renaud and colleagues, in a study of 453 CAP patients, noted that the 28-day mortality rate was 11.7% for those who were directly admitted to the ICU with an obvious need for ICU care, a value significantly lower than the 23.4% mortality rate experienced among those initially without obvious need for ICU care whose admission to the ICU was delayed.[36] In their analysis, Hraiech and associates divided CAP patients into those requiring MV within 72 hours of the onset of CAP and those with progressive respiratory failure who required invasive MV 4 or more days after the onset of CAP.[37] There was a significant difference in mortality between the early respiratory failure group compared with late (28% vs. 51%, $P = .03$), suggesting that delay in identification of respiratory failure, delay of transfer to the ICU, or the development of progressive symptoms have deleterious effects on patient outcome.

Cardiac events, including acute myocardial infarction (AMI), are common in patients with SCAP. Ramirez and colleagues reported a 15% incidence in patients with severe CAP.[38] In another study including 55,276 patients, Carr and colleagues noted 8% of cardiac arrests occurred in pneumonia patients, and in this population, 62% of cardiac arrests occurred in patients admitted to the ICU. Approximately 50% were on vasopressors or required MV.[39] Cardiac arrests occurred earlier in the ICU than on the ward (at a median of 18.9 versus 28.4 hours) and were generally characterized by a "not shockable" rhythm (asystole or pulseless electrical activity). These findings suggest that patients with CAP in the hospital, or even the ICU, commonly have cardiac ischemia and that ischemic events may occur without warning. In another study, a restrictive red blood cell transfusion strategy (target hemoglobin level 7–9 g/dL in all patients except those with acute myocardial infarcts or unstable angina) was associated with better outcomes for CAP patients.[40]

Waterer and colleagues studied avoidable factors that contributed to CAP-specific short-term mortality from a large prospective study of acute respiratory infection with image confirmation across five hospitals in the United States.[41] The overall inpatient mortality was 2.2% (52/2320) but was higher among patients ≥65 years of age (4%, 33/832) and those with more than three severe comorbidities (Pneumonia Severity Index [PSI] risk classes IV and V). Investigators noted that only two patients who died had an identifiable lapse in quality of inpatient pneumonia care characterized by no administration of antibiotic within 1 hour in the presence of shock or the use of antibiotics not consistent with the IDSA/ATS 2007 CAP guidelines. These observations suggest that most CAP-related mortality is unavoidable and is determined by older age and comorbidities.

In a recent study evaluating the changes in pneumonia-related hospitalizations from 2001 to 2014, the average annual age-adjusted and pneumonia-associated hospitalization rate was 464.8 per 100,000 (95% confidence interval [CI] 452.5–467.1), with an inpatient mortality of 7.4%.[8] In this study, factors associated with increased mortality were male sex and having a colisting of immunocompromised state and lower income status.[8] There was a significant decrease in age-adjusted pneumonia-related hospitalizations over the study period, despite a significant increase in sepsis or respiratory failure. Age-adjusted hospitalizations were highest during the months of December to March; however, the inpatient mortality rate was highest in July (8.2%) and lowest in March, April, and May (7.1%).

When these findings are viewed together, they suggest some general principles. Mortality is more likely in CAP patients who have severe physiologic derangements, serious underlying illnesses, and delay in the initiation of appropriate antimicrobial therapy or MV and the presence of atypical clinical features. This last factor suggests that an unusual clinical presentation (low fever, nondistinct respiratory symptoms) is associated with mortality, which may be the result of its reflecting an inadequate inflammatory response to infection and because such a presentation can delay the recognition of pneumonia and the need to institute appropriate therapy.

PATHOGENESIS

Pneumonia results when host defenses are overwhelmed by an infectious pathogen. This may occur because the patient has an inadequate immune response, often as the result of underlying comorbid illness, anatomic abnormalities, acute illness-associated immune dysfunction, or therapy-induced dysfunction of the immune system. Pneumonia can also occur in patients who have an adequate immune system if the host defense system is overwhelmed by a large inoculum of microorganisms or if the patient encounters a particularly virulent organism to which he or she has no preexisting immunity or to which the patient has an inability to form an adequate acute immune response.[42,43]

Microaspiration of infected oropharyngeal secretions is the most common mechanism associated with pneumonia. Other routes of entry include inhalation (which applies primarily to viruses, *Legionella pneumophila, Mycobacterium tuberculosis*), hematogenous dissemination from extrapulmonary sites of infection (e.g., right-sided endocarditis), and direct extension from contiguous sites of infection (such as liver abscess). Thus previously healthy individuals develop infection with virulent pathogens such as viruses and *L. pneumophila, Mycoplasma pneumoniae, Chlamydia pneumoniae,* and *Streptococcus pneumoniae*. On the other hand, chronically ill patients can be infected by these organisms, and in addition by organisms that commonly colonize patients but only cause infection when immune responses are

inadequate. These organisms include enteric gram-negative bacteria (e.g., *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Acinetobacter* spp.) and fungi.

Studies evaluating the normal lung immune response to infection have shown that in most patients with unilateral CAP, the inflammatory response is limited to the site of infection.[43] In patients with localized pneumonia, tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6, and IL-8 levels were increased in the pneumonic lung and generally not increased in the uninvolved lung or in the serum.[44,45] On the other hand, in patients with severe pneumonia, the immune response is characterized by a "spillover" of the immune response into the systemic circulation, reflected by increases in serum levels of TNF-α and IL-6.[46] It remains uncertain why localization does not occur in all individuals and why some patients develop diffuse lung injury (e.g., acute respiratory distress syndrome [ARDS]) or systemic sepsis as a consequence of pneumonia. These complications may result from an inability to develop a brisk lung immune response as a consequence of specific bacterial virulence factors, inadequate or delayed therapy, or genetic polymorphisms that affect the immune response.[47] There is a growing body of evidence suggesting polymorphonuclear neutrophils (PMNs) not only have defensive properties through phagocytosis of invading microorganisms or releasing reactive oxygen species, antimicrobial peptides, and neutrophil extracellular traps, but also they can modify the adaptive immune system, causing both T-cell suppression and activation, thereby influencing lung injury.[48]

CLINICAL FEATURES

Symptoms and Physical Findings

Patients with CAP and an intact immune system have a normal pulmonary response to infection and generally have respiratory symptoms such as cough, sputum production, and dyspnea, along with fever and other complaints. Cough is the most common finding and is present in up to 80% of all patients, but is less common in those who are elderly, those with serious comorbidity, or patients coming from nursing homes.[49] Pleuritic chest pain is also common in patients with CAP, and in one study its absence was identified as a poor prognostic finding.[50] The elderly generally have fewer respiratory symptoms than younger individuals, and, as mentioned, the absence of clear-cut respiratory symptoms and an afebrile status have themselves been predictors of an increased risk of death.[1,51] In elderly patients, pneumonia can have a nonrespiratory presentation with symptoms of confusion, falling, failure to thrive, altered functional capacity, or deterioration in a preexisting medical illness, such as congestive heart failure.[49,52,53]

Physical findings of pneumonia include tachypnea, crackles, rhonchi, and signs of consolidation (egophony, bronchial breath sounds, dullness to percussion). Patients should also be evaluated for signs of pleural effusion. In addition, extrapulmonary findings should be sought to rule out metastatic infection (arthritis, endocarditis, meningitis) or to add to the suspicion of an "atypical" pathogen, such as *M. pneumoniae* or *C. pneumoniae,* which can lead to complications such as bullous myringitis, rash, pericarditis, hepatitis, hemolytic anemia, or meningoencephalitis. In the elderly, an elevation of respiratory rate can be the initial presenting sign of pneumonia, preceding other clinical findings by as much as 1–2 days.[54] In fact, in one study, tachypnea was the most common finding in elderly patients with pneumonia, being present in over 60% of all patients and occurring more often in the elderly than in younger patients with pneumonia.[49]

RADIOGRAPHIC FEATURES

For most patients, CAP is defined by a combination of clinical symptoms and the presence of a new radiographic infiltrate, but not all patients with this illness will have such findings when first evaluated. Even when the radiograph is negative, if the patient has appropriate symptoms and focal physical findings, pneumonia may still be present. Some studies have suggested that febrile and dehydrated patients can have a normal chest radiograph when first admitted with pneumonia. The presence of alveolar densities (lobar or bronchopneumonic) has been associated with a high likelihood of a bacterial etiology, but it is extremely difficult to distinguish among specific pathogens by using patterns of radiographic abnormalities.[55] The chest radiograph may have prognostic value in patients with severe pneumonia. Multilobar infiltrates or rapid progression of infiltrates serve as poor prognostic signs, helping to identify patients who require intensive care.[1,10]

Chest computed tomography (CT) generally has a higher sensitivity in diagnosing occult pneumonia, with an initially negative chest radiograph.[56] Chest CT can also have value in the critically ill patient in situations when a noninfectious process is being considered or when complications such as pneumothorax, empyema, or abscess are suspected. CT can suggest certain alternative noninfectious diagnoses such as granulomatous vasculitis, acute eosinophilic pneumonia, and bronchiolitis obliterans with organizing pneumonia. Upchurch and associates compared "CT-only" pneumonia with a negative chest x-ray in hospitalized CAP patients (present in 3% of patients) with pneumonia diagnosed via chest x-ray (in 97% of patients) and noted similar pathogens (bacterial 12% and 13.6% and viruses 30.3% and 26.1%, respectively), and clinical outcomes, including disease severity, death, need for ICU admission, vasopressor use, and invasive MV.[57] A lower percentage of patients with "CT-only" pneumonia had received antibiotics within 6 hours, compared with those with overt pneumonia on chest x-ray (59% vs. 83%, $P < .01$). Thus in the right clinical setting, pneumonia may need to be treated even with a negative chest radiograph.

Although a variety of radiographic patterns can be seen in pneumonia, specific findings cannot generally be used to predict the microbial etiology in CAP; however, there are certain patterns to keep in mind. Focal consolidation can be seen with infections caused by pneumococcus, *Klebsiella* species, aspiration (especially if in the lower lobes or other dependent segments), *S. aureus, Haemophilus influenzae, M. pneumoniae,* and *C. pneumoniae*. Interstitial infiltrates should suggest viral pneumonia in addition to infection resulting from *M. pneumoniae, C. pneumoniae, Chlamydia psittaci,* and *Pneumocystis jirovecii*. Lymphadenopathy with an interstitial pattern should raise concerns about anthrax, *Francisella tularensis*, and *C. psittaci,* whereas adenopathy can be seen with focal infiltrates in tuberculosis, fungal pneumonia, anthrax, and bacterial pneumonia. Cavitation can be the result of an aspiration lung abscess, infection with *S. aureus* or aerobic gram-negatives (including *P. aeruginosa*), tuberculosis, fungal infection (*Aspergillus*), nocardiosis, and actinomycosis.

Lung ultrasound (LUS) has increasingly been adopted for diagnosing pleural and pulmonary diseases. Various patterns with B- and M-mode ultrasound techniques, including "tissue sign," "shred or fractal sign," and " dynamic air bronchograms," are seen with pulmonary consolidation, whereas the "sinusoidal sign" and "quad sign" are seen with even small pleural effusions.[58] In a prospective, multicenter study including 362 patients with suspected CAP, LUS had a sensitivity of 93.4% and specificity of 97.7% compared with chest x-ray and chest CT.[59] In that study, the combination of LUS and auscultation decreased the negative likelihood ratio to 0.04 (95% CI 0.02–0.09), but the technique is operator dependent, and about 8% of pneumonic lesions are not visualized by LUS. The noninvasive nature of the test and the rapidity with which it can be performed make this another tool in the armamentarium for critical care physicians. A meta-analysis of 10 studies with 1172 patients supports the use of LUS by skilled

practitioners.[60] A recent meta-analysis including 5108 emergency department patients showed a sensitivity of 92% and specificity of 93% for the diagnosis of CAP using LUS.[61] Another cluster-randomized study using the biomarker PCT and LUS as a combination for decision on antibiotic prescription in patients with CAP is underway and could provide more insight into LUS use in the primary care setting.[62]

SEVERITY SCORING IN CAP

Although there is no uniformly accepted definition for SCAP, this term generally refers to any patient who is admitted to the ICU because of CAP. Most of these patients have severe sepsis or "respiratory failure," defined by the presence of hypoxemia or hypercarbia, but not all such patients require MV. Some patients with CAP are treated in the ICU because the pneumonia has led to clinical instability of an underlying disease, but the pneumonia itself may not be severe. Bacteremia does not always correlate with more severe illness, and its presence alone is not always a predictor of a poor outcome, with most episodes of bacteremia being the result of pneumococcus. However, in the elderly with pneumococcal pneumonia, bacteremia is present in one-fourth of patients with CAP and is often associated with azotemia and multilobe involvement.[63] When an infection, such as pneumonia, is complicated by severe sepsis or septic shock (not just bacteremia), outcome is adversely affected, with increases in mortality, LOS, and costs for survivors.

One approach to evaluating CAP patients is to use a scoring system to define prognosis and predict the risk of death. The most widely used prognostic scoring systems are the PSI and a modification of the British Thoracic Society (BTS) scoring system, the CURB-65 score. Other prediction rules, such as the ATS/IDSA criteria for severe CAP, the Australian SMART-COP, the Japanese A-DROP scoring system, CAPPIRO, and the Spanish CURXO-80, have also been developed for risk prognostication and help with appropriate resource utilization.[1,64–66]

The investigators in the Pneumonia Outcomes Research Team (PORT) study have developed a mortality prediction rule that classifies all patients into one of five groups (PSI classes I to V), each with a different risk for death.[67] Patients in classes IV and V have a predicted mortality risk of 8.2%–9.3% and 27%–31.1%, respectively, whereas those in classes I and II have a mortality risk of 0.1%–0.4% and 0.6%–0.7%, respectively. To use this scoring system, patients have points calculated based on such factors as age, sex, the presence of comorbid medical disease, certain physical findings, and laboratory data.[67] Although the PORT scoring system has been shown to be accurate for predicting mortality and prognosis, it does not directly measure severity of illness, and there is poor correlation between mortality risk and the need for ICU admission.[68,69] In general, the PSI V patients who need the ICU tend to get more of their points from acute illness, whereas those not needing the ICU tend to score points because of chronic disease factors. In addition, in young patients without comorbid illness, the pneumonia must be particularly severe to place the patient in a high-mortality risk group, and certain vital sign thresholds must be exceeded to accumulate points toward a poor prognosis.

For the critical care physician, underestimating the severity of illness is a serious concern, and the use of the CURB-65 approach, modified from the BTS rule, is a simple and accurate way to address this issue. CURB-65, an acronym for the clinical features used to assess pneumonia severity and prognosis, assigns 1 point, on a 5-point scale, to confusion, BUN greater than 19 mg/dL, respiratory rate greater than or equal to 30 breaths/min, blood pressure of $<$90 mm Hg systolic or $\leq$60 mm Hg diastolic, and age greater than or equal to 65 years. In one study, when the score was 0–1, the mortality rate was 0%, whereas mortality was more than 20% for a score of 3 or higher, and those with a score of 2 had a mortality risk of 8.3%.[70] The use of the CURB-65 rules may be a problem in the elderly, reflecting the altered clinical presentations of pneumonia in this population. Interestingly, although the rule was not optimal in an elderly population and did not work as well as it did in other populations, it had a higher sensitivity for predicting mortality than the PSI, derived from the PORT study. Some studies have compared the PSI with CURB-65 and found them to be similar for identifying low-risk populations, but the CURB-65 may be more discriminating for identifying poor prognosis in those with severe illness, compared with the PSI.[71] An amended version of the CURB-65 without the use of laboratory measurement of BUN—CRB-65—has also been found to be similarly accurate.[72] Chalmers and colleagues in a meta-analysis including 40 studies reported CURB-65 and CRB-65 to be superior to PSI in identifying high-risk patients, whereas PSI was superior in identifying low-risk patients.[73] An expanded version of CURB-65 that includes the three additional variables: platelet count $<100 \times 10^9$/L, lactate dehydrogenase (LDH) levels $>$230 u/L, and albumin $<$3.5 g/dL, was recently shown to have improved accuracy in identifying higher mortality risk among hospitalized CAP patients.[74]

The A-DROP scoring system uses a 6-point scale that stratifies the severity of CAP, and it includes age (male 70 years, female 75 years); dehydration (BUN $\geq$21 mg/dL); respiratory failure (SaO_2 $<$90% or PaO_2 $<$60 mm Hg); orientation disturbance (confusion); and low blood pressure (systolic blood pressure $<$90 mm Hg).[75] Basically it is a modification of CURB-65 with the inclusion of hypoxemia as a variable in place of respiratory rate and with different gender-based thresholds for age in risk assessment. The sensitivity, specificity, and 30-day mortality predictive value of the A-DROP scoring tool is similar to CURB-65.[64] The CORB scoring system is a simple predictive tool that does not require invasive testing and removes bias regarding patient age.[76] The CORB tool does not use variables of age and BUN levels but does add oxygen saturation as a variable in the risk calculation. In both the derivation and validation cohorts, risks of mortality and/or requirement for ventilatory or inotropic support were systolic blood pressure $<$90 mm Hg (OR 3.49); acute confusion (OR 5.48); SaO_2 $\leq$90% (OR 3.49); and respiratory rate $\geq$30/min (OR 2.65). Dwyer and colleagues developed the "DS-CRB 65" criteria to improve the sensitivity and negative predictive value of CRB-65 by adding 1 point (D criterion) for the presence of any underlying disease according to the PSI rule and 1 point if SaO_2 was $<$90% (S criterion).[77]

The 2019 ATS/IDSA CAP guidelines endorse using a validated clinical prediction rule plus clinical judgment in decision making regarding outpatient vs. inpatient care in immunocompetent CAP patients.[4] The guideline supports PSI over CURB-65 based on the PSI's ability to identify a large proportion of patients at lower risk and increased precision for mortality decision making (strong recommendation with moderate-quality evidence).[4] In the new Sepsis-3 guidelines, the qSOFA score has been proposed to predict sepsis outcome. This score is similar to CURB but with the criteria being altered mental status, respiratory rate $>$22/min, and systolic blood pressure $<$100 mm Hg. In one study of 152 ICU patients, the qSOFA score was a good mortality predictor—in fact better than traditional systemic inflammatory response syndrome (SIRS) criteria.[78] In another study of 6574 CAP patients, the qSOFA score did not perform as well as CURB-65 to identify mortality risk.[79]

Other prognostic scoring systems have been developed to define the presence of severe pneumonia. Espana and associates estimated the need for ICU admission by the presence of one of two major criteria: arterial pH $<$7.30 or systolic blood pressure $<$90 mm Hg.[66] In the absence of these criteria, SCAP can also be identified by the presence of two of six minor criteria, which are confusion, BUN $>$30 mg/dL, respiratory rate $>$30/min, PaO_2/FiO_2 ratio $<$250, multilobar infiltrates, and

age of at least 80 years. When these criteria were met, the tool was 92% sensitive for identifying those with SCAP and was more accurate than the PSI or CURB-65 criteria, although not quite as specific as the CURB-65 rule.[66] Using this approach, some criteria (acidosis and systolic hypotension) are weighted more heavily than others, which contrasts with some of the other approaches to define SCAP.

A different method than assessing risk for death is to use scoring systems to define the need for ICU interventions, such as intensive respiratory and vasopressor support (IRVS). The SMART-COP tool was developed to predict the need for IRVS.[65] Using a multivariate model, eight clinical features were associated with the need for IRVS: systolic blood pressure <90 mm Hg, multilobar infiltrates, albumin <3.5 g/dL, respiratory rate elevation (>25 for those less than age 50, and >30 for those greater than age 50), tachycardia (>125/min), confusion, low oxygen (<70 mm Hg if less than age 50 or <60 mm Hg if greater than age 50), and arterial pH <7.35. The abnormalities in systolic blood pressure, oxygenation, and arterial pH each received 2 points, and the five other criteria received 1 point each, and, with this system, the need for IRVS was predicted by a SMART-COP score of at least 3 points. Using this cutoff, the sensitivity for need for IRVS was 92.3% and the specificity 62.3%, with a positive and negative predictive value of 22% and 98.6%, respectively. The PSI and CURB-65 did not perform as well overall for predicting the need for IRVS.

The 2007 IDSA/ATS guidelines for CAP suggested that ICU care be considered if the patient has one of two major criteria (need for MV or septic shock with the need for vasopressors), or three of nine minor criteria.[1] The minor criteria are respiratory rate ≥30 breaths/min, PaO_2/FiO_2 ratio ≤250, multilobar infiltrates, confusion/disorientation, uremia (BUN level ≥20 mg/dL), leukopenia (white blood cell [WBC] count <4000 cells/mm^3), thrombocytopenia (platelet count <100,000 cells/mm^3), hypothermia (core temperature <36°C), and hypotension requiring aggressive fluid resuscitation. Other factors to consider in the decision-making process are hypoglycemia (in a nondiabetic patient), hyponatremia, acute alcohol intoxication, cirrhosis, asplenia, and unexplained metabolic acidosis. The use of these minor criteria alone requires validation, with one study showing that patients who met only minor criteria for ICU admission did not have an increase in mortality, whereas in another study, use of four minor criteria instead of three improved the accuracy in defining the need for ICU admission.[80,81] Phua and colleagues showed that the ATS minor criteria had greater discriminatory power in the prediction of severity, ICU admission, and mortality than the PSI and CURB.[82] Brown and associates noted that both the positive and negative predictive value of minor criteria exceeded 80% if four criteria were used to define the need for ICU admission rather than just three criteria.[81] In another study, investigators simplified the ATS/IDSA criteria by excluding variables that occurred in <5% of cases—leukopenia, thrombocytopenia, and hypothermia—and noted similar predictive value for mortality and intensive care admission as compared with the original ATS/IDSA criteria.[83] In the same study, addition of another variable—acidosis (pH <7.35)—improved the prediction for mortality and for ICU admission.

Rello and associates evaluated the CAP-PIRO score calculated within 24 hours of ICU admission.[84] In this study, 1 point was assigned for each variable: comorbidities (COPD, immunocompromise), age greater than 70 years, multilobar opacities on chest radiograph, shock, severe hypoxemia, acute renal failure, bacteremia, and ARDS. Patients were stratified into four levels of risk: (a) low, 0–2 points; (b) mild, 3 points; (c) high, 4 points; and (d) very high, 5–8 points. The PIRO score performed well as a 28-day mortality prediction tool in patients with CAP requiring ICU admission, with a better performance than APACHE II and the IDSA/ATS criteria. CAP-PIRO can further stratify patients in PSI class V and differentiate patients requiring more intense care.

The Risk of Early Admission to ICU (REA-ICU) index was derived from a data set of nearly 5000 patients and is helpful as a tool on admission to identify patients who had no obvious indication for ICU management but subsequently required ICU care. It categorizes individuals into four risk groups based on 11 criteria independently associated with ICU admission: male gender, age younger than 80 years, comorbid conditions, respiratory rate of 30 breaths/min or higher, heart rate of 125 beats/min or higher, multilobar infiltrate or pleural effusion, WBC less than 3 or 20,000/L or above, hypoxemia (oxygen saturation <90% or PaO_2 <60 mm Hg), BUN of 11 mmol/L or higher, pH <7.35, and serum sodium concentration <130 mEq/L.[85] The mortality and likelihood of needing ICU care increased with each risk group, with the highest in class IV with a score ≥9. In a study including 850 CAP patients who had no obvious need for ICU care on admission, the REA-ICU index performed better than PSI but was similar to other tools (like SMART-COP, CURXO-80, the 2007 IDSA/ATS minor severity criteria, and CURB-65) at defining the need for early ICU admission.[86] The need for sensitive criteria to define severe illness in CAP patients is important because the benefit seems most certain if patients are admitted to the ICU early in the course of severe illness. The 2019 ATS/IDSA guidelines recommend direct admission to ICU for those who require IRVS, and for those who do not require it, using the 2007 ATS/IDSA minor criteria plus clinical judgment in making a decision on ICU care.[4]

ROLE OF BIOMARKERS IN SEVERE CAP

Measurement of serum levels of biomarkers such as C-reactive protein (CRP), midregional proadrenomedullin, midregional pro-atrial natriuretic peptide (MR-proANP), proarginine-vasopressin (copeptin), proendothelin-1, or PCT may be valuable in guiding management of antibiotics for CAP. PCT is an acute-phase reactant synthesized in the liver in response to bacterial, but not viral, infection. Studies in CAP have documented that serial measurement of levels of PCT can guide the duration of antibiotic therapy, allowing cessation of therapy once levels fall and leading to a marked reduction in the duration of therapy, compared with unaided clinical judgment.[87,88] In patients with SCAP, measurement of initial and serial levels can help to define those with a poor prognosis, and a low PCT value may distinguish which patients in PSI classes IV and V might be safely managed outside the ICU.[89] Kruger and colleagues reported nonsurvivors had significantly higher median PCT levels on admission than survivors (0.88 vs. 0.13 ng/mL; $P = .0001$).[90] Low PCT accurately predicted patients at very low risk of death, even in patients falling in a high prognostic scoring category by the CURB-65 evaluation. Given its high negative predictive potential (98.9% with PCT level of <0.228 ng/mL), patients with low initial PCT might be safely treated outside the ICU.[90] Huang and colleagues found that 23.1% (126/546) of high-risk patients defined by PSI had low PCT levels on the first hospital day, and this subgroup had very low mortality, similar to low-risk patients.[91]

Ramirez and associates, in a prospective study of 685 CAP patients, evaluated the relationship between biomarkers and ICU admission.[92] Inflammatory biomarkers helped identify patients needing intensive care monitoring, including those requiring delayed ICU admission. No patient with ≥3 ATS minor severity criteria and PCT levels below the cutoff (0.35 ng/mL) needed ICU admission compared with 14 (23%) with levels above the cutoff ($P = .032$).[92] In another study, the authors compared the levels of three biomarkers—N-terminal pro-B-type natriuretic peptide (NT-proBNP), MR-proANP, and B-type natriuretic peptide (BNP)—with the PSI and CURB-65 score for predicting short- and long-term mortality.[93] The levels of NT-proBNP, MR-proANP, and BNP increased with the severity of pneumonia, and patients who died

had a higher level of all three biomarkers. A combined assessment using categorical PSI score and NT-proBNP levels seemed beneficial over a single-marker approach for short- and long-term risk stratification. In a recent meta-analysis of seven studies including 1075 patients using a PCT-based regimen in patients with severe sepsis or septic shock, the 28-day mortality was not different between the PCT-based regimen and standard treatment groups, but the PCT-guided group had a shorter duration of antimicrobial therapy.[94] Using a PCT-based strategy led to more de-escalation and a shorter duration of antibiotic therapy, with no adverse impact on mortality.

In the EPIC study of CAP, 1770 patients had PCT measured on admission, and the results were combined with the ATS minor severity criteria to best identify patients needing ICU care.[95] Patients with three or more ATS minor severity criteria plus a PCT level ≥0.83 ng/mL were admitted to the ICU 41.1% of the time, whereas those in this group with a PCT <0.83 ng/mL needed the ICU only 14.6% of the time. In those with fewer than three minor criteria and a low PCT level, the ICU was used by only 3.5%.

In another study, Mendez and associates studied the time-related changes on systemic concentrations of inflammatory cytokines and biomarkers since onset of self-reported symptoms in two different prospective, longitudinal CAP cohorts (derivation $n = 541$ and validation $n = 398$).[96] Because bacterial growth is exponential within the first 48 hours, investigators divided the patient population as early presenters (<3 days) vs. not. They noted CRP levels were higher ≥3 days (18 vs. 13.2, $P = .005$ in derivation and 18.8 vs. 13.6, $P = .006$ in validation) in both groups, whereas the PCT levels were higher in early presenters (,5 vs. 0.3, $P = .023$ and 0.9 vs. 0.4, $P = .028$). This finding was not affected by prior antibiotic use. Taken together, the inflammatory responses of cytokines and biomarkers appear to depend on time since onset of symptoms. There is a risk of underestimating the inflammatory profile based on the cytokine tested for CAP clinical trials if the time since onset of symptoms is not taken into account.

Using biomarkers to adjudicate severity is best done in conjunction with clinical, microbiologic, and pathologic data. A combined approach that includes severity scores and biomarkers can aid clinicians in assessing severity of illness and the need for using antibiotics, and serial measurements can be used to assess treatment response. However, PCT or other biomarkers are not specific for pneumonia itself and can be elevated in other infectious or inflammatory conditions. Levels should be interpreted with particular caution in patients with cardiac and renal failure. Based on the reported sensitivity of PCT to detect bacterial infection that ranges from 38% to 91%, the ATS/IDSA 2019 guidelines do not recommend withholding empiric antibiotics, regardless of the initial PCT levels in suspected CAP patients.[4] In ICU patients, the decision to start antibiotics should never be guided by biomarkers, but biomarkers can be used along with other data to decide to stop or shorten the duration of antibiotic therapy. In a randomized Dutch study of over 1500 ICU patients, PCT guidance for antibiotic therapy duration was compared with standard care, and it led to reductions in antibiotic use, antibiotic duration, and 28-day mortality.[97]

ETIOLOGIC PATHOGENS

Even with extensive diagnostic testing, an etiologic agent is defined in only about half of all patients with CAP, pointing out the limited value of diagnostic testing and the possibility that we do not yet know all the organisms that may cause CAP.[1,98] In the past 4 decades, a variety of new pathogens for this illness have been identified, including *L. pneumophila, C. pneumoniae,* Middle East respiratory syndrome coronavirus (MERS-CoV), avian-origin influenza A – H7N9, novel H1N1, H3N2 influenza, hantavirus, and severe acute respiratory syndrome coronavirus (SARS-CoV-2). In addition, antibiotic-resistant variants of common pathogens, such as *S. pneumoniae,* have become increasingly common. However, recent data indicate that ICU mortality decreased for pneumococcal CAP between 2000 and 2013, probably as a reflection of appropriate identification of SCAP, early antibiotic prescription, and increased use of combination therapy.[99]

The likely pathogens for infection vary, depending on patient risk factors for specific microorganisms and the presence of certain comorbid illnesses, but for all patient groups, including those with SCAP, pneumococcus remains the most common pathogen.[1,100] Recent studies, however, have shown an increasing frequency of viral CAP, including among those admitted to the ICU. The incidence of antibiotic-resistant pneumococci has increased in recent years, and up to 40% of these organisms can have reduced sensitivity to penicillin or other antibiotics, although the clinical relevance of in vitro resistance is still uncertain.[1,101,102] Although *S. pneumoniae* is the most common bacterial organism causing CAP, the frequency of pneumococcal pneumonia has declined, probably because of effective vaccination practices and a decreased incidence of smoking in adults.[103] Identified risk factors for drug-resistant *S. pneumoniae* (DRSP) include beta-lactam therapy received in the past 3 months, alcoholism, age older than 65 years, immune suppression, multiple medical comorbidities, and contact with a child in daycare.[1,104,105] Other common infecting organisms in those with SCAP include viruses (e.g., influenza, respiratory syncytial virus [RSV], and various coronavirus illnesses), *L. pneumophila, M. pneumoniae, M. tuberculosis,* and *H. influenzae* (especially in smokers). In the setting of severe pneumonia, patients can be infected with *S. aureus* (including methicillin-resistant forms, or MRSA) or enteric gram-negatives and, rarely, anaerobes. In the elderly, including those with aspiration pneumonia and in those with underlying cardiopulmonary disease, enteric gram-negative organisms are frequently encountered.

Although aspiration has often been considered a risk factor for anaerobic infection, studies of SCAP in elderly patients with aspiration risk factors suggested that this population is very likely to have aerobic gram-negative infection.[106,107] Risk factors for gram-negative organisms causing CAP are probable aspiration, previous hospital admission within 30 days of admission, previous antibiotics within 30 days of admission, presence of pulmonary comorbidity, smoking, and hyponatremia.[108,109] In a study of 3272 episodes of CAP, Falguera and associates found that 2% were caused by enteric gram-negatives (most commonly *P. aeruginosa*) and the risk factors for these organisms were COPD, current use of corticosteroids, prior antibiotic therapy, tachypnea >30 breaths/min, and septic shock on admission.[110] Patients with these organisms needed ICU care more often and had a higher risk for mortality and extended LOS than those without these pathogens present. Changes in the airway microbiome with different illnesses may result in a change in the lung microbiota and could potentially impair pulmonary defenses. A macro aspiration event in those with reduced reflexes or impaired mentation could then overwhelm the homeostasis created by an altered microbiome, resulting in pneumonia.[111]

Primary pulmonary infection with atypical pathogens has been reported for patients with SCAP for many years. In fact, in one ICU in Spain, atypical pathogens were present in almost 25% of all patients, but the organisms responsible varied over time. *Legionella* was the most common atypical pathogen leading to SCAP in 14% of patients during one period, but in the same hospital a decade later, it was seen in only 2%, having been replaced by *Mycoplasma* and *Chlamydophila* infection. The latter were found in 17% of patients, compared with only 6% a decade earlier.[20] Several studies have shown that even if bacterial pathogens lead to CAP, they can be accompanied by atypical pathogens in the form of mixed infection.[112,113] Atypical pathogens can include *C. pneumoniae, M. pneumoniae,* and *L. pneumophila,* and some studies have

shown that these infections are common in patients of all ages, not just young and healthy individuals. These organisms have even been reported among the elderly in nursing homes.[1,112,114] When mixed infection is present, it may lead to a more complex course and a longer LOS than if a single pathogen were present, which may explain the increasing number of studies that show a reduction in CAP mortality, including those in the ICU, when initial therapy provides coverage for these organisms, compared with regimens that do not.[115,116] Mixed infections with bacteria and viruses may also increase mortality, and in one study of 117 SCAP patients, 15.4% had mixed viral and bacterial infection.[117] This group had a 14-fold higher mortality in multivariate analysis, compared with culture-negative patients, emphasizing that even with documented viral infection, empiric antibiotics are necessary in severely ill patients to address possible bacterial coinfection. Interestingly, multiple retrospective studies of pneumococcal bacteremia have shown a reduced mortality when dual therapy (usually involving a macrolide) rather than monotherapy is used, raising the possibility that even these patients have mixed infection with atypical pathogens.[118,119] The frequency of atypical pathogens can be as high as 60%, with as many as 40% of all CAP patients having mixed infection.[113] These high incidence numbers have been derived using serologic testing, which is of uncertain accuracy. Atypical organism pneumonia may not be a constant phenomenon, and the frequency of infection may vary over the course of time and with geographic location.

In the past, *S. aureus* was an uncommon but often life-threatening cause of CAP. In the past several years, a community-acquired strain of MRSA (CA-MRSA) has emerged as a cause of SCAP, particularly in patients without a history of previous hospitalization or chronic illness, often as a complication of influenza infection.[1,120,121] The organism can lead to a severe, bilateral, necrotizing pneumonia, often related to toxin production by the organism. This organism is distinct from the nosocomial strain of MRSA and is clonal in origin, usually due to the USA 300 strain. In a study including 3702 patients from the Global Initiative for MRSA Pneumonia (GLIMP) database collected from 54 countries worldwide, Aliberti and colleagues noted the prevalence of confirmed MRSA pneumonia was ~3.0%, varying among different countries.[122] The three risk factors associated with MRSA pneumonia were previous MRSA infection or colonization (OR = 6.21), recurrent skin infections (OR = 2.87), and severe pneumonia (OR = 2.39). The investigators also assessed the risk factors and characteristics of immunocompromised patients admitted with CAP from the GLIMP database.[123] *S. pneumoniae* was the most prevalent pathogen causing CAP, but immunocompromised patients had more frequent *P. aeruginosa,* RSV, pneumocystis, *Aspergillus fumigatus,* and *Nocardia* species compared with immunocompetent patients. Interestingly, multidrug-resistant (MDR) pathogens were similarly isolated from both groups and the rates of bacteremia between the groups were not different. Pathogens not covered by usual CAP therapy were more common in those with COPD and in patients with tracheostomy or severe pneumonia. Fungal infections were associated with AIDS and hematologic cancers, whereas viruses other than influenza were associated with hematologic cancer and severe pneumonia. Nontuberculous mycobacteria were associated with AIDS and malnutrition, and *M. tuberculosis* with malnutrition. As one in five hospitalized patients have an immunocompromised status, it would be prudent to assess both at the time of admission, and treatment should be tailored to avoid treatment failure.

RISK FACTORS FOR SPECIFIC PATHOGENS

Table 67.3 summarizes the common pathogens causing CAP in hospitalized patients, including those admitted to the ICU. The classification is based on the presence of clinical risk factors for specific pathogens, referred to as "modifying factors." In predicting the likely etiologic pathogens for those admitted to the ICU, patients are divided into a population at risk for pseudomonal infection and a population without this organism being likely. The risk factors for *P. aeruginosa* infection are structural lung disease, corticosteroid therapy (>10 mg prednisone/day), broad-spectrum antibiotic therapy for more than 7 days in the past month, and malnutrition.[1] From the GLIMP database, Restrepo and associates found the prevalence of *P. aeruginosa* and antibiotic-resistant *P. aeruginosa* CAP was 4.2% and 2.0%, respectively.[124] The risk factors associated with *P. aeruginosa* CAP were prior infection or colonization because of *P. aeruginosa* and one of the three chronic lung conditions: tracheostomy, bronchiectasis, and/or very severe COPD. In another study, Aliberti and colleagues showed patients with at least one risk factor for MDR pathogens had more severe pneumonia on admission and a higher prevalence of severe sepsis compared with those without (45% vs. 29%, P <.001; 31% vs. 21%, P = .001). Of all risk factors, hospitalization in the preceding 90 days (OR 4.87) and residence in a nursing home (OR 3.55) were the best independent predictors of infection with a resistant pathogen and mortality.[125] Table 67.4 shows that certain clinical conditions are associated with specific pathogens, and these associations should be considered in all patients when obtaining an intake history.[1]

TABLE 67.3 Common Pathogens Causing Community-Acquired Pneumonia

Inpatient, with no Cardiopulmonary Disease or Modifying Factors
Streptococcus pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae, Chlamydophila pneumoniae, mixed infection (bacteria plus atypical pathogen), viruses (including influenza), *Legionella* species, and others (*Mycobacterium tuberculosis,* endemic fungi, *Pneumocystis jirovecii*)
Inpatient, with Cardiopulmonary Disease and/or Modifying Factors
All of the ones listed earlier, but drug-resistant *S. pneumoniae* (DRSP) and enteric gram-negative organisms are more of a concern
Severe Community-Acquired Pneumonia, with no Risks for *Pseudomonas aeruginosa*
S. pneumoniae (including DRSP), *Legionella* species, *Haemophilus influenzae,* enteric gram-negative bacilli, *Staphylococcus aureus* (including MRSA), *M. pneumoniae,* respiratory viruses (including influenza), others (*C. pneumoniae, M. tuberculosis*, endemic fungi)
Severe CAP, with Risks for *P. aeruginosa*
All of the pathogens noted earlier plus *P. aeruginosa.*

CAP, Community-acquired pneumonia; *MRSA*, methicillin-resistant *Staphylococcus aureus*.

FEATURES OF SPECIFIC PATHOGENS

Streptococcus pneumoniae

The most common bacterial pathogen for CAP, this organism is a gram-positive, lancet-shaped diplococcus, of which there are 84 different serotypes, each with a distinct antigenic polysaccharide capsule. Eighty-five percent of all pneumococcal infections are caused by the 23 serotypes included in a polysaccharide vaccine. Infection is most common in the winter and early spring, which may relate to the finding that up to 70% of patients have a preceding viral illness. The organism spreads from person to person and commonly colonizes the oropharynx before it

TABLE 67.4 Clinical Associations With Specific Pathogens

Condition	Commonly Encountered Pathogens
Alcoholism	*Streptococcus pneumoniae* (including penicillin-resistant), anaerobes, gram-negative bacilli (possibly *Klebsiella pneumoniae*), tuberculosis
Chronic obstructive pulmonary disease/current or former smoker	*S. pneumoniae, Haemophilus influenzae, Moraxella catarrhalis*
Residence in nursing home	*S. pneumoniae*, gram-negative bacilli, *H. influenzae, Staphylococcus aureus, Chlamydia pneumoniae;* consider *Mycobacterium tuberculosis.* Consider anaerobes, but less common
Poor dental hygiene	Anaerobes
Bat exposure	*Histoplasma capsulatum*
Bird exposure	*Chlamydia psittaci, Cryptococcus neoformans, H. capsulatum*
Rabbit exposure	*Francisella tularensis*
Travel to southwestern USA	*Coccidioidomycosis;* hantavirus in selected areas
Exposure to farm animals or parturient cats	*Coxiella burnetii* (Q fever)
Postinfluenza pneumonia	*S. pneumoniae, S. aureus* (including CA-MRSA), *H. influenzae*
Structural disease of lung (e.g., bronchiectasis, cystic fibrosis)	*P. aeruginosa, P. cepacia,* or *Staphylococcus aureus*
Sickle cell disease, asplenia	Pneumococcus, *H. influenzae*
Suspected bioterrorism	Anthrax, tularemia, plague
Travel to Asia	Severe acute respiratory syndrome (SARS), tuberculosis, melioidosis

CA-MRSA, Community-acquired methicillin-resistant *Staphylococcus aureus*.

leads to pneumonia. Pneumonia develops when colonizing organisms are aspirated into a lung that is unable to contain the aspirated inoculum. Bacteremia is present in up to 20% of hospitalized patients, and extrapulmonary complications include meningitis, empyema, arthritis, endocarditis, and brain abscess. The burden of pneumococcal disease is often underestimated, because most studies report the incidence of bacteremic or invasive pneumococcal disease (IPD). In a systematic review and meta-analysis, Said and colleagues estimated the proportion of CAP attributable to pneumococcus at 27.3%, and using urine antigen testing helped diagnose an additional 11.4% of pneumococcal CAP beyond conventional techniques.[126] In that study, 24.8% of all cases were bacteremic. Bloodstream invasion was more common among those with severe illness, no prior antibiotics, and a positive HIV status. As mentioned elsewhere, in recent years there has been a trend towards improved survival of severe pneumococcal CAP in the ICU, perhaps owing in part to improved antibiotic prescription practices and a decrease in smoking.[99]

Since the mid 1990s, antibiotic resistance among pneumococci has become increasingly common, and penicillin resistance, along with resistance to other common antibiotics (macrolides, trimethoprim/sulfamethoxazole, selected cephalosporins), is present in over 40% of these organisms.[1,101,102,104,105] Fortunately, most penicillin resistance is of the "intermediate" type (penicillin minimal inhibitory concentration [MIC] of 0.1–1.0 mg/L) and not of the high-level type (penicillin MIC >2.0 mg/L). Although the clinical impact of in vitro resistance is uncertain, one large database indicated that only organisms with a penicillin MIC of more than 4 mg/L led to an increased risk of death.[101] The definitions of resistance have been changed for nonmeningeal infection, with sensitive being defined by a penicillin MIC ≤2 mg/L, intermediate as an MIC of 4 mg/L, and resistant as an MIC ≥8 mg/L.[127] The clinical impact of resistance on outcomes such as mortality has been difficult to show using older definitions. Nonetheless, although very few pathogens will be defined as resistant using the newer criteria, those that are so classified would logically seem likely to adversely affect outcome. Yet in a study including 118 patients that used the new definition for resistance, there was no apparent difference in 30-day mortality between penicillin-susceptible and -resistant groups.[128] The penicillin-resistant group had a higher frequency of having received antibiotics within the last 2 weeks, but, interestingly, it was the susceptible group who had a higher frequency of worse initial presentation, such as ICU admission and bacteremia. In this cohort both groups received equally broad-spectrum antibiotic regimens, such as extended-spectrum cephalosporins, vancomycin, and a carbapenem.

The relationship of prior antibiotic use to subsequent pneumococcal resistance is well-known, and prior therapy with macrolides, beta-lactams, and quinolones has been identified as a predisposing factor for subsequent resistance to the same class of antibiotic.[104,129–131] The risk appears no lower for therapy received in the preceding 6 months compared with therapy in the past 1 month.[131] Other studies have shown that quinolone therapy can predispose to subsequent pneumococcal resistance to this class of antibiotics.[129,130] Seok and colleagues report risk factors for levofloxacin-resistant pneumococcal pneumonia to be recent hospitalization, bronchopulmonary disease, cerebrovascular disease, and prior antibiotic use within 3 months.[132] In another study of patients with pneumococcal bacteremia, resistance to beta-lactams (penicillins and cephalosporins), macrolides, and quinolones was more likely if the patient had received the same agent in the preceding 3 months.[129] Although some studies have indicated that discordant therapy of drug-resistant pneumococcus can be a risk factor for mortality, one study suggested that discordant therapy was less likely if patients were treated with ceftriaxone or cefotaxime, compared with other therapies.[133] Thus in clinical practice, resistance is not highly likely to affect outcome, because current guidelines for SCAP recommend the use of these effective agents as empiric therapy. Macrolide-resistant pneumococci have also been described, and can be either low- or high-level resistant, depending on whether the mechanism of resistance is efflux or ribosomal alteration, respectively. Although high-level resistance may be clinically relevant, this is generally not an issue in the management of ICU CAP, because all patients who receive macrolide therapy do so in combination with a highly active beta-lactam effective against pneumococcus, even if macrolide resistance is present.

Legionella pneumophila

This small, weakly staining, gram-negative bacillus was first characterized after an epidemic in 1976 and can occur either sporadically or in epidemic form. Although multiple serogroups of the species *L. pneumophila* account for 90% of all cases of legionnaires' disease, serogroup 1 is responsible for most cases. The other species that commonly causes human illness is *L. micdadei*. The organism is water-borne and can emanate from air-conditioning equipment, drinking water, lakes and river banks, water faucets, and shower heads.[134] Infection is generally caused by inhalation of an infected aerosol generated by a contaminated water source. When a water system becomes infected in an institution, endemic outbreaks may occur. In its sporadic form, *Legionella* may account for 7%–15% of all cases of CAP, being a particular

concern in patients with severe forms of illness.[1,20,134] Recent studies show an increase in the reported cases of *Legionella,* especially in populous cities like New York, with a higher incidence in diabetic patients and in those from poor neighborhoods.[135]

The classic *Legionella* syndrome is characterized by high fever, chills, headache, myalgias, and leukocytosis.[134] The diagnosis is also suggested by the presence of pneumonia with preceding diarrhea, along with mental confusion, hyponatremia, relative bradycardia, and liver function abnormalities. Symptoms progress rapidly, and the patient may appear to be quite toxic. This classic syndrome is not always present, so the diagnosis should always be considered in patients admitted to the ICU with CAP and in those with rapidly progressive radiographic abnormalities. To establish this diagnosis serologically, it is necessary to collect both acute and convalescent titers. The urinary antigen test (UAT) is the single most accurate acute diagnostic test for *Legionella,* but is specific only for serogroup 1 infection. It does not detect other types of *Legionella,* so a negative result does not rule out infection from another sero-class. In recent years, most cases have been diagnosed with UAT and there has been less reliance on blood serology and culture.[136] With increased availability of UAT, the case fatality rate of *Legionella* has fallen, in part reflecting the diagnosis of less severe illness than in the past.[136]

Staphylococcus aureus

S. aureus leads to severe forms of CAP, which can cause necrotizing cavitary pneumonia and disseminate hematogenously to multiple extrapulmonary sites. The organism can also seed the lung hematogenously from valvular vegetations in patients with right-sided endocarditis or from septic venous thrombophlebitis (from central venous catheter or jugular vein infection). When a patient develops post–influenza pneumonia, *S. aureus* can lead to secondary bacterial infection and, in the United States, CA-MRSA strains have emerged. These primarily affect skin and soft tissues but also may cause SCAP. CA-MRSA is a clonal disease, emanating from the USA300 clone of *S. aureus* and is clinically and bacteriologically different from the strains of MRSA that cause nosocomial pneumonia.[120] In addition, it can infect previously healthy individuals, and the classic clinical presentation of this pathogen as CAP occurs as a complication of a preceding viral or influenza infection.

The illness is characterized by a severe, bilateral, necrotizing pneumonia, which may relate to staphylococcal virulence factors, such as the Panton–Valentine leukocidin (PVL). In a prospective study of 627 patients from 12 emergency departments across the United States during two influenza seasons, the authors isolated CA-MRSA from 2.4% of all patients and 5% of patients admitted to the ICU. The mortality rate was 14%, and all isolates were of the USA300 strain.[137] CA-MRSA patients had severe infections with multiple infiltrates or cavities on chest imaging, were intubated or required vasopressors, and compared with other patients were more likely to develop illness after nursing home admission within the previous year or after close contact in the previous month with someone with a skin infection. Because the pathogenesis of pneumonia resulting from this organism may be related to toxin production by the bacteria, therapy may need to involve both an antibacterial agent and an antitoxin-producing agent.[121] Sicot and associates, in a study of 133 patients with PVL-positive CAP, found similar mortality rates for patients who had MRSA and methicillin-susceptible *S. aureus* (MSSA). However, treatment with antibiotics having antitoxin effects (clindamycin, rifampin, and linezolid) was associated with a reduced mortality, compared with those who did not get antitoxin therapy (6.1% vs. 52.3%, P <.001). Notably, only about one-third of patients received this therapy.[138] The frequency of this illness is still relatively low, but it does occur sporadically, with certain geographic areas having a high occurrence frequency, especially during influenza season.

OTHER ORGANISMS

The incidence of viral pneumonia is difficult to define, but one careful study of over 300 nonimmunocompromised CAP patients looked for viral pneumonia by paired serologies and found that 18% had viral pneumonia, with about half being pure viral infection and the others being mixed with bacterial pneumonia.[139] Influenza (A more than B), parainfluenza, and adenovirus were the most commonly identified viral agents. The multicenter EPIC study of CAP found that viral infection was more common than bacterial infection, but among the 482 admitted to the ICU, 45% had an identified pathogen, with viral infection in 22% and bacterial infection alone in 19%, and 4% with mixed infection. The viral pathogens were rhinovirus (8%), influenza (6%), metapneumovirus, RSV, parainfluenza, coronavirus, and adenovirus.[140] Viral illnesses that can lead to respiratory failure in addition to influenza include RSV (which can affect the elderly), varicella (a particular concern in pregnant females with chickenpox), and hantavirus (endemic in the Four Corners area of New Mexico).[141] In a study of patients with severe pneumonia using polymerase chain reaction (PCR) techniques, the authors found viral infection to be common: 36.4% ($n = 72$) had positive viral markers and 9.1% ($n = 18$) had bacterial and viral coinfections.[142]

It is important to always consider the diagnosis of tuberculosis in patients with SCAP and to be aware of fungal infections with coccidioidomycosis and histoplasmosis in endemic areas, especially among HIV-infected persons. Several rickettsiae can also cause CAP, including Q fever (*Coxiella burnetii*), which occurs worldwide; Rocky Mountain spotted fever (RMSF); and scrub typhus (*Rickettsia tsutsugamushi*) in Asia and Australia. Transmission typically involves an intermediate vector, often ticks (Q fever, RMSF) or mites (scrub typhus), but also sheep, cows, and contaminated milk (Q fever). These infections have variable incubation periods, ranging from days to a few weeks, and are characterized by a febrile syndrome that may have a pneumonic component and a maculopapular rash (Q fever and RMSF).

INFLUENZA

Influenza should always be considered during epidemic periods and can lead to a primary viral pneumonia or to secondary bacterial infection with pneumococcus, *S. aureus,* or *H. influenzae*. In April 2009, an outbreak of H1N1 influenza infected approximately 61 million people worldwide, with as many as 13,000 deaths. H1N1 influenza, in contrast to seasonal flu, affected younger people more often than the elderly, and high-risk populations included pregnant women and those with obesity.[143] In one series, 12% of all hospitalized patients with H1N1 infection were mechanically ventilated and 6% of hospitalized patients died.[144] Antiviral therapy with zanamivir and oseltamivir may reduce the severity of these illnesses, particularly if given early, and the role of corticosteroids for patients with severe illness is controversial.[143,145] MacIntyre and colleagues report during the pandemic of influenza A(H1N1)pdm09, a mean prevalence of bacterial coinfection in 19% of patients admitted to the ICU and in 12% of hospitalized patients not requiring ICU care. *S. pneumoniae* was the most common cause in both groups.[146] Muscedere and associates evaluated the risk of coexistent or secondarily acquired bacterial respiratory tract or bloodstream-positive cultures in 681 patients with 2009 influenza A (H1N1) infection.[147] In that study, 38% of patients had at least a positive blood or respiratory culture during their ICU stay even though almost all patients had received antibiotics. Patients with any positive culture experienced higher

morbidity, with more days on the ventilator, longer ICU and hospital LOS, and higher hospital mortality compared with those with negative cultures. During the spring of 2013, infection with novel avian-origin influenza A (H7N9) emerged in China and was strongly related to exposure to live animals, including chickens (82%).[148] It was linked with a high incidence of respiratory failure and ICU admission, especially in those with comorbid conditions, and mortality ranged from 27% to 34% among ICU patients.[148,149] Use of steroids as an adjunctive treatment in influenza is controversial. Although the results of most studies have been prone to confounding by indication, recent evidence suggests that steroid use is associated with greater mortality risk in influenza patients with pneumonia.[150,151]

SEVERE ACUTE RESPIRATORY SYNDROME

In late 2003, a respiratory viral infection caused by a coronavirus emerged in parts of Asia and was termed *severe acute respiratory syndrome (SARS).* The illness affected people from a variety of endemic areas in Asia, but was encountered in North America when an outbreak occurred in Toronto, Canada, after exposure to an infected traveler returning from Asia. Importantly, worldwide as many as 20% of affected patients were healthcare workers, particularly those caring for patients admitted to the ICU. Although transmission risk was greatest during emergent intubation, it also occurred during noninvasive ventilation, making this latter modality of therapy contraindicated when SARS is suspected.[152] Infection control may be quite effective in preventing the spread of SARS to healthcare workers and includes the careful handling of respiratory secretions, ventilator circuits, the use of N-95 respirator masks, and careful gowning and gloving.[153] Even more elaborate infection control measures, including personal air exchange units, are needed for healthcare workers involved in high-risk procedures such as intubation. The mortality rate for ICU-admitted SARS patients was over 30%, and, when patients died, it was generally from multiple system organ failure and sepsis. A similar experience has accompanied the COVID-19 pandemic.

MIDDLE EAST RESPIRATORY SYNDROME CORONAVIRUS

A new coronavirus outbreak, subsequently named "Middle East respiratory syndrome coronavirus" (MERS-CoV), started September 2012 in the Arabian Peninsula.[154] Patients presented with severe acute pneumonia with hypoxemic respiratory and renal failure. MERS-CoV pneumonia can occur sporadically in the community in addition from healthcare–associated human-to-human transmission.[155] The infection was associated with a very high fatality rate (up to 60%), especially in patients with medical comorbidities. The majority of patients required invasive respiratory support and had extrapulmonary manifestations, mainly kidney failure.[156] The effectiveness of steroids, oseltamivir, ribavirin, and interferon for treatment of this illness has remained uncertain.

BIOTERRORISM CONSIDERATIONS

Certain airborne pathogens can cause pneumonia as the result of deliberate dissemination by the aerosol route, in the form of a biologic weapon, and present a clinical syndrome of CAP. The pathogens that are most likely to be used in this fashion and that can lead to severe pulmonary infection are *Bacillus anthracis* (anthrax), *Yersinia pestis* (plague), and *F. tularensis* (tularemia).[157–161] The Centers for Disease Control and Prevention (CDC) has classified these agents as category A pathogens because of their high mortality rate and their potential impact on public health.[157] Other pneumonic pathogens could also serve as agents of biologic warfare but are potentially less serious and are category B, and include *C. burnetii* and *Brucella* species. Certain emerging pathogens are category C agents and are not widely available as weapons but have the potential for high morbidity and mortality and include hantavirus and MDR tuberculosis. Some agents of bioterrorism can be spread via the aerosol route but do not generally present as pneumonia. These include smallpox and viral hemorrhagic fevers (Ebola, Marburg).

DIAGNOSTIC EVALUATION

As discussed, the diagnosis of CAP is suggested by the history and physical examination and confirmed by chest radiograph. The history may call to mind certain pathogens on the basis of epidemiologic considerations (see Table 67.4), but the clinical features and chest radiograph cannot nail down an exact etiologic diagnosis. In the patient with SCAP, diagnostic testing is done to define the presence of pneumonia, the severity of illness and its complications, and the etiologic pathogen. Although defining a specific etiologic diagnosis of CAP allows for focused antibiotic therapy, most patients never have a specific pathogen identified, and in many who do, the diagnosis may be made days or weeks later when the results of cultures or serologic testing become available. An etiologic diagnosis is best established if blood or pleural fluid cultures identify a pathogen, if bronchoscopic techniques demonstrate an organism in high concentrations, or if serologic testing confirms a fourfold rise in titers to specific pathogens (comparing acute and convalescent samples collected weeks apart).

For ICU-admitted patients, after a chest radiograph establishes the presence of pneumonia, testing should include an assessment of oxygenation (pulse oximetry or blood gas if retention of carbon dioxide is suspected), routine admission blood work, and two sets of blood cultures[1] (Table 67.5). Although blood cultures are positive in only 10%–20% of CAP patients, they can be helpful when they define a specific diagnosis and may indicate the presence of drug-resistant pneumococci.[1,101] Blood cultures are not routine for all admitted patients, but should be done in those with severe illness, especially if the patient has not received antibiotics before admission, because the incidence of a true positive result is higher in this population.[162] Current IDSA/ATS 2019 guidelines discourage obtaining blood cultures in outpatient and inpatient settings, unless the patient has severe CAP, is being empirically treated for or has a history of infection with MRSA or *P. aeruginosa,* or has a history of being hospitalized and has received parenteral antibiotics within the preceding 90 days of admission.[4] If the patient has a significantly large ipsilateral pleural effusion, this should be tapped and the fluid sent for culture and biochemical analysis.

The role of Gram stain of sputum to guide initial antibiotic therapy is controversial, but this test has its greatest value in guiding the interpretation of sputum culture and can be used to define the predominant organism present in the sample. Gram stain can be used to broaden initial empiric therapy by enhancing the suspicion for organisms that are not covered in routine empiric therapy (such as *S. aureus* being suggested by the presence of clusters of gram-positive cocci, especially during a period of epidemic influenza).[1] Sputum culture can help identify the presence of a drug-resistant or unusual pathogen and should be obtained from all critically ill patients who are intubated.[1] IDSA/ATS 2019 guidelines extend the same recommendation as with blood culture for Gram stain of sputum and culture to be done in patients with SCAP who are being empirically treated for or have a history of infection with MRSA or *P. aeruginosa* or have a history of being hospitalized and have received parenteral antibiotics within the preceding 90 days before admission.[4] UAT for pneumococcus or

TABLE 67.5 Diagnostic Testing for Community-Acquired Pneumonia

Test	Sensitivity	Specificity	Comment
Chest radiograph	65%–85%	85%–95%	Computed tomography is more sensitive to infiltrates. Recommended for all patients.
Computed tomography	Gold standard	Not infection specific	Should not be done routinely but helpful to identify cavitation and loculated pleural fluid. Recommended in the evaluation of nonresponding patients.
Blood cultures	10%–20%	High when positive	Usually shows pneumococcus (in 50%–80% of positive samples) and defines antibiotic susceptibility. Recommended in patients with severe CAP, particularly if not on antibiotic therapy at the time of testing.
Sputum Gram stain	40%–100% depending on criteria	0%–100% depending on criteria	Can correlate with sputum culture to define predominant organism and can use to identify unsuspected pathogens. Recommended if sputum culture obtained. May not be able to narrow empiric therapy choices.
Sputum culture			Use if suspect drug-resistant or unusual pathogen, but positive result cannot separate colonization from infection. Obtain via tracheal aspirate in all intubated patients
Oximetry or arterial blood gas			Both define severity of infection and need for oxygen; if hypercarbia is suspected, a blood gas sample is needed. Recommended in severe community-acquired pneumonia.
Serologic testing for *Legionella, Chlamydia pneumoniae, Mycoplasma pneumoniae*, viruses			Accurate, but usually requires acute and convalescent titers collected 4–6 weeks apart. Not routinely recommended.
Legionella urinary antigen	50%–80%		Specific to serogroup 1, but the best acute diagnostic test for *Legionella*
Pneumococcal urinary antigen	70%–100%	80%	False positives if recent pneumococcal infection. Can increase sensitivity with concentrated urine.
Serum procalcitonin			Not a routine test, but if done, should be measured with the highly sensitive KRYPTOR assay. May help guide duration of therapy and need for ICU admission.

CAP, Community-acquired pneumonia; *ICU*, intensive care unit.

Legionella has some potential value for providing a rapid diagnosis. *Legionella* urinary antigen is specific to serogroup 1 infection and is only positive in a little more than half of all infected patients, but it is the one test that is most likely to be positive in the setting of acute illness.[163] UAT is also available for detection of capsular polysaccharide of *S. pneumoniae* and has 77%–88% sensitivity in patients with bacteremic pneumococcal pneumonia, but is only 64% positive with nonbacteremic pneumococcal pneumonia.[103,164] The sensitivity of pneumococcal UAT increases if concentrated urine is examined, and it can be positive even in the presence of antibiotic therapy. False-positive tests can occur in patients who have had recent pneumococcal infection.[165] In a randomized study of 177 patients treated based on UAT for *Legionella* and *S. pneumoniae* compared with empiric guideline-directed treatments, there was no difference in mortality, need for ICU level of care, or hospital LOS. Nonetheless, targeted treatment was associated with a slightly higher overall cost and lower exposure to broad-spectrum antimicrobials.[166] IDSA/ATS 2019 guidelines discourage routine UAT testing in all adults with CAP, but recommend it for those with SCAP and for those with high-risk epidemiologic factors, such as recent travel or *Legionella* outbreak in the community.[4]

Routine serologic testing is not recommended.[1] Nucleic acid amplification tests and PCR assays provide rapid test results in CAP for atypical agents such as viruses, *Mycoplasma, Chlamydophila,* and *Legionella*. Cultureless, rapid diagnostic tests such as new nucleic acid amplification platforms, real-time computer-assisted microscopy, next-generation sequencing, and high-throughput mass spectrometry are being developed for early detection and pathogen-specific therapy.[167] The usefulness of these techniques in managing CAP has not yet been proven. The concern with using this method is that it is so sensitive that if a respiratory sample is positive, it cannot distinguish colonization from infection. However, the test may be valuable if negative, because the absence of a suspected pathogen by PCR may permit a more focused antibiotic therapy approach.

Bronchoscopy is not indicated as a routine diagnostic test and should be restricted to immunocompromised patients and to selected individuals with severe forms of CAP. Several studies[168,169] have not shown improvement in outcome when a specific etiologic diagnosis is made for patients with SCAP. Rather, outcome is improved if the initial empiric therapy is accurate and the patient has a prompt clinical improvement.[169] However, patients who have rapidly progressive lung infection in spite of therapy may benefit from invasive diagnostic testing. Again, however, a favorable impact of this testing on patient outcome has not been demonstrated. One population that should be considered for invasive testing is the corticosteroid-treated COPD patient who has a slowly responding or nonresponding pneumonia, because these individuals are at risk for infection with *Aspergillus,* and this organism usually can be recovered from a bronchoscopic lavage sample. In addition, bronchoscopy may have value for the nonresponding patient or other immunesuppressed individuals.[170]

In patients with SCAP, diagnostic testing may be valuable for guiding modifications of antibiotic therapy, rather than affecting the choice of initial therapy.[171] In one study, nearly 40% of patients had no pathogen identified. Pathogen-directed therapy had no overall impact on mortality or LOS, but led to fewer adverse events than empiric therapy and also was accompanied by a lower incidence of

mortality for patients admitted to the ICU.[172] In addition, studies have emphasized mortality benefit from prompt administration of effective antibiotic therapy.[173] Thus, therapy should never be delayed for the purpose of diagnostic testing, and the diagnostic workup should be streamlined, with all patients receiving empiric therapy based on algorithms as soon as possible.

TREATMENT

Initial antibiotic therapy for SCAP is necessarily empiric, with the goal of targeting the likely etiologic pathogens, based on the considerations listed in Tables 67.3 and Table 67.4, which categorize patients on the basis of severity of illness and risk factors for specific pathogens. The likelihood of organisms such as DRSP, enteric gram-negative organisms, and *P. aeruginosa* is determined by the presence of cardiopulmonary disease or "modifying factors."[1] A set of likely pathogens can be predicted for each patient (see Table 67.3), and this information can be used to guide initial empiric therapy. If diagnostic testing shows the presence of a specific pathogen, broad-coverage therapy can be narrowed and focused.

In choosing empiric therapy of CAP, certain principles and therapeutic approaches should be followed (Table 67.6).[1,174] All individuals should be treated for DRSP and atypical pathogens, but only those with appropriate risk factors (see earlier) should receive coverage for *P. aeruginosa*, and patients with bilateral necrotizing pneumonia occurring after influenza need coverage for CA-MRSA.[1] All patients admitted to the ICU require combination therapy, using a beta-lactam with either a macrolide or quinolone, with the addition of other agents, depending on the clinical setting.[1,4,175] The recommendation to avoid monotherapy is based on the fact that the efficacy (especially for meningitis complicating pneumonia), effective dosing, and safety of any single agent, including quinolone monotherapy, has not been established for ICU-admitted CAP patients. From the available data, it appears that adding either a macrolide or a quinolone to a beta-lactam leads to similar results. Some data in patients with bacteremic CAP, especially with pneumococcus, suggest that a macrolide may have particular advantages to adding a quinolone, possibly because of its antiinflammatory effects.[118,119,176,177]

In one study of 529 patients with ICU-admitted CAP, combination therapy with a beta-lactam plus either a macrolide or quinolone led to improved survival for the population with shock needing pressors (279 patients), compared with the use of monotherapy.[178] Another study of SCAP patients (not all pneumococcal) also confirmed the benefit of adding a macrolide as part of initial empiric therapy, but not a quinolone, for reducing mortality.[179] In a study comparing the impact of dual (beta-lactam plus macrolide or fluoroquinolone [$n = 394$]) versus monotherapy (beta-lactam alone [$n = 471$]) in immunocompetent SCAP, there was no difference in 60-day mortality between the two groups.[180] However, there was a survival advantage for patients who had initial adequate antibiotic therapy, and those who received dual therapy had a higher frequency of initial adequate antibiotics. In one study comparing high-dose levofloxacin with a beta-lactam/quinolone combination, the single-agent regimen was overall effective. However, patients in septic shock were excluded, and there was a trend to a worse outcome with monotherapy for individuals receiving MV.[175] In a meta-analysis of SCAP, the addition of a macrolide to a beta-lactam was associated with reduced mortality compared with other regimens.[181] In another systematic review that included 17 studies with 16,684 patients, no difference in outcomes was noted between combination beta-lactam plus macrolide versus beta-lactam plus fluoroquinolone.[182] If *Legionella* is suspected, then the use of a quinolone may be preferable, because these agents have been highly successful in treating pneumonia caused by this organism—possibly more effective than macrolides.[183] Also, IDSA/ATS 2019 guidelines do not recommend adding antibiotics for anaerobic coverage for suspected aspiration pneumonia in inpatient settings, except when lung

TABLE 67.6 Empiric Therapy Regimens for Severe Community-Acquired Pneumonia

No Pseudomonal Risk Factors

Selected beta-lactam (ampicillin + sulbactam 1.5–3 g every 6 h, cefotaxime 1–2 g every 8 h, ceftriaxone 1–2 g daily, or ceftaroline 600 mg every 12 h)
Plus
Intravenously administered macrolide (azithromycin 500 mg daily or clarithromycin 500 mg twice daily) *or* quinolone (levofloxacin 750 mg daily or moxifloxacin 400 mg daily)

Pseudomonal Risk Factors Present or Prior Pseudomonal Colonization or the Presence of Local Etiologic and Risk Factor Data

Selected antipseudomonal beta-lactam (piperacillin-tazobactam [4.5 g every 6 h], cefepime [2 g every 8 h], ceftazidime [2 g every 8 h], aztreonam [2 g every 8 h], meropenem [1 g every 8 h], or imipenem [500 mg every 6 h])
Plus
Intravenously administered antipseudomonal quinolone (ciprofloxacin or levofloxacin)
Or selected antipseudmomonal beta-lactam
Plus
Aminoglycoside
Plus
Antipneumonoccal quinolone or macrolide

MRSA Risk Factors Present or Prior Isolation of MRSA

Vancomycin (15 mg/kg every 12 h, adjust based on trough levels 15–20) or linezolid (600 mg every 12 h).
Note: Although routine MRSA coverage is NOT recommended for all cases of severe CAP, consider CA-MRSA, especially after influenza and with bilateral necrotizing pneumonia, and if toxin-mediated infection suspected, treat by adding either linezolid or the combination of vancomycin and clindamycin.

CAP, Community-acquired pneumonia; *CA-MRSA*, Community-acquired MRSA; *MRSA*, methicillin-resistant *Staphylococcus aureus*.

abscess or empyema is suspected, as the majority of these pneumonias are caused by gram-negative pathogens.[4]

Although they should not be used as monotherapy for ICU-admitted CAP patients, the antipneumococcal quinolones have assumed great importance because they can cover pneumococcus (including DRSP), nonpseudomonal gram-negative organisms, and atypical pathogens.[1] Quinolones penetrate well into respiratory secretions and are highly bioavailable, achieving similar serum levels with either oral or intravenous therapy and facilitating a rapid switch to oral therapy in responding patients. The available intravenous agents that are active against pneumococcus are moxifloxacin and levofloxacin.[184] Based on in vitro activity, the recommended doses for moxifloxacin are 400 mg daily and for levofloxacin 750 mg daily, with the need to adjust dosing of levofloxacin (but not moxifloxacin) in patients with renal insufficiency.

For patients with pseudomonal risk factors, effective therapy can be provided with a two-drug regimen, using an antipseudomonal beta-lactam (cefepime, imipenem, meropenem, piperacillin/tazobactam) plus ciprofloxacin (the most active antipseudomonal quinolone) or levofloxacin. Alternatively, a three-drug regimen can be used, combining an antipseudomonal beta-lactam plus an aminoglycoside plus either an intravenous antipneumocccal quinolone (moxifloxacin or levofloxacin) or a macrolide.[1] If CA-MRSA is suspected, effective therapy can be provided with either vancomycin or linezolid, although other agents might be effective, because this pathogen is not as antibiotic resistant as nosocomial MRSA. However, because CA-MRSA is in part a toxin-mediated illness, the use of an agent that inhibits toxin production along with an antibacterial effect is recommended by some.[121] To do this, linezolid can be used alone (because it acts to inhibit protein synthesis), or clindamycin can be added to vancomycin. IDSA/ATS 2019 guidelines recommend empiric coverage for *Pseudomonas* and MRSA based on locally validated epidemiologic risk factors for either pathogen to be present.[4] Guidelines do not recommend prior categorization of HCAP and empiric therapy with broad-spectrum antibiotics. Maruyama and colleagues applied a simple therapeutic algorithm for all pneumonia patients based on MDR risks in a prospective study of 1089 patients including 656 CAP patients and found that 30-day mortality was not associated with site of classification such as CAP, HCAP, hospital-acquired pneumonia (HAP), or ventilator-acquired pneumonia (VAP). Therapy was based on five risk factors—namely, advanced age, hematocrit <30%, malnutrition, dehydration, and chronic liver disease—in addition to shock or prior inappropriate therapy.[185] Using this algorithm, inappropriate empiric therapy was given in less than 5% of all patients.

Patients admitted with influenza should be treated with appropriate antiviral agents, regardless of the duration of illness before diagnosis.[4] There is a high incidence of postinfluenza bacterial pneumonia, with mortality rates approaching 10% with both seasonal and pandemic influenza.[186] In addition, antibiotics should be started, even in confirmed influenza, with a special focus on *S. aureus, S. pneumoniae, H. influenzae*, and group A streptococcus to account for the possibility of coinfection. However, the guidelines allow consideration for de-escalation of antibiotics in those with no evidence of bacterial superinfection and clinical stability after 48–72 hours of initiation of antibiotics.[4]

Several newer antibiotics are on the horizon for the treatment of CAP, including solithromycin, lefamulin, omadacycline, ceftobiprole, ceftazidime-avibactam, ceftolozane-tazobactam, and delafloxacin.[187] Solithromycin is a novel fourth-generation macrolide. In two recent double-blind, randomized controlled, noninferiority trials, its effectiveness was comparable to oral moxifloxacin in patients with mild to moderate CAP (PORT scores II–IV).[188,189] Lefamulin is a novel semi-synthetic antibiotic in the pleuromutilin class. In the phase 3 "LEAP 2" randomized clinical trial comparing early clinical responses in CAP patients with PORT risk class of II, III, or IV, 5 days of oral lefamulin was not inferior to 7-day oral treatment with moxifloxacin.[190] Omadacycline is an aminomethycycline, and in a recent randomized, double-blind trial conducted in CAP patients (PORT risk class of II, III, or IV), a comparison of omadacycline (100 mg intravenously every 12 hours for two doses, then 100 mg intravenously every 24 hours) with moxifloxacin (400 mg intravenously every 24 hours) demonstrated similar early clinical responses with both antibiotics.[191] Ceftobiprole is an extended-spectrum cephalosporin available in intravenous form. In a double-blind controlled trial with 706 hospitalized CAP patients, ceftobiprole medocaril was found noninferior to ceftriaxone with or without linezolid.[192] Nemonoxacin is a novel nonfluorinated quinolone. In a phase III study of CAP patients randomized to nemonoxacin ($n = 356$) or levofloxacin ($n = 171$) there was no difference in clinical or microbiologic cure rates between the groups at 7–10 days; adverse side effects were comparable.[193] Delafloxacin is another novel fluoroquinolone, and in a phase III study in CAP patients, there was 16-fold greater activity with delafloxacin compared with moxifloxacin for gram-positive and fastidious gram-negative pathogens. Retained activity was observed against resistant phenotypes found in S. *pneumoniae* (penicillin-resistant, macrolide-resistant, MDR), *Haemophilus* species (beta-lactamase producing, macrolide-nonsusceptible), and *S. aureus* (MRSA, fluoroquinolone-nonsusceptible MSSA).[194] Both ceftazidime-avibactam and ceftolozane-tazobactam are agents in development for treating nosocomial pneumonia, and both have excellent activity against *P. aeruginosa*. These agents will be important newer options over the next decade, given increasing concerns regarding drug resistance. But for now, the workhorse of CAP treatment in the critical care setting remains the beta-lactam plus macrolide or beta-lactam plus fluoroquinolone combinations.

TIMELINESS OF INITIAL THERAPY

For inpatients with CAP, timely and accurate therapy is essential to reduce mortality. In patients with SCAP, improved survival has been shown to occur if initial empiric therapy is accurate and if it leads to a rapid clinical response.[115,169,173] In one study, if initial therapy led to a clinical response within 72 hours, mortality of SCAP was approximately 10%, compared with a mortality rate of 60% in patients who received ineffective therapy initially.[169] For CAP in general, early therapy is associated with reduced mortality compared with therapy given later; if the patient has pneumonia with sepsis and hypotension, mortality rises by nearly 8% for every hour of delay in starting therapy.[195]

DURATION OF THERAPY

There is little information on the proper duration of therapy in patients with CAP, especially those with severe illness. Even in the presence of pneumococcal bacteremia, short durations of therapy may be possible, with a rapid switch from intravenous to oral therapy in those who respond.[196] Generally, *S. pneumoniae* can be treated for 5–7 days if the patient responds rapidly and has received the correct dose of an appropriate therapy. Initial PCT level may accurately predict a positive blood culture in pneumonia patients, and serial measurements help with antibiotic de-escalation and withdrawal in CAP patients.[197,198] In a randomized trial of antibiotic therapy in the ICU, PCT guidance reduced the duration of therapy compared with standard care in all patients, including those with SCAP.[199] A meta-analysis of 14 randomized trials favored a PCT-based treatment algorithm for

antibiotic de-escalation without an increase in either mortality or treatment failure.[200] In a recent meta-analysis of 19 randomized controlled trials of CAP including 4861 patients there were no differences in clinical cure rates between short-course treatment defined as ≤6 days and treatment for ≥7 days irrespective of patient setting or severity of pneumonia.[201] In that study, short-course treatment was associated with fewer serious adverse events (relative risk [RR] = 0.73; 95% CI 0.55–0.97) and potentially lower mortality than long-course treatment (RR = 0.52; 95% CI 0.33–0.82). The IDSA/ATS 2019 guideline recommends clinicians continue antibiotics until the patient achieves stability using a validated measure of clinical stability, including normalization of vital sign abnormalities, oxygen saturation, ability to eat, and normal mentation. The duration is not less than a total of 5 days.[4]

The presence of extrapulmonary infection (e.g., meningitis, empyema) and the identification of certain pathogens (such as bacteremic *S. aureus* and *P. aeruginosa*) may require a longer duration of therapy. Identification of *L. pneumophila* pneumonia may require at least 14 days of therapy, depending on severity of illness and host defense impairments, but shorter durations with quinolone therapy have been effective. Most therapy in the ICU will be given intravenously; however, recent studies, using a variety of antibiotics, have suggested that oral therapy may be instituted after as early as 2–3 days of parenteral therapy, assuming that the patient's condition has stabilized and the patient is afebrile.[1] The switch to oral therapy, even in severely ill patients, may be facilitated by the use of quinolones that are highly bioavailable and achieve similar serum levels with oral therapy as with intravenous therapy.

ADJUNCTIVE THERAPY MEASURES

In addition to antibiotic therapy, the patient with SCAP may require chest physiotherapy, especially if the patient has either an excessive volume of purulent sputum (>30 mL/day) or severe respiratory muscle weakness resulting in ineffective cough.[202] Aerosolized humidification has been used to reduce sputum viscosity, thereby enhancing clearance in patients who have generally ineffective cough, and nebulized hypertonic saline may promote cough and expectoration of sputum. However, it is likely that much of the generated water vapor is deposited in the upper airway, where it is likely to stimulate cough but unlikely to influence the rheologic properties of sputum. Bronchodilator therapy, which also enhances mucociliary clearance and ciliary beat frequency, is most likely to be of benefit in patients with pneumonia complicating COPD. A recent Cochrane review did not find convincing evidence supporting the role of chest physiotherapy in pneumonia patients.[203]

Previous studies looking into the use of adjunctive corticosteroids in patients with SCAP have shown mixed results.[204,205] Although the role of corticosteroids as routine therapy for CAP is not established, steroids may be beneficial in patients with sepsis and relative adrenal insufficiency, which occurs in a high proportion of patients with SCAP.[206] A recent meta-analysis of nine trials involving 1001 patients did not support routine use of corticosteroids in CAP patients, but may improve mortality in a subset with SCAP.[207] Another setting in which corticosteroids may have benefit is in pneumococcal pneumonia that is complicated by meningitis, where pretreatment with corticosteroids before antibiotic therapy may lead to more favorable neurologic outcomes.[208] In a randomized, prospective study, Torres and associates found that in patients with SCAP and elevated CRP >150 mg/L at admission, administration of intravenous methylprednisolone (bolus of 0.5 mg/kg every 12 hours) led to less treatment failure, compared with placebo.[209] In that study, there was no significant difference in hospital mortality between the two groups. The IDSA/ATS 2019 guideline gives a strong conditional recommendation against routine use of adjunctive steroids in patients treated for CAP.[4] Even if corticosteroids are given to selected SCAP patients, they should probably be withheld in those with documented influenza, unless there is another specific indication (e.g., adrenal insufficiency). Adjunctive immune therapy with granulocyte colony-stimulating factor (G-CSF) has also been used in SCAP, with no benefit in mortality or in the course of illness resolution.[210]

EVALUATION OF RESPONSE TO THERAPY

The majority of patients will respond rapidly to appropriate empiric therapy within 24–72 hours. Clinical response is defined as improvement in symptoms of cough, sputum production, and dyspnea, along with ability to take medications by mouth, declining WBC count, and an afebrile status on at least two occasions 8 hours apart.[1] In the critically ill patient, improvement in oxygenation may be one of the earliest signs of response to therapy, although few studies have examined mechanically ventilated patients.[1] Radiographic improvement lags behind clinical improvement, and in general, 50% of patients with pneumococcal pneumonia have radiographic clearing at 5 weeks, whereas the majority clear in 2–3 months. With bacteremic disease, 50% of patients have a clear chest radiograph at 9 weeks, and most are clear by 18 weeks.[211] Radiographic resolution is most influenced by the number of lobes involved and the age of the patient. Radiographic clearance of CAP decreases by 20% per decade after age 20, and patients with multilobar infiltrates take longer to clear than those with unilobar disease.[211]

If the patient fails to respond to appropriate therapy in the expected time interval, then it is necessary to consider infection with a drug-resistant or unusual pathogen (tuberculosis, *C. burnetii*, *Burkholderia pseudomallei*, *C. psittaci*, endemic fungi, or hantavirus); a pneumonic complication (lung abscess, endocarditis, empyema); or a noninfectious process that mimics pneumonia (bronchiolitis obliterans with organizing pneumonia, hypersensitivity pneumonitis, pulmonary vasculitis, bronchoalveolar cell carcinoma, lymphoma, pulmonary embolus).[1] The evaluation of the nonresponding patient should be individualized, but may include CT of the chest, pulmonary angiography, bronchoscopy, and, occasionally, open lung biopsy.

PREVENTION

Prevention of CAP is important for all groups within the population but especially for the elderly patient, who is at risk for both a higher frequency of infection and a more severe course of illness. Appropriate patients should be vaccinated with both pneumococcal and influenza vaccines, and cigarette smoking should be stopped in all at-risk patients. Even for the patient who is recovering from CAP, immunization while in the hospital is appropriate to prevent future episodes of infection, and the evaluation of all patients for vaccination need and the provision of information about smoking cessation have been performance standards used to evaluate the hospital care of CAP patients.[1]

PNEUMOCOCCAL VACCINE

Pneumococcal capsular polysaccharide vaccine can prevent pneumonia in otherwise healthy populations, as was initially demonstrated in South African gold miners and American military recruits.[1,212] The benefits in individuals of advanced age or with underlying conditions in nonepidemic environments are less clearly defined. Efficacy of the polysaccharide vaccine has ranged from 65% to 84% in patients with diabetes mellitus, coronary artery disease, congestive heart failure,

chronic pulmonary disease, and anatomic asplenia.[212] In immunocompetent patients over the age of 65, effectiveness has been documented to be 75%. In the immunocompromised patient, effectiveness has not been proven, and this includes patients with sickle cell disease, chronic renal failure, immunoglobulin deficiency, Hodgkin disease, lymphoma, leukemia, and multiple myeloma. A single revaccination is indicated in a person who is older than age 65 years who initially received the vaccine more than 5 years earlier and was younger than age 65 on first vaccination.[1,105] If the initial vaccination was given at age 65 or older, revaccination is indicated, and the second dose is given at least 5 years after the original dose.

The available polysaccharide pneumococcal vaccine is widely underutilized, especially as the 23-valent pneumococcal vaccine contains 23 pneumococcal serotypes that cause 85% of all infections resulting from pneumococcus. Two protein-conjugated pneumococcal vaccines have been licensed and are more immunogenic than the older vaccine, but contain only 7 and 13 serotypes.[1] However, the conjugate vaccine has had benefit for adults, even when given to only children, demonstrating a "herd immunity" effect.[213] In a recent study, investigators studied the influence of conjugate vaccine on pneumonia-related hospitalizations compared with nonpneumonia hospitalizations over five study intervals: prevaccine period, availability of PCV-7 for private purchase, public funding of PCV-7, replacement of PCV-7 with PCV-10, and replacement of PCV-10 with PCV-13 using a difference-in-differences approach.[214] They noted that although the hospitalization rates and costs for pneumonia were similar to nonpneumonia hospitalizations during the prevaccine period for all age groups, there was a drastic difference in the postvaccination period. The impact of indirect effects was seen also among those ineligible to receive vaccination, with statistically significant reductions in hospitalizations and related costs across all age groups.

The 13-valent pneumococcal conjugate vaccine (PCV-13) was approved by the Food and Drug Administration (FDA) in late 2011 for use among adults aged ≥50 years.[215] Based on the recent report from the randomized, placebo-controlled trial evaluating the efficacy of PCV-13 for preventing CAP among adults aged ≥65 years (CAPITA: Community Acquired Pneumonia Immunization Trial in Adults), the Advisory Committee on Immunization Practices has recommended routine use of PCV-13 among adults aged ≥65 years since August 2014.[215] PCV-13 should be administered in series with the 23-valent pneumococcal polysaccharide vaccine, giving PCV-13 first, if possible. More recent recommendations suggest that the decision to use PCV-13 in patients over age 65 be a shared decision with the patient and physician, because of a decline in pneumococcal infection rates as a result of current immunization practices.[216] PCV-13 and pneumococcal polysaccharide vaccine 23-valent vaccination are also recommended in patients with chronic pulmonary diseases on steroids or receiving immunomodulating therapy, or who have concurrent sickle cell disease or other hemoglobinopathies, primary immunodeficiency disorders, human immunodeficiency virus (HIV) infection/acquired immunodeficiency syndrome (AIDS), nephrotic syndrome, and hematologic or solid malignancies.[217]

Hospital-based immunization could be highly effective, because over 60% of all patients with CAP have been admitted to the hospital, for some indication, in the preceding 4 years, and hospitalization could be defined as an appropriate time for vaccination. Pneumococcal vaccine can be given simultaneously with other vaccines, such as influenza vaccine, but each should be given at a separate site. The vaccine can, and often should, be given before discharge in the patient admitted for CAP.

INFLUENZA VACCINATION

Influenza epidemics contribute to morbidity and mortality, both by causing direct infection and by leading to postinfluenza complications. The influenza vaccine preparations are revised annually to account for changes in the antigenic nature of the virus (antigenic drift) that is present each season. Three strains are represented in each vaccine preparation: two influenza A strains (H3N2 and H1N1) and one influenza B strain. Vaccination should be given to all patients older than age 65 and to those with chronic medical illness (including nursing home residents) and to those who provide health care to patients at risk for complicated influenza.[1] It is given yearly, usually between September and mid-November. Although the traditional influenza vaccine contains an inactivated virus, there is now an intranasal vaccine containing a live attenuated influenza virus. It is currently approved for individuals ages 5 to 49 years who are not immune suppressed or chronically ill and who do not have asthma. When the vaccine matches the circulating strain, it can prevent illness in 70%–90% of healthy persons younger than age 65.[1,218] For older persons with chronic illness, the efficacy is less, but the vaccine can still attenuate the influenza infection and lead to fewer lower respiratory tract infections and the associated morbidity and mortality that follow influenza. In many studies, the vaccine has been shown to be cost-effective and able to prevent severe illness and death and to reduce the occurrence of secondary pneumonia and hospitalization.[218] For those above 65 years of age a higher-dose influenza vaccine (60 μg of hemagglutinin per strain) has been shown to provide better protection.[219,220] In a randomized study including 31,989 participants, the high-dose vaccine induced significantly higher antibody responses and provided better protection against laboratory-confirmed influenza illness than standard vaccine.[219] In another study, Izurieta and colleagues examined a large Medicare database of patients aged ≥65 years and found that those who had received high-dose inactivated influenza vaccine during the 2012–13 influenza seasons were less likely to have influenza-related medical encounters and hospitalization than those who received the standard-dose vaccine.[221]

KEY POINTS

- CAP is a common illness, but only about 20% of all affected patients are admitted to the hospital, and only 10%–20% of admitted patients require ICU care.
- Risk factors for SCAP include smoking, alcohol abuse, serious comorbid medical illnesses, and advanced age.
- Risk factors for CAP mortality include severe physiologic abnormalities, delays in the initiation of appropriate antibiotic therapy, advanced age, genetic abnormalities in the immune response, rapid radiographic progression, the development of respiratory failure, and the presence of certain high-risk pathogens.
- Prognostic scoring systems are useful for predicting CAP mortality but are less accurate for identifying patients who require ICU care. ICU care is needed for patients with respiratory failure, multilobar infiltrates, severe hypoxemia (PaO_2/FIO_2 ratio <250), and systolic blood pressure less than 90 mm Hg. Early recognition of SCAP may allow the ICU to be used in a fashion that can reduce the mortality of this illness.
- The failure to localize infection to a single site in the lung, with excessive systemic and pulmonary inflammation, is a common feature in patients with severe forms of CAP.
- Clinical features of pneumonia cannot help to predict the microbial etiology, especially in older patients with impaired immune response, who commonly have less dramatic clinical findings than younger patients with a similar severity of illness.
- The most common pathogens causing SCAP include pneumococcus, atypical pathogens (*Legionella* spp., *M. pneumoniae,* and *C. pneumoniae*), enteric gram-negatives (including *P. aeruginosa*), *S. aureus* (including community-acquired methicillin-resistant strains), and *H. influenzae,* but infection can also be the result of viral illness (influenza, coronaviruses such as SARS), bioterrorism (anthrax), and other miscellaneous organisms.
- Antibiotic-resistant pneumococci are increasingly common and must be considered in the choice of initial antibiotic therapy for SCAP; however, the impact of resistance on the outcomes of patients is uncertain.
- It may be difficult to establish an exact etiologic diagnosis in patients with SCAP, but diagnostic testing should always include a chest radiograph, oxygenation assessment, blood cultures, and, in selected patients, sputum Gram stain and culture, bronchoscopic culture, and UAT for *Legionella* and pneumococcus.
- Therapy for SCAP must be done promptly and empirically, using multiple antibiotics directed against pneumococcus, atypical pathogens, enteric gram-negative organisms, and, in some patients, *P. aeruginosa* and CA-MRSA. This usually requires the combination of a specific beta-lactam with either a macrolide or a quinolone and sometimes the addition of other agents. Quinolone monotherapy is not recommended for the empiric management of SCAP. In patients with SCAP after influenza, CA-MRSA should be considered.
- On serial measurements, biomarkers like PCT can help with antibiotic de-escalation.
- Nonresponse in severe CAP can be recognized as early as 24–48 hours and requires consideration of unusual or drug-resistant pathogens, noninfectious diseases that mimic pneumonia, and pneumonia complications.
- Prevention of pneumonia can be accomplished by focusing on smoking cessation and immunization for pneumococcus and influenza, with consideration of a hospital-based immunization program. The 13-valent pneumococcal conjugate vaccine (PCV-13) was approved by the FDA in late 2011 for use among adults aged ≥50 years, and recent evidence suggests using PCV-13 in series with 23-valent pneumococcal polysaccharide vaccine among patients ≥65 years of age.

References for this chapter can be found at expertconsult.com.

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Nosocomial Pneumonia

Gianluigi Li Bassi, Miguel Ferrer, and Antoni Torres

DEFINITIONS

Nosocomial pneumonia is an infection of the pulmonary parenchyma caused by pathogens acquired in hospital settings.[1,2] Nosocomial pneumonia develops in patients admitted to the hospital for more than 48 hours, and the incubation period usually is no longer than 2 days. Among nosocomial pneumonias, ventilator-associated pneumonia (VAP), which is the main focus of this chapter, develops in intensive care unit (ICU) patients who have been mechanically ventilated for at least 48 hours. Recently, an additional subpopulation of patients with severe nosocomial pneumonia who ultimately require mechanical ventilation has been recognized and defined as those who ultimately require invasive mechanical ventilation (VHAP). Of note, causative pathogens and outcomes associated with VHAP more closely resemble VAP than nosocomial pneumonia.[1–4] Ventilator-associated tracheobronchitis (VAT) is characterized by signs of respiratory infection without new radiologic infiltrates.[5] American studies[6] have suggested that patients hospitalized for 2 days or more within the preceding 90 days; residents in a nursing home or extended care facility; or those undergoing home infusion therapy, chronic dialysis, home wound care, or have contact with subjects colonized by multidrug-resistant (MDR) pathogens may be at risk of acquiring healthcare–associated pneumonia (HCAP) caused by MDR microorganisms, similar to pathogens isolated in hospitalized patients or critically ill patients. European data[7] have also found substantial similarities in the etiology of HCAP and community-acquired pneumonia, challenging the definition of HCAP.

Nosocomial pneumonia is a classification based on the presence of microorganisms isolated from respiratory surveillance cultures and includes the following categories[8]:

1. Primary endogenous pneumonia: causative microorganisms are carried in the nasopharynx and upper airways and isolated in cultures taken on admission.
2. Secondary endogenous pneumonia: causative microorganisms are nosocomial pathogens not present on admission but colonize the patient during a hospital stay.
3. Exogenous pneumonia: caused by microorganisms not originally isolated from surveillance cultures; hence the patient is not a previous carrier.

The time of onset for nosocomial pneumonia reflects possible etiologies, empirical antimicrobial treatment, and outcomes. Previously, VAP has been categorized as either early or late onset.[9] In contrast, Trouillet and colleagues[10] demonstrated that three variables were significant for predicting infection with MDR: duration of mechanical ventilation (MV) ≥7 days (odds ratio [OR] = 6.0), prior antibiotic use (OR = 13.5), and prior use of broad-spectrum antimicrobial agents (OR = 4.1). Subsequent studies[11,12] challenged this classification and reported comparable microbial etiologies in patients with early- or late-onset VAP. This similarity may relate to the worldwide rise in MDR and emphasizes that the local ICU ecology is the most important determinant for acquiring MDR pathogens, irrespective of the duration of intubation.

EPIDEMIOLOGY

Incidence and Associated Burden

Nosocomial pneumonia is the second most common nosocomial infection and the leading cause of death from nosocomial infections among critically ill patients. Incidence ranges from 5 to more than 20 cases per 1000 hospital admissions,[1,2] with the highest rates in immunocompromised, surgical, and elderly patients. Approximately one-third of nosocomial pneumonias are acquired in the ICU, with VAP being the majority of these. Epidemiology studies from the United States report a VAP incidence density between 2 and 16 episodes per 1000 ventilator-days. In the last decade, according to the US Centers for Disease Control and Prevention's National Healthcare Safety Network (NHSN),[13] and before the 2019 SARS-CoV-2 pandemic, the incidence of VAP was consistently decreasing, down to 0.9 VAP cases per 1000 ventilator-days in medical ICUs. In surgical ICUs, the reported incidence declined from 5.2 to 2.0. These figures are not in line with international reports,[14] and as suggested by Metersky and colleagues,[15] optimistic percentages reported from NHSN diverge from the Medicare Patient Safety Monitoring System data, which suggest that the rate of VAP remained stable among ventilated patients between 2005 and 2013 (10.8% during 2005 to 2006 versus 9.7% during 2012 to 2013). Cook and colleagues[16] estimated that the risk of VAP is 3% during the first 5 days on MV, 2% from the fifth to the tenth days, and 1% for subsequent days. Nosocomial pneumonia, and particularly VAP, increases both healthcare costs and the duration of hospitalization. Worsened clinical outcomes associated with VAP have been consistently reported.[17,18] As a result, mean hospital charges per VAP patient have been estimated to increase by approximately US$40,000.

VAP in Coronavirus Disease 2019

In 2019 a novel coronavirus, namely SARS-CoV-2, was isolated from patients in China who presented with pneumonia of unknown cause.[19] The viral infection was found to cause a multisystemic condition named *coronavirus disease (COVID-19)*. Patients with COVID-19 are potentially at risk for concomitant pulmonary infections for several reasons.[20,21] First, SARS-CoV-2 causes substantial damage to respiratory ciliated cells, potentially impairing the mucociliary escalator and facilitating bacterial adhesion and colonization. Second, a significant proportion of hospitalized COVID-19 patients require prolonged MV[22,23] and, specifically during the early phase of the pandemic, have

been treated with a broad range of immunosuppressants. To date, there are still uncertainties on the exact risk of acquiring pulmonary infections in patients with COVID-19. In a few early small case series, a higher incidence of VAP in COVID-19 patients was noted,[24,25] but conflicting lower figures have been demonstrated in subsequent reports.[26–29] In addition, the stated impact of VAP on mortality is variable across these studies, and understanding has been limited by the competing high risk of mortality associated with COVID-19 itself, especially during the early phase of the pandemic. In a meta-analysis by Lansbury and collaborators that pooled data from more than 3800 COVID-19 hospitalized patients,[30] 7% had bacterial coinfection. Yet the incidence of bacterial coinfection increased to 14% in ICU patients. The most common bacteria were *Mycoplasma pneumoniae, Pseudomonas aeruginosa,* and *Haemophilus influenzae*. Finally, in an interesting small case study in COVID-19 patients on MV,[31] *Aspergillus* spp. were detected in up to 21.4% of the patients through galactomannan antigens assay in bronchoalveolar lavage (BAL) fluid. At the time this chapter is written, there is an urgent need for further appraisal of the incidence of concomitant pulmonary infections in the COVID-19 ventilated population and accurate assessment of the impact of VAP on major outcomes.

Mortality

One-third to one-half of all VAP-related deaths are the direct result of the infection, with a higher mortality rate in cases caused by *P. aeruginosa* and *Acinetobacter* spp., abetted by inappropriate or delayed antibiotic therapy.[32,33] Several other factors such as severity of illness and multilobar, cavitating, or rapidly progressive lung infection and comorbidities significantly affect mortality risk.[34–37] Attributable VAP mortality has been defined as the percentage of deaths that would not have occurred in the absence of the infection. The impact of VAP on mortality has required in-depth analysis, because many critically ill patients die from their underlying disease rather than VAP.[38–40] In particular, as mentioned earlier, the risk of VAP is time-dependent, possibly causing a significant time-dependent bias, because mortality and ICU discharge act as competing endpoints. Thus comprehensive analyses reported an attributable mortality associated with VAP of 10%,[38,39] with surgical patients and patients with mid-range severity of illness at the highest associated risk. Lisboa and collaborators proposed a useful tool to assess severity and predict mortality associated with VAP.[41] The authors included parameters to assess predisposition, insult, response, and organ dysfunction (PIRO), and they stratified mortality risk into mild, high, or very high. The hazard ratio for mortality in the very high-risk group was 4.63 (95% confidence interval [CI] 2.68–7.99), and the area under the receiver operating characteristic (ROC) curve (AUROC) corroborated mortality discrimination by the VAP PIRO score (AUROC = 0.81; 95% CI 0.77–0.85).

PATHOGENESIS

Extensive laboratory and clinical work has determined the key pathogenic mechanisms of VAP. Pathogens must first gain access to the airways to cause pneumonia, and intubated patients are at high risk for aspiration of colonized oropharyngeal secretions. In healthy, nonintubated patients, colonization by bacteria that gain access to the respiratory tract is prevented by defense mechanisms such as a cough, mucus clearance, and cellular and humoral immune responses. Critically ill and intubated patients are already at a high risk for infection because of underlying illness, comorbidities, malnutrition, and invasive devices or procedures. However, tracheal intubation is the *conditio sine qua non* for the development of VAP, because it facilitates aspiration of pathogens and hinders intrinsic respiratory defenses.

The Role of the Endotracheal Tube in the Pathogenesis of VAP

Pulmonary aspiration of the colonized oropharyngeal secretions across the endotracheal tube (ETT) cuff is the main pathogenic mechanism for the development of VAP. The most commonly used ETT for long-term mechanically ventilated patients comprises a high-volume, low-pressure (HVLP) cuff. HVLP cuffs were originally designed to prevent tracheal injury.[42] However, because the potential diameter of the HVLP cuff is two to three times greater than the tracheal diameter, folds invariably form along the inflated cuff surface, predisposing to aspiration of oropharyngeal secretions.[43]

Pathogens may also grow on the internal surface of the ETT, and these ultimately translocate into the lungs. Bacteria easily adhere to the ETT internal surface to form a structure called a *biofilm*[44] (Fig. 68.1). Biofilm is composed of sessile bacteria embedded within a self-produced exopolysaccharide matrix.[45] Biofilm on the internal surface of an ETT can be identified early after tracheal intubation.[46,47] Sessile bacteria undergo phenotypic differentiation from their planktonic counterparts to enable their survival. Indeed, sessile bacteria are difficult to eradicate by the host's immune response or antibiotics.[48] During MV, biofilm particles may dislodge into the airways as a result of the inspiratory airflow[49] and invasive medical interventions, such as tracheal aspiration.[50] Several studies[46,47,51] have confirmed that the ETT biofilm constitutes a persistent source of colonization.

Sources of Colonization

Patients are colonized exogenously by contaminated respiratory equipment, the ICU environment, and the hands of the ICU staff. Several reports have described ICU outbreaks caused by colonized bronchoscopes,[52,53] water supply,[54] respiratory equipment,[55] humidifiers,[56] ventilator temperature sensors,[57] respiratory nebulizers,[58] and the contaminated ICU environment.[59]

Endogenous colonization is the primary pathogenic mechanism for VAP development. In the critically ill patient, the oral flora shifts early to a predominance of aerobic gram-negative pathogens,[60] *P. aeruginosa*, and methicillin-resistant *Staphylococcus aureus* (MRSA). Pulmonary aspiration of oropharyngeal contents increases the risk for airway colonization and infection. After aspiration and colonization of the airways, the occurrence of VAP primarily depends on the size of the inoculum, functional status of the patient, and competency of host defenses. Controversy remains regarding the exact sequence of colonization and source of infection in the pathogenesis of VAP. Early studies by Feldman and colleagues[61] found that in patients undergoing MV, the oropharynx is the first site to be colonized by pathogens (36 hours), followed by the stomach (36–60 hours), the lower respiratory tract (60–84 hours), and the ETT thereafter (60–96 hours).

Oropharyngeal Colonization

In ICU patients, several oropharyngeal defense mechanisms are dramatically altered. First, comorbidities and inherent patient characteristics, such as alcohol abuse,[62] diabetes,[63] and chronic obstructive pulmonary disease (COPD),[64] are well-known risk factors for gram-negative oropharyngeal colonization. Elderly patients,[65] patients with disabilities,[66] and patients tracheally intubated for extended periods are at increased risk for overgrowth of oropharyngeal pathogens because of their inability to carry out effective oral care. Additionally, the extensive use of antibiotics in critical care settings promotes overgrowth of oropharyngeal pathogens.[67,68] Second, during critical illness, the antimicrobial effectiveness of saliva is highly impaired because of a dramatic reduction in the salivary flow,[69] decreased pH,[70] and increased amount of proteases released by host immune cells and periodontal bacteria.[71,72] Bacteria that colonize the oropharynx also

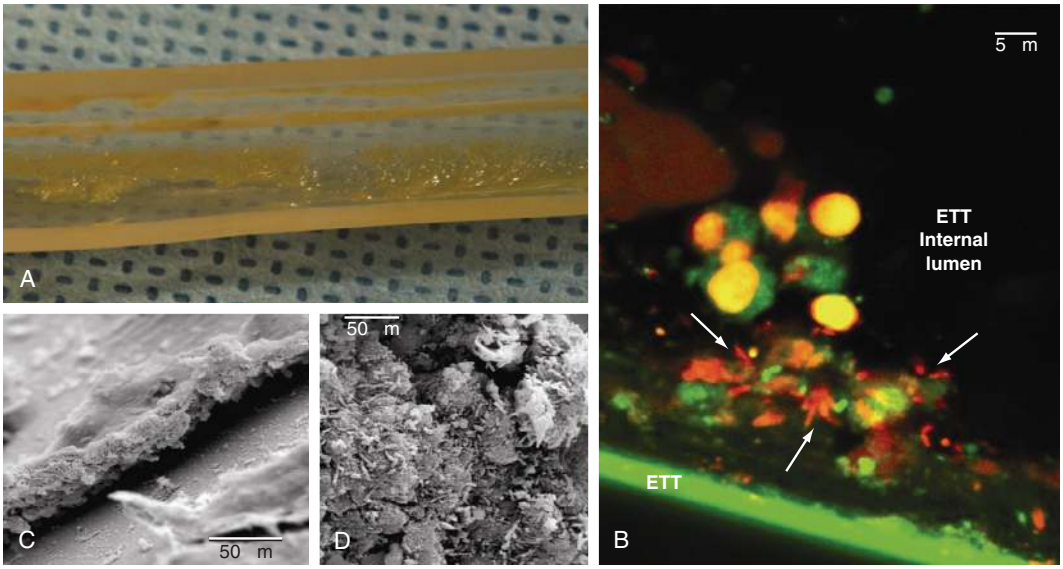

Fig. 68.1 Laboratory Studies to Assess Biofilm Formation on the Internal Surface of the Tracheal Tube After Oropharyngeal Challenge in Pigs of *Pseudomonas Aeruginosa* (Strain PAO1) and 72 Hours of Mechanical Ventilation. **A,** Internal surface of the tracheal tube at extubation, largely covered by respiratory secretions. **B,** Cross section of tracheal tube stained with LIVE/DEAD BacLight bacterial viability kit and imaged with confocal scanning laser microscopy. Bacterial biofilm adheres to internal endotracheal tube (*ETT*) surface. *White arrows* indicate bacteria embedded into biofilm matrix. **C,** Scanning electron microscopy of tracheal tube lumen. Note the presence of amorphous deposits on most of the surface. **D,** Higher magnification of tracheal tube lumen through scanning electron microscopy. *P. aeruginosa* sessile cells are clearly visible within biofilm extracellular polymeric substance.

produce a large variety of hydrolases that lead to increased expression of key receptors for bacterial adhesion.[73,74]

Fourrier and collaborators[75] found that prolonged ICU stay increased the risk for oropharyngeal colonization, which ultimately led to nosocomial pulmonary infection. Azarpazhooh and colleagues[76] found evidence of an association between pneumonia and poor oral health (OR = 1.2–9.6, depending on oral health indicators); improved oral hygiene reduced the occurrence of respiratory infection among high-risk elderly adults. Interestingly, in a study by Heo and colleagues,[77] oral respiratory pathogens were often genetically identical to pathogens recovered from the lower airways, and rapid changes of bacterial species occurred in both oral and pulmonary sites.

Sinuses

The association between sinusitis and VAP has long been debated.[78] Several studies have confirmed that orotracheal as compared with nasotracheal intubation is associated with a decreased incidence of sinusitis[79–81] and that the incidence of VAP is lower in patients who do not develop sinusitis.[82] A study by Holzapfel and colleagues[83] evaluated the incidence of nosocomial maxillary sinusitis and pneumonia in patients who underwent either nasotracheal or orotracheal intubation. The authors found that sinusitis increased the risk of nosocomial pneumonia by a factor of 3.8. Presently, only a small proportion of patients are nasotracheally intubated; hence the incidence of sinusitis in mechanically ventilated patients and associated risks of VAP may now be lessened.

Stomach

According to the gastropulmonary hypothesis of colonization, the stomach of ICU patients is colonized by pathogens because of gastric alkalinization associated with enteral nutrition and drugs for the prevention of gastrointestinal (GI) bleeding.[84] Gastroesophageal reflux facilitates translocation of microbes into the oropharynx, which is then aspirated across the ETT cuff. Early studies have shown that in tracheally intubated patients, gastric pH higher than 4 was consistently associated with gastric colonization.[85,86] However, the association between gastric colonization and VAP reported in very early studies[87,88] has been challenged.[89,90] Overall, this area remains highly controversial, and several studies have not found that bacteria causing VAP first originated in the stomach. Recently, in a large randomized clinical trial,[91] Krag and collaborators randomized 3298 ICU patients to daily pantoprazole versus placebo and found pneumonia rates identical between the groups.

Impairment of Respiratory Defense During Critical Illness and Tracheal Intubation

In healthy subjects, the anatomic laryngeal barrier prevents aspiration of pathogen-laden oropharyngeal contents. After intubation, the ETT completely bypasses these anatomic barriers. A cough is one of the most efficient mechanisms to prevent further translocation of pathogens that may have gained access to airways. Tracheal intubation prevents the closure of the glottis and sudden, high-velocity expulsions. Hence, it hinders cough[92]; moreover, intubated patients are often sedated and unable to generate high expiratory flows.

Mucociliary clearance is the primary innate airway defense mechanism to clear pathogens. In young, healthy nonsmokers, the mucociliary velocity ranges between 10 and 20 mm/min. Studies in animals have shown that inflation of the ETT cuff lowers mucociliary velocity by 50% after only 2 hours.[93] Clinical studies[94] in critically ill patients have found similar reductions of mucociliary velocity (0.8–1.4 mm/min) accompanied by higher risks for pulmonary complications.

As previously mentioned, the daily hazard rate for developing VAP is higher during the first days of MV.[16] Investigators have found that a temporary immunoparalysis can be found early in the course of the

critical illness and sepsis.[95,96] In particular, researchers have assessed human leukocyte antigen-DR (HLA-DR) expression on peripheral monocytes as a marker of immune function.[97] Low levels of HLA-DR expression have been found in patients who subsequently developed nosocomial pneumonia.[98]

Respiratory Dysbiosis and Nosocomial Pneumonia

The diverse and dynamic ecosystem of bacteria within the respiratory system has been highlighted by novel culture-independent technologies.[99] The respiratory system microbiome presents a higher level of complexity than previously thought, and it is continuously challenged by microaspiration of pharyngeal microbiota.[100] These potential invaders are ultimately cleared by effective coughing, mucociliary clearance, and the innate and adaptive host defenses. In recent years, investigators have focused on the dynamics of the respiratory microbiome during critical illness and nosocomial pneumonia and emphasized that the microbial burden, diversity, community composition, and host's response are variably impaired.[101] In particular, there is evidence regarding dysbiosis resulting from substantial changes of the predominant bacterial taxa before and after hospitalization. A progressive depletion of biodiversity toward dominant pathogens progressively increases their biomass, and in the context of altered respiratory immunity could ultimately lead to an infection.[102]

Etiology of Nosocomial Pneumonia

Nosocomial pneumonia may be caused by a variety of pathogens; also, in many patients, more than one pathogen may be isolated. Microorganisms responsible for nosocomial pneumonia differ according to the ICU population, the durations of hospital and ICU stays, and the specific diagnostic method(s) used. VAP is commonly caused by aerobic pathogens, often MDR, including *P. aeruginosa*, *Acinetobacter* species, carbapenemase-containing *Klebsiella pneumoniae*, and MRSA.[1,2] Data from 8135 patients with suspected or proven infections (60% with respiratory tract infection) have confirmed that *Klebsiella* species (27%), *Escherichia coli* (25%), *Pseudomonas* species (24%), and *Acinetobacter* species were the most commonly detected pathogens and *S. aureus* was isolated in 5% of the patients, predominantly in North America.[103]

Esperatti and colleagues[3] prospectively evaluated 315 ICU patients with hospital-acquired pneumonia (HAP) admitted to an ICU; among those, 52% were invasively ventilated, whereas 48% were either breathing spontaneously or receiving noninvasive ventilation (NIV). Interestingly, the proportion of causative pathogens was similar between groups, except for a higher proportion of *Streptococcus pneumoniae* in patients not invasively ventilated. In another report[104] that concerned 200 patients with HAP who were eventually admitted to the ICU and either received or did not receive invasive MV, MDR pathogens were identified in 41% and 39% of the isolates, respectively, emphasizing similar risks of harboring these pathogens between HAP and VHAP when critical care is required. Thus it seems that in ICU-acquired pneumonia, the overall frequency of MDR pathogens and MRSA is sufficiently high to warrant the use of broad empirical therapy.

The high rate of polymicrobial infection in VAP has been shown repeatedly. Combes and colleagues[105] studied 124 ICU patients, of whom 52% had monomicrobial VAP and 48% had polymicrobial VAP. In most patients, two different bacterial species were isolated (34%); however, up to four different bacterial species coexisted in seven patients (6%). Interestingly, no differences were detected in mortality rate at 30 days among patients with polymicrobial or monomicrobial infection. A study by Teixeira and colleagues[106] investigated risk factors for inadequate empirical antimicrobial therapy in 151 ICU patients and found that inadequate antimicrobial treatment was associated with polymicrobial VAP (OR = 3.67; 95% confidence interval [CI] = 1.21–11.12; $P = .02$) and higher mortality.

Underlying diseases may predispose patients to infection with specific organisms. Patients with COPD are at increased risk for *H. influenzae*, *Moraxella catarrhalis*, *P. aeruginosa*, and *S. pneumoniae* infections.[107,108] Patients with acute respiratory distress syndrome (ARDS) are at higher risk for developing VAP caused by *S. aureus*, *P. aeruginosa*, and *Acinetobacter baumannii*, and often in these patients, VAP is caused by multiple pathogens.[109,110] Finally, trauma and neurologic patients are at increased risk for *S. aureus*, *Haemophilus*, and *S. pneumoniae* infections.[111–113]

Causative pathogens of VAP that are potentially multiresistant are *P. aeruginosa*, MRSA, *Acinetobacter* spp., *Stenotrophomonas. maltophilia, Burkholderia cepacia*, and *K. pneumoniae.*[11,103] Conversely, *S. pneumoniae*, *H. influenzae*, methicillin-sensitive *S. aureus* (MSSA), and antibiotic-sensitive Enterobacteriaceae are not considered MDR pathogens. In the majority of cases, resistance to third- and fourth-generation cephalosporins in carbapenem-susceptible strains of *E. coli* and *K. pneumoniae* is caused by the acquisition of plasmidic Ambler class A extended-spectrum beta-lactamases or AmpC-like cephalosporinases.[114] Resistance to carbapenems in Enterobacteriaceae is caused by the acquisition of plasmidic carbapenemases, either of Ambler class A (mainly *K. pneumoniae* carbapenemase), B, or D.[114] Importantly, plasmids harboring extended-spectrum beta-lactamase (ESBL)–encoding and/or carbapenemase-encoding genes often carry other resistance genes, which ultimately confer pan-drug resistance. Conversely, carbapenem resistance in *P. aeruginosa* and *A. baumannii* may be caused by loss of outer membrane porins, hyperexpression of efflux pump systems, and carbapenemase production. In 2010 linezolid-resistant MRSA was reported,[115] caused by a plasmid harboring the chloramphenicol-florfenicol resistance gene.[116–118]

Patients at risk of being colonized by MDR pathogens often present with several comorbidities, and many have received antibiotics during their hospitalization. The incidence of MDR pathogens is also closely linked to local factors and varies widely from one institution to another.[119] Therefore clinicians must be aware of their ICU's local ecology and antibiotic susceptibility so as to avoid the administration of inadequate initial antimicrobial therapy.

Legionella pneumophila as the cause of nosocomial pneumonia should be considered, particularly in immunocompromised patients.[120] Often, the source of legionellosis outbreaks within the hospital is a water system that has become colonized by the microorganism.[121]

A primary mechanism for VAP development is through aspiration of oropharyngeal contents, and the oropharynx is highly colonized by anaerobes. Robert and colleagues[122] studied 26 mechanically ventilated patients and found that 15 patients became colonized with 28 different anaerobic strains. Similarly, Doré and colleagues[123] found anaerobic bacteria in 30 (23%) of 130 patients diagnosed with VAP but always in association with aerobic pathogens. Importantly, empirical antibiotic therapy active against anaerobic bacteria appears to improve short-term outcomes in patients with VAP. The role of anaerobes in VAP has been consistently controversial in the reported literature.[124] Yet more advanced molecular techniques to appraise lung microbiota during acute disease are corroborating the role of anaerobes in the development of VAP.[125]

Rarely, VAP is caused by fungi. *Candida* spp. and *Aspergillus fumigatus*[126] are the most commonly isolated fungi, predominantly in immunocompromised patients. *Candida* promotes the development of pneumonia by creating biofilms that facilitate bacterial colonization.[127] Moreover, *Candida* seems to reduce host immune response.[128] Thus clinical studies have shown that *Candida* colonization increases

the risk of VAP by *P. aeruginosa*.[129] Yet in a postmortem study of patients with evidence of pneumonia at autopsy and isolation of *Candida* from respiratory samples, no case of *Candida* pneumonia was found.[130] Interestingly, colonization by *Candida* has also been associated with longer MV, ICU and hospital stays, and rates of in-hospital mortality.[131–133] Some investigators argue that the presence of *Candida* is merely a marker of severity rather than a true etiologic factor for VAP.[134] The role of *Aspergillus* spp. in the pathogenesis of VAP has been recently reappraised.[31] In an interesting study by Loughlin and collaborators,[135] 24 out of the 194 mechanically ventilated patients (12.4%) met the definition of *Aspergillus* infection, corroborated by positive galactomannan in either BAL fluid or serum. These figures are in line with postmortem findings corroborating invasive pulmonary aspergillosis often clinically undiagnosed antemortem.[136]

Viruses may also cause VAP. Herpes simplex virus type-1 (HSV-1) nosocomial pneumonia is more frequently reported in immunocompromised patients and patients with ARDS,[137] major surgery,[138,139] or extensive burns.[140] Luyt and colleagues demonstrated in 201 patients with clinical suspicion of VAP that 21% had HSV-1 pneumonia.[141] Several studies[142–145] have reported a high incidence of active cytomegalovirus (CMV) infection in mechanically ventilated patients. Chiche and colleagues[144] studied 242 immunocompetent ICU patients and found active CMV infection in 39 (16%) individuals. At 28 days, only 15% of the patients with active CMV infection were weaned and alive, in comparison to 52% of patients free of CMV infection ($P < .001$).

PREVENTION

Nosocomial pneumonia is associated with high rates of morbidity and mortality and constitutes an important burden for the healthcare system. Therefore preventive strategies should be implemented to reduce the overall incidence of the disease (Box 68.1). The Institute for Healthcare Improvement recommends that approaches with proven efficacy in infection control be implemented together as a "bundle" because when combined, they are expected to result in better outcomes than when implemented individually. Designing a preventive bundle is just a first step that must be followed by a continuous assessment of healthcare personnel compliance and by improvements to implement interventions. An interesting report by Klompas and colleagues[146] that appraised the effects of certain components of various bundles found that the association of head-of-bed elevation, sedative infusion interruptions, spontaneous breathing trials, and thromboembolism prophylaxis were the most beneficial elements within bundles. Several reports[147–149] have found consistent reductions in the incidence of VAP after the implementation of VAP preventive bundles.

BOX 68.1 Preventive Strategies for Nosocomial Pneumonia

- Implementation, as a bundle, of nosocomial pneumonia preventive strategies that have proven efficacy in reducing morbidity and mortality
- Implementation of educational programs for caregivers and frequent performance feedbacks and compliance assessment
- Strict alcohol-based hand hygiene
- Avoidance of tracheal intubation and use of NIV when indicated
- Daily sedation vacation and implementation of liberation from mechanical ventilation protocols
- No ventilatory circuit tube changes unless the circuit is soiled or damaged
- Use of tracheal tube with cuff made of novel materials and shapes
- Use of silver-coated tracheal tube
- Application of low-level PEEP during tracheal intubation
- Aspiration of subglottic secretions
- Internal cuff pressure maintained within the recommended range and carefully controlled during transport of patients outside the ICU
- Oral care with chlorhexidine
- Avoid stress ulcer prophylaxis in very low-risk patients for gastrointestinal bleed, and consider use of sucralfate when indicated
- Semirecumbent patient positioning
- Continuous lateral rotation therapy
- Postpyloric feeding in patients who have impaired gastric emptying
- SDD for patients requiring >48 hours of mechanical ventilation

ICU, Intensive care unit; *NIV,* noninvasive ventilation; *PEEP,* positive end-expiratory pressure; *SDD,* selective digestive decontamination.

General Prophylactic Measures

Maintaining high levels of education among ICU personnel relating to VAP pathophysiology and preventive strategies can be effective in reducing its incidence.[150] Needleman and colleagues[151] studied administrative data from 799 hospitals in 11 states (covering 5,075,969 discharges of medical patients and 1,104,659 discharges of surgical patients) and found that a higher proportion of hours of care per day provided by registered nurses, compared with licensed practical nurses and nurses' aides, was associated with lower incidence of pneumonia.

Adherence to simple infection control measures, such as alcohol-based hand disinfection,[152,153] effectively reduces cross-transmission of pathogens and incidence of VAP. The World Health Organization has endorsed hand hygiene as the single most important element of strategies to prevent healthcare–associated infections.[154] Overall, most studies have demonstrated a temporal association between implementation of alcohol-based hand hygiene and reduction of nosocomial infections in ICU environments.[148,155]

Investigators have reported that transporting the patient outside the ICU was associated with increased risk for VAP.[156,157] Clinicians and nursing staff should carefully check the internal pressure of the ETT cuff before and during patient transport. Also, ventilator circuits should be carefully manipulated to prevent the aspiration of colonized fluids from within the circuit.

Daily interruption or lightening of sedation[158–160] and early mobilization,[161] in addition to avoidance of paralytic agents, are highly recommended to avoid impairment of respiratory defenses, prolonged tracheal intubation, and VAP.

There is evidence of shorter length of MV, reduced rates of failed extubation, and decreased incidence of VAP when protocol-driven liberation from the ventilator is implemented.[162,163] Marelich and colleagues[163] randomized 385 patients to receive either a protocol-driven weaning procedure or standard care and found that duration of MV was decreased from a median of 124 hours for the control group to 68 hours in the protocol-driven weaning group ($P = .0001$). Moreover, a trend toward less VAP was found in the treatment group ($P = .061$).

Noninvasive Ventilation

Tracheal intubation and MV are the main risks for nosocomial pneumonia and should therefore be avoided whenever possible. NIV is an attractive alternative for patients with acute exacerbations of COPD or mild to moderate acute hypoxemic respiratory failure and for some immunocompromised patients with pulmonary infiltrates and respiratory failure.[164–168] NIV can also be safely used to facilitate early extubation and curtail extended invasive weaning. A meta-analysis[169] confirmed that noninvasive weaning is associated with reduced mortality, VAP, and length of stay in the ICU and hospital. Other reports[170,171] have emphasized the role of NIV in preventing reintubation of recently extubated patients at risk for relapse and respiratory failure. Kohlenberg et al.[172] pooled data of 400 ICUs in Germany and found a mean

pneumonia incidence of 1.58 and 5.44 cases per 1000 ventilator days for NIV and invasive MV, respectively. Therefore when indicated, NIV should be attempted to avoid tracheal intubation and reduce the overall duration of tracheal intubation.

Tracheal Tube Cuff

In current critical care settings, patients are intubated with ETTs that are sealed by HVLP cuffs. Upon inflation, folds form along the cuff surface, and colonized oropharyngeal secretions may leak through these folds.[173] ETT cuffs made of polyurethane,[174] silicone,[175] and latex[176] have been developed and tested in the laboratory and clinical trials. In particular, the polyurethane cuff has a thickness of 5 to 10 μm, in comparison with 50 μm for polyvinyl chloride (PVC) cuffs. Hence, upon inflation, smaller folds form with polyurethane cuffs, and aspiration of secretions above the cuff can be prevented or reduced. Some investigators have attempted to prevent aspiration by modifying the shape of the cuff.[177] In comparison with standard cuffs with cylindrical shapes, cuffs designed with a smooth, tapering shape allow elimination of folds for a full circumference of the trachea or cuff contact zone, irrespective of the cuff material.

Assessments in medical ICU patients have shown that polyurethane cuffs reduce risks of developing VAP.[178] The polyurethane-cuffed ETT has also been reported to show benefits in reducing early postoperative pneumonia in cardiac surgical patients.[179,180] Results from earlier studies have been contradicted by a landmark multicenter study[181] that compared preventive benefits of cuffs of cylindrical PVC, cylindrical polyurethane, conical PVC, or conical polyurethane and found no reduction of VAP with the use of polyurethane or conical cuffs. Likewise, Monsel and colleagues did not find any advantage in using conical-shaped ETT cuffs.[182] In our opinion, because of the lack of clear clinical evidence regarding the benefits of better-quality cuffs, their use should be only limited to specific patients at very high risk of developing VAP.

It is important to maintain the internal ETT cuff pressure between 25 and 30 cm H_2O to prevent aspiration of contaminated secretions into the lower airways and to avoid tracheal injury. Several studies[183,184] have demonstrated that the ETT cuff is frequently underinflated or hyperinflated using standard management. Continuous control of internal cuff pressure reduces risks of significant deflation and pulmonary aspiration.

Ventilatory settings may play a role in the pathogenesis of VAP. In particular, positive end-expiratory pressure (PEEP) may decrease the incidence of VAP by counteracting hydrostatic pressure exerted by oropharyngeal secretions above the ETT cuff, hence reducing pulmonary aspiration.[185,186] Lucangelo and colleagues[187] assessed the effects of 5–8 cm H_2O PEEP in normoxemic ventilated patients and showed a reduction in the rate of VAP. Thus in the absence of major contraindications, a low level of PEEP should be maintained.

Tracheal Tubes Coated With Antimicrobial Agents

Coating the ETT with antimicrobial agents, such as silver, is a promising strategy to prevent biofilm formation on its internal surface and VAP.[44] Olson and colleagues[188] tested a silver-coated ETT in dogs challenged with *P. aeruginosa* instilled into the oropharynx. Using the new tube, the investigators were able to postpone colonization of the ETT's inner surface and reduce pulmonary bacterial burden. Similarly, Berra and colleagues[189] studied a silver sulfadiazine/chlorhexidine–coated ETT in sheep. After 24 hours of MV, standard ETTs and ventilatory circuits were heavily colonized, whereas the novel coated ETT fully avoided colonization. Interestingly, the efficacy of silver-based coatings seems to decrease over time. Indeed, animal studies reported heavy colonization of silver-coated ETTs after 72 hours of MV. To date, only one laboratory study[190] has shown the absence of ETT biofilm formation up to 168 hours of MV when silver sulfadiazine ETTs were regularly cleaned with the Mucus Shaver.[191] The North American Silver-Coated Endotracheal Tube (NASCENT) randomized trial[192] compared the preventive effects of a silver-coated vs. conventional ETT. The silver-coated ETT was associated with a lower incidence of microbiologically confirmed VAP (4.8% vs. 7.5%; $P = .03$), for a relative risk reduction of 35.9%. A retrospective cohort analysis by Afessa and colleagues[193] showed that the silver-coated ETT was associated with reduced mortality in patients with VAP (14% vs. 36% in silver and control ETT, respectively, $P = .03$). Mortality was higher in those without VAP. In conclusion, ETT coated with antimicrobial agents could reduce the incidence of VAP, but the evidence supporting its use comes only from one study, with significant limitations.[194] Thus clinicians should carefully consider benefits and limitations of these ETTs and properly direct the use of silver-coated tubes to patients expected to be ventilated for longer periods and with higher risks for nosocomial pneumonia. Shorr and colleagues[195] analyzed the cost-effectiveness of the silver-coated ETT and found that per each prevented VAP, US$12,840 was saved.

Aspiration of Subglottic Secretions

Aspiration of colonized subglottic secretions through dedicated ETTs potentially prevents leakage across the cuff. A meta-analysis[196] has shown that drainage of subglottic secretions reduced the overall risk ratio (RR) for VAP by half (RR = 0.55; 95% CI = 0.46–0.66; $P < .01$). In a multicenter trial by Lacherade and colleagues,[197] 333 patients were randomized to be intubated with either an ETT that allowed drainage of subglottic secretions or a standard ETT. Microbiologically confirmed VAP occurred in 14.8% of the patients in the treatment group, compared with 25.6% of the patients intubated with a standard tube ($P = .02$). Interestingly, subglottic secretion drainage has been consistently associated with tracheal injury in clinical[198,199] and laboratory studies.[43,200]

Tracheostomy

Tracheostomized patients present the same risks for aspiration of pathogen-laden secretions pooled above the cuff as orotracheally intubated patients. A meta-analysis[201] that assessed outcomes of early versus late tracheostomy found that early tracheostomy did not reduce the incidence of VAP. Early tracheostomy may improve patient comfort, ability to communicate, and capability for oral feeding reduce the need for sedation and analgesia and airway resistance in comparison with standard ETTs. These factors are of paramount importance during the weaning period to shorten the duration of tracheal intubation.

Ventilator Circuit Management

Clinical trials in adults[202–204] and meta-analyses[205] have demonstrated that a routine change of the ventilator circuit does not decrease risks for VAP or costs. Therefore circuits should not be changed unless soiled or damaged. Importantly, inadvertent flushing of the contaminated condensate into the lower airways (or by nebulizers) should always be avoided by careful emptying of ventilator circuits and water traps.[206]

A meta-analysis[207] that assessed the effects of heated humidifiers (HHs) and heat and moisture exchangers (HMEs) on prevention of nosocomial pneumonia showed no differential effect on pneumonia prevention. To date, neither humidification strategy can be recommended as a pneumonia prevention tool. However, it is rational to deliver inspiratory gases at body temperature or slightly below and at the highest relative humidity to prevent loss of heat and moisture from the airways, adverse change in rheologic properties of secretions, and

impairment of mucociliary clearance. The use of HH is selectively indicated in patients with hypothermia, prolonged MV, thick secretions, and chronic respiratory disorders. Finally, studies[208–210] testing less frequent changes of HMEs have not found increased risks for VAP. HMEs should be changed periodically (i.e., every 72 hours or when overtly contaminated) to ensure good performance.

Closed tracheal suctioning systems have been introduced in clinical settings to avoid adverse events associated with ventilator disconnection during open tracheal suctioning in addition to exogenous contamination by suction catheters entering the ETT. Various meta-analyses[211–213] have compared the closed and the open tracheal suction system in mechanically ventilated patients and found no advantage of either for VAP prevention.

The use of a saline solution instilled into the ETT before tracheal suctioning remains controversial. A systematic review[214] reported decreased patient oxygenation in most studies. One study[215] found a lower incidence of microbiologically proven VAP (saline instillation versus no treatment: 23.5% vs. 10.8%; $P = .008$). Likewise, a later study found that when closed tracheal suction systems with HMEs were used, saline instillation was advantageous in reducing the incidence of VAP.[216] Importantly, in sedated patients in the semirecumbent position and with the ETT internal surface highly colonized, saline instillation may increase risks for translocation of pathogens into the airways.

Body Position

Early studies demonstrated that intubated patients are at higher risk for gastropulmonary aspiration when placed in the supine position (0 degrees) as compared with a semirecumbent position (45 degrees).[84,217,218] One randomized trial[219] demonstrated a reduction in the incidence of VAP in patients positioned in the semirecumbent position as opposed to completely supine, particularly during enteral feeding. A later randomized trial[220] found limited feasibility of the intervention and no differences in VAP incidence. Given available evidence,[221] intubated patients should be preferentially kept in the semirecumbent position (30–45 degrees) rather than supine (0 degrees), especially when receiving enteral feeding.

Laboratory reports[222,223] have challenged the preventive benefits of the semirecumbent position. Theoretically, a tracheal orientation above horizontal might facilitate aspiration across the ETT cuff. The Gravity-VAP study was a randomized trial that studied 194 endotracheally intubated patients positioned in the lateral-Trendelenburg position (LTP) in comparison with 201 in the standard semirecumbent position. The authors found that the LTP could further reduce VAP, specifically in patients with healthy lungs upon intubation, but LTP feasibility appeared challenging.[224]

Rotating Bed

Several ICU beds permit the rotation of patients along the longitudinal axis from one lateral position to the other. These appear to reduce extravascular lung water, improve the ventilation-perfusion ratio, and enhance mobilization of airway secretions. Meta-analyses[225,226] have shown a significant reduction in the incidence of VAP among patients undergoing rotation therapy. Staudinger and colleagues[227] studied the effects of continuous lateral rotation therapy and found a VAP incidence of 11% in the rotation group and 23% in the control group ($P = .048$). Those authors also found that the duration of ventilation (8 ± 5 vs. 14 ± 23 days; $P = .02$) and length of stay (25 ± 22 days vs. 39 ± 45 days; $P = .01$) were significantly shorter in the rotational group. In conclusion, in patients at higher risk for prolonged immobilization and respiratory infection, continuous lateral rotation therapy may add to other preventive measures for VAP.

Stress Ulcer Prophylaxis and Enteral Feeding

Sucralfate, histamine type 2 blockers (H_2 blockers), and proton pump inhibitors (PPIs) are the most common medication for stress ulcer prophylaxis. Of these, sucralfate is the only treatment that does not cause gastric alkalinization. Early studies found a higher incidence of pneumonia in patients with alkalinized gastric contents,[87,88] whereas others have not.[90] Cook and colleagues[228] found a higher risk of GI bleeding using sucralfate and no significant difference in VAP incidence: 19.1% and 16.2% in patients treated with H_2 blockers or sucralfate, respectively. Likewise, in a meta-analysis,[229] PPIs were more effective than H_2 blockers at reducing upper GI bleeding, without differences in VAP (RR = 1.06; 95% CI = 0.73–1.52; $P = .76$). Krag and colleagues[91] recently studied 3298 ICU patients who were randomized to receive either pantoprazole or placebo. At 90 days, the RR of mortality was 1.02; 95% CI 0.91–1.13; $P = .76$ and no difference was found in the development of respiratory infections between groups. In conclusion, GI bleeding is a serious complication in critically ill patients. The actual risk for VAP is unknown when appropriate methods of enteral feeding (i.e., avoiding large gastric residual volumes) or other preventive measures are used in combination with stress ulcer prophylaxis. Therefore clinicians should probably limit stress ulcer prophylaxis to high-risk patients and weigh the potential benefit of sucralfate (with potentially less VAP and more GI bleeding) versus H_2 blockers/PPIs (with potentially more VAP and less GI bleeding).

Enteral nutrition has been considered a risk factor for the development of VAP because of increased incidence of gastric alkalinization, gastroesophageal reflux, and gastropulmonary aspiration. However, its alternative, parenteral nutrition, is associated with higher risks for catheter-related infections, complications of line insertions, higher costs, and loss of intestinal villous architecture, which may facilitate enteral microbial translocation. A large meta-analysis[230] of 11 studies comprising more than 500 critically ill patients found that the use of parenteral nutrition was associated with more infectious complications, compared with early enteral nutrition (OR = 1.47; 95% CI = 0.90–2.38; $P = .12$). Conversely, studies in medical ICU patients have demonstrated a higher risk for VAP with early enteral feeding.[231,232] Therefore in medical ICU patients, the benefits of early nutrition should be balanced with associated increased risks for VAP.

Many ICU patients experience impaired gastric emptying. Placement of the feeding tube beyond the pylorus has the potential to achieve nutrition goals without increased risks for gastropulmonary aspiration. A meta-analysis by Jiyong and colleagues[233] found that small bowel feedings were associated with a lower incidence of pneumonia (RR = 0.63; 95% CI = 0.48–0.83; $P = .001$). In an interesting report by Davies and collaborators,[234] in mechanically ventilated patients with mildly elevated gastric residual volumes who were already receiving nasogastric nutrition, early postpyloric nutrition did not increase energy delivery or reduce the frequency of pneumonia. Therefore postpyloric feeding should be preferred only when impaired gastric emptying is present. Finally, a landmark study[235] challenged the utility of routine monitoring of residual gastric volume in 449 patients receiving invasive MV and early enteral nutrition. VAP occurred in 16.7% of the patients without routine monitoring, in comparison with 15.8% in the control group.

Modulation of Oropharyngeal and Gastrointestinal Colonization

Given the pivotal role of oropharyngeal colonization in the development of VAP, many decontamination strategies have been developed, which include caregiver handwashing, oral hygiene and tooth brushing,[236] selective oral decontamination with topical nonabsorbable antibiotics,[237] and oropharyngeal rinsing with antiseptics.[238] Chlorhexidine

is a cationic chlorophenyl *bis*-biguanide antiseptic that has long been used as an inhibitor of dental plaque formation and gingivitis. A meta-analysis[238] of studies assessing the benefits of chlorhexidine on the reduction of VAP reported fewer lower respiratory tract infections in cardiac surgery patients (RR = 0.56; 95% CI = 0.41–0.77) but without a significant mortality difference (RR = 0.88; 95% CI = 0.25–2.14). Results in noncardiac ICU populations have been inconsistent. Most of the studies described in earlier years used chlorhexidine concentrations up to 0.2%. This concentration may not be effective in most ICU patients with high levels of oropharyngeal colonization. Studies[239,240] have demonstrated significant reductions in VAP rates when chlorhexidine concentration was increased to 2%. Importantly, in recent years, arguments have been raised against the use of chlorhexidine because of associated increased mortality risk.[241] These findings could be misleading or imply that extensive pulmonary aspiration of chlorhexidine might occur in patients in the semirecumbent position. Additional data are needed to resolve this issue.

Selective digestive decontamination (SDD) comprises a combination of nonabsorbable antibiotics against gram-negative pathogens (i.e., tobramycin and polymyxin E) plus either amphotericin B or nystatin. These agents are administered into the GI tract to prevent oropharyngeal and gastric colonization with aerobic gram-negative bacilli and *Candida* spp. while preserving the anaerobic flora. Some regimens include a short course of systemic antibiotics (i.e., cefotaxime). SDD was originally applied to oncologic and hematologic patients with severe immunosuppression.[242,243] In the early 1980s Stoutenbeek and colleagues introduced this practice into critical care medicine.[244] Since then, a remarkable number of clinical trials and meta-analyses confirmed the benefits associated with the use of SDD, which has been associated with reduced incidence of VAP, bacterial bloodstream infections, and mortality.[245] Currently, SDD is primarily applied in a minority of European centers with low levels of MDR.

Randomized clinical trials[237,246,247] and meta-analyses[245] confirmed that SDD confers protection against nosocomial pneumonia. Several factors, however, should be taken into account before advocating its use worldwide. First, investigations on the intestinal microbiota highlight the variability, interactions, and complexity of GI bacterial colonies and systemic consequences of changes in gut colonization.[248–250] Indeed, it is known that more than 10^{11} bacteria per gram of feces, comprising more than 1000 different species, are present in our intestinal system.[251] Large interindividual variations in bacterial patterns are evident even among humans living in the same geographic region.[252] Considering the increasing interest of the critical care field on individualized medicine, the implementation of a unit-wide single SDD regimen for all ICU population subtypes seems unwise. In addition, even the selectivity of SDD against aerobic gram-negative bacteria has been challenged.[253] Thus the impact of SDD on the intestinal microbiota and the resulting alterations of bacterial diversity need further evaluation. Second, one of the most recurrent arguments for not using SDD is that microorganisms not addressed by the regimen may be selected (i.e., MRSA and *Enterococcus* spp.) or MDR for the applied antibiotics may increase. An increase in anaerobic flora antibiotic resistance genes during SDD, particularly highly transferable genes conferring resistance to aminoglycosides, has been corroborated.[248] In line with these results, Oostdijk and collaborators[246] found increases in aminoglycoside-resistant gram-negative bacteria during SDD use. Finally, in one older study[254] by the same group that explored recolonization after SDD, increased intestinal colonization occurred with gram-negative bacteria resistant to ceftazidime, tobramycin, or ciprofloxacin. Likewise, resistance to ceftazidime increased gradually in the respiratory tract during SDD and even further postintervention for all three antibiotics used in the SDD regimen. This suggests that there are still several unknown effects of SDD that need to be addressed. Of note, in a recent study[255] the effects of SDD/SOD (selective oropharyngeal contamination) on bloodstream infections was conducted in ICUs with high prevalence of antibiotic resistance. Mortality rate was not affected by the interventions, and antibiotic resistance did not vary throughout the study periods. Only one study[256] has demonstrated that a short course of cefuroxime in patients with structural coma or severe burns was an effective prophylactic strategy to decrease the VAP rate. However, routine use of parenteral antibiotics is not recommended until more data become available.

Several clinical trials have attempted to modify GI and oropharyngeal growth of pathogens through the use of probiotics. Probiotics are innocuous microorganisms that can be administered either as individual strains or in various combinations. These microorganisms are often administered with nondigestible food ingredients that facilitate bacterial growth and activity (prebiotics). Products containing both probiotics and prebiotics are called *synbiotics*. A meta-analysis[257] on the effects of probiotics suggests that probiotics may reduce the incidence of VAP. The low quality of the evidence does not enable one to draw firm conclusions regarding utility.

DIAGNOSIS

How best to establish the diagnosis of VAP remains controversial.[258–261] Clinical signs suggestive of pneumonia, such as fever, tachycardia, and leukocytosis, are nonspecific in critically ill patients.[262,263] Moreover, the chest radiograph is often difficult to interpret, and it may not reveal subtle lung infiltrates, which are better detected by computed tomography (CT) scans.[264] When infiltrates are evident, the differential diagnosis is challenging (i.e., cardiogenic and noncardiogenic pulmonary edema, pulmonary contusion, and atelectasis).

Few studies have examined the accuracy of portable chest radiographs for making the diagnosis of VAP.[265,266] In mechanically ventilated patients with autopsy-proven VAP, no single radiographic sign had a diagnostic accuracy greater than 68%.[267] In patients with ARDS, marked heterogeneity of radiographic abnormalities has been reported. A clinical study showed the presence of lung infection in only 42% of the patients with clinically suspected VAP.[268] The presence of air bronchograms may increase the specificity of chest radiographs in ARDS patients.

The Clinical Pulmonary Infection Score (CPIS) is based on six clinical assessments.[269] The CPIS showed a good correlation ($r = 0.84$; $P < .0001$) with quantitative bacteriology of BAL samples. Moreover, a value ≥6 was the threshold to accurately identify patients with pneumonia. In recent years the value of CPIS in the diagnosis of VAP has been reconsidered,[104] and it should be emphasized that the score remains to be validated in a large prospective study, especially in patients with bilateral pulmonary infiltrates. Several diagnostic biomarkers have also been investigated to improve diagnostic accuracy. In 2016 results of the BioVAP study, a multicenter study that investigated the kinetics of biomarkers to predict VAP, were published.[270] The authors found that C-reactive protein (CRP) and CRP slopes over time presented moderate diagnostic accuracy, whereas procalcitonin, pro-adrenomedullin, and soluble urokinase plasminogen receptor (SUPAR)[271] performed poorly. Finally, in the recent VAPrapid2 multicenter, randomized controlled trial (RCT),[272] 214 patients were randomized to biomarker-guided recommendations on antibiotics, quantifying interleukin (IL)-1-beta and IL-8 in BAL fluid, or routine use of antibiotics. The authors did not find any difference in antibiotic-free days in the 7 days after BAL.

The presence of bacteria in the lower airways of intubated patients is not sufficient to diagnose VAP, because it could be only nonpathogenic colonization or VAT. In one study, cultures of endotracheal

aspirate from patients with respiratory failure and histologically documented pneumonia simultaneously obtained from the trachea and lung tissue agreed in only 40% of cases, with a 82% sensitivity and 27% specificity.[273] Similarly, in another study, only 23% of colonized patients subsequently developed VAP.[60] The use of Gram staining for the diagnosis of VAP has also been debated. In a meta-analysis pooling data from 21 studies,[274] sensitivity and specificity of Gram staining were only 79% and 75%, respectively, with a positive predictive value of 40%. Yet the diagnostic accuracy seems higher when narrowed to the diagnosis of VAP caused by *S. aureus*. In a recent meta-analysis[275] pooling data from 1665 respiratory samples, overall sensitivity and specificity were 68% and 95%, respectively. However, in clinical scenarios with *S. aureus* prevalence between 5% and 20%, a negative predictive value of 95% was found.

Many sampling procedures of respiratory secretions, such as sputum collection, endotracheal aspirates, BAL, and protected specimen brush (PSB), are available. In addition, there are several microbiologic techniques, including Gram staining and intracellular organism count, for specimens obtained via BAL. Each diagnostic technique has advantages and limitations and provides different diagnostic specificity and sensitivity.

Qualitative cultures of endotracheal aspirates have a high percentage of false-positive results. Conversely, quantitative culture techniques are more reliable if appropriate cutoff criteria are applied. When patients develop pneumonia, pathogens are present in the lower respiratory tract secretions at concentrations of at least 10^5 to 10^6 colony-forming units (CFU)/mL.[276–279] The current diagnostic threshold proposed for tracheal aspirates is 10^6 CFU/mL. Similarly, PSB collects between 0.001 and 0.01 mL of secretions. Therefore the presence of more than 10^3 bacteria in the originally diluted sample (1 mL) represents 10^5 to 10^6 CFU/mL in pulmonary secretions. Finally, 10^4 CFU/mL is considered the cutoff for BAL, which collects 1 mL of secretions in 10–100 mL of effluent.

In one study,[279] only 40% of the microorganisms cultured in endotracheal aspirate samples coincided with those obtained from PSB specimens. Also, when quantitative cultures of different lower respiratory tract specimens were compared with postmortem quantitative lung biopsy cultures, all techniques for detecting VAP were of limited value.[280]

A major problem in the management of patients with suspicion of VAP is the concurrent use of antibiotics. The indiscriminate administration of antimicrobial agents for patients in the ICU may contribute to the emergence of MDR pathogens and raise the risk of superinfections with increased morbidity and mortality and expose the patient to antibiotic-related adverse effects and higher costs.[281] On the other hand, correct and prompt treatment of pneumonia results in better patient survival.[33,282,283] Inadequate empirical antibiotic treatment, initiated before obtaining the results of cultures from respiratory secretions, was associated with greater hospital mortality compared with antibiotic regimens that provided adequate antimicrobial coverage based on microbiologic culture results.[284–287] However, the choice of initial antibiotic treatment is often difficult because of previous antibiotic treatment,[288] prevalence of MDR pathogens, and colonizing pathogens.[289,290]

Several rapid molecular techniques (i.e., polymerase chain reaction [PCR]) have been developed to expedite identification of causative pathogens of nosocomial pneumonia through microbial DNA, helping to guide prompt administration of appropriate antibiotic therapy.[291] The available assays are either pathogen specific (i.e., to identify MRSA)[292] or are aimed to identify, through multiplex PCR assays, a broad spectrum of pathogens that cause nosocomial pneumonia.[293–295] Further studies and clinical validation are needed to help identify for the clinician when and how PCR can be used. In a remarkable study by Paonessa and colleagues,[274] the impact of a novel rapid diagnostic MRSA testing was compared with usual care in a small population of 45 patients. Duration of anti-MRSA antibiotics was reduced using the rapid test, and although the study was underpowered, hospital mortality was 13.6% in the intervention group and 39.1% for usual care (95% CI of difference, −3.3 to 50.3, $P = .06$). Additionally, efforts have been made to detect rapidly the most important MDR genes, such as *mecA, blaKPC, blaIMP, blaVIM,* and *blaOXA*.[296] Finally, a Spanish study tested a rapid E-test antibiogram for six antibiotic agents that could provide antibiotic susceptibility within 24 hours and found that the use of this technique resulted in more appropriate and reduced use of antibiotics in VAP patients.[297]

Ventilator-Associated Events Surveillance Algorithm

The Centers for Disease Control introduced the ventilator-associated events (VAEs) surveillance definition algorithm[298] to monitor complications in mechanically ventilated patients (Fig. 68.2). This new algorithm was developed to monitor objectively pulmonary complications associated with worse outcomes in mechanically ventilated patients. Importantly, reports had demonstrated poor concordance between infection-related ventilator-associated condition (IVAC), possible and probable VAP, and VAP diagnosed with standard criteria.[299,300] In a study by Bouadma and collaborators,[301] sensitivity and specificity of diagnosing VAP were 0.92 and 0.28 for the ventilator-associated condition and 0.67 and 0.75 for IVAC, respectively. Boyer and colleagues[302] studied 1209 patients ventilated for ≥2 calendar days with 5.5% VAE. The most common causes of VACs included IVACs (50.7%), ARDS (16.4%), pulmonary edema (14.9%), and atelectasis (9.0%). The sensitivity of the VAE algorithm for the detection of VAP was only 25.9% (95% CI = 16.7%–34.5%). Thus the VAE algorithm should be considered a powerful benchmarking tool that has only marginal value for the diagnosis of VAP.

Diagnostic Strategies for Hospital-Acquired Pneumonia

Recommendations regarding diagnostic strategies to be applied in patients with clinical suspicion of VAP diverge between the most recent American[1] and European guidelines.[2] In particular, based on the results of a large meta-analysis on diagnostic techniques,[303] the latest American guidelines recommend (weak recommendations with low-quality evidence) noninvasive sampling with semiquantitative cultures. The European guidelines, by contrast, recommend distal quantitative sampling (i.e., BAL) before antibiotic use. The intent of that approach is to reduce overall use of antibiotics, because several previous studies in this field were limited by the lack of antimicrobial de-escalation upon obtaining positive or negative culture results.

An ideal diagnostic strategy for patients with clinical suspicion of HAP should reach the following objectives:

1. Accurately identify patients with true pulmonary infection and isolate the causative microorganisms to initiate appropriate antimicrobial coverage and subsequently to optimize therapy based on the susceptibility of the pathogens.
2. Identify patients with extrapulmonary sites of infection.
3. Withhold and/or withdraw antibiotics in patients without infection.

The diagnosis of nosocomial pneumonia begins with clinical suspicion. The presence of new or progressive radiographic infiltrates plus at least two of three clinical criteria (fever/hypothermia, leukocytosis/leukopenia, and purulent secretions) represents the starting point to begin diagnostic procedures.

Based on our clinical expertise and recognizing potential heterogeneity in worldwide practice in this field, two diagnostic algorithms could be used when there is clinical suspicion of nosocomial pneumonia. The

Patient has a baseline period of stability or improvement on the ventilator, defined by ≥ 2 calendar days of stable or decreasing daily minimum FiO_2 or PEEP values. The baseline period is defined as the 2 calendar days immediately preceding the first day of increased daily minimum PEEP or FiO_2

↓

After a period of stability or improvement on the ventilator, the patient has at least one of the following indicators of worsening oxygenation: 1) Minimum daily FiO_2 values increase > 20 over the daily minimum FIO_2 in the preceeding 2 calendar days (the baseline period) for ≥ 2 calendar days

↓

Ventilator-Associated Conditions (VAC)

On or after calendar day 3 of mechanical ventilation and within 2 calendar days before or after the onset of worsening oxygenation, the patient meets both of the following criteria:

1) Temperature ≥ 38°C or ≤ 36°C or white blood cell count ≥ 12,000 cells/mm³ or ≤ 4000 cells/mm³

AND

2) A new antimicrobial agent(s) is started and is continued for ≥ 4 days

↓

Infection-Related Ventilator-Associated Complication (IVAC)

On or after calendar day 3 of mechanical ventilation and within 2 calendar days before or after the onset of worsening oxygenation, ONE of the following criteria is met:

1) Purulent respiratory secretions (from one or more specimen collections), defined as secretions from the lungs, bronchi, or trachea that contain ≥ 25 neutrophils and < 10 squamous epithelial cells per low power field [lpf x 100] (or corresponding semi-quantitative results)
2) Positive culture (qualitative, semi-quantitative or quantitative) of sputum, endotracheal aspirate, bronchoalveolar lavage, lung tissue, or protected specimen brushing

Exclude: Normal respiratory/oral flora, mixed respiratory/oral flora or equivalent; *Candida* species or yeast not otherwise specified; Coagulase-negative *Staphylococcus* species; *Enterococcus* species

↓

Possible VAP

On or after calendar day 3 of mechanical ventilation and within 2 calendar days before or after the onset of worsening oxygenation, ONE of the following criteria is met:

1) Purulent respiratory secretions (from one or more specimen collections – and defined as for possible VAP)

AND one of the following:

- Positive quantitative culture of endotracheal aspirate ≥ 10^5 cfu/mL or equivalent semiquantitative and follow result
- Positive quantitative culture of BAL ≥ 10^4 cfu/mL or equivalent semi-quantitative result
- Positive quantitative culture of lung tissue ≥ 10^4 cfu/gr mL or equivalent semi-quantitative result
- Positive quantitative culture of PSB ≥ 10^3 cfu/mL or equivalent semi-quantitative results

Same organism exclusions as noted for possible VAP

2) One of the following (without requirements for purulent respiratory secretions):

- Positive pleural fluid culture (where specimen was obtained during thoracentesis or initial placement of chest tube and NOT from an indwelling chest tube)
- Positive lung histopathology
- Positive diagnostic test for *Legionella* spp.
- Positive diagnostic tests on respiratory secretions for influenza virus, respiratory syncytial virus, adenovirus, parainfluenza virus, rhinovirus, human metapneumovirus, coronavirus

↓

Probable VAP

Fig. 68.2 Ventilator-Associated Events Surveillance Protocol. *BAL*, Bronchoalveolar lavage; *CFU*, colony-forming unit; *FiO_2*, fraction of inspired oxygen; *PEEP*, positive end-expiratory pressure; *VAP*, ventilator-associated pneumonia. (Full surveillance protocol available at http://www.cdc.gov/nhsn/acute-care-hospital/vae/index.html for eligible antimicrobials.)

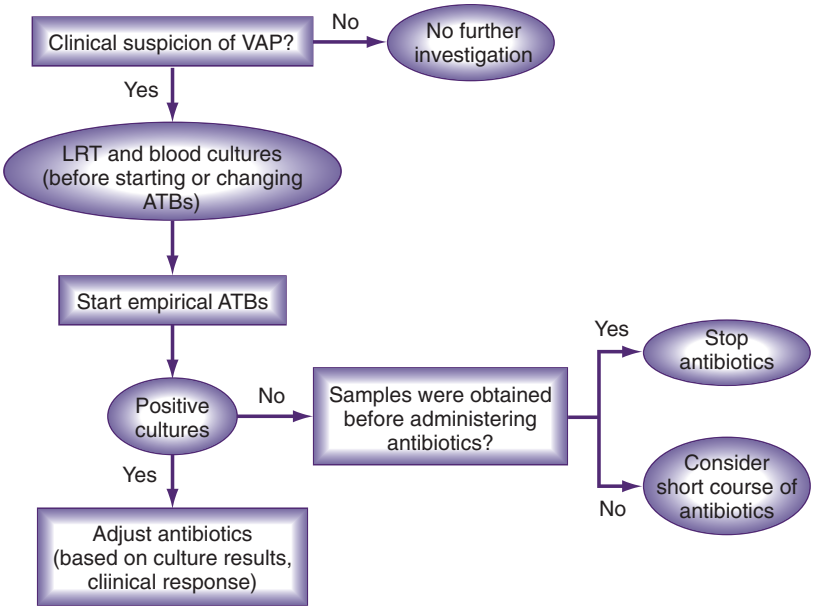

Fig. 68.3 Clinical Noninvasive Strategy for Diagnosis and Management of VAP. *ATBs,* Antibiotics; *LRT,* lower respiratory tract; *VAP,* ventilator-associated pneumonia. (Adapted from American Thoracic Society. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med.* 2005;171:388–416.)

clinical approach recommends treating every patient suspected of having a pulmonary infection with new antibiotics even when the likelihood of infection is low (Fig. 68.3). However, samples of respiratory secretions (e.g., endotracheal aspirate or sputum) should be obtained before the initiation of antibiotic treatment. In this strategy, the selection of appropriate empirical therapy is based on risk factors and local resistance patterns. The etiology of pneumonia is defined by semiquantitative cultures of endotracheal aspirates or sputum, with an initial microscopic examination of the Gram stain. Antimicrobial therapy is adjusted according to culture results or clinical response. The semiquantitative culture of tracheal aspirates has the advantage that no specialized microbiologic techniques are required, and the sensitivity is high. This clinical strategy provides antimicrobial treatment to the majority of the patients with suspicion of HAP and yields a low rate of false negatives. If the tracheal aspirate culture does not demonstrate pathogens and the patient has not received new antibiotics within the previous 72 hours, the diagnosis of pneumonia is unlikely.[304] This strategy is useful in centers where bronchoscopic methods are not always available. The main drawback of this strategy is that the high sensitivity of semiquantitative cultures of tracheal aspirates leads to an overestimation of the incidence of HAP and overuse of antibiotics.

Bacteriologic strategies are based on the results of quantitative cultures of lower respiratory secretions (Fig. 68.4). The procedure used to collect the samples (endotracheal aspirate, BAL, or PSB) may be invasive (bronchoscopic) or noninvasive (blind procedures). The bacteriologic strategy attempts to identify accurately patients with true HAP so that only infected patients are treated and clinical outcomes are improved.[286,305] Such an approach reduces the risks for overuse of antibiotics, because quantitative cultures yield fewer microorganisms above the threshold in comparison to semiquantitative cultures. Among the disadvantages of the bacteriologic strategy is the possibility of obtaining false-negative results that lead to delayed antibiotic treatment in a patient with pneumonia. Moreover, results using the bacteriologic strategy may lack reproducibility, and often no microbiologic information is available at the time that empirical antibiotic therapy is initiated.

Four RCTs[286,306–308] have assessed the impact of diagnostic strategies on antibiotic use and outcome in patients with clinically suspected VAP. In three small studies,[286,306,307] invasive diagnostic techniques resulted in a greater number of antibiotic changes than noninvasive techniques; however, no differences in mortality and morbidity were found when either invasive (PSB and/or BAL) or noninvasive (quantitative endotracheal aspirate cultures) techniques were used. In contrast, a larger trial[308] showed a reduction in mortality, reduced use of antibiotics, and increased number of antibiotic-free days using invasive diagnostic techniques. This study was limited, however, by the use of qualitative cultures of tracheal aspirates, thereby limiting comparison with other clinical trials. Irrespective of the methods used to obtain respiratory samples, it is strongly recommended that samples be obtained before starting new antibiotics, or a lower sampling threshold should be used in patients with recent antibiotic changes.[309,310]

In a noteworthy trial,[311] quantitative culture of BAL fluid and culture of endotracheal aspirate were compared in critically ill patients with suspected VAP. This study was part of a larger 2-by-2 factorial design also comparing empirical antimicrobial monotherapy (a carbapenem) and combination therapy (a carbapenem plus a fluoroquinolone). A total of 740 patients in 28 ICUs throughout Canada and the United States were enrolled. The authors found no difference in the 28-day mortality rate between the BAL group and the endotracheal aspiration group (18.9% and 18.4%, respectively; $P = .94$). The BAL group and the endotracheal aspiration group also had similar rates of targeted therapy and days alive without antibiotics. At least 40% of the screened patients were excluded because they were at risk for colonization with *Pseudomonas* spp. or MRSA or were immunosuppressed. Therefore translation of these findings into clinical practice is challenging because many ICU patients evaluated for suspected VAP fall into these latter categories. In a key meta-analysis,[303] no differences in mortality rates were uncovered for using quantitative cultures versus qualitative cultures (RR = 0.91; 95% CI = 0.75–1.11), nor were differences found regarding the number of days on MV, the length of ICU stay, or antibiotic changes. Likewise, there was no effect of invasive versus noninvasive diagnostic methods. Yet results from many included studies were limited by inadequate de-escalation upon obtaining culture results.

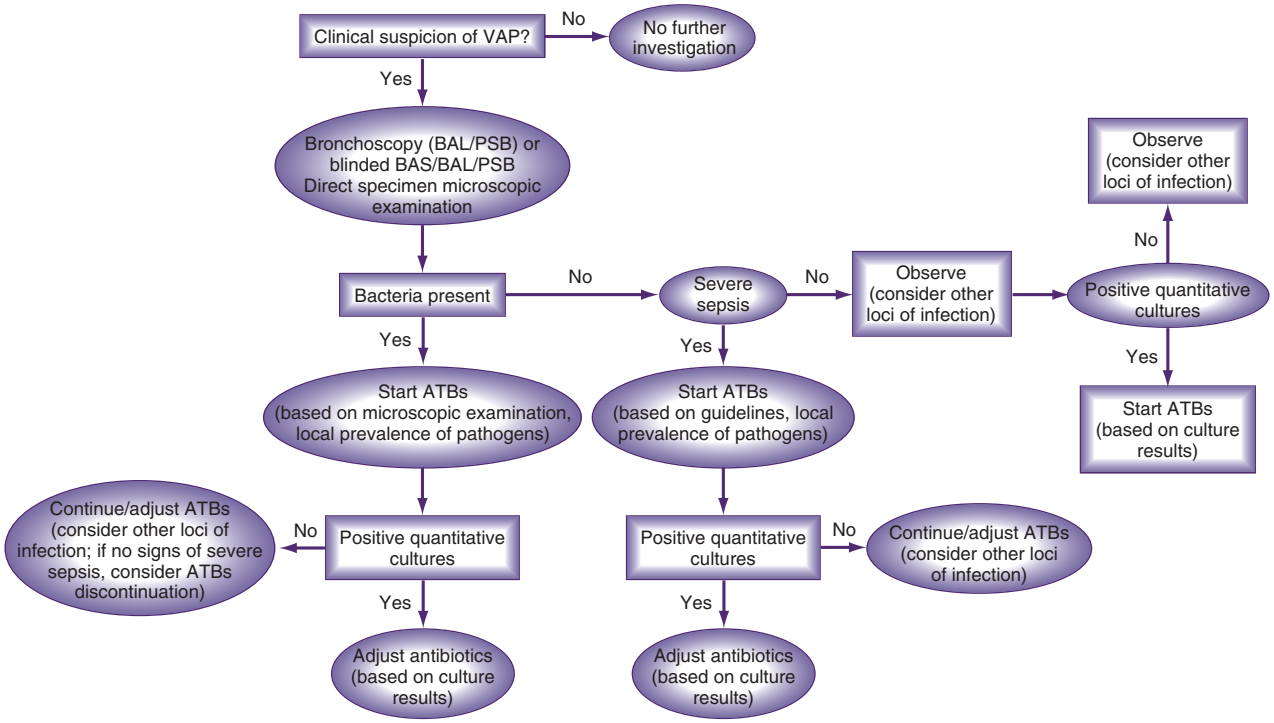

Fig. 68.4 Invasive and Quantitative Culturing Strategy for Diagnosis and Management of VAP. *ATBs,* Antibiotics; *BAL,* bronchoalveolar lavage; *BAS,* bronchial aspirate; *PSB,* protected specimen brush; *VAP,* ventilator-associated pneumonia. (Adapted from American Thoracic Society. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med.* 2005;171:388–416.)

Practical Implementation of a Diagnostic Strategy in Suspected VAP or VHAP

In clinical practice, the development of local guidelines can combine both clinical and bacteriologic strategies (Box 68.2). The diagnostic protocol begins with clinical suspicion of a nosocomial respiratory infection (Fig. 68.5). In mechanically ventilated patients, the presence of an infiltrate on chest radiograph differentiates between the possible presence of pneumonia and tracheobronchitis. The next step is to sample the lower respiratory tract (Table 68.1) to identify the causative microorganism. Respiratory tract specimens can be obtained by expectoration, bronchial aspirate, BAL, or PSB. The latter two techniques can be performed with bronchoscopy or blindly through a protected telescoping. Several other samples should also be collected, as noted in Box 68.2.

TREATMENT

Once the clinical decision to initiate antimicrobial therapy has been made, the following issues should be considered to achieve the best antimicrobial efficacy and reduce overuse of antibiotics:

- The most likely etiologic microorganisms
- Choice of the empirical antimicrobials likely to be active against these microorganisms

BOX 68.2 Diagnostic Protocol to Combine Clinical and Bacteriologic Strategies for the Diagnosis of Ventilator-Associated Pneumonia

1. As soon as pneumonia or infection associated with mechanical ventilation is suspected and before initiating new empirical antibiotic treatment, collect samples as follows*:
   - Expectoration
   - Tracheobronchial aspirate (BAS)**
   - Bronchoalveolar lavage (BAL) or mini-BAL**
   - Protected brush specimen (PBS)**
2. Two blood cultures
3. In cases of evidence for parapneumonic effusion, obtain pleural fluid sample
4. Obtain *Legionella pneumophila* and *Streptococcus pneumoniae* antigens in urine
5. In patients on long-term mechanical ventilation with previous antibiotic treatment, corticosteroid administration, and chronic lung comorbidities, galactomannan in serum and BAL could be assayed to identify invasive pulmonary aspergillosis
6. Other laboratory tests: complete blood cell count, serum electrolytes, liver and renal function tests, C-reactive protein, procalcitonin, arterial blood gases

*Samples should be sent immediately to the microbiology department or, if not available, maintained in a refrigerator at 4°C (only respiratory samples) for a maximum of 1 hour for Gram staining, intracellular organism counting (only in BAL and mini-BAL), and quantitative cultures. The collection of lower respiratory secretion samples should not delay the initiation of empirical treatment in patients with severe sepsis.

**These techniques may be performed by bronchoscopy or blind procedures. Quantitative cultures are performed with the respiratory secretions obtained by BAS, BAL, or PBS. The cutoff count to diagnose pneumonia is the following: BAS 10^6 CFU/mL, BAL 10^4 CFU/mL, and PSB 10^3 CFU/mL. *CFU,* Colony-forming unit.

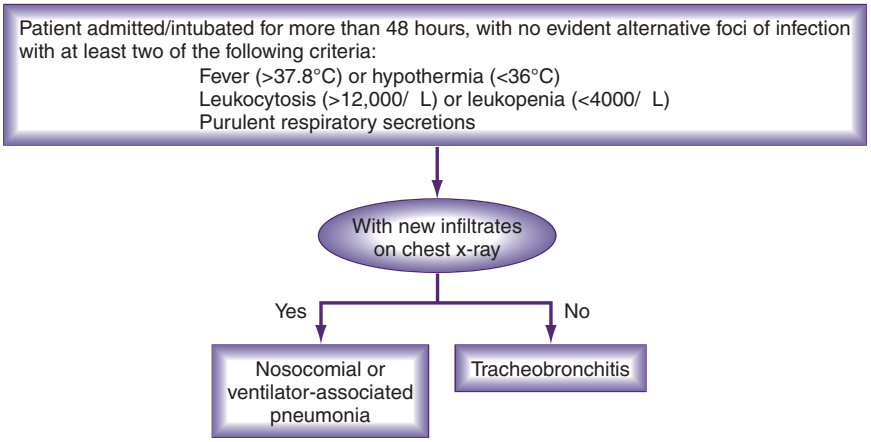

Fig. 68.5 Clinical Suspicion of Nosocomial Respiratory Infection.

TABLE 68.1 Initial Empirical Antibiotic Treatment in Nosocomial and Ventilator-Associated Pneumonia of Early Onset in Patients Without High Severity or Risk Factors for Infection by Multidrug-Resistant Pathogens

Probable Microorganism	Recommended Antibiotic
Streptococcus pneumoniae	Ceftriaxone/cefotaxime
Haemophilus influenzae	*or*
Methicillin-sensitive *Staphylococcus aureus*	Levofloxacin, moxifloxacin
Enteric gram-negative bacilli	*or*
Escherichia coli	Ampicillin/sulbactam
Klebsiella pneumoniae	*or*
Enterobacter spp.	Ertapenem
Proteus spp.	
Serratia marcescens	

Adapted from International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia. *Eur Respir J.* 201750(3):1700582.

MDR, Multidrug resistant; *VAP,* ventilator-associated pneumonia.

- Adjustment of therapy after microbiologic results and duration of treatment

Likely Etiologic Microorganisms

As detailed in previous paragraphs, microorganisms causing VAP originate from the oropharyngeal flora of the patient. Underlying chronic diseases, specific risk factors, acute inflammatory processes, and factors specific to each hospital or ICU can facilitate abnormal bacterial colonization of the oropharynx and may predispose patients to infection with specific organisms. Therefore the selection of initial antimicrobial therapy must be tailored to the local prevalence of pathogens and antimicrobial patterns of resistance at each institution.[119] The dynamics of change of oropharyngeal flora during hospital stay can be described as follows (Fig. 68.6):

1. Healthy subjects are colonized with normal oropharyngeal flora, among which pathogenic microorganisms, such as *S. pneumoniae*, group A streptococci, or meningococci, may be transiently found.
2. Patients with chronic comorbidities or an acute inflammatory process have impaired immune responses. As a result, *S. aureus* and Enterobacteriaceae can colonize the oropharynx.
3. Patients who have received antibiotic treatment frequently become colonized with resistant pathogens, including ESBL + Enterobacteriaceae, *Enterobacter* spp., *P. aeruginosa*, or MRSA.
4. Patients who have received broad-spectrum antibiotics for more than 7 days are often colonized by MDR microorganisms (i.e., *A. baumannii, S. maltophilia, B. cepacia,* and gram-positive microorganisms).

Changes in the oropharyngeal flora tend to occur progressively; the presence of microorganisms during one stage often overlaps with the next stage.

Choice of Empirical Antimicrobials Likely to Be Active Against Causative Microorganisms

The American[1] and European guidelines[2] concur that before the commencement of antibiotic therapy, patients should be stratified according to their risks of being infected with MDR pathogens. American guidelines emphasize several risk factors for MDR, as shown in Box 68.3. European guidelines, however, classify as "high-risk HAP/VAP" patients those who require broad-spectrum antibiotic coverage, those with septic shock, >15% mortality risk,[3,12] or specific risk factors for MDR (see Box 68.3). Conversely, patients without risk factors for MDR and 15% or less chance of mortality are classified as low-risk HAP/VAP. Potential limitations of guidelines and recommendations should be taken into account when used for the prediction of possible causative pathogens. Ekren and colleagues[104] validated the 2016 Infectious Disease Society of America/American Thoracic Society (IDSA/ATS) guidelines[1] using a Spanish repository of HAP/VAP and found high sensitivity for detecting MDR pneumonia using recommended risk factors but very low specificity, potentially increasing the risk of overtreatment or use of inappropriate antibiotics. The antibiotics recommended by the latest American and European guidelines are shown in Table 68.1 and Table 68.2. Recommendations are similar, yet the American guidelines advocate empiric treatment for MRSA in ICUs where MRSA is isolated in at least 10% of the samples, in comparison with 25% for the European guidelines. In addition, as for the empiric treatment against gram-negative pathogens, European guidelines suggest use of monotherapy even in patients with high risk of mortality and/or risks of harboring MDR gram-negative pathogens, assuming a single agent is active for >90% of the gram-negative

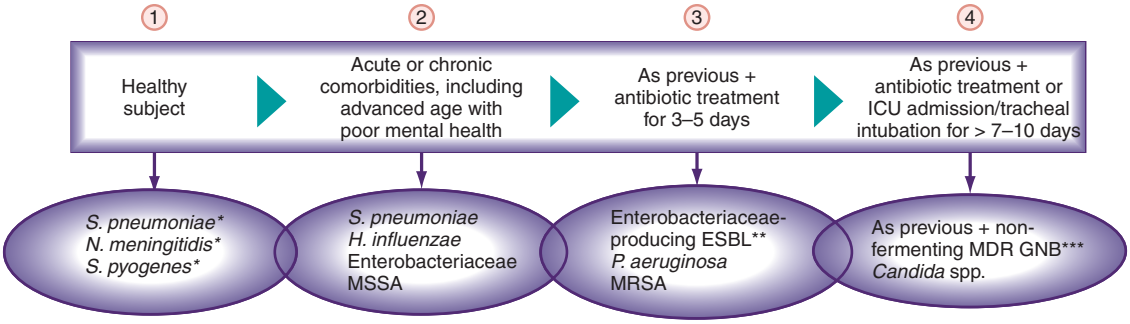

Fig. 68.6 Evolution of Potentially Pathogenic Microorganisms Present in Oropharyngeal Flora Related to Comorbidity, Antibiotic Treatment, and Colonization Pressure. *Transiently present in healthy carriers. **Producers of ESBL or with type ampC chromosomal beta-lactamases. ***_Pseudomonas aeruginosa_, _Stenotrophomonas_ spp., _Acinetobacter_ spp., _Burkholderia_ spp. _ESBL,_ extended-spectrum beta-lactamase; _GNB,_ gram-negative bacilli; _MDR,_ multidrug resistant; _MRSA,_ methicillin-resistant _Staphylococcus aureus_; _MSSA,_ methicillin-sensitive _S. aureus_.

BOX 68.3 Risk Factors for Multidrug-Resistant Pathogens Causing Nosocomial Pneumonia

American Guidelines	European Guidelines
• Septic shock at the time of VAP	• Septic shock at the time of VAP
• Acute respiratory distress syndrome	• Mortality risk >15%
• Renal replacement therapy preceding VAP	• Hospital/ICU settings with more than 25% rate of MDR pathogens
• Intravenous antibiotic use within the previous 90 days	• Previous antibiotic use
• At least 5 days of hospitalization before development of VAP	• Recent prolonged hospital stay (>5 days of hospitalization)
	• Previous colonization with MDR pathogens

Adapted from Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis.* 2016;63(5):e61–e111 and International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia. *Eur Respir J.* 2017;50(3):1700582.
ICU, Intensive care unit; *MDR,* multidrug resistant; *VAP,* ventilator-associated pneumonia.

pathogens isolated in the ICU. Furthermore, American guidelines discourage the use of aminoglycosides if alternative agents are available because of possible low epithelial lining fluid concentrations of this class of antibiotics.[313] European guidelines highlight aminoglycosides as an appropriate second anti–gram-negative agent. Another difference between the American and European guidelines is in the use of colistin. Americans recommend against the use of colistin for VAP because of potential nephrotoxicity and need to reduce risk for resistance for this last-line antibiotic. European guidelines instead recommend colistin in VAP caused by *Acinetobacter* spp.

An algorithm for the initial management of patients with nosocomial respiratory infection and selection of appropriate antimicrobials is shown in Fig. 68.7. Adequate dosing of antibiotics for empirical therapy is summarized in Table 68.3. Broad-spectrum empirical antibiotic therapy should be rapidly de-escalated as soon as microbiologic data become available, with the intent to limit the emergence of resistance in the hospital. Fig. 68.7, Table 68.1, and Table 68.2 detail empirical therapy, which should be based on the patient's risk of colonization by MDR organisms. With regard to the need for dual therapy against gram-negative pathogens, Aarts and colleagues[314] performed a meta-analysis of 11 trials randomizing 1805 patients. No mortality difference was detected for patients receiving monotherapy versus combination therapy (RR = 0.94, 0.76–1.16). Likewise, there was no significant difference in treatment failure in patients with clinically suspected pneumonia (RR = 0.88, 0.72–1.07; see Fig. 68.4) or microbiologically proven pneumonia (RR = 0.86, 0.63–1.16).

Novel Intravenous Antibiotics

Drug resistance is increasing worldwide, and several drugs are at various stages of clinical research and development aimed at appropriately treating infections caused by microorganisms resistant to our current arsenal. Several antimicrobials against gram-positive (i.e., tedizolid) and gram-negative pathogens (i.e., cefiderocol or plazomicin) are being tested in phase III clinical trials.[315] In a pivotal multicenter noninferiority trial,[316] 726 patients with VAP were randomly assigned to receive either 3 g of ceftolozane-tazobactam or 1 g meropenem intravenously every 8 hours up to 14 days. At 28 days, 24% of patients in the ceftolozane-tazobactam group and 25% in the meropenem group had died (weighted treatment difference 1.1%, 95% CI −5.1 to 7.4), and similar rates of serious treatment-related adverse events were observed. In another noninferiority trial, ceftazidime-avibactam was compared with meropenem for the treatment of HAP/VAP.[317] Sixty-nine and seventy-three percent of the patients who received ceftazidime-avibactam or meropenem, respectively, achieved the positive primary outcomes set for the study. In studies that focused on outcomes other than respiratory infections, ceftazidime-avibactam has also compared favorably against colistin for positive outcomes in treating carbapenem-resistant Enterobacteriaceae[271] and as a salvage therapy against *K. pneumoniae* carbapenemase enzyme producers.[271] In the TANGO II clinical trial,[318] meropenem-vaborbactam was compared with standard therapy in a multicenter clinical study in patients with infections caused by carbapenem-resistant Enterobacteriaceae, including HAP/VAP. Lower 28-day all-cause mortality and nephrotoxicity

TABLE 68.2 Initial Empirical Antibiotic Treatment for Nosocomial and Ventilator-Associated Pneumonia in Patients With High Mortality Risk and/or Risk Factors for Infection by Multidrug-Resistant Pathogens and Septic Shock

Probable Microorganism	Combined Antibiotic Treatment
Microorganisms from Table 68.1 plus:	Antipseudomonal cephalosporin (ceftazidime or cefepime)*
Pseudomonas aeruginosa	*or*
Klebsiella pneumoniae (ESBL+)†	Carbapenem (imipenem, meropenem)*
Acinetobacter spp.†	*or*
Other nonfermenting gram-negative bacilli	Beta-lactam/beta-lactamase inhibitor (piperacillin-tazobactam)*
Methicillin-resistant *Staphylococcus aureus* (MRSA)	+
Legionella pneumophila‡	Antipseudomonal fluoroquinolone (ciprofloxacin, levofloxacin)**
	or
	Aminoglycoside** (amikacin), gentamicin
	±
	Linezolid or vancomycin***

*The choice of beta-lactam is made as follows: patients who have not received any antipseudomonal beta-lactam within the last 30 days should be administered piperacillin-tazobactam or an antipseudomonal cephalosporin. Patients who have received these drugs should be given empirical therapy with a carbapenem. Patients with infection by ESBL-producing microorganisms should be treated with carbapenem regardless of the results of the antibiogram.
** American guidelines discourage the use of aminoglycosides as first choice for the second antipseudomonal therapy, whereas European guidelines are in favor. Potential use of an antipseudomonal fluoroquinolone should be considered in cases of renal failure or concomitant use of vancomycin.
***American guidelines recommend empirical therapy aimed against MRSA in units in which >10% of *S. aureus* isolates are methicillin resistant. European guidelines recommend empirical therapy aimed against MRSA in units in which >25% of *S. aureus* isolates are methicillin resistant. The antibiotic of choice is either vancomycin (except in patients allergic to this medication, with creatinine values ≥1.6 mg/dL, or in patients presenting with signs of empirical treatment failure after 48 hours of antibiotic therapy) or linezolid. (ψ) For epidemiologic surveillance, nasal and perineal cultures should be performed on admission and at 1-week intervals thereafter while remaining in the ICU.
†If an ESBL+ strain, such as *K. pneumoniae* or *Acinetobacter* spp. is suspected, a carbapenem is the first choice.
‡If *L. pneumophila* is suspected, the combination antibiotic regimen should include a macrolide (e.g., azithromycin), or a fluoroquinolone (e.g., ciprofloxacin, levofloxacin) should be used rather than an aminoglycoside.
ESBL, Extended-spectrum beta-lactamase; *GNB,* gram-negative bacilli.

were found in comparison with standard intravenous antibiotics (25% versus 44%) in the subcohort of patients with HAP/VAP. An innovative algorithm based on the evidence gathered from clinical trials on the use of novel antibiotics against nosocomial pneumonia has been recently proposed by Zaragoza and collaborators.[271] The algorithm envisions future empirical and targeted treatment for critically ill patients with nosocomial pneumonia, which could be potentially recommended in the next decade.

Nebulized Antibiotics

Intravenous administration of antibiotics for nosocomial pneumonia has several limitations, including insufficient lung distribution, development of adverse side effects, and exerting selective pressure for development of MDR. Additionally, intravenous antibiotics are often underdosed in critically ill patients because of sepsis-related higher volumes of drug distribution and the influence of hyperdynamic states. Coadministration of nebulized antibiotics is a potential therapeutic alternative[319] to overcome these limitations. Additionally, systemic exposure to antibiotics and potential adverse effects are dramatically reduced by the aerosol route. Finally, nebulized antibiotics can potentially reduce the risk of developing MDR infections.[320] In laboratory models, nebulized amikacin reached pulmonary concentrations 30 times higher than intravenous administration. In a pivotal study by Lu and colleagues,[321] 20 patients with susceptible or intermediate-resistant gram-negative pathogens received nebulized ceftazidime and amikacin, whereas 17 patients infected with susceptible strains received intravenous ceftazidime and amikacin. After 8 days of treatment, cure rates were similar among tested groups. However, acquisition of treatment-associated antibiotic resistance was higher in the intravenous cohort. In a later study, Niederman and colleagues[322] randomized 69 mechanically ventilated patients with gram-negative VAP to receive aerosolized amikacin concomitantly with systemic antibiotics. They found that amikacin distributed well throughout the lung parenchyma, with high tracheal and alveolar levels but with a serum concentration below the renal toxicity threshold. Several factors play a critical role in lung deposition of nebulized antibiotics during MV.[323] First, the extent and severity of lung infection critically affect their lung distribution.[324] Second, vibrating plate nebulizers increase the efficiency of aerosol delivery to 40%–60%.[325,326] Finally, humidification and angular geometry of the ventilatory circuit should be taken into account during nebulization. In addition, ventilatory settings that ensure laminar inspiratory flow provide better distal lung deposition of aerosolized particles.[327] Irrespective of the potential benefits of nebulized antibiotics and advances in the field, two large RCTs recently failed to find any improvement in major outcomes during treatment with nebulized antibiotics.[328,329] As a good example, Niederman and collaborators[328] randomized 508 VAP patients to receive aerosolized amikacin every 12 hours as an adjunct to standard intravenous antibiotics and found that mortality up to 32 days from commencement of therapy did not differ between study groups (OR + 0.841; 95% CI 0.55–1.27; $P = .43$). In accordance with those marginal results, the latest American guidelines[1] recommended against the use of nebulized

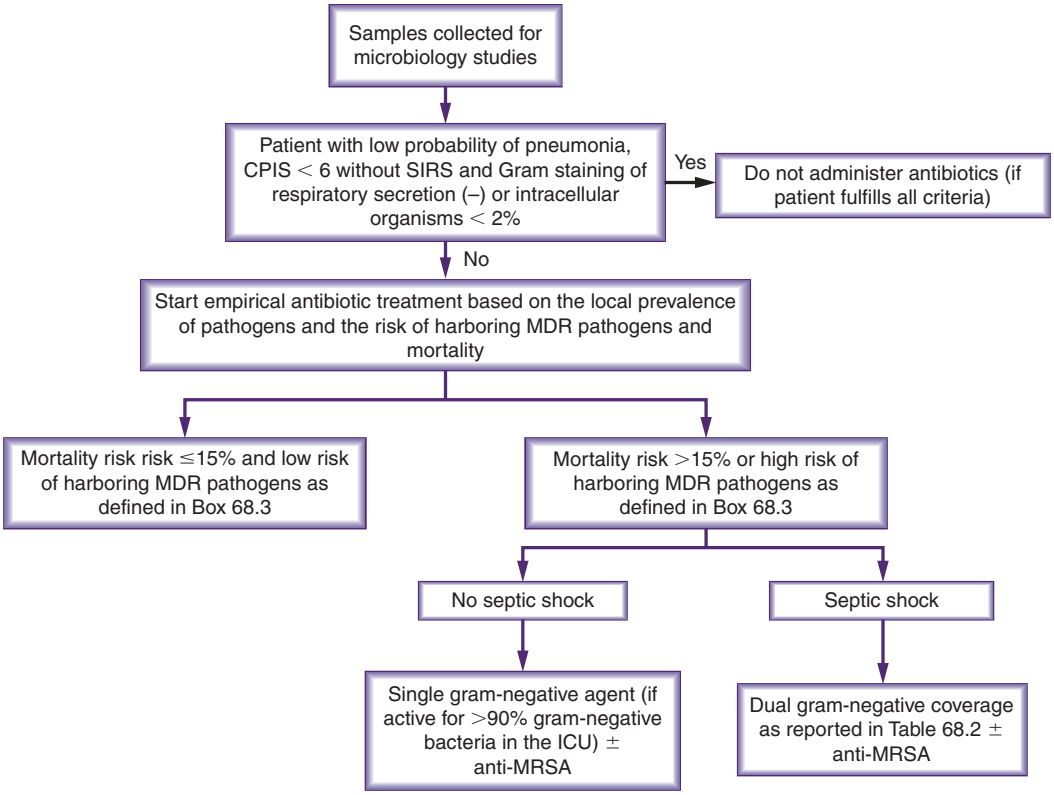

Fig. 68.7 Algorithm for the Treatment of Patients with Suspicion of Nosocomial Respiratory Infection. SIRS comprises at least two of the following: temperature >38°C or <36°C; heart rate >90 beats/min; respiratory rate >20 breaths/min or partial pressure of carbon dioxide ($PaCO_2$) <32 mm Hg; and leukocytes >12,000/mm^3, <4000/mm^3, or the presence of >10% immature neutrophils. *CPIS*, Clinical Pulmonary Infection Score; *ICU*, intensive care unit; *MDR*, multidrug resistant; *MRSA*, methicillin-resistant *Staphylococcus aureus*. *SIRS,* Systemic inflammatory response syndrome.

TABLE 68.3 Recommended Initial Intravenous Antibiotic Dosage for Empirical Treatment of Patients With Nosocomial and Ventilator-Associated Pneumonia

Antibiotic	Doses	Interval of Administration	Perfusion Time
Non-Antipseudomonal Cephalosporins			
Ceftriaxone	2 g	24 hours	½–1 hour
Cefotaxime	2 g	6 hours	½–1 hour
Antipseudomonal Cephalosporins and other Classes			
Ceftazidime	2 g	8 hours	2–3 hours
Cefepime	1–2 g	8 hours	2–3 hours
Imipenem	0.5 or 1 g	6 or 8 hours	1 hour
Meropenem	1 g	8 hours	2–3 hours
Piperacillin-tazobactam	4–0.5 g	6 hours	2–3 hours
Fluoroquinolones			
Levofloxacin	500 mg	12 hours*	½ hour
Ciprofloxacin	400 mg	8 hours	½ hour
Amikacin	15–20 mg/kg	24 hours**	½–1 hour
Gentamicin	5-7 mg/Kg^	24 hours	1/2 hour
Vancomycin	15 mg/Kg	8–12 hours***	1–3 hours
Linezolid	600 mg	12 hours	1 hour

*Administer this dose for 3 days and after continue with 500 mg/24 h. Alternatively, administer 750 mg every 24 hours.
**Adjust the dosage according to pharmacokinetic/pharmacodynamic (PK/PD) parameters.
***Initiate this dose within 24 hours, measure trough blood levels before the following dosage, and adjust the levels according to values. Dosages are based on normal renal and hepatic function.
^In case of multiple daily dosing (3 mg/Kg load, then 2 mg/kg every 8 hours), therapeutic monitoring is recommended to acheive goal peak >8 mcg/ml and through < 2mcg/ml

antibiotics in VAP, whereas European guidelines[2] favored inhaled antibiotics in addition to systemic therapy in VAP caused by gram-negative bacilli that are not responding to intravenous treatment alone (weak recommendation with low-quality evidence).

Antimicrobial Therapy in Special Situations

In geographic areas with a documented presence of community-acquired MRSA, severe pneumonia with radiologic images of cavitation, and presence of gram-positive cocci in respiratory secretions, empirical treatment with linezolid or vancomycin may be appropriate. Recently, an outbreak of MRSA and linezolid-resistant *S. aureus* (LRSA) was reported in an intensive care department of a 1000-bed tertiary care university teaching hospital in Madrid, Spain, and was associated with nosocomial transmission and extensive usage of linezolid.[115,116] Tigecycline may be a useful alternative in this setting, but clinical experience is scanty.

Infections by *L. pneumophila* serogroup 1 can be diagnosed by a *Legionella* urinary antigen test. This test should be routinely obtained if the hospital water supply is known to be colonized with *L. pneumophila* serogroup 1. A fluoroquinolone or a macrolide would be an appropriate treatment for *L. pneumophila* infection.

Modifications of Therapy and Duration of Treatment

A suggested flowchart for the follow-up of patients with nosocomial pneumonia is shown in Fig. 68.8. After 72 hours, treatment should be adjusted based on microbiologic results. The initial beta-lactam should be continued if the microorganism is susceptible to the empirical beta-lactam originally prescribed. If not, another beta-lactam should be introduced. The empirical antibiotic against MRSA should be discontinued if the presence of this pathogen is not confirmed by cultures. Discontinuation of the fluoroquinolone, and especially the aminoglycoside, should be considered after 3–5 days of treatment. The bactericidal activity of aminoglycosides and fluoroquinolones leads to a rapid reduction in the bacterial load during the first days of treatment. After this time, monotherapy may be sufficient. This tapering approach would decrease the emergence of resistant mutants and minimize nephrotoxicity caused by aminoglycosides.

The majority of VAP infections that occur in patients without immunodeficiency, cystic fibrosis, empyema, lung abscess, cavitation, or necrotizing pneumonia can be effectively treated with 8 days or less of antimicrobial therapy, provided that a good clinical response to therapy has been observed.[2] In a meta-analysis[330] that pooled data from four RCTs comparing short (7–8 days) with long (10–15 days) treatment periods, no difference in mortality was found. There was an increase in antibiotic-free days for the short-course treatment, and a trend to lower relapse rates in the long-course treatment was observed (OR = 1.67; 95% CI = 0.99–2.83; P = .06).

Four situations may justify prolonged treatment: (1) infection by intracellular microorganisms, such as *Legionella* spp.; (2) the presence of biofilms or prosthetic devices; (3) development of tissue necrosis, formation of abscesses, or infection within a closed cavity, such as empyema; and (4) the persistence of the original infection (such as perforation or endocarditis). If the clinical course from the pneumonia is favorable, as defined by defervescence, improvement in partial pressure of oxygen/fraction of inspired oxygen (PaO_2/FiO_2), and reduction in CRP levels within the first 3–5 days of antimicrobial therapy, treatment may be withdrawn

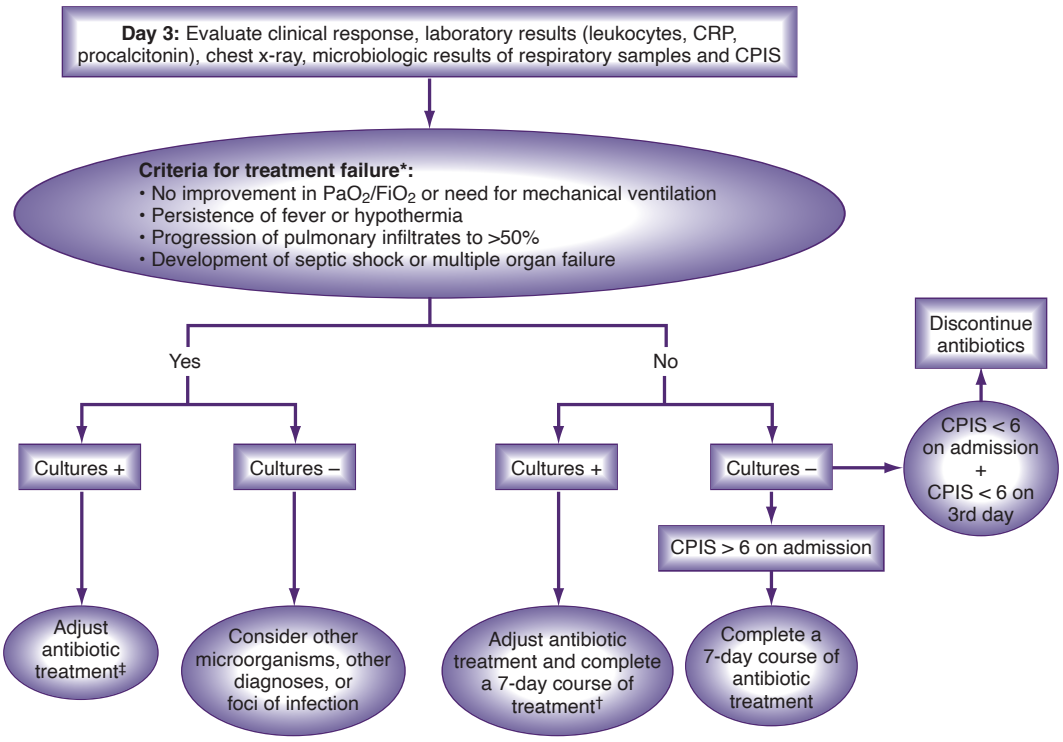

Fig. 68.8 Suggested Algorithm for the Follow-Up of Patients with Nosocomial Pneumonia and VAP. *Criteria of treatment failure taken from Ioanas M, Ferrer M, Cavalcanti M, et al. Causes and predictors of non-response to treatment of the ICU-acquired pneumonia. *Crit Care Med.* 2004;32:938–945. †In cases in which the etiologic agent is *Pseudomonas aeruginosa* or *Acinetobacter* spp., treatment should be maintained for 14 days. ‡Patients with criteria of treatment failure and in whom MRSA is isolated should be administered linezolid. If a GNB is isolated, consultation is recommended. *CPIS,* Clinical Pulmonary Infection Score; *CRP,* C-reactive protein; *FiO_2,* fraction of inspired oxygen; *GNB,* gram-negative bacilli; *MRSA,* methicillin-resistant *Staphylococcus aureus*; *PaO_2,* partial pressure of oxygen; *VAP,* ventilator-associated pneumonia.

after 7 days. If the causative microorganism is a nonfermenting gram-negative bacillus, the treatment can be extended beyond 14 days. A large prospective, multicenter, randomized trial study comparing the efficacy of 8-day and 15-day antibiotic regimens for treating VAP suggested that an 8-day regimen reduces antibiotic use and decreases the emergence of pulmonary MDR bacteria without modification of the prognosis.[331] However, this study observed that in cases of pneumonia produced by nonfermenting gram-negative bacilli, eradication of these microorganisms from bronchial secretions was less complete with the shorter regimen. On the other hand, the 14-day treatment regimen was associated with a trend toward colonization by MDR pathogens and a higher frequency of reinfection. Finally, antimicrobials may be withdrawn in patients with clinical suspicion of ICU-acquired pneumonia who have a CPIS lower than 6 on the third day of treatment. In this setting, the patient likely does not have pneumonia, or the pneumonia is sufficiently mild such that prolonged antibiotic treatment is not required. Finally, most recent European guidelines[2] suggest that procalcitonin—an inflammatory biomarker investigated both for the diagnosis of VAP and response to treatment[271]—could play a role in appropriately shortening or prolonging duration of treatment in specific circumstances, such as inappropriate antibiotic treatments, infections caused by MDR or extensively drug-resistant microorganisms, or when using second-line antibiotics such as colistin and tigecycline.

Treatment Failure

At least 3 days of antibiotic treatment are needed to achieve clinical improvement. Thus treatment failure should be assessed between 3 and 5 days after the initiation of antibiotic therapy. The rate of treatment failure ranges between 30% and 50%, which highlights the severity and complexity of this pulmonary infection. In our previous observations,[3] we developed a systematic definition of treatment failure composed of the following: (1) no improvement in PaO_2/FiO_2 or need for intubation because of pneumonia; (2) persistence of fever or hypothermia, together with purulent respiratory secretions; (3) increase in the pulmonary infiltrates on chest radiograph of greater than or equal to 50%; or (4) occurrence of septic shock or multiple organ dysfunction syndrome. Thus we found that no improvement in the Sequential Organ Failure Assessment (SOFA) score and PaO_2/FiO_2 highly predicted worse 28-day mortality. Importantly, treatment failure could be a surrogate endpoint for clinical trials to compare novel treatments. Upon evidence of treatment failure, respiratory samples should be reobtained and the initial empirical therapy rapidly readjusted. CT scan or lung ultrasound[332,333] may help to detect cavitation, pleural effusion, and other causes for treatment failure.

Implementation of Therapeutic Guidelines

Although guideline-recommended strategies may provide significant benefits for patients, their implementation is often difficult to achieve.[334] Soo Hoo and colleagues[335] developed hospital protocols to manage patients with severe HAP based on the 1996 ATS guidelines.[336] After the guidelines were introduced into clinical settings, the authors found that adequate antibiotic therapy was administered in more than 81% of the patients with pneumonia, compared with 46% before implementation ($P < .01$). Moreover, a lower mortality at 14 days was found after implementation of the guidelines ($P = .03$). Similarly, Ibrahim and coworkers developed a protocol to provide appropriate initial antibiotic treatment for patients with VAP and encouraged a 7-day course of treatment.[337] Patients with VAP who were treated as directed by the protocol more often received adequate antimicrobial treatment than those treated empirically (94%, in comparison to 48% before protocol implementation; $P < .001$). The length of treatment was reduced by 6 days, and a second episode of VAP was less likely to occur after implementation.

KEY POINTS

- Nosocomial pneumonia is a common complication occurring in critically ill patients and is the leading cause of nosocomial infection–related death. VAP develops in tracheally intubated patients.
- Etiologic agents for VAP differ according to the population of ICU patients, duration of hospital stay, and prior antimicrobial therapy. Nosocomial pneumonia caused by MDR pathogens is associated with the highest morbidity and mortality.
- Preventive strategies, grouped as bundles, should be implemented in hospital settings. Several preventive strategies have shown efficacy in decreasing the incidence of pneumonia. In particular, the most effective strategies focus on reduction of cross-transmission, diminishing the likelihood of aspiration across the tracheal tube cuff, and decreasing bacterial load in the oropharynx.
- In the presence of clinical suspicion of nosocomial pneumonia, diagnostic strategies should include an early collection of respiratory samples *before* starting or changing antibiotics.
- The choice of empirical treatment should be based on the most likely etiologic microorganisms and the antimicrobials likely to be active against these microorganisms. Response to therapy should be reassessed after 3–5 days and antimicrobials adjusted or de-escalated to reduce the burden of the disease.

References for this chapter can be found at expertconsult.com.

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International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia: guidelines for the management of hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) of the European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Asociacion Latinoamericana del Torax (ALAT). *Eur Respir J.* 2017;50(3):1700582.
Latest European guidelines published by a joint committee of the ERS, ESICM, ESCMID, and ALAT. As highlighted and inclusively described in the chapter, several recommendations differ from the American guidelines.

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A meta-analysis investigating the effect of oral antiseptics in the prevention of ventilator-associated pneumonia. Overall, antiseptic use resulted in a significant risk reduction of ventilator-associated pneumonia (RR = 0.67; 95% CI = 0.50–0.88; P 5 0.004). In particular, chlorhexidine application was shown to be effective especially in cardiosurgical patients, whereas the effects associated with povidone-iodine remain unclear.

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Muscedere J, Rewa O, McKechnie K, et al. Subglottic secretion drainage for the prevention of ventilator-associated pneumonia: a systematic review and meta-analysis. *Crit Care Med.* 2011;39(8):1985–1991.
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Oostdijk EA, de Smet AM, Blok HE, et al. Ecological effects of selective decontamination on resistant gram-negative bacterial colonization. *Am J Respir Crit Care Med.* 2010;181(5):452–457.
The authors studied the effects of selective digestive decontamination (SDD) and selective oropharyngeal decontamination (SOD) on the development of antibiotic resistance after ICU discharge. During SDD, average proportions of patients with intestinal colonization with pathogens resistant to either ceftazidime, tobramycin, or ciprofloxacin were 5%, 7%, and 7%, respectively, and increased to 15%, 13%, and 13% post intervention (P = .05), respectively. During SDD and SOD, resistance levels in the respiratory tract were not more than 6% for all three antibiotics, but increased gradually for ceftazidime during the intervention and to levels of 10% or more for all three antibiotics post intervention (P 5 0.05). Thus SDD and SOD have a marked rebound effect of ceftazidime resistance after discontinuation of intervention.

Philippart F, Gaudry S, Quinquis L, et al. Randomized intubation with polyurethane or conical cuffs to prevent pneumonia in ventilated patients. *Am J Respir Crit Care Med.* 2015;191(6):637–645.
Multicenter, prospective, randomized clinical study in 621 patients with expected ventilation longer than 2 days randomized to be intubated with a cuff composed of cylindrical polyvinyl chloride, cylindrical polyurethane, conical polyvinyl chloride, or conical polyurethane. No differences in tracheal colonization and VAP were found among groups.

Price R, MacLennan G, Glen J, SuDDICU Collaboration. Selective digestive or oropharyngeal decontamination and topical oropharyngeal chlorhexidine for prevention of death in general intensive care: systematic review and network meta-analysis. *BMJ.* 2014;348:doi:10.1136/bmj.g2197.
Latest meta-analysis of randomized controlled trials that recruited adult patients in general intensive care units and studied selective digestive decontamination (SDD), selective oropharyngeal decontamination (SOD), or oropharyngeal chlorhexidine compared with standard care or placebo. SDD was the only intervention that decreased mortality (OR = 0.73; 95% CI = 0.64–0.84).

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69

Core Principles of Cardiovascular Physiology and Pathophysiology in Critical Illness

Sheldon Magder

INTRODUCTION

Metabolism in almost all living organisms is energized by the chemical reduction of oxygen (O_2). As such, provision of O_2 to tissues is of central importance for living beings, especially in the high O_2 consumption (VO_2) of mammals and birds. Accordingly, VO_2 has evolved to be tightly related to the organism's energy demands. The Fick principle, a statement of conservation of mass, indicates that VO_2 is determined by the flow of blood and the extraction of O_2 by tissues. As such, maintenance of appropriate blood flow to match tissue needs is fundamental to normal homeostasis. This is evident in the tight linear relationship between cardiac output and VO_2 under normal physiologic conditions.

It might be expected that there would be widespread agreement on the regulation of such a key factor as the control of cardiac output. However, two conflicting conceptual approaches remain. One is that of Levy and others,[1,2] which argues that the arterial pressure produced by the heart is the force that determines blood flow in the circulation. The alternative approach is that of Arthur Guyton.[3,4] He argued that the primary role of the heart in the generation of blood flow is to allow venous blood to drain back to the heart. In his argument, the heart can never pump out more than what comes back to it. The main force in Guyton's approach is the recoil pressure created by the volume filling the veins and venules because this force determines what comes back to the heart to be pumped out again (Fig. 69.1). Arterial pressure then is determined by pumping a stroke volume against the vascular resistance. The arterial pressure itself, though, does not determine the amount of flow in the circulation (except by acting as an afterload and inhibiting ejection) and, more importantly, what comes back to the heart. As a simple illustration of this point, the right ventricle (RV) and left ventricle (LV) produce the same blood flow but with very different pressures. This chapter presents the Guytonian view of the circulation universe.

THE GUYTONIAN UNIVERSE

Central to the Guytonian view is that the volume that fills vasculature structures creates an elastic recoil force by stretching the walls of vessels (Fig. 69.2).[5] This elastic force is present even when there is no blood flow. Evidence for this is that blood will flow from a cut vein in a person with an arrested heart. The average elastic recoil pressure that fills all vascular structures when there is no flow is called the *mean circulatory filling pressure* (MCFP). The role of the heart in this concept is "permissive" in that by emptying the blood from the ventricles, the upstream volume in the veins can return to the heart (see Fig. 69.2). This volume is then pumped out again.

Over 70% of blood volume resides in small veins and venules. Thus the elastic recoil force of these vessels, as determined by the volume distending them and the compliance of their walls, or its inverse elastance, is the major determinant of the elastic recoil force. When blood is flowing, blood volume redistributes among the different vascular compartments based on the resistance into and out of each region and their relative compliances. Under flow conditions, the pressure in the veins and venules directly upstream from the heart is called the *mean systemic filling pressure* (MSFP, note the "S" instead of "C") and is a major determinant of the return of blood flow to the heart. Under normal conditions, MCFP and MSFP are similar, but the relationship can change with alterations in cardiac function because of the changes in distribution of blood volume.

By lowering right atrial pressure (Pra) and central venous pressure (CVP), the heart allows venous volume to return to the heart. The heart, though, obviously has a second key function, which is its "restorative" function, in that it puts the blood back into the system (see Fig. 69.2). The compliance of arterial vessels is less than 1/40th of venous vessels. Thus putting the relatively small stroke volume into stiff arteries produces the high arterial pressure, but there is very little change in the pressure in the veins and venules, that is the MSFP, when this volume is removed from the massive systemic venous volume. As already mentioned, in the Guyton model arterial pressure does not determine cardiac output, but rather cardiac output and the downstream systemic arterial resistance determine arterial pressure. The stroke volume then distributes throughout the vasculature based on the distribution of regional vascular resistances.[6] There is an additional determinant of arterial pressure, and that is a critical closing pressure proximal to the microcirculation (Fig. 69.3).[6,7] This factor affects the position of the vascular resistance line and magnifies or offsets changes in the slope of the resistance line. The actual cardiac output is determined by the interaction of the return of blood to the heart from the veins and venules, which is called the *return function,* and cardiac function as defined by Ernest Starling.

Venous Return

It may seem strange that vascular compliance, a static property, is so important for the generation of blood flow in the circulation. The explanation is that pulsatile flow in a tube occurs from a region with a

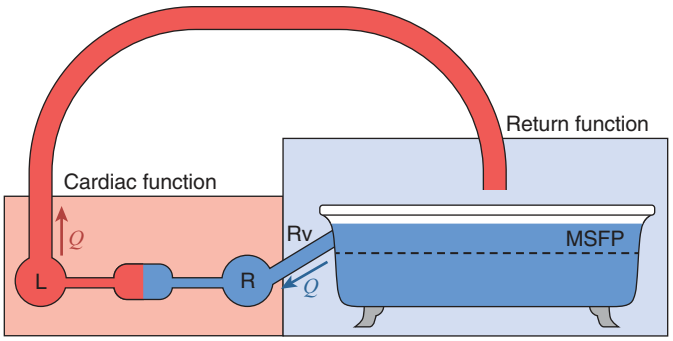

Fig. 69.1 General model of the circulatory system. Cardiac output is determined by the interaction of a pump function, *left side*, and a return function, *right side*. ***L,*** Left heart; ***MSFP,*** mean systemic filling pressure; ***Q,*** cardiac output; ***R,*** right heart; ***Rv,*** resistance to venous return.

high pressure to an area with a lower pressure. If the closed loop vasculature was made up only of stiff vessels, the pressure wave produced with each stroke volume would be instantaneously transmitted through the system and there would be no pressure difference to drive flow (Fig. 69.4). Thus for flow to occur, the pressure wave and volume pulse have to be transiently taken up in a region that has a higher compliance; that region is the veins and venules, which have a large volume at a low pressure and as such are very compliant (see Fig. 69.4). This is analogous to the characteristics of a bathtub (see Fig. 69.2). Drainage from a bathtub is determined by the height of the water above the hole at the bottom. Inflow from the tap only increases outflow from the tub by adding volume and raising the height of water in the tub, but the pressure coming out of the taps does not alter flow from the drain. Similarly, the pressure going into the veins and venules does not determine outflow from the veins; only the volume entering per time (i.e., flow) does this.

Based on this discussion, the determinants of the return function are the volume that stretches the vascular walls, the compliance of the walls of the veins and venules, and the resistance to flow between the venous system and the RV (see Fig. 69.2). The compliance of arteries and capillaries only add a very small component to the total vascular compliance and can be ignored for simplification.

Guyton provided a useful graphical approach to understanding the return function (Fig. 69.5). He plotted Pra on the *x*-axis because he considered it to be the variable being controlled, and thus the independent variable. The *y*-axis is flow (or venous return). The *x*-intercept is the MSFP. The lower the Pra, the greater the flow. The slope of the venous return line is −1/venous resistance (−1/Rv). This inverted relationship occurs because the inflow pressure, MSFP, remains relatively constant and the outflow pressure, Pra, is lowered by the heart. The function then is plotted against the outflow pressure, which is Pra. When Pra falls below its surrounding pressure, which is atmospheric pressure when breathing spontaneously, the floppy veins collapse where they enter the thoracic cavity, which has a negative pressure relative to atmospheric pressure. This does not stop flow but creates a flow limitation, what is called a *vascular waterfall*.[8] When that happens, lowering Pra further does not increase venous return. This can be very evident when attempts are made to increase the speed of a mechanical device supporting the heart and there is insufficient upstream pressure to support the flow. When intrathoracic pressure is raised by mechanical ventilation, the collapse of veins occurs when Pra is less than pleural pressure.

It is important to introduce another term, and that is capacitance (Fig. 69.6). By now it should be clear that the volume stretching veins and venules determines flow, rather than total blood volume. The reason is that under resting conditions 70% of blood volume simply rounds out vessel walls but does not stretch them. This is called "*unstressed*" *volume*.[9,10] Thus only about 30% of blood volume—the

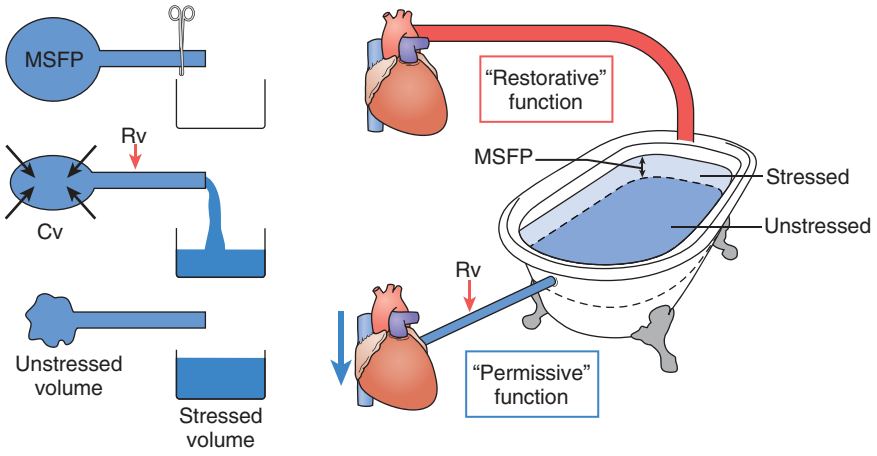

Fig. 69.2 Role of the heart and venous elastic recoil in the determination of cardiac output. The *left side* shows the principle of venous elastic recoil. In the *top part* an elastic balloon is clamped; the elastic recoil creates a pressure, which would be the equivalent of mean systemic filling pressure (*MSFP*) in veins and venules. In the *middle part*, the clamp is removed and flow occurs based on the compliance of the wall of the balloon (*Cv*) and the resistance draining it (*Rv*). The *bottom part* shows that after emptying is finished, the volume that came out is the volume that stretched the balloon (i.e., *stressed volume*), and the volume remaining in the balloon is *unstressed volume*.

The *right side* shows the equivalent of a bathtub in the veins and venules. Here the height is equivalent to MSFP and is produced by the volume (*stressed*) above the outlet on the side of the tub. The volume below the hole is *unstressed*. By lowering right atrial pressure (i.e., emptying the ventricle), the heart is permissive and allows volume to flow back to the heart. It also is (*restorative*), in that it puts the volume it got back into the circulation during systole.

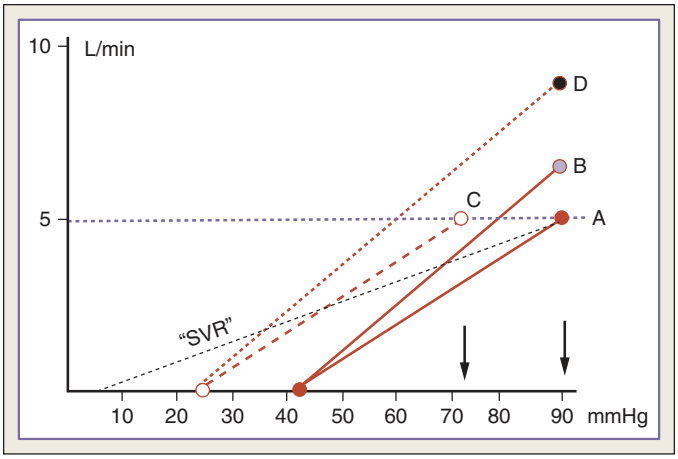

Fig. 69.3 Pressure-flow relationship of systemic arterial vasculature. The *line* labeled *SVR* (systemic vascular resistance) shows the standard line of the inverse of vascular resistance from mean arterial to Pra/CVP (right atrial pressure/central venous pressure; 5 mm Hg in this example). *A* shows what the inverse resistance line would be if there is a critical closing pressure in arterioles of 42 mm Hg; the actual resistance is much less. *B* shows the effect of a decrease in this resistance; there is a rise in flow for the same mean pressure. *C* indicates what happens if the slope of the line did not change but the critical closing pressure decreased. The same flow ***(horizontal dotted line)*** can occur with a much lower mean arterial pressure. *D* shows what happens when there is both a decrease in resistance (*the slope*) and a fall in the critical closing pressure. There is a much higher flow for the same initial mean arterial pressure.

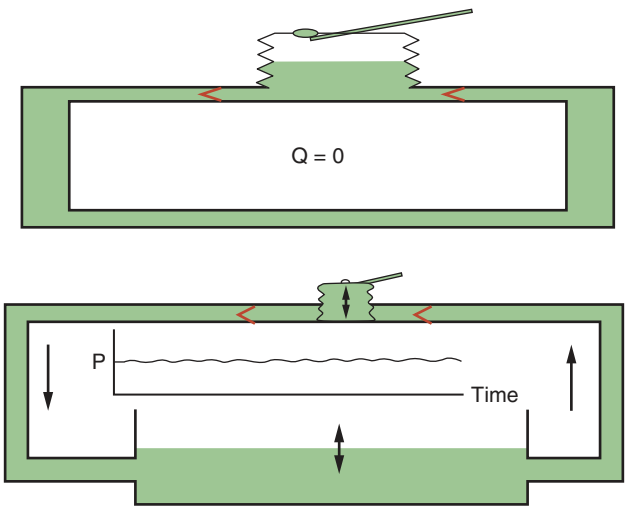

Fig. 69.4 Importance of a compliance in a closed loop system with pulsatile flow. The figure shows a circuit with a "bellows" to pump the fluid, valves to control the direction of flow, and stiff pipes. When the bellows are pumped, no flow occurs because there is no region that can transiently take up volume and pressure, which is necessary to allow the pulse to go through the system. In the *bottom part*, there is an opening that allows a change in volume with a change in height, which is the equivalent of pressure. This is the equivalent of a compliance and allows pulsatile flow (*insert* shows mild pressure waves in this very compliant region).

stressed volume—actually stretches vessel walls.[9] This means that in a 70-kg person, only about 1.3–1.4 L of a total blood volume of 5.5 L actually creates MSFP, the force that is critical for the return of blood to the heart. This needs to be considered when infusing liters of volume to increase cardiac output.

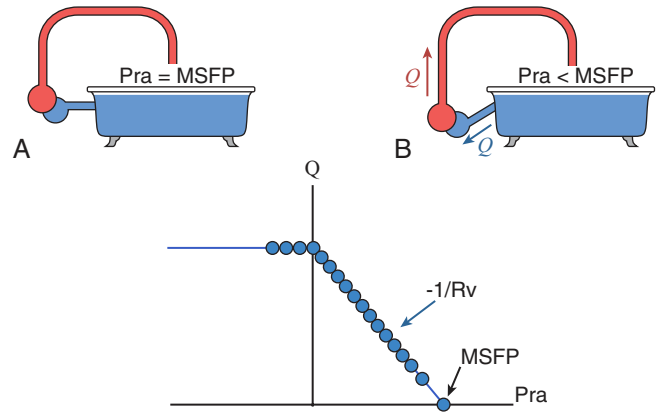

Fig. 69.5 Guyton's venous return curve. Guyton placed cardiac output (*Q*) on the *y*-axis and the right atrial pressure (*Pra*) on the *x*-axis. When Pra = mean systolic filling pressure (*MSFP*), there is no flow (*x*-intercept). The lower the Pra, the greater the flow to a maximum value that occurs when the pressure inside the great vessels is less than the pressure surrounding them (atmospheric when breathing with room air). In the collapse range, flow does not stop; it just does not increase with more negative Pra. The slope of the venous return line before the collapse is −1/venous resistance (−1/*Rv*). Q refers to flow.

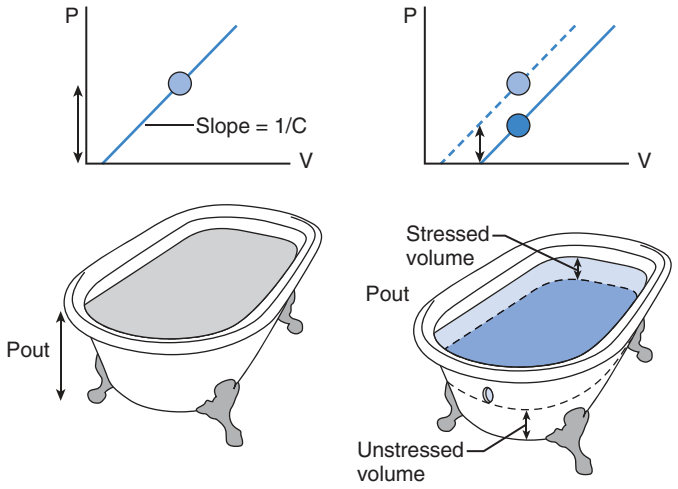

Fig. 69.6 Concept of capacitance. The *bottom part* shows a tub with the hole on the bottom and another with the hole on the side. When the hole is on the bottom, the force driving fluid out is the height of the water above the bottom (*Pout*). This is graphically shown with pressure (*P*) versus volume (*V*) in the *upper part* of the figure. When the hole is on the side, only the volume above the hole (stressed volume) generates Pout and comes out.

Cardiac Function

Output from the heart is determined by the rate of contractions (heart rate) and the amount ejected per beat (stroke volume), which in turn is determined by preload, afterload, and contractility[11] (Fig. 69.7). The fundamental role of preload was demonstrated by Otto Frank and later by Ernest Starling.[12] They appreciated that the greater the initial stretch of cardiac muscle before the onset of contraction, the greater the force produced by the muscle. Starling even correctly hypothesized that this was because stretch of muscle fibers increases overlap of chemically active sites, an insight obtained without knowing about the existence of actin and myosin in sarcomeres, which are the basis of the

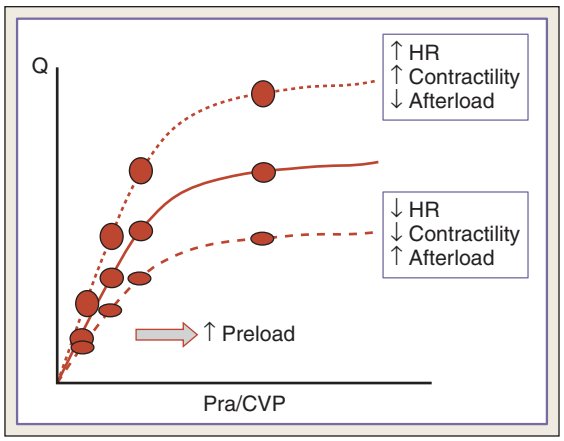

Fig. 69.7 Cardiac function curve. The plot shows the change in cardiac output (*Q*) with a change in right atrial pressure (*Pra*) or central venous pressure (*CVP*). An increase in heart rate (*HR*), contractility, or decrease in afterload move the curve upward, and the opposite actions move the curve down. Each curve is a set of outputs for a given preload with HR, contractility, and afterload constant.

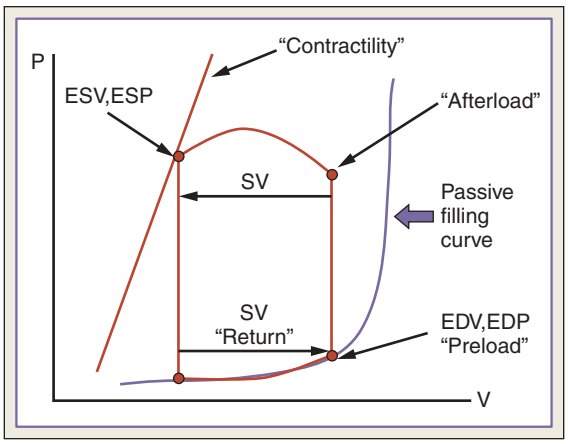

Fig. 69.8 The ventricular pressure (P) versus volume (V) plot. In diastole there is a passive filling curve which has a sharp break. Systole begins at the end-diastolic volume-pressure (V-P) point with an isovolumetric rise in pressure until the aortic valve opens ***(closed circle).*** Blood is then ejected and ventricular volume decreases until the end-systolic volume-pressure line is reached. This is at the end-systolic volume-pressure point. The outflow valve then closes, and there is isovolumetric relaxation back to the passive filling curve. The equivalents of preload, afterload, and contractility are shown. Forward stroke volume must match stroke return if all other factors are constant. ***SV,*** Stroke volume.

current sliding filament hypothesis for muscle force development.[12,13] The significance of this length-tension property is that the exact volume that fills the heart during diastole is ejected on the next beat if all other properties, which are heart rate, contractility, and afterload, stay the same. Although the initial muscle length directly determines the force of contraction and the volume emptied, preload refers to a force, so that preload should be defined as the pressure required to stretch the sarcomere at a given compliance and not by the volume. This "law of the heart" provides perfect matching of what can be called the "stroke return" to the heart and the "stroke output," or stroke volume. It also ensures that in the steady-state stroke output from the LV perfectly matches that of the RV. The importance of this can be understood by some simple calculations. If the RV pumps 100 mL per beat with a heart rate of 70 beats/min and the LV pumps 99 mL per beat—a 1% difference—and total blood volume is 5.5 L, in an hour and a half the total blood volume would be in the lungs! Thus matching of RV and LV outputs must be perfect over time. This can be a significant clinical problem when mechanical devices are used to bypass the ventricles. Unlike cardiac muscle, these devices have minimal "preload" responsiveness. If RV output is set greater than LV output, pulmonary edema rapidly develops.

Unlike skeletal muscle, cardiac muscle cannot be stretched beyond a defined limit. Thus there is a maximal end-diastolic volume and consequently maximal stroke volume. When this limit is reached, further volume loading only increases the diastolic pressure but does not increase muscle length and thus does not change stroke volume. Most often, cardiac filling is limited by the RV, which is very compliant within the range of normal diastolic volumes but has a sharp decrease in its compliance when filling becomes limited[14,15] (see Fig. 69.7). This limit to RV filling normally occurs partially because of a limit to stretch imposed by the pericardium, but also by the limit to stretch imposed by the myocardial wall. When RV filling is limited, stroke volume of the LV is also affected because the LV only can put out what the RV heart transfers to it. This RV limitation provides a protective mechanism that prevents overfilling of the LV and a consequent increase in pulmonary capillary pressures and pulmonary edema.

Ernest Starling provided a useful graphical approach to help illustrate the preload responsiveness of the heart (see Fig. 69.7). Right atrial diastolic pressure is plotted on the *x*-axis and the output of blood from the LV on the *y*-axis. (Starling actually plotted the output on the *x*-axis and Pra on the *y*-axis, but the real independent variable is Pra, which should be on the *x*-axis.[16]) This plot shows that cardiac output in response to an increase in preload rises to a maximum value; beyond that point a sharp plateau appears. No further increase in cardiac output occurs with further increases in Pra/CVP. The plot assumes that contractility, afterload, and heart rate remain unchanged. In this plot, the status of everything between the right atrium and the aortic output are included (see Fig. 69.1).

Another other way to understand function of the heart is through an analysis of the pressure-volume relationship of the ventricles (Fig. 69.8). In this analysis, there is a passive diastolic filling curve, a phase of isovolumetric contraction until the ventricular outflow valve opens, ejection of the stroke volume, then isovolumetric relaxation, followed again by the phase of passive filling. The pressure-volume plot gives a clear explanation for why the steady-state stroke volume must match stroke return. It also indicates the roles of preload, afterload, contractility, and heart rate.

Preload is the final pressure before the onset of systole and, as such, determines the final stretch of myocardium before the onset of contraction. The passive filling curve also indicates the limit to ventricular filling (Figs. 69.8 and 69.9).

Afterload refers to the force (pressure) the myocardium faces after it begins to contract. The value is approximated by the pressure at the opening of the outflow valves from the ventricles (pulmonary valve for the RV and aortic valve for the LV). The afterload really should be the generated tension, but because ventricular volume during ejection is falling while the pressure is rising, the tension is quasi-constant. The greater the afterload, the smaller the stroke volume (see Figs. 69.8 and 69.9). This restriction relates to the time available for contraction after valve opening, which will become clearer in the discussion that follows on contractility. Under normal conditions, changes in LV afterload only have a small effect on stroke volume, but the effect is much greater when contractility of the heart is decreased.

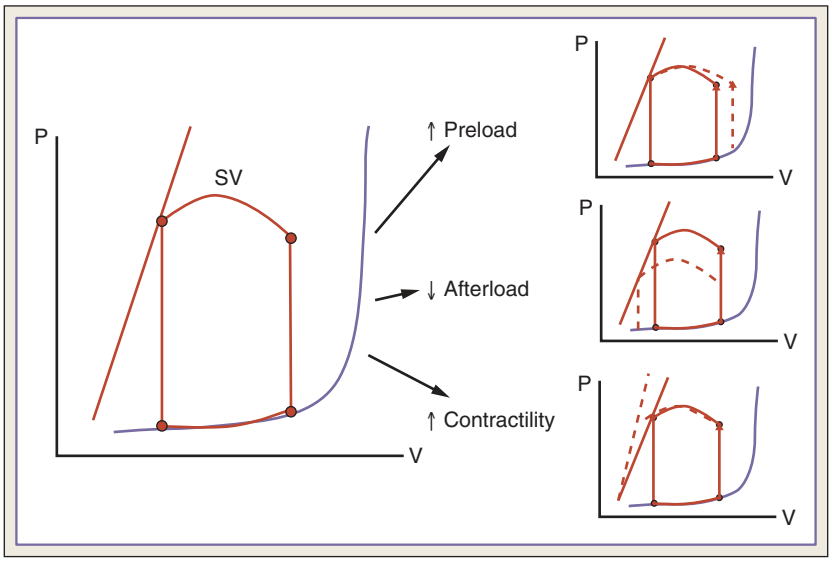

Fig. 69.9 Effects of increased preload, decreased afterload, and increased contractility on the volume (*V*)-pressure (*P*). relationship of the ventricles. All three of these increase stroke volume (*SV*).

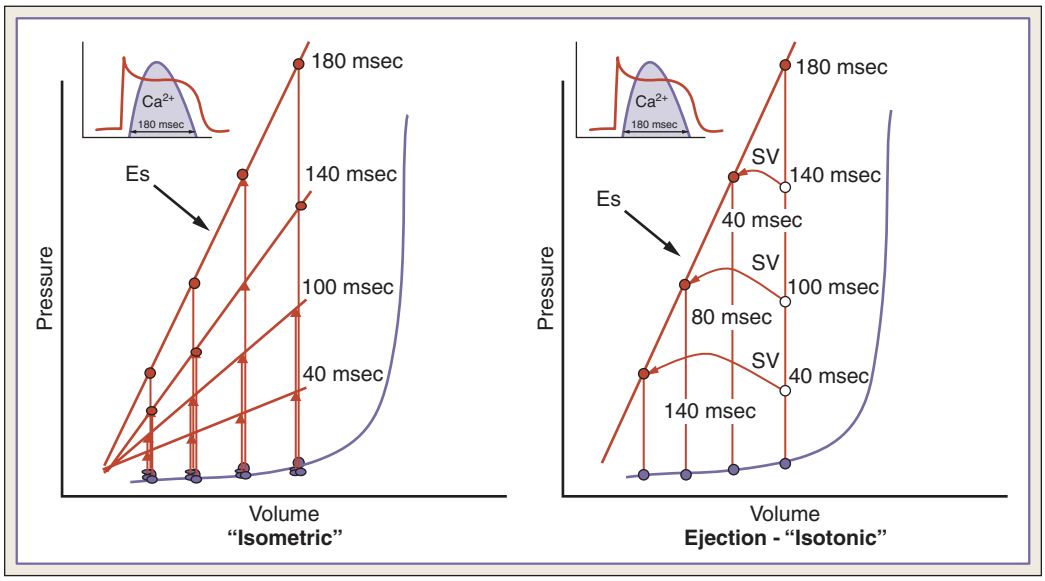

Fig. 69.10 Suga and Sagawa's concept of time-varying elastance. The slope of a line on the pressure versus volume relationship is elastance. During the contraction phase, at each instant during systole, all pressure-volume points fall on the same elastance. The numbers indicate the time during the cycle for each line. The *top insert* shows Ca^{2+} moving into the cell during the plateau of the action potential. In this case, the inflow lasts 180 msec, which is what determines the time to the maximum elastance for the cycle. The *left side* shows isovolumetric contraction (i.e., no ejection). The *right side* shows the outflow valve opening at different times. The total cycle time is still always 180 msec, but the lower the opening pressure, the more the time to eject blood, and stroke volume (*SV*) thus is larger.

The third property is contractility. This refers to the speed and extent of shorting of the muscle for a given afterload and preload. This property is best explained by what Suga and Sagawa called "a time varying elastance" (Fig. 69.10).[11,17,18] In very careful studies in isolated hearts from rabbits, they showed that the ventricular muscle becomes progressively stiffer (i.e., increases its elastance) during the contractions phase and then relaxes. On a plot of developed pressure versus ventricular volume, this appears as an elastance line that becomes steeper and steeper during the cardiac contraction cycle and then relaxes. The steepest elastance line gives the maximum possible pressure for any volume in the ventricle. The steepness of the line is determined by how quickly the muscle can stiffen in the time available for myocardial contraction. That time of contraction in turn depends on the amount of time for Ca^{2+} to be released into the cytoplasm, the amount of Ca^{2+} released, and how fast it is taken up during each cycle. These factors regulate the turnover of actin and myosin binding sites.

Depression of cardiac function means that a lower maximum elastance slope is inscribed during the cycle. The consequence is a lower stroke volume for the same preload, afterload, and heart rate. The normal end-systolic elastance slope for the LV is very steep, which is why changes in afterload only have a small effect on stroke volume in a normal heart (see Fig. 69.9). The effect of afterload on the RV, though, is much greater because the maximum elastance of the RV is only about a third of that of the LV. The lesser slope of the elastance line of the RV accounts for the systolic pressure sensitivity of this ventricle.

Another factor that is considered by some to be a determinant of cardiac output is aortic elastance.[19] This value is estimated from a line drawn from its end-diastolic volume and pressure point to the end-systolic volume-pressure point. It thus incorporates stroke volume and the pressure generated in the aorta at the end of systole; the change in pressure for change in volume gives elastance units. However, this is simply a reflection of ventricular afterload, which is already considered in the pressure-volume analysis of the ventricle and is likely better estimated by aortic valve opening. Based on Sagawa's concept of a time-varying elastance, the pressure generated in the aorta or pulmonary artery by ventricular ejection can never be higher than the pressure generated by the ventricle so that the aortic properties do not provide a load but do affect aortic valve opening. Furthermore, what is being called aortic elastance is a dynamic elastance and is dominated by vascular resistance and the downstream critical closing pressure. Finally, active LV ejection ends in the middle to two-thirds of systole so that the ventricle is relaxing before the end-systolic pressure-volume point. The aortic elastance analysis therefore adds little information to the simple consideration that aortic valve opening gives an estimate of LV coupling with the aorta, and this is easily seen at the end-diastolic pressure.

Right Ventricular Limitation Versus Dysfunction

In critically ill patients, RV output is frequently the limiting factor for cardiac output. This is especially so in patients with sepsis and in those who are post cardiac surgery. Three terms need to be distinguished. If a normal RV with normal end-systolic elastance is excessively filled, RV output becomes limited by the diastolic passive filling curve. Giving more volume will not increase LV output, but this is not failure of the RV. It is rather the physical limitation of its filling. When RV dysfunction is present, the end-systolic pressure-volume line is flatter and Pra/CVP must be greater for a given stroke volume, but if RV filling is not limited, stroke volume still can increase when there is an increase in venous return, allowing the LV stroke volume also to rise. When RV dysfunction is present, the limit of RV filling occurs at a lower Pra so that stroke volume is constrained to a lower range. The term *RV failure* should be used to indicate that there is both RV dysfunction and RV limitation so that the RV cannot provide adequate filling to the LV. It needs to be remembered that even if there is complete failure of RV contraction, Pra/CVP can never be higher than MSFP so that a high Pra/CVP only can occur by excessive volume administration and an MSFP that rises above normal values.

INTERSECTION OF RETURN AND CARDIAC FUNCTION

Actual cardiac output is determined by the interaction of the cardiac function and the return function. This is well described by Guyton's graphical analysis, which provides a mathematical solution to the interaction of these two functions (Fig. 69.11). Because the cardiac function

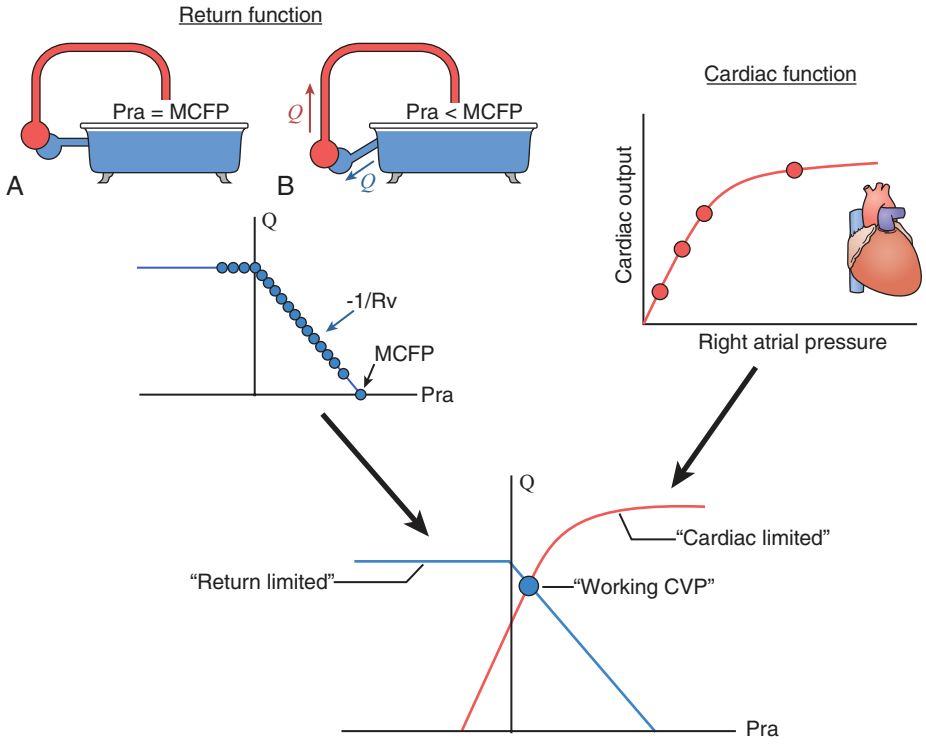

Fig. 69.11 Interaction of the cardiac function and venous return curves and the determination of cardiac output (*Q*). The *upper left* part shows the return curve, and the *upper right* part shows cardiac function. The two have the same axis so that they can be plotted together. This allows a graphical solution to determining the intersection of the two functions and the determination of the "working" cardiac output, "working" Pra/CVP, and "working" venous return. *CVP*, Central venous pressure; *MSVP*, mean systolic filling pressure; *PRa*, right atrial pressure; *Rv*, venous resistance.

and venous return curves share the same vertical axis, they can be plotted together (see Fig. 69.11). Where they intersect gives the "working" cardiac output, Pra, and venous return. With this analysis, respective changes in Pra/CVP and cardiac output indicate whether the process is the result of a primary change in cardiac function or in the return function.

Changes in Return Function

Role of Volume

One of the most common interventions in critically ill patients is the administration of a bolus of a fluid intended to increase cardiac output and arterial pressure, but this often is done without consideration of what volume can and cannot do. As in equation 1, a rise in blood pressure with a volume infusion must occur by increasing cardiac output because a volume infusion should not increase systemic vascular resistance. Any rise in cardiac output occurs by increasing MSFP and shifting the venous return curve to the right. This results in the venous return curve intersecting the cardiac function curve at a higher Pra/CVP and cardiac output. However, there are important caveats to seeking this response (Fig. 69.12). As already discussed (see Figs. 69.7 and 69.11), the cardiac function curve has a steep rise and a sharp plateau. When the VR curve intersects the plateau of the cardiac function curve, further increases in Pra/CVP do not change cardiac output and only provide "wasted preload": that is, a rise in Pra/CVP with no change in cardiac output. Without an increase in cardiac output, there should be no change in blood pressure, and the only physiologic accomplishment is increased fluid filtration at the capillary level and consequent congestion of upstream organs and dilution of the hemoglobin concentration. It also needs to be emphasized that the ascending part of the cardiac function curve (see Fig. 69.7) is steep, so that even a 1 mm Hg increase in CVP should produce close to a 0.5 L/min increase in cardiac output and 2 mm Hg rise in Pra—a 1 L/min increase. Thus if Pra/CVP is increased by 2 mm Hg with a volume bolus and cardiac output does not increase, more volume is not the clinical answer and is only harmful. As a last point, cardiac output frequently rises without a change in blood pressure, especially when the systolic pressure exceeds 100 mm Hg. This likely occurs because the baroreceptors have become reset at a lower threshold so that the rise in arterial pressure produces peripheral dilatation to maintain a constant arterial pressure. It can be shown in modeling studies that the maintenance of blood pressure allows for a larger increase in cardiac output because there is no associated increase in afterload to offset the increase in stroke volume.

There is an intrinsic mechanism for increasing stressed volume, and that control is to change capacitance (Figs. 69.6 and 69.13). A baroreceptor-induced activation of sympathetic pathways can contract the smooth muscle in the walls of small venules and veins, especially in the splanchnic region. This recruits unstressed volume into the stressed vascular volume, which is called a *decrease in capacitance.* A strong sympathetic response by this mechanism can recruit 10 mL/kg of unstressed volume into the stressed compartment. To put this into better perspective, in a 70-kg male this transfer would increase a stressed volume of 1400 mL by 700 mL:, a 50% increase, and this occurs in seconds because it is a reflex response. To do the equivalent with an infusion of a crystalloid would require over 2 L of fluid because of the distribution of the fluid between the vascular space and interstitial space. Capacitance also can be decreased by alpha-agonists such as norepinephrine. The importance of capacitance is that administration of alpha-adrenergic blocking drugs or narcotics removes this venous tone and can result in a rapid increase in capacitance, fall in MSFP, and fall in cardiac output. The clinical response should then be to give a volume bolus. Importantly, vascular smooth muscle only can constrict the vessel to some limit. When that limit is reached, this mechanism cannot be used by the body to defend its stroke volume. Furthermore, whenever MSFP is increased, it is likely that there also is increased capillary filtration and loss of vascular volume.

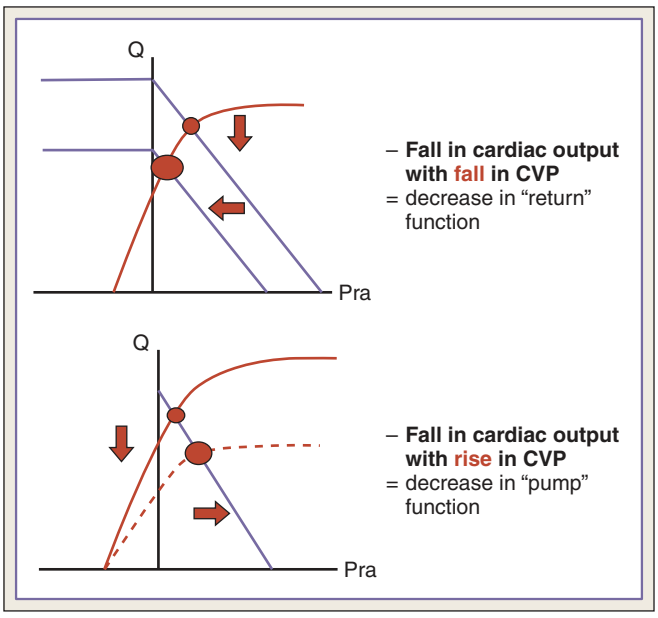

Fig. 69.12 Comparison of a change in cardiac function versus change in return function on cardiac output (*Q*) and right atrial pressure (*Pra*). When cardiac function changes, the change in cardiac output and Pra/CVP go in opposite directions. When the venous return function changes, the changes in cardiac output and Pra/CVP go in the same direction. *CVP*, Central venous pressure; Q, cardiac output.

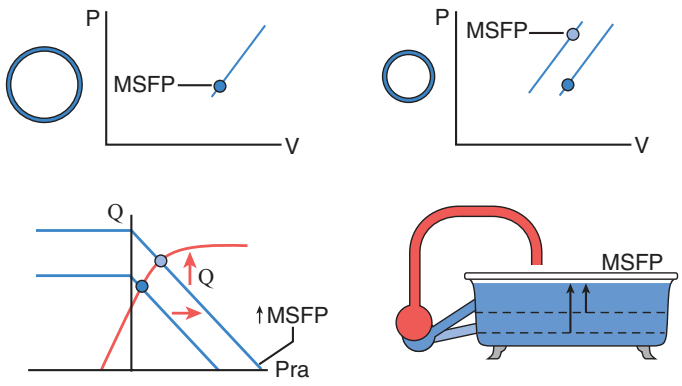

Fig. 69.13 Effect of a decrease in capacitance on cardiac output (*Q*). The *bottom right* is a cartoon of the major vascular components. A change in capacitance is the equivalent of lowering the opening on the side of the tub, which means mean systolic filling pressure (*MSVP*) is increased. The *upper left* shows the pressure vs. volume relationship (*P-V*) of the vasculature. The *upper right* shows a decrease in capacitance in a vessel, which occurs if the circumference is reduced (note *reduced circle*). This produces a leftward shift of the P-V line and rise in MSFP for the same volume. The *bottom left* is the venous return–cardiac function relationship. A decrease in capacitance shifts the venous return curve to the right, which intersects the cardiac function curve at a higher value and thus increases cardiac output (1) by the Starling mechanism. *PRa*, Right atrial pressure.

Venous Resistance

The pressure gradient from the MSFP to the right atrium normally is only in the 4–8 mm Hg range because venous resistance is low, but it still is physiologically significant. A decrease in venous resistance can increase cardiac output because the VR curve then intersects the cardiac function curve at a higher Pra/CVP. This likely is a factor in the high-cardiac-output states of early sepsis and liver disease. However, as with a rise in MSFP and rightward shift of the VR curve, this only is effective if the VR curve intersects the ascending part of the cardiac function curve.

Change in Cardiac Function

When cardiac function changes, changes in Pra/CVP and cardiac output occur in opposite directions. For example, better cardiac function is associated with a fall in Pra/CVP and a rise in cardiac output (see Fig. 69.12). Large increases in cardiac output under physiologic conditions, such as during exercise, primarily occur by heart rate increasing. The associated upward shift of the cardiac function curve with an increase in heart rate makes the heart much more "preload sensitive" because the ascending part of the cardiac function curve is much steeper and the plateau higher. In a normal heart, any increase in contractility, as characterized by a steeper end-systolic elastance curve, only mildly increases cardiac output (see Fig. 69.9). This underwhelming response takes place because the end-systolic pressure-volume line is already very steep, and making it steeper adds little to the stroke volume. However, if cardiac contractility is depressed, as in a patient who is septic or has another cause of depressed contractility, the effect of an inotrope can be marked.

In most shock states the blood pressure, and thus the afterload, is already low and little is gained by lowering systemic vascular resistance further; more often, clinicians try to increase resistance. However, some patients with cardiogenic shock present with an elevated systemic vascular resistance. In these patients carefully lowering vascular resistance with a drug such as nitroprusside can be helpful. This also argues for not raising arterial pressure more than is physiologically necessary in cardiogenic shock because the rise in arterial pressure decreases stroke volume to a greater extent when contractility is depressed.

PHYSIOLOGICALLY BASED APPROACH AT THE BEDSIDE

A good place to start is with the consideration that arterial pressure is determined by the product of cardiac output and the systemic vascular resistance (Fig. 69.14). Because a decrease in blood pressure triggered the clinical concern and systemic vascular resistance is a calculated value, the first key variable to evaluate is cardiac output. If the cardiac output is normal or elevated, the primary pathologic process is a fall in systemic vascular resistance. Unfortunately, most of the time it is not easy to directly measure cardiac output, but it is still possible to make a clinical judgment of the cardiac output status based on peripheral temperature, lactate, central venous saturation, organ function, and clinical context. However, when the situation is critical and the assessment of cardiac output uncertain, some measure of cardiac output is advantageous. It is important to appreciate that ejection fraction does indicate stroke volume or cardiac output, the variables that count. Thus if using echocardiography, a flow measurement may also be necessary. If the problem is deemed to be primarily a decrease in systemic vascular resistance, that is, distributive shock, the differential diagnosis is very clear and is listed in Box 69.1. The primary therapy then is to restore peripheral resistance, and for that, norepinephrine is an appropriate drug. The assumption is that the increased systolic pressure will result in a more normal distribution of blood flow by local metabolic regulation. Some increase in cardiac output can be helpful, too, but when this is done by trying to increase preload with fluids, it must be remembered that fluid loading is also likely to increase capillary leak.

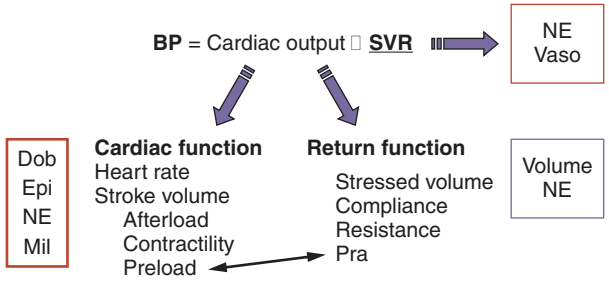

Fig. 69.14 Approach to managing shock. See text for details. ***BP,*** Blood pressure; ***Dob,*** dobutamine; ***Epi,*** epinephrine; ***Mil,*** milrinone; ***NE,*** norepinephrine; ***SVR,*** systemic vascular resistance; ***Vaso,*** vasopressin.

If a decrease in the cardiac output is considered the primary problem, it next needs to be determined whether the inadequate cardiac output is the result of decreased pump function or decreased return function (see Fig. 69.14). The Pra/CVP and clinical context give an indication of which it is. If the Pra/CVP is on the high side with a low cardiac output, the primary problem is depressed cardiac function, and inotropic therapy with dobutamine, epinephrine, or milrinone is indicated. It also is important to make sure that a low heart rate is not part of the problem. If Pra/CVP is on the low side, the return function is likely the primary problem and volume boluses are appropriate. In sepsis, norepinephrine also can be helpful because it constricts capacitance vessels and thereby recruits unstressed into stressed volume and acts like a volume infusion without giving volume.[20] Furthermore, norepinephrine does not increase venous resistance and may even decrease it, and it has a modest inotropic effect on the heart.

In this discussion only the Pra/CVP and not the pulmonary artery occlusion pressure has been used to assess preload status, even when the pulmonary occlusion pressure can be measured. This choice is made because Pra/CVP indicates the interaction of the heart as a whole with the venous return function.[21] Concentrating on Pra/CVP is especially important when cardiac limitation occurs at the right heart because once there is RV limitation, filling of the left heart is not a variable that can be manipulated to improve cardiac output. If a pulmonary artery occlusion pressure can be obtained, that value can be a useful indicator of the risk of pulmonary edema and can be used to modify fluid therapy, or even encourage diuresis, but a low value may prove a flawed indication for giving volume.

It is not within the scope of this chapter to delve into the heart-lung interactions of shock, but one important physiologic concern must be

BOX 69.1 Causes of a Distributive Vascular State

- Sepsis
- Drugs (vasodilators)
  - Milrinone
  - Nitroprusside
  - Hydralazine
- Arterial-venous shunts
- Spinal/epidural anesthetics
- Spinal injury
- Cirrhosis
- Thyroid disease (hyperthyroidism)
- Anaphylaxis
- Corticosteroid deficiency
- Anemia (severe, long-standing)
- Beriberi (thiamine, B_1) deficiency

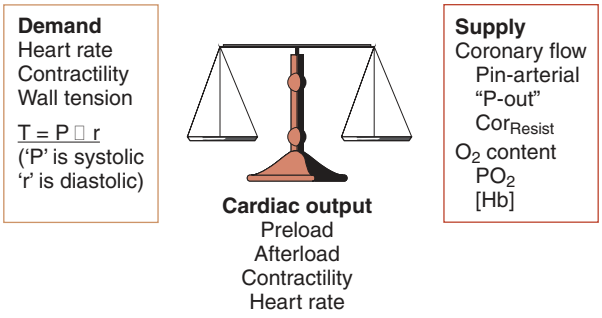

Fig. 69.15 Supply-demand balance of the heart. The *left side* shows the determinants of myocardial oxygen demand, and the *right side* shows the determinants of the supply of blood through the coronary circulation. The *middle* shows the determinants of cardiac function; these overlap with the demand factors. *T* is tension; *P* is systolic pressure; *r* is the ventricular radius; *Pin* is the arterial pressure perfusing the coronary arteries; *P-out* is the outflow pressure, which is a critical closing pressure in the myocardial wall; Cor_{Resist} is the coronary vascular resistance; and *[Hb]* is hemoglobin concentration.

highlighted. When RV limitation is present and there is "wasted preload," application of a mode of positive-pressure ventilation can decompress the heart by shifting the intersection of cardiac function and venous return function. Because the person's right heart likely is on the flat part of its function curve, lowering Pra/CVP will not decrease cardiac output. The decrease in transmural Pra/CVP may improve left-sided filling pressure. Ventricular decompression also may improve coronary flow.

SUPPLY–DEMAND CONSIDERATIONS

The heart has high aerobic demands and minimal anaerobic reserves. Thus demand for O_2 must be closely matched by the delivery of O_2. The major determinants of cardiac O_2 demand are heart rate, contractility, and ventricular wall tension[22] (Fig. 69.15). Wall tension is determined by the systolic pressure and the ventricular radius. Therefore it should be evident that the determinants of myocardial O_2 demand overlap with the determinants of cardiac function, which are heart rate, preload, afterload, and contractility. An increase in heart rate, rate of rise of systolic pressure, peak systolic pressure, or ventricular diameter all increase myocardial O_2 demand. Delivery of O_2 to the heart is determined by the hemoglobin concentration, arterial O_2 saturation, the pressure difference from the aorta to the myocardial wall, and the coronary vascular resistance. When coronary vessels are normal, coronary vasodilatory reserves are very large; blood flow to heart can increase fivefold from resting heart rates to the maximum.[23] However, this is not true when there are proximal coronary artery stenoses. In that situation the adverse impact of raising heart rate or arterial pressure needs to be considered. The effect of inotropes is complicated. The increase in contractility and heart rate increase myocardial O_2 demand, but this can be offset by reducing the ventricular radius, which acts to reduce wall stress. The inotrope may increase a very low arterial pressure because of inadequate cardiac output, but in the setting of coronary narrowing it also will improve coronary perfusion, potentially improving contractile function. On the other hand, use of high doses of vasoconstrictor drugs may override local metabolic dilatation in heart muscle and decrease coronary perfusion while increasing myocardial O_2 demand. Thus any interventions made in patients with obstructive coronary disease must be done with careful monitoring and consideration of all positive and negative consequences.

CONCLUSION

In the Guytonian universe it always is necessary to consider the effects of the underlying processes and treatments on cardiac function and return function. Directional changes in cardiac output and Pra/CVP give an indication of how these two functions are behaving. When managing cardiogenic shock, it is best to start by considering whether the problem is primarily distributive—that is a decrease in vascular resistance—or primarily inadequate cardiac output. If it is primarily inadequate cardiac output, the question becomes is the problem primarily with cardiac function or the return function. The directional changes in cardiac output and Pra/CVP give the answer in a physiologically based approach to shock.

KEY POINTS

- The four determinants of cardiac function are heart rate, preload, afterload, and contractility.
- The determinants of venous return are stressed volume, compliance of the systemic venous compartment, resistance to venous return, and right atrial pressure.
- The volume stretching the systemic veins creates the MSFP.
- The working cardiac output is determined by the intersection of cardiac function and return function.
- The heart only can pump out what comes back to it—in the steady state, stroke volume must equal stroke return.
- Stroke output by the ventricles is constrained by the limit of diastolic filling, and usually this occurs in the right heart.
- Venous return becomes limited when the pressure inside the great veins is less than their surrounding pressure; this is atmospheric pressure when not intubated.
- Normally only about 30% of blood volume is stressed, and it is this stressed volume that creates the force returning blood to the heart.
- Unstressed vascular volume can be recruited into stressed volume by reflex or alpha-adrenergic drugs; this is called a decrease in vascular capacitance.
- Capacitance can be increased by drugs that reduce sympathetic tone, MSFP, and the venous return function.
- Capacitance cannot be measured in an intact person and only can be estimated clinically.
- The determinants of myocardial oxygen demand include heart rate, wall tension (which is determined by the ventricular radius and systolic pressure), and contractility; these same variables are key determinants of cardiac function.

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Acute Coronary Syndromes: Therapy

Brian Baturin and Steven M. Hollenberg

DEFINITION AND CLINICAL MANIFESTATIONS

Acute coronary syndromes are a family of disorders that share similar pathogenic mechanisms and represent different points along a common continuum. They include ST elevation myocardial infarction (STEMI), non–ST segment elevation acute coronary syndrome (NSTE-ACS), and unstable angina (UA) pectoris. These syndromes account for nearly 2 million hospitalizations annually in the United States, and if patients who die before reaching the hospital are included, the mortality may be as high as 25%. The common link among the various acute coronary syndromes is the rupture of a vulnerable, but previously quiescent, coronary atherosclerotic plaque. Exposure of plaque contents to the circulating blood pool triggers the release of vasoactive substances and activation of platelets and the coagulation cascade. The extent of resultant platelet aggregation, thrombosis, vasoconstriction, and microembolization dictates the clinical manifestations of the syndrome.

Acute coronary syndromes were traditionally classified by the presence or absence of Q waves, but more recently the classification has shifted and has become based on the initial electrocardiogram (ECG). Patients are divided into three groups: (1) those with STEMI, (2) those without ST elevation but with enzyme evidence of myocardial damage (NSTE-ACS), and (3) those with UA. Classification according to a presenting ECG coincides with current treatment strategies because patients presenting with ST elevation benefit from immediate reperfusion and should be treated with fibrinolytic therapy or urgent revascularization. In contrast, fibrinolytic agents are not effective in patients without ST elevation.

PATHOPHYSIOLOGY OF ACUTE CORONARY SYNDROMES

Myocardial ischemia results from an imbalance between oxygen supply and demand and usually develops in the setting of obstructive atherosclerotic coronary artery disease, which limits blood supply. The pathophysiology of unstable coronary syndromes and myocardial infarction (MI) usually involves dynamic partial or complete occlusion of an epicardial coronary artery because of acute intracoronary thrombus formation.

The inciting event underlying the development of acute coronary syndromes is the rupture of an intracoronary atherosclerotic plaque.[1] The possible sequelae of plaque rupture include thrombus formation with a total occlusion resulting in STEMI, or dissolution of the thrombus, healing of the fissure, and clinical stabilization with subtotal occlusion, which can lead to either NSTE-ACS or UA.

Atherosclerotic plaques are composed of a lipid core, which includes cholesterol, oxidized low-density lipoproteins (LDLs), macrophages, and smooth muscle cells, covered by a fibrous cap. Plaque rupture occurs when external mechanical forces exceed the tensile strength of the fibrous cap. After plaque rupture, the clinical consequences depend largely on the balance between prothrombotic and antithrombotic forces.[2,3] The lipid core contains tissue factor and other thrombogenic materials that lead to platelet activation and aggregation. Fibrinolytic factors, such as tissue plasminogen activator, prostacyclin, and nitric oxide, act to counteract the potential for thrombosis. A major factor in the outcome of plaque rupture is blood flow. With subtotal occlusion, high-grade stenosis, or vasospasm, thrombus begins to propagate downstream in the arterial lumen. In contrast to the initial thrombi that are platelet rich, these thrombi contain large numbers of red cells enmeshed in a web of fibrin. The former would be expected to respond best to antiplatelet therapy and the latter to antithrombotic and fibrinolytic therapy.

STEMI

Epidemiology

STEMI comprises approximately 25%–40% of ACS presentations, although more recent data show a decline in the percentage of ACS caused by STEMI between 1999 and 2008.[4,5] In-hospital mortality and 1-year mortality rates from STEMI have decreased significantly with improvements in reperfusion therapy and guideline-directed medical therapy (GDMT); current in-hospital mortality can be as low as 4%–6%, and 1-year mortality ranges from 7% to 18%.[6,7] Nonetheless, not all eligible patients with STEMI receive reperfusion therapy; registry data from 2017 estimated an overall early ECG miss rate of 7%, with the majority of those patients being elderly, and variability up to 30% between multiple large-volume emergency departments.[8]

Women, people with diabetes, and patients with renal disease appear to have worse outcomes when presenting with STEMI. Approximately 23% of patients with STEMI in the United States have diabetes mellitus, and three-fourths of all deaths among patients with diabetes mellitus are related to coronary artery disease. Patients with chronic renal disease, particularly those on dialysis, are less likely to receive GDMT; only 45% of eligible patients on dialysis received reperfusion therapy, and only 70% received aspirin on admission. At discharge, only 67% of patients on dialysis were prescribed aspirin, and only 57% were prescribed beta-blockers.[7,9] Women and patients on dialysis tend to have higher bleeding complications associated with antithrombotic therapy.[9,10]

Diagnosis and Treatment of STEMI

Symptoms suggestive of MI may be similar to those of ordinary angina but are typically greater in intensity and duration. Nausea, vomiting, and diaphoresis may be prominent features, and malaise and even

stupor attributable to low cardiac output can occur. Compromised left ventricular function may result in pulmonary edema with the development of pulmonary bibasilar crackles and jugular venous distention; a fourth heart sound can be present with small infarcts or even mild ischemia, but a third heart sound is usually indicative of more extensive damage.

A consensus group to standardize the definition of MI defines the changes diagnostic of STEMI as new ST elevation at the J-point ≥1 mm (0.1 mV) in at least two contiguous leads, except leads V_2–V_3, where the threshold is higher (≥1.5 mm in women and ≥2 mm in men) or new left bundle branch block (LBBB).[10,11] The specificity of new LBBB has been challenged by a multicenter, longitudinal study published in which 4% of patients presenting with possible ACS had an LBBB presumed to be new, and of these, only 39% were diagnosed with ACS.[12] Similar findings have been reported elsewhere.[13] In the GUSTO-1 trial, of the 26,003 North American patients presenting with possible ACS, 131 (0.5%) with confirmed acute MI had an LBBB.[14] A new or presumed new LBBB should not be considered diagnostic of acute MI in isolation, but when the clinical presentation strongly suggests ACS, and especially when shock is present, LBBB should be regarded as a STEMI equivalent.

Patients presenting with suspected myocardial ischemia should undergo a rapid evaluation, continuous monitoring, and reassessment. (See Fig. 70.1 for an algorithm for the initial evaluation and management of STEMI). The 2013 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Guidelines for the Management of ST-Elevation Myocardial Infarction emphasize the importance of choosing some type of reperfusion therapy as soon as possible when appropriate. In addition to antiplatelet therapy, an early decision to perform percutaneous coronary intervention (PCI), transfer to a PCI-capable facility, or administer fibrinolytic therapy should be made. The timeliness of reperfusion is as important as the choice of therapy.[15]

The preferred method for reperfusion in STEMI is PCI if it can be done in a timely manner, defined as the time from first medical contact (FMC) to device of less than 90 minutes. Emergency medical services (EMS) transport directly to a PCI-capable hospital for primary PCI is the recommended triage strategy for patients with STEMI.[9] If a patient initially presents to a non–PCI-capable hospital and door in–door out time is anticipated to be less than 30 minutes, transfer to a PCI-capable hospital should be arranged if the FMC to device time is anticipated to be less than or equal to 120 minutes. If the FMC to device time is longer than 120 minutes, fibrinolytics should be considered, with probable transfer to a PCI-capable facility after fibrinolytic therapy for STEMI.[9] Practical considerations regarding transport to a PCI-capable facility should be reviewed carefully before foregoing fibrinolytics for PCI.

Fibrinolytic Therapy

Evidence from multiple clinical trials demonstrates the ability of fibrinolytic agents administered early in the course of an acute MI to reduce infarct size, preserve left ventricular function, and reduce

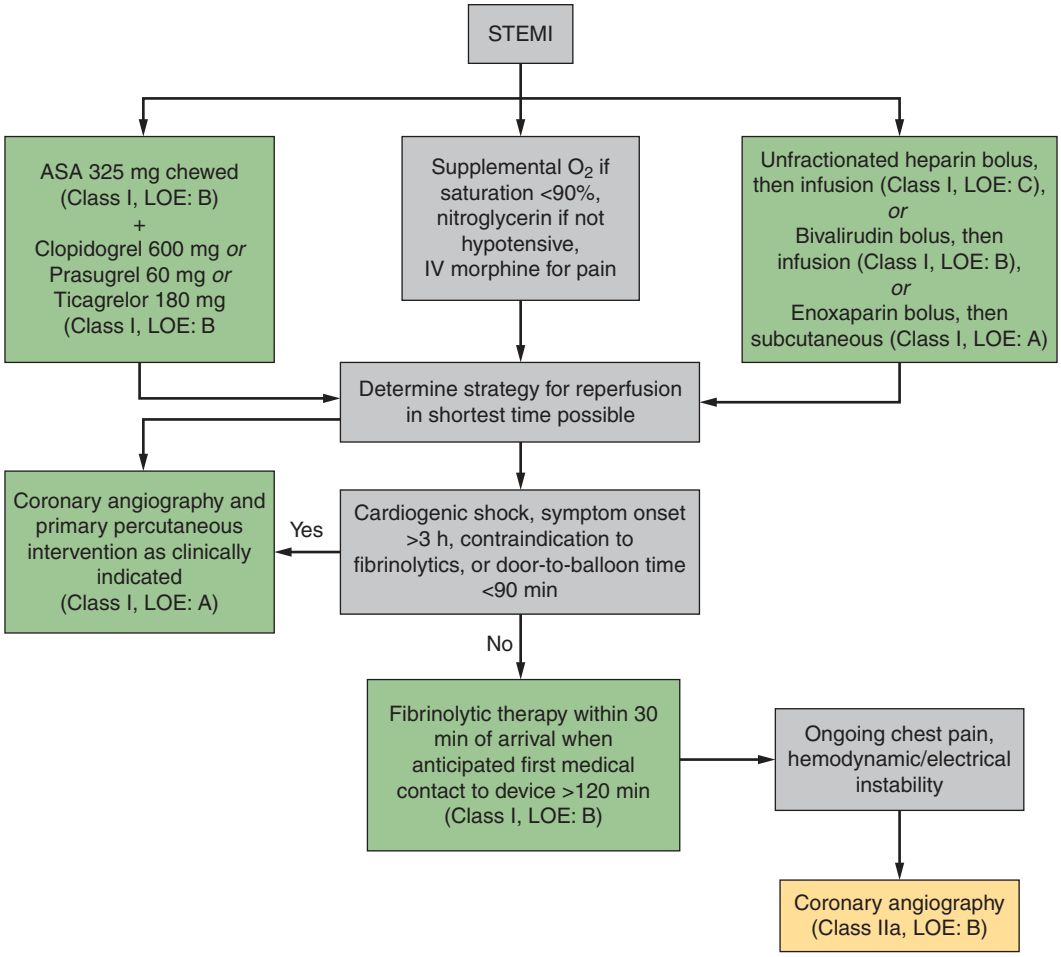

Fig. 70.1 Algorithm for the initial management of patients with ST elevation myocardial infarction (*STEMI*). *ASA*, Acetyl salicylic acid; *IV*, intravenous; *LOE*, level of evidence.

Box 70.1 Indications for and Contraindications to Fibrinolytic Therapy in ST Elevation Myocardial Infarction

Indications for Fibrinolytic Therapy When There Is a >120-Minute Delay From First Medical Contact to Primary Percutaneous Coronary Intervention

- Presentation within 12 hours of symptom onset (COR 1, LOE A)
- Evidence of ongoing ischemia 12–24 hours after symptom onset and a large area of myocardium at risk or hemodynamic instability (COR IIa, LOE C)
- Fibrinolytics are contraindicated for the treatment of ST depression (non–ST elevation acute coronary syndrome), except if true posterior myocardial infarction or when associated with ST elevation in lead aVR (COR III, LOE B)

Contraindications

Absolute

- Any prior intracranial hemorrhage
- Known structural cerebral vascular lesion (e.g., arteriovenous malformation)
- Known malignant intracranial neoplasm (primary or metastatic)
- Ischemic stroke within 3 months (EXCEPT acute ischemic stroke within 4.5 hours)
- Suspected aortic dissection
- Active bleeding or bleeding diathesis (excluding menses)
- Significant closed-head or facial trauma within 3 months
- Intracranial or intraspinal surgery within 2 months
- Severe uncontrolled hypertension (unresponsive to emergency therapy)
- For streptokinase, prior treatment within the previous 6 months

Relative

- History of chronic, severe, poorly controlled hypertension
- Significant hypertension on presentation (SBP >180 mm Hg or DBP >110 mm Hg)
- History of prior ischemic stroke >3 months
- Dementia
- Known intracranial pathology not covered in absolute contraindications
- Traumatic or prolonged (>10 minutes) cardiopulmonary resuscitation
- Major surgery (<3 weeks)
- Recent (within 2–4 weeks) internal bleeding
- Noncompressible vascular punctures
- Pregnancy
- Active peptic ulcer
- Oral anticoagulant therapy

COR, Class of recommendation; *DBP,* diastolic blood pressure; *LOE,* level of evidence; *SBP,* systolic blood pressure.

short-term and long-term mortality.[16–18] Patients treated early derive the most benefit.[18]

Indications for and contraindications to fibrinolytic therapy are listed in Box 70.1. Because of the small, but nonetheless significant, risk of bleeding complications (most notably, intracranial hemorrhage, which occurs in 0.7%–1.8% of high-risk patients treated with fibrinolytics), the selection of patients with acute MI for the administration of a fibrinolytic agent should be undertaken with prudence and caution.[19] This is of special importance in intensive care unit (ICU) patients, who may have a predisposition to bleeding complications because of multiple factors. In this setting, emergent coronary angiography (with PCI as clinically indicated) is usually preferable.

Commonly administered fibrinolytics include the fibrin-specific agents tenecteplase, reteplase, and alteplase; the non–fibrin-specific agent streptokinase is infrequently used. After the administration of fibrinolytics for STEMI, the patient should be monitored for signs and symptoms of adequate reperfusion, as indicated by relief of symptoms and/or hemodynamic/electrical instability coupled with resolution of the highest initial ST elevation (preferably 50%, but at least some).[20] Complete (or near-complete) ST segment resolution at 60 or 90 minutes after fibrinolytic therapy is a useful marker of a patent infarct artery.[21–23] If signs of adequate reperfusion are not evident within 90 minutes ("failed fibrinolysis"), patients should be urgently transferred to a PCI-capable facility with intent to perform rescue PCI.[9] In patients with clinically successful fibrinolysis, trial data suggest that death, recurrent MI, recurrent ischemia, new or worsening heart failure (HF), or shock at 30 days is reduced with routine angiography compared with patients who underwent an ischemia-guided approach, with the greatest benefit in high-risk patients.[24–27]As such, in centers without angiographic capability, transfer to a PCI-capable facility after fibrinolytic therapy is recommended.

Patients with STEMI and signs of shock or severe HF should be immediately transferred to a PCI-capable facility irrespective of when the MI occurred or when fibrinolytics were given.[28]

In contrast to the treatment of STEMI, fibrinolytics have shown no benefit and an increased risk of adverse events when used for the treatment of NSTE-ACS or UA.[29] Based on these findings, there is currently no role for fibrinolytic agents in these latter syndromes.

Primary PCI in Acute Myocardial Infarction

The major advantages of primary PCI over fibrinolytic therapy include a higher infarct artery patency with a higher rate of normal flow, lower rates of recurrent ischemia, reinfarction, the need for emergency repeat revascularization, and a lower risk of intracranial hemorrhage.[17,30] Placement of drug-eluting stents is now routine.[31,32] Coronary angiography also affords the ability to stratify risk based on the severity and distribution of coronary artery disease. Data from several randomized trials have indicated that PCI is preferable to fibrinolytic therapy for acute MI patients at a higher risk.[30]

Achieving reperfusion in a timely manner correlates with improvement in the infarct size, left ventricular function, and survival.[20,33] The ultimate goal is to restore adequate blood flow through the infarct-related artery to the infarct zone and to limit microvascular damage and reperfusion injury. The latter is accomplished with adjunctive and ancillary treatments that are discussed later.

Previous clinical practice guidelines recommended against PCI of non–culprit artery stenoses at the time of primary PCI in patients with STEMI. Recent randomized controlled trials since this recommendation have demonstrated that multivessel PCI at the time of culprit artery PCI or as a staged procedure may be safe and beneficial. The largest of these trials was the COMPLETE study, which demonstrated a significant decrease in a composite outcome of cardiovascular (CV) death or MI in those patients with complete revascularization.[34] Given these findings, PCI of a non-culprit vessel may be considered either at the time of primary PCI or as a staged procedure in patients presenting with a STEMI.[34,35] In patients with cardiogenic shock, however, multivessel PCI was not shown to be effective, and so this is not recommended in this setting.[36]

Coronary Artery Bypass Graft Surgery in Patients With STEMI

Subsets of patients who present with STEMI are better served with coronary artery bypass graft (CABG) surgery. Patients with failed PCI

TABLE 70.1 Timing of Urgent Coronary Artery Bypass in Patients With ST Elevation Myocardial Infarction in Relation to the Use of Antiplatelet Agents

Drug	Recommendation	COR	LOE
Aspirin	Aspirin should not be withheld before urgent CABG	I	C
Clopidogrel or ticagrelor	Discontinue at least 24 hours before urgent on-pump CABG	I	B
Eptifibatide or tirofiban	Discontinue at least 2 to 4 hours before urgent CABG	I	B
Abciximab	Discontinue at least 12 hours before urgent CABG	I	B

CABG, Coronary artery bypass grafting; *COR,* class of recommendation; *LOE,* level of evidence.
Adapted from O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guidelines for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2013;127:e362–e425.

or whose coronary anatomy is not amenable to PCI but who have ongoing symptoms of ischemia, cardiogenic shock, severe HF, or other high-risk features should be considered for CABG.[37] CABG is also recommended in patients who require not only revascularization but also the repair of a mechanical defect, such as a ventricular septal defect, free wall rupture, or papillary muscle rupture.[9] The previously reported increased mortality in CABG patients who recently had a STEMI needs to be balanced against the need for revascularization. Consideration must be given to the timing of urgent CABG in relation to the administration of antiplatelet agents in patients with a recent STEMI. Table 70.1 provides a summary of these recommendations. The risk of major bleeding and mediastinal re-exploration is higher in patients on dual antiplatelet therapy, but if therapy can be held for 3–5 days, the magnitude of this risk is uncertain.[38,39] The risk of postoperative bleeding may be higher in patients previously given prasugrel.[40]

Adjunctive Therapy

Aspirin

Aspirin is the best known and the most widely used of all the antiplatelet agents because of its low cost and relatively low toxicity. Aspirin inhibits the production of thromboxane A_2 by irreversibly acetylating the serine residue of the enzyme prostaglandin H_2 synthetase. Aspirin has been shown to reduce the mortality in acute infarction to the same degree as fibrinolytic therapy, and its effects are additive to fibrinolytics.[41] In addition, aspirin reduces the risk of reinfarction.[42,43] Unless contraindicated, all patients with a suspected ACS should be given aspirin as soon as possible at a dose of 162–325 mg of a non–enteric-coated preparation. The maintenance dose is typically 81 mg daily.

Adenosine Diphosphate $P2Y_{12}$ Receptor Blockers

Dual antiplatelet therapy with addition of an adenosine diphosphate $P2Y_{12}$ receptor blocker is routine. $P2Y_{12}$ inhibitors include clopidogrel, prasugrel, and ticagrelor.[9]

Clopidogrel is a prodrug that is converted in the liver to the active thiol metabolite via the cytochrome P-450 (CYP) 3A, 1A, 2B, and 2C subfamilies. The active metabolite binds irreversibly to the $P2Y_{12}$ component of the adenosine diphosphate (ADP) receptor on the platelet surface, preventing the activation of the GPIIb/IIIa receptor complex and reducing platelet aggregation for the remainder of the platelet's lifespan, which is approximately 7–10 days. The onset of the inhibition of platelet aggregation is dose-dependent, within 2 hours of a loading dose, although peak effect is closer to 6 hours. A 600-mg loading dose of clopidogrel provides more rapid platelet inhibition and is preferred to a 300-mg loading dose.[44]

Prasugrel is a thienopyridine that irreversibly binds to the $P2Y_{12}$ component of the ADP receptor with a more rapid onset of action.[45] Like clopidogrel, prasugrel is a prodrug metabolized to both an active and inactive metabolite, but a higher proportion is metabolized to an active metabolite, resulting in a higher level of inhibition of platelet aggregation than clopidogrel. The onset of inhibition of platelet aggregation can be achieved in less than 30 minutes with a loading dose of 60 mg, but peak effect occurs in approximately 4 hours.[46]

Ticagrelor is a reversible, non-thienopyridine $P2Y_{12}$ receptor antagonist that does not require metabolic conversion to the active drug. Like prasugrel, ticagrelor has a more rapid onset of action than clopidogrel with ~41% inhibition of platelet aggregation within 30 minutes of an 180-mg loading dose and peak effect in approximately 2 hours.

Which $P2Y_{12}$ receptor antagonist to use is dependent on the chosen reperfusion strategy. In those patients receiving fibrinolysis, early concomitant administration of clopidogrel has shown clear evidence of benefit with reduced endpoints of death, MI, or recurrent ischemia.[47,48] The TREAT trial compared the use of ticagrelor or clopidogrel after fibrinolysis after initial administration of clopidogrel in most (90%) patients. There was no difference in major, fatal, or intracranial bleeding at 30 days and 1 year, and the composite outcome (vascular death, MI, or stroke) was also similar.[49]

When primary PCI is intended, recent randomized trials have demonstrated improved outcomes with the use of ticagrelor or prasugrel, as discussed later. The choice of agent depends on various factors, including familiarity, local practice, and cost. In the randomized, double-blind TRITON-TIMI 38 trial, patients treated with prasugrel had a significant reduction in nonfatal MI when compared with those treated with clopidogrel.[50] The rate of major bleeding was higher in the prasugrel group, as was the rate of life-threatening bleeding. A post hoc analysis of the TRITON-TIMI 38 trial identified either harm in patients with a history of transient ischemic attack (TIA) or stroke and no benefit in patients either older than 75 years or those weighing less than 60 kg. The Food and Drug Administration (FDA) has labeled a history of TIA and/or stroke as an absolute

contraindication to prasugrel use, whereas weight less than 60 kg or age over 75 years remain relative contraindications.[51]

The PLATO trial compared ticagrelor with clopidogrel in 18,000 patients presenting with ACS, 38% of whom had a STEMI; the primary endpoint (MI, stroke, or CV death) occurred less often with ticagrelor, although there were more strokes and episodes of intracranial hemorrhage with ticagrelor.[52] Interestingly, ticagrelor was less effective in North America than in the rest of the world, probably because of an interaction with the aspirin maintenance dose (more patients in the United States took a median aspirin dose ≥300 mg/dL).[53] Hence, when ticagrelor is used with aspirin as a component of dual antiplatelet therapy, the dose of aspirin should not exceed 100 mg.[54]

The ISAR-REACT-5 trial compared prasugrel with ticagrelor in 4018 patients who presented with ACS (41% of patients with STEMI) and showed an increased rate of the primary endpoint (a composite of death, MI, or stroke at 1 year) in the ticagrelor arm with similar rates of bleeding in both groups.[55] This result was not expected based on the results of the PLATO and TRITON-TIMI 38 trials and might be explained by an open-label design or relatively fewer patients.

Dual antiplatelet therapy with aspirin and $P2Y_{12}$ inhibition is given to all patients undergoing fibrinolysis or PCI, as described earlier. However, the data suggest that even patients not undergoing reperfusion benefit from the addition of clopidogrel or ticagrelor to aspirin.[48,56] COMMIT-CCS-2 randomized over 45,000 patients, most with STEMI but only 54% treated with fibrinolytics and almost none treated with PCI, to 75 mg of clopidogrel daily.[48] All-cause mortality was significantly reduced from 8.1% in the placebo group to 7.5% in the clopidogrel group, without increased bleeding in the clopidogrel group. A subanalysis of PLATO demonstrated benefit of ticagrelor compared with clopidogrel in patients with ACS and no reperfusion.[56] On the basis of these data, patients presenting with MI should be considered for clopidogrel or ticagrelor regardless of whether or not they underwent reperfusion therapy. Prasugrel has not shown superiority to clopidogrel in patients with ACS without reperfusion.

Glycoprotein IIb/IIIa Receptor Antagonists

Glycoprotein IIb/IIIa receptor antagonists inhibit the final common pathway of platelet aggregation, blocking the cross-linking of activated platelets.[57] In the era of dual antiplatelet therapy using $P2Y_{12}$ inhibitors and aspirin, the role of the addition of a glycoprotein IIb/IIIa inhibitor in primary angioplasty for STEMI is uncertain. Upstream use (before PCI) has failed to show benefit and is no longer recommended. Current guidelines suggest that use of a glycoprotein IIb/IIIa inhibitor at the time of PCI for STEMI cannot be recommended as routine but may be beneficial and is typically considered on an individual patient basis. For example, the use of a glycoprotein IIb/IIIa inhibitor at the time of PCI may be appropriate if the patient has a large thrombus burden, has no or slow reflow, or there was insufficient loading with a $P2Y_{12}$ receptor antagonist.[58]

Anticoagulants in Patients Undergoing PCI

For patients undergoing PCI who have already been treated with aspirin and a $P2Y_{12}$ inhibitor, both unfractionated heparin (UFH) and bivalirudin are acceptable anticoagulant regimens.[58] Bivalirudin is a direct thrombin inhibitor (DTI) that inhibits both clot-bound and circulating thrombin. It is an alternative to UFH in patients with a history of heparin-induced thrombocytopenia (HIT). Previous studies have concluded that bivalirudin is at least equivalent to heparin plus a glycoprotein IIb/IIIa inhibitor in reducing ischemic events.[59–61] More recent trials, which reflect contemporary practices such as more frequent potent antiplatelet agent use (ticagrelor or prasugrel), a radical approach to PCI, and decreased use of IIb/IIIa glycoprotein inhibitors, have concluded that compared with bivalirudin, heparin is similar in or reduces the incidence of major adverse ischemic events in the setting of primary PCI, with no increase in bleeding complications.[62,63] A 2017 registry study evaluated outcomes in more than 65,000 patients with STEMI with an even distribution of administration of UFH and bivalirudin. After adjustment, there was no difference in outcomes but a higher rate of stent thrombosis with bivalirudin.[64] Table 70.2 gives doses of antiplatelet and anticoagulant therapy for the management of STEMI.

Other Medical Therapies

Nitrates

Nitrates have a number of beneficial effects in acute MI. They reduce myocardial oxygen demand by decreasing preload and afterload and may also improve myocardial oxygen supply by increasing subendocardial perfusion and collateral blood flow to the ischemic region.[65] Patients with ST elevation caused by occlusive coronary artery spasm may have dramatic resolution of ischemia with nitrates. In addition to their hemodynamic effects, nitrates reduce platelet aggregation. Despite these benefits, the GISSI-3 and ISIS-4 trials failed to show a significant reduction in mortality from routine acute and chronic nitrate therapy.[66,67] Nonetheless, nitrates remain the first-line agents for the symptomatic relief of angina pectoris and when myocardial infarction is complicated by hypertension or congestive heart failure. Nitrates should be avoided in patients with right ventricular infarct, hypotension (systolic blood pressure [SBP] <90 mm Hg or >30 mm Hg below baseline), hypertrophic cardiomyopathy, severe aortic stenosis, or phosphodiesterase-5-inhibitor use within the previous 24–48 hours.

Beta-Blockers

Beta-blockers are beneficial both in the early management of MI and as long-term therapy. In the prefibrinolytic era, early intravenous atenolol was shown to significantly reduce reinfarction, cardiac arrest, cardiac rupture, and death.[68] However, more recent data have shown that although the early administration of intravenous beta-blockers followed by oral dosing may lower the reinfarction rate at 4 weeks, there may be an increase in the risk of developing HF and cardiogenic shock.[69] Based on these findings, routine use of intravenous beta-blockers in the absence of systemic hypertension is no longer recommended. However, oral beta-blockers should be administered to patients within the first 24 hours of having a STEMI as long as the following conditions are not present: signs of HF, cardiogenic shock or a low-output state, significant atrioventricular (AV) conduction disease, or active wheezing because of reactive airway disease.[9] Unless contraindicated, beta-blockers should be continued beyond the hospitalization.

Renin–Angiotensin–Aldosterone System Inhibitors

The renin–angiotensin–aldosterone system (RAAS) inhibitors include angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and aldosterone antagonists. ACE inhibitors decrease circulating angiotensin II levels and increase levels of bradykinin, which in turn stimulates production of nitric oxide by endothelial nitric oxide synthase. In the vasculature, ACE inhibition promotes vasodilation and tends to inhibit smooth muscle proliferation, platelet aggregation, and thrombosis.

ACE inhibitors have been shown unequivocally to improve hemodynamics, functional capacity and symptoms, and survival in patients with chronic congestive heart failure and to prevent the development of congestive heart failure in patients with asymptomatic left ventricular dysfunction.[70–72] This information was the spur for trials evaluating

TABLE 70.2 Adjunctive Antiplatelet and Anticoagulant Therapy to Support Reperfusion With Primary Percutaneous Coronary Intervention

Drug	Dosing	COR	LOE
Antiplatelet Therapy			
Aspirin	162–325 mg loading	I	B
Aspirin	81 to 325 mg daily maintenance	I	A
Clopidogrel	600 mg loading	I	B
	75 mg daily maintenance for 1 year	I	B
Prasugrel	60 mg loading	I	B
	10 mg daily maintenance for 1 year	I	B
Ticagrelor	180 mg loading	I	B
	90 mg twice a day maintenance for 1 year	I	B
GP IIb/IIIa Receptor Antagonists in Conjunction with Unfractionated Heparin or Bivalirudin in Selected Patients			
Abciximab	Bolus, then infusion	IIa	A
Tirofiban	Bolus, then infusion; reduce infusion by 50% with CrCl < 30 mL/min	IIa	B
Eptifibatide	Double bolus 10 minutes apart, then infusion; reduce infusion by 50% with CrCl < 50 mL/min	IIa	B
Anticoagulant Therapy			
Unfractionated heparin	Bolus to achieve therapeutic ACT	I	C
Bivalirudin	Bolus, then infusion with or without prior treatment with UFH; reduced dose with renal impairment	I	B
Fondaparinux	Not recommended as the sole anticoagulant for primary PCI	III: Harm	B

ACT, Activated clotting time; *COR,* class of recommendation; *LOE,* level of evidence; *PCI,* percutaneous coronary intervention; *UFH,* unfractionated heparin.

Adapted from O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guidelines for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2013;127:e362–e425.

the benefit of the prophylactic administration of ACE inhibitors in the post-MI period.

The ACE inhibitor captopril was shown to improve survival in patients with left ventricular dysfunction (ejection fraction <40%) after MI in the SAVE trial.[73] A smaller but still significant reduction in mortality was seen when all patients were treated with captopril in the ISIS-4 study, with greater benefits in patients with left ventricular dysfunction.[67] The mechanisms responsible for the benefits of ACE inhibitors probably include limitation in the progressive left ventricular dysfunction and enlargement (remodeling) that often occur after infarction, but a reduction in ischemic events was seen as well.

Immediate intravenous ACE inhibition, particularly with enalaprilat, has not been shown to be beneficial,[74] but oral ACE inhibition should be started early in the hospital course after STEMI. An ACE inhibitor should be administered within the first 24 hours to all patients with a STEMI and left ventricular dysfunction or HF.[9] Possible contraindications to ACE inhibitor use include hypotension, shock, or a history of renal failure or hyperkalemia with ACE inhibitor or ARB use. Baseline renal function should be taken into consideration when initiating an ACE inhibitor or an ARB, but renal failure is not an absolute contraindication to their use. Patients should be started on low doses of oral agents and titrated to maximally tolerated doses. STEMI patients who are intolerant to an ACE inhibitor should be given an ARB. In particular, valsartan has been shown to be noninferior to captopril in the VALIANT (Valsartan in Acute Myocardial Infarction) trial.[75]

Aldosterone has also been implicated in deleterious left ventricular remodeling after MI. Early initiation (<7 days post MI) of the aldosterone antagonist eplerenone has a proven mortality benefit and should be given to patients with STEMI and no contraindications who are already receiving an ACE inhibitor and beta-blocker and who have a left ventricular ejection fraction (EF) less than or equal to 40% and either symptomatic HF or diabetes mellitus.[9,76] More recent data have pointed towards some benefit with aldosterone antagonists in patients presenting with a STEMI without HF,[77,78] but the guidelines do not recommend their use in STEMI patients when HF is not present. Contraindications to the use of an aldosterone antagonist include creatinine greater than 2.5 mg/dL in men and more than 2.0 mg/dL in women or potassium higher than 5.0 mEq/L.

Lipid-Lowering Agents

Multiple studies have shown that statin use in patients after ACS can prevent death, recurrent MI, and stroke.[79,80] Use of a high-intensity statin is preferred and should be initiated before discharge to improve compliance.[7,9] In patients with ACS, high-intensity statin therapy should be given regardless of the LDL level. Among the currently available statins, only high-dose atorvastatin (80 mg daily) has been studied in clinical trials and shown to reduce death and ischemic events among patients with ACS.[81,82] It is uncertain if this represents a class effect or is specific to atorvastatin. High-intensity rosuvastatin (20–40 mg daily) is known to lower LDL comparably to atorvastatin and may be used particularly in patients with intolerance to the latter.[83] Contraindications to statin use include a history of statin-induced rhabdomyolysis or significant myopathy and/or acute liver injury.

Calcium Channel Blockers

Randomized clinical trials have not demonstrated that routine use of calcium channel blockers improves survival after MI.[84] In fact, meta-analyses suggest that high doses of the short-acting dihydropyridine nifedipine increased mortality in MI.[85] Adverse effects of calcium channel blockers include bradycardia, AV block, and an exacerbation of HF.

Oxygen

When given to normoxic patients with MI, supplemental oxygen has the potential to exert a direct vasoconstrictor effect on the coronary arteries.[86] The AVOID trial randomized 441 patients with confirmed STEMI to supplemental oxygen or none regardless of oxygen saturation and showed an increase in recurrent MI and cardiac arrhythmias and an increase in myocardial infarct size on CMR with oxygen.[87,88] The DETO2X trial randomized 6629 patients with MI and oxygen saturation >90% to supplemental oxygen or none and found no difference in all-cause mortality at 1 year with oxygen use.[88,89] Supplemental oxygen therapy in patients with STEMI but without hypoxia is no longer recommended.[88,89]

UA AND NSTE-ACS

UA and NSTE-ACS should be considered part of the spectrum of ACS, with elevated cardiac troponin differentiating NSTE-ACS from UA. The key to the initial management of patients with ACS who present without ST elevation is risk stratification. The overall risk of a patient is related to both the severity of preexisting heart disease and the degree of plaque instability. Risk stratification is an ongoing process, which begins with hospital admission and continues through discharge (Fig. 70.2).

The risk of ACS increases with age. ST segment depression on the ECG identifies patients at higher risk for clinical events.[90] However, a normal 12-lead ECG does not exclude an NSTE-ACS and is seen in approximately 1%–6% of patients with ACS.[91] For example, a left circumflex coronary artery occlusion can be "electrically silent" and may only be detected using posterior leads V_7–V_9. If there is a high clinical suspicion for ACS, a repeat ECG should be done in 15- to 30-minute intervals for the first hour.[92] Nonspecific ST- and T-wave changes can be seen on ECG in the absence of ACS. See Table 70.3 for non-ACS causes of ST- and T-wave changes.

Cardiac Biomarkers in NSTE-ACS

Biochemical markers of cardiac injury are predictive of outcome. The preferred biomarker for the diagnosis of myocardial necrosis is troponin. Cardiac troponin T and cardiac troponin I are sensitive markers of cardiac injury, particularly when used with the recommended diagnostic cut point of the 99th percentile of healthy controls.[93,94] Newer high-sensitivity assays are now being used and have led to decreasing diagnosis of UA and an increase in the diagnosis of NSTE-ACS.[11,95] Elevated levels of troponin T are associated with an increased risk of cardiac events and a higher 30-day mortality.[96] Conversely, low levels are associated with low event rates, although the absence of troponin elevation does not guarantee a favorable prognosis and is not a substitute for good clinical judgment. Troponins are elevated in MI as early as 2–4 hours after symptom onset and may persist for several days after the initial event.

An elevated cardiac troponin level in the absence of overt ischemic heart disease is a common finding in both acute and nonacute processes, particularly with newer, high-sensitivity assays. When serum cardiac troponin is present but the clinical information does not suggest ACS, the clinician should look for other causes.

Approach to Revascularization of NSTE-ACS

Two predominant pathways have emerged in the management of patients with NSTE-ACS and are referred to as an *early invasive approach* or an *ischemia-guided approach*. An early invasive approach is defined as coronary angiography within 24 hours of admission with PCI if appropriate.

Risk stratification is the key to managing patients with NSTE-ACS. Patients with NSTE-ACS who have refractory angina, hemodynamic or electrical instability, severe HF, or worsening mitral regurgitation and who lack serious comorbidities or contraindications should be taken urgently for cardiac catheterization.[92] Recent subanalyses of trials examining when to perform coronary angiography in UA/NSTE-ACS have demonstrated improved outcomes with an early invasive strategy in patients with elevated risk scores (TIMI >2 or GRACE >140) without contraindications.[97,98] When considering an invasive strategy, the patient's ability to tolerate anticoagulation, antiplatelet, or antithrombotic therapy must be considered. An early invasive strategy should not be considered for patients who are deemed low risk or who have significant comorbidities such as bleeding, advanced liver or renal failure, end-stage lung disease, or advanced-stage cancer such that the risk of PCI outweighs the benefit.

When no indication for immediate angiography is present, patients should then undergo risk assessment with a risk calculator, most commonly the Thrombolysis in Myocardial Infarction (TIMI) risk score or the Global Registry of Acute Coronary Events (GRACE) risk score. These tools take into account patient and clinical factors to provide a prognosis after UA/NSTE-ACS.[99,100] An initial strategy of medical management with attempts at stabilization and delayed invasive strategy is warranted in patients with a lower risk.

Guideline-Directed Medical Therapy for UA/NSTE-ACS

Standard medical therapy for the early management of patients presenting with UA/NSTE-ACS includes analgesics, nitrates, and antiplatelet and antithrombotic therapy. Other medications that should be considered include high-dose statin, beta-blockers, and renin–angiotensin blockers. See Table 70.4 for a summary of recommendations for the use of medications in UA/NSTE-ACS.

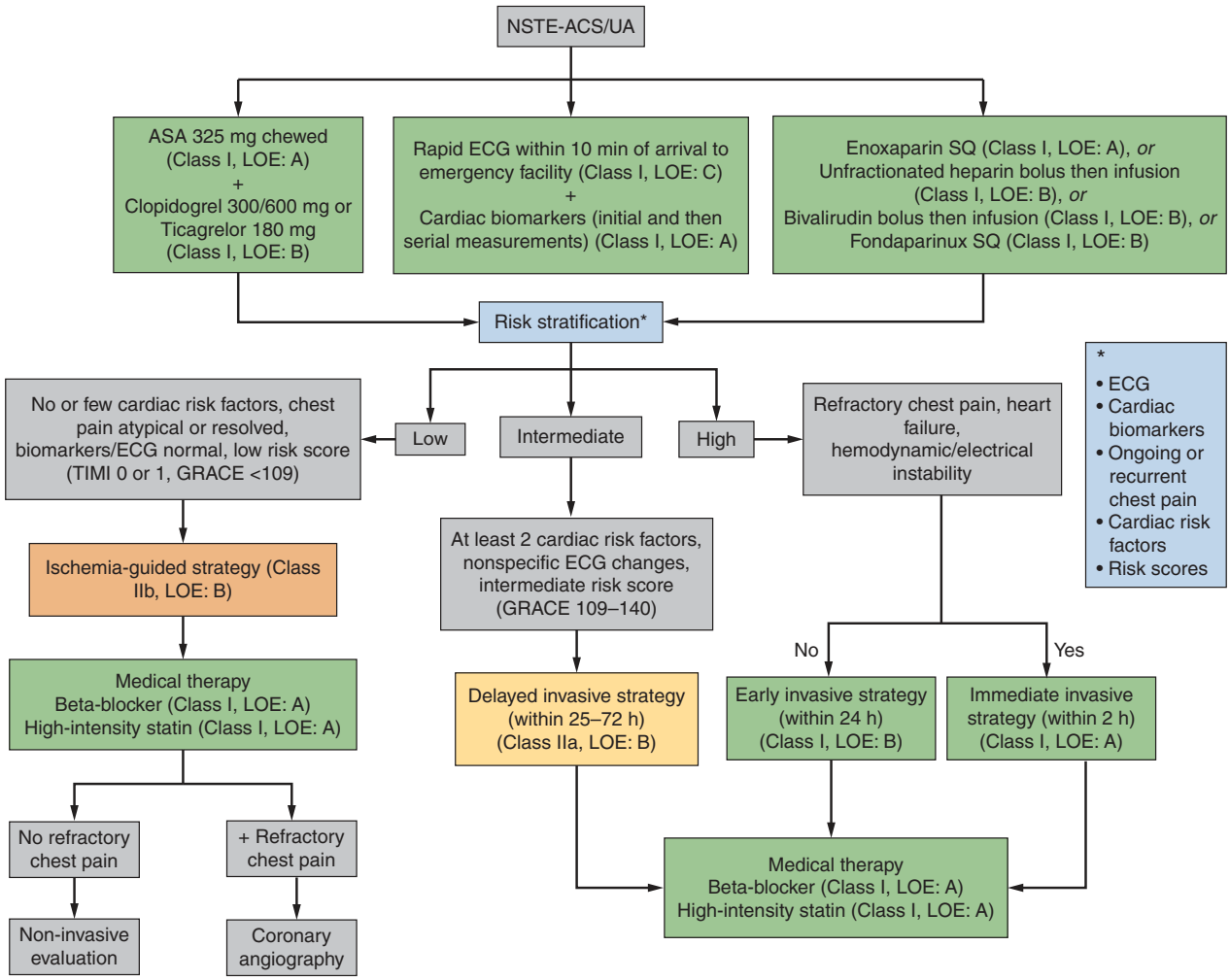

Fig. 70.2 Algorithm for management of patients with definite or likely non–ST elevation acute coronary syndrome/unstable angina (*NSTE-ACS/UA*). Based on risk stratification. *ASA,* Acetyl salicylic acid; *ECG,* electrocardiogram; *GRACE,* Global Registry of Acute Coronary Events (GRACE) risk score; *LOE,* level of evidence; *SQ,* subcutaneous; *TIMI,* Thrombolysis in Myocardial Infarction (TIMI) risk score.

TABLE 70.3 Non–Acute Coronary Syndrome Causes of ST- and T-Wave Changes on Electrocardiogram

Disease/Condition	ECG Finding
Left ventricular aneurysm	ST elevation in precordial leads, Q waves, T-wave inversions (low amplitude)
Pericarditis or myocarditis	Widespread concave ST elevation and PR depression throughout most of the leads Reciprocal ST depression and PR elevation in lead aVR (± V_1)
Right bundle branch block	ST depressions and T-wave inversions in the right precordial leads
Left ventricular hypertrophy	Downsloping ST segments into an inverted T wave in the lateral leads ("LV strain pattern") ST elevations and tall positive T waves are also common findings in leads V_1 and V_2
Hyperkalemia	Peaked T waves
Prinzmetal angina	ST elevation in an anatomic distribution
Stress-induced cardiomyopathy	ST elevation
Brugada pattern	"Coved" ST elevation in V_1–V_3
CNS disease	Deep T-wave inversions ST depression
Early repolarization	J-point elevation of ≥0.1 mV in two adjacent leads Widespread concave ST elevation, most prominent in the mid-to-left precordial leads (V_2–V_5) No reciprocal ST depression to suggest ST elevation myocardial infarction (except in aVR)

CNS, Central nervous system.

TABLE 70.4 Recommendations for the Use of Medications in Non–ST Elevation Myocardial Infarction/Unstable Angina

Therapy	COR	LOE
Oxygen		
Oxygen, only if SpO_2 < 90% or respiratory distress	I	C
Nitrates		
Sublingual nitroglycerin	I	C
IV nitroglycerin for persistent ischemia, heart failure, or hypertension	I	B
Nitrates are contraindicated with recent phosphodiesterase inhibitor use	III: Harm	B
Analgesics		
Morphine sulfate for ongoing ischemic pain despite maximal medical therapy	IIb	B
Nonsteroidal antiinflammatory drugs (except aspirin) should not be initiated or should be discontinued	III: Harm	B
Beta-Blockers		
Oral beta-blockers should be initiated within the first 24 hours, in the absence of contraindications*	I	A
Use of metoprolol succinate, carvedilol, or bisoprolol is recommended in patients with non-ST-elevation acute coronary syndrome and reduced systolic function with stabilized heart failure	I	C
Reasonable to continue beta-blocker therapy in patients with normal left ventricular function with non-ST-elevation acute coronary syndrome	IIa	C
Intravenous beta-blockers are contraindicated in patients with risk factors for or evidence of shock	III	B
Statin Therapy		
Initiate or continue high-intensity statin therapy† in patients with no contraindications	I	A
Obtain a fasting lipid profile, preferably within 24 hours	IIa	C
Renin–Angiotensin–Aldosterone Inhibitors		
Angiotensin-converting enzyme inhibitors should be started and continued indefinitely in all patients with left ventricular ejection fraction < 40% and those with hypertension, diabetes mellitus, or stable chronic kidney disease unless contraindicated	I	A
Angiotensin receptor blockers should be given to patients intolerant to angiotensin-converting enzyme inhibitors with a left ventricular ejection fraction < 40%	I	A
Aldosterone blockade is recommended in patients post myocardial infarction without significant renal dysfunction who have a left ventricular ejection fraction < 40%, diabetes mellitus, or heart failure who are receiving therapeutic doses of angiotensin-converting enzyme inhibitors and beta-blockers	I	A

*Decompensated heart failure, low-output state, risk for cardiogenic shock, bradycardia, evidence of atrioventricular nodal conduction disease.
†Atorvastatin or rosuvastatin.
COR, Class of recommendation; *IV,* intravenous; *LOE,* level of evidence; *SpO_2,* arterial blood oxygen saturation.
Adapted from Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guidelines for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;130:e344–e426.

Initial Antiplatelet/Anticoagulant Therapy in Patients With Definite or Likely NSTE-ACS

Antiplatelet Therapy

Antiplatelet therapy includes aspirin, $P2Y_{12}$ receptor inhibitors, and glycoprotein IIb/IIIa inhibitors. As previously noted, aspirin is a mainstay of therapy for all ACSs. A loading dose of 162 mg to 325 mg non–enteric-coated aspirin is the initial antiplatelet therapy. Both the VA Cooperative Study Group[42,101] and the Canadian Multicenter Trial[102] showed that aspirin reduces the risk of death or MI by approximately 50% in patients with UA or NSTE-ACS. Aspirin also reduces events after resolution of an ACS, and 81 mg should be continued indefinitely if not contraindicated. In patients who are aspirin-intolerant (allergy or significant gastrointestinal [GI] intolerance), a loading dose of clopidogrel followed by a daily maintenance dose should be administered.[9]

Similar to patients with STEMI, patients with NSTE-ACS and UA benefit from the use of $P2Y_{12}$ receptor inhibitors in addition to aspirin. This benefit—a decrease in CV death, MI, or stroke—was established in the CURE trial and was seen not only in patients who underwent PCI but also in those managed medically.[103]

Ticagrelor has a faster onset of action when compared with clopidogrel and has a faster recovery of platelet function. Patients with NSTE-ACS in the PLATO trial showed a reduction in the composite outcome of death from vascular causes, MI, or stroke in patients treated with ticagrelor compared with clopidogrel.[52] Major bleeding events did not differ between the groups, although bleeding not related to CABG occurred more often with ticagrelor.

Prasugrel has a more rapid onset of action and can achieve a greater level of platelet inhibition when compared with clopidogrel. Taking into account the results of the TRITON-TIMI 38 and ISAR-REACT 5 trials, prasugrel can be a useful alternative to clopidogrel considering that approximately 20%–25% of the population may be resistant to clopidogrel.[104] It is reasonable to administer prasugrel if diagnostic coronary angiography and PCI are intended. However, the use of prasugrel is not recommended for "up-front" therapy before planned PCI in patients with NSTE-ACS because of an increase in bleeding complications without a significant reduction in composite endpoints when compared with dosing at the time of PCI.[105] The TRILOGY ACS trial compared prasugrel with clopidogrel in UA/NSTE-ACS patients treated with a noninvasive strategy and demonstrated no difference in the primary efficacy endpoint (a composite of death from CV causes, nonfatal MI, or nonfatal stroke).[106] Table 70.5 summarizes the dosing of clopidogrel, prasugrel, and ticagrelor in the treatment of UA/NSTE-ACS.

Anticoagulant Therapy

Heparin is an important component of primary therapy for patients with unstable coronary syndromes without ST elevation. When added to aspirin, heparin has been shown to reduce refractory angina and the development of MI,[42] and a meta-analysis of the available data indicates that the addition of heparin reduces the composite endpoint of death or MI.[107]

UFH, however, can be difficult to administer because the anticoagulant effect is unpredictable in individual patients. Therefore activated partial thromboplastin time (APTT) or factor Xa levels must be monitored closely. The potential for heparin-associated thrombocytopenia is also a safety concern. The recommended regimen is weight-based and adjusted using a standardized nomogram.

Low-molecular-weight heparins (LMWHs) have several advantages over UFH. Because they bind less avidly to heparin-binding proteins, there is less variability in the anticoagulant response and a more predictable dose-response curve, obviating the need to monitor APTT. The incidence of thrombocytopenia is lower (but not absent), and patients with HIT with antiheparin antibodies cannot be switched to LMWH. LMWH is less susceptible to inactivation by platelet factor 4. Finally, LMWHs have longer half-lives and can be given by subcutaneous injection.

Several trials have documented beneficial effects of LMWH therapy in unstable coronary syndromes.[108,109] Specific considerations with the use of LMWH include a decreased clearance in renal insufficiency and the lack of a commercially available test to measure the anticoagulant effect. Enoxaparin is dosed by weight and in the presence of impaired renal function (CrCl <30 mL/min) the dose should be reduced.

TABLE 70.5 Dosing of Clopidogrel, Prasugrel, and Ticagrelor in Patients With NSTEMI

Drug	Loading Dose	Maintenance Dose
Clopidogrel	300 mg or 600 mg	75 mg
Prasugrel†	60 mg*	10 mg
Ticagrelor‡	180 mg	90 mg BID

*Recommended to be given at time of coronary angiography when percutaneous coronary intervention is intended.

†Net harm in patients with a history of cerebrovascular events and no clinical benefit in patients older than 75 years of age or those with low body weight (<60 kg) (Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med.* 2007;357:2001–2015.)

‡The recommended maintenance dose of aspirin to be used with ticagrelor is 81 mg daily.

Adapted from Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guidelines for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2014; 130:e344–e426.

Direct Thrombin Inhibitors

Bivalirudin is a DTI. As opposed to heparin, bivalirudin binds directly to both circulating and clot-bound thrombin and inhibits the conversion of fibrinogen to fibrin in the final step of the clotting cascade. DTIs have several theoretical advantages over heparin. Heparin binds to a number of tissue and plasma proteins, which alters its bioavailability and clearance. Heparin may also have a platelet-activating effect in ACS. Lastly, DTIs do not bind to platelet factor 4 and therefore avoid the problem of HIT.

Bivalirudin is the only DTI indicated for use in ACS and is recommended in the setting of HIT. When an early invasive strategy is employed, more contemporary data have shown similar outcomes as compared with heparin without a difference in bleeding. Given this, in the era of DAPT and radial artery access, both bivalirudin and heparin are reasonable when coronary angiography is planned. When pursuing a conservative approach without intention of revascularization, LMWH or UFH should be used in preference to bivalirudin.[92]

Glycoprotein IIb/IIIa Antagonists

Previous studies had suggested reduced incidence of a composite outcome of death and MI with glycoprotein IIb/IIIa inhibition in NSTE-ACS,[110] but these studies were conducted before the era of dual

antiplatelet therapy, which is now standard practice. The most recent data suggest a glycoprotein IIb/IIIa inhibitor can be given in addition to aspirin and an anticoagulant if the patient is considered high risk (troponin positive) and not pretreated with a $P2Y_{12}$ inhibitor. If a high-risk patient is pretreated with a $P2Y_{12}$ inhibitor, a glycoprotein IIb/IIIa inhibitor can be given at the time of PCI in addition to aspirin and an anticoagulant.[92,111]

Complications of Acute Myocardial Infarction

Ventricular Free Wall Rupture

Ventricular free wall rupture typically occurs during the first 5 days after an infarction and within 2 weeks in over 90% of cases. The incidence of left ventricular free wall rupture in all comers with STEMI is low (about 1%). Not surprisingly, the incidence in those who die after STEMI is much higher, ranging from 7% to 26%.[112–114] The classic patient is elderly, female, and presents with an anterior wall infarction. Early use of fibrinolytic therapy reduces the incidence of cardiac rupture, but late use may actually increase the risk. Pseudoaneurysm with leakage may be heralded by chest pain, nausea, and restlessness, but frank free wall rupture presents as a catastrophic event with shock and electromechanical dissociation. Pericardiocentesis may be necessary to relieve acute tamponade, ideally in the operating room, because the pericardial effusion may tamponade the bleeding. Salvage is possible with expeditious thoracotomy and repair, either with a patch or by direct suturing.[115] For those patients who make it to the operating room for repair, mortality approaches 60%.[9]

Ventricular Septal Rupture

Septal rupture presents as severe HF or cardiogenic shock, with a loud pansystolic murmur and parasternal thrill. Ventricular septal rupture most commonly occurs within 24 hours of reperfusion (typically with fibrinolytic therapy) in patients with a STEMI.[116] The hallmark finding is a left-to-right intracardiac shunt ("step up" in oxygen saturation from the right atrium to the right ventricle), but the diagnosis is most easily made with echocardiography. Rapid institution of supportive pharmacologic measures and mechanical support, such as intraaortic balloon pumping, is necessary. Operative repair is the only viable option for long-term survival. Even if surgical repair is done promptly, mortality remains high, ranging from 20% to 87%.[116–118]

Acute Mitral Regurgitation

Ischemic mitral regurgitation is usually associated with inferior myocardial infarction and ischemia or infarction of the posterior papillary muscle because of its singular blood supply. An anterior papillary muscle rupture can also occur, although is less common, as it is typically supplied by two coronary arteries. Papillary muscle rupture has a bimodal incidence, either within 24 hours or 3–7 days after an acute MI. It presents dramatically with pulmonary edema, hypotension, and cardiogenic shock. When a papillary muscle ruptures, the murmur of acute mitral regurgitation may be limited to early systole because of a rapid equalization of pressures in the left atrium and ventricle. More important, the murmur may be soft or inaudible, especially when the cardiac output is low.[119]

Echocardiography is extremely useful in the differential diagnosis, which includes free wall rupture, ventricular septal rupture, and infarct extension with pump failure. Hemodynamic monitoring with pulmonary artery catheterization may also be helpful. Management includes afterload reduction with an intraaortic balloon pump or another mechanical circulatory support device as a temporizing measure. Inotropic or vasopressor therapy may also be needed to support cardiac output and blood pressure. Definitive therapy, however, is surgical valve repair or replacement, which should be undertaken as soon as possible because clinical deterioration can be sudden.[119,120]

RIGHT VENTRICULAR INFARCTION

Right ventricular infarction occurs in up to 30% of patients with an inferior infarction and is clinically significant in 10%.[121] The combination of a clear chest radiograph with jugular venous distention in a patient with an inferior wall MI should lead to the suspicion of a coexisting right ventricular infarct. The diagnosis is substantiated by demonstration of ST segment elevation in the right precordial leads (V_{3R}–V_{5R}) or by characteristic hemodynamic findings on right heart catheterization (elevated right atrial and right ventricular end-diastolic pressures with normal to low pulmonary artery occlusion pressure and low cardiac output). Echocardiography can demonstrate depressed right ventricular contractility.[122] Patients with cardiogenic shock on the basis of right ventricular infarction have a better prognosis than those with left-sided pump failure.[120] This may be caused in part by the fact that the right ventricular function tends to return to normal over time with supportive therapy, although such therapy may need to be prolonged.[123]

In patients with right ventricular infarction, right ventricular preload should be maintained with fluid administration. In some cases, however, fluid resuscitation may increase pulmonary capillary occlusion pressure but may not increase cardiac output, and overdilation of the right ventricle can compromise left ventricular filling and cardiac output.[123] Inotropic therapy may be more effective in increasing cardiac output in some patients, and monitoring with serial echocardiograms may also be useful to detect right ventricular overdistention. Maintenance of AV synchrony is also important in these patients to optimize right ventricular filling.[122] For patients with continued hemodynamic instability, intraaortic balloon pumping may be useful, particularly because elevated right ventricular pressures and volumes increase wall stress and oxygen consumption and decrease right coronary perfusion pressure, exacerbating right ventricular ischemia. Immediate reperfusion of the occluded coronary territory is also crucial.[124] Percutaneous right ventricular mechanical support may be an option in selected cases as well.

CARDIOGENIC SHOCK

Epidemiology and Pathophysiology

Cardiogenic shock, resulting either from left ventricular pump failure or mechanical complications, represents the leading cause of in-hospital death after MI.[125,126] Cardiogenic shock should be considered in the presence of persistent hypotension (SBP $<$90 mm Hg or mean arterial pressure 30 mm Hg lower than baseline) with reduced cardiac index ($<$1.8 L/min/m^2 without support or $<$2.2 L/min/m^2 with support) and adequate or elevated filling pressures.[127] Patients may have cardiogenic shock at initial presentation, but shock most often evolves over several hours.[128]

Cardiac dysfunction in patients with cardiogenic shock is usually initiated by MI or ischemia. The initial ischemic event leads to myocardial dysfunction, which in turn worsens the ongoing ischemia, creating a downward spiral (Fig. 70.3). Compensatory mechanisms that retain fluid in an attempt to maintain cardiac output may add to the vicious cycle and further increase diastolic filling pressures. The interruption of this cycle of myocardial dysfunction and ischemia forms the basis for the therapeutic regimens for cardiogenic shock. Early recognition of cardiogenic shock and timely management (revascularization) are paramount to improved mortality.

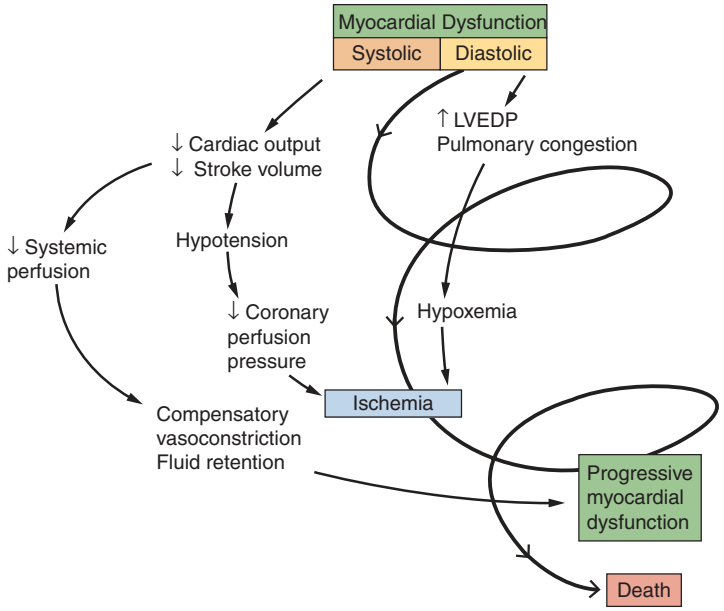

Fig. 70.3 The "downward spiral" in cardiogenic shock. Stroke volume and cardiac output fall with left ventricular (LV) dysfunction, producing hypotension and tachycardia that reduce coronary blood flow. Increasing ventricular diastolic pressure reduces coronary blood flow, and increased wall stress elevates the myocardial oxygen requirements. All of these factors combine to worsen ischemia. The falling cardiac output also compromises systemic perfusion. Compensatory mechanisms include sympathetic stimulation and fluid retention to increase preload. These mechanisms can actually worsen cardiogenic shock by increasing myocardial oxygen demand and afterload. Thus a vicious circle can be established. ***LVEDP,*** Left ventricular end-diastolic pressure. (Adapted with permission from Hollenberg SM, Kavinsky CJ, Parrillo JE. Cardiogenic shock. *Ann Intern Med.* 1999;131:47–59.)

Initial Management

Maintenance of adequate oxygenation and ventilation is critical. Many patients require intubation and mechanical ventilation if only to reduce the work of breathing and facilitate sedation and stabilization before cardiac catheterization. Electrolyte abnormalities should be corrected, and morphine (or fentanyl if systolic pressure is compromised) used to relieve pain and anxiety. Arrhythmias and a heart block may have important effects on cardiac output and should be corrected promptly with antiarrhythmic drugs, cardioversion, or cardiac pacing. Amiodarone is the preferred antiarrhythmic drug for sustained ventricular or atrial tachyarrhythmias in the setting of cardiogenic shock.

Both pharmacologic and mechanical forms of circulatory support should be used to reverse hypotension and maintain organ and coronary artery perfusion. Patients are commonly diaphoretic, and relative hypovolemia may be present in as many as 20% of patients with cardiogenic shock, so fluid boluses, titrated to clinical endpoints of heart rate, urine output, and blood pressure, should be considered as an initial measure unless frank pulmonary edema is present. Patients who do not respond rapidly to initial fluid boluses or those with poor physiologic reserve should be considered for invasive hemodynamic monitoring. Optimal filling pressures vary from patient to patient; hemodynamic monitoring can be used to construct a Starling curve at the bedside, identifying the filling pressure at which the cardiac output is maximized. Maintenance of adequate preload is particularly important in patients with a right ventricular infarction.

Vasopressor and inotropic agents remain the mainstay of first-line therapy in the management of cardiogenic shock. Catecholamine agents, such as norepinephrine, epinephrine, dopamine, dobutamine, and phenylephrine, have both vasopressor and inotropic effects, but it is useful to distinguish vasopressor effects (those aimed at maintaining blood pressure) and inotropic effects (those aimed at increasing myocardial contractility and thus cardiac output) to allow for titration of dose to effect. When arterial pressure remains inadequate, therapy with vasopressor agents may be required to maintain coronary perfusion pressure to break the vicious cycle of progressive hypotension with further myocardial ischemia. The most commonly used vasopressors include norepinephrine, phenylephrine, and epinephrine. Norepinephrine acts on both α_1- and β_1-adrenergic receptors, thus producing potent vasoconstriction in addition to a modest increase in cardiac output[129] and is the preferred first-line agent. A subgroup analysis of a multicenter randomized trial comparing norepinephrine with dopamine in patients with shock demonstrated a lower 28-day mortality with norepinephrine.[130] Phenylephrine, a selective α_1-adrenergic agonist, acts as a potent vasoconstrictor that augments systemic vascular resistance (SVR) without greatly affecting contractility or cardiac output. Phenylephrine may be used when tachyarrhythmias limit therapy with other vasopressors. Epinephrine has potent β_1-adrenergic receptor activity and moderate β_2- and α_1-adrenergic receptor effects. The net effect can be an increase in cardiac output and decreased SVR, with escalating doses causing a greater increase in SVR. Epinephrine is typically used in addition to norepinephrine in septic shock and for the management of hypotension after CABG.

Vasopressor infusions need to be titrated carefully in patients with cardiogenic shock to maximize coronary perfusion pressure with the least possible increase in myocardial oxygen demand. Hemodynamic monitoring, with serial measurements of cardiac output, filling pressures, and other parameters, such as mixed venous oxygen saturation, can allow for titration of the dosage of vasoactive agents to the minimum dosage required to achieve the chosen therapeutic goals.[131] However, reperfusion therapy should not be delayed for the placement of a pulmonary artery catheter.

After initial stabilization and restoration of adequate blood pressure, tissue perfusion should be assessed. If tissue perfusion is adequate but significant pulmonary congestion remains, diuretics may be employed.

Vasodilators such as intravenous nitroglycerin or nitroprusside can be considered as well, depending on the blood pressure.

If tissue perfusion remains inadequate, cardiovascular support with inotropic agents should be initiated. There is no firm guideline-based recommendation regarding which inotropic agent to use in the setting of cardiogenic shock. Typically used inotropes include dobutamine, dopamine, and norepinephrine (which can act as both a vasopressor and inotrope). Dobutamine, a selective β_1-adrenergic receptor agonist, can improve myocardial contractility and increase cardiac output. Dobutamine may exacerbate hypotension in some patients and can precipitate tachyarrhythmia. Dobutamine is typically reserved for patients with SBP >80 mm Hg. Epinephrine can increase cardiac output but often at the expense of a substantial increase in myocardial oxygen demand. In some situations, a combination of a vasopressor and an inotrope can be more effective than either agent used alone. Phosphodiesterase inhibitors such as milrinone are less arrhythmogenic than catecholamines but have the potential to cause hypotension and should be used with caution in patients with tenuous clinical status.

Mechanical Support in Cardiogenic Shock

Intraaortic balloon counterpulsation (IABP) reduces the systolic afterload and augments diastolic perfusion pressure, increasing cardiac output and improving coronary blood flow, without an increase in oxygen demand.[132] IABP does not, however, produce a significant improvement in blood flow distal to a critical coronary stenosis.[132,133] The timing and utility of IABP in patients with STEMI complicated by cardiogenic shock, however, remain uncertain.[134,135] The IABP-SHOCK II trial randomized 600 patients with cardiogenic shock complicated by acute MI to either IABP or no IABP at the time of PCI. There was no difference in all-cause mortality at 30 days or 12 months: nor was there any significant difference in any of the subgroups.[136] Some randomized patients in this trial received an IABP after PCI when they were hemodynamically stable and might not have been expected to derive great benefit. In addition, 10% of patients in the control group crossed over to IABP therapy. IABP is widely available, is easy to place, and has a lower cost compared with other support devices; as such, IABP may still have some role in the stabilization of selected patients with cardiogenic shock.

In appropriate settings, more intensive support with mechanical circulatory support devices may also be implemented. Such devices include left ventricular assist devices (LVADs), such as the TandemHeart percutaneous left atrial–to–femoral arterial ventricular assist device or the Impella percutaneous transvalvular left ventricular assist device, and percutaneous cardiopulmonary bypass support with the use of extracorporeal membrane oxygenation (ECMO). The percutaneous LVADs provide better hemodynamics compared with IABP, with higher cardiac indices and mean arterial pressures and lower filling pressures and improve metabolic parameters. Percutaneous LVADs, however, have not been shown to improve mortality in randomized trials.[137]

Reperfusion Therapy

Although fibrinolytic therapy reduces the likelihood of the subsequent development of shock after the initial presentation, it is clearly less effective in patients with cardiogenic shock than in those without[138] and has not been shown to reduce mortality in patients with established cardiogenic shock.[66,139]

To date, emergency percutaneous revascularization is the only intervention that has been shown to reduce mortality rates consistently in patients with cardiogenic shock. An extensive body of observational and registry studies has shown consistent benefits from revascularization.[140] These data have been confirmed in the SHOCK study, a randomized, multicenter international trial that assigned patients with cardiogenic shock to receive optimal medical management (including IABP and fibrinolytic therapy) or to cardiac catheterization with revascularization using percutaneous transluminal coronary angioplasty (PTCA) or CABG.[29,141] The trial enrolled 302 patients and was powered to detect a 20% absolute decrease in 30-day all-cause mortality rates. Mortality at 30 days was 46.7% in patients treated with early intervention and 56% in patients treated with initial medical stabilization, but this difference did not quite reach statistical significance ($P = .11$).[28] At 6 months, the absolute risk reduction with early invasive therapy in the SHOCK trial was 13%, and this risk reduction was maintained at 12 months.[141] The subgroup analysis showed a substantial improvement in mortality rates in patients younger than 75 years of age at both 30 days and 6 months.[141] Put into perspective with the results from other randomized controlled trials of patients with acute MI, an important point emerges: despite the moderate relative risk reduction (0.72, confidence interval [CI] 0.54–0.95) the absolute benefit is important, with 9 lives saved for 100 patients treated at 30 days (number needed to treat 10.8) and 13.2 lives saved for 100 patients treated at 1 year in the SHOCK trial (number needed to treat 7.6). Based on these data, the presence of cardiogenic shock in the setting of acute MI is an indication for emergency revascularization, either by percutaneous intervention or CABG.[9]

See Box 70.2 for a summary of complications caused by acute MI.

Box 70.2 Complications Caused by Acute Myocardial Infarction

- Cardiogenic shock
- Mechanical
  - Rupture of the left ventricular free wall
  - Rupture of the interventricular septum
  - Acute mitral regurgitation
- Left ventricular aneurysm
- Ventricular arrhythmia
- Bradycardia or atrioventricular block
- Pericarditis
- Bleeding

KEY POINTS

- ACSs are a family of disorders that exist along a clinical continuum. Prompt recognition and early initiation of treatment are paramount to decrease morbidity and mortality.
- Acute STEMI is a medical emergency requiring urgent treatment with revascularization of the ischemic territory. After initial management, multiple medical therapies have been shown to provide clinical benefit.
- Improvements and advancements in reperfusion therapy and GDMT has greatly decreased the mortality attributable to STEMI.
- In patients with NSTE MI or UA, clinical trials have demonstrated improved outcomes with prompt antiplatelet and antithrombotic therapy. Reperfusion strategy is dependent on multiple factors, which dictate the decision between an early invasive or ischemic-guided approach.
- Complications of acute MI include ventricular free wall rupture and acute mitral regurgitation often the result of papillary muscle rupture. The treatment for the majority of mechanical complications is generally surgical, with poor overall survival.
- Cardiogenic shock related to acute MI is a consequence of a hemodynamic spiral as a result of ischemia begetting myocardial dysfunction, which begets further ischemia. Therapeutic interventions include prompt revascularization, pharmacologic vasopressor and inotropic support, and various forms of mechanical circulatory support.

References for this chapter can be found at expertconsult.com.

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The guideline statement document for the management of patients with non–ST elevation ACS syndromes, including updated recommendations for which patients to pursue early invasive strategy and which to pursue delayed invasive or ischemic-guided strategy.

Kofoed KF, Kelbaek H, Hansen PR, et al. Early versus standard care invasive examination and treatment of patients with non-ST-segment elevation acute coronary syndrome. *Circulation.* 2018;138(24):2741–2750.
Randomized trial evaluating optimal timing for coronary angiography and reperfusion in patients with NSTE-ACS that showed no difference in outcomes between a very early PCI strategy (,12 hours) and a delayed strategy (24–72 hours) except in higher-risk patients (GRACE score .140), in whom benefit from earlier intervention was found.

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Update to guideline statement on primary percutaneous coronary intervention in patients with STEMI. This update changed recommendations for PCI to non–culprit arteries to IIb from III. This was based on multiple randomized controlled trials showing reduction in cardiovascular composite outcomes with multivessel PCI. The statement also addresses aspiration thrombectomy during STEMI and makes routine use of this a class III recommendation.

O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: Developed in collaboration with the American College of Emergency Physicians and Society for Cardiovascular Angiography and Interventions. *Catheter Cardiovasc Interv.* 2013;82(1):E1–E27.
The latest clinical guideline statement for care of patients with STEMI clearly displays current recommendations for the management of these patients with the discussion regarding the clinical trials that led to the class of recommendation.

Thiele H, Akin I, Sandri M, et al. PCI strategies in patients with acute myocardial infarction and cardiogenic shock. *N Engl J Med.* 2017;377(25):2419–2432.
Although the benefit of revascularization in patients with STEMI and cardiogenic shock is well established by the SHOCK trial, this randomized trial studied the utility of intervening on nonculprit vessels at the time of revascularization in patients with cardiogenic shock. Nonculprit PCI in this setting led to an increased incidence of death or severe renal failure requiring dialysis compared with culprit PCI only, suggesting that this strategy should not be employed routinely in patients with shock.

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71

Supraventricular Arrhythmias

Irina Savelieva

CLASSIFICATION AND EPIDEMIOLOGY

Supraventricular arrhythmias include rhythms arising from the sinus node and the adjacent atrial tissue (inappropriate sinus tachycardia, sinoatrial reentry tachycardia), both the right and left atria (atrial tachycardia, flutter, and fibrillation), the atrioventricular (AV) node (AV nodal reentry tachycardia, accelerated ectopic junctional rhythm), and the AV node with involvement of an accessory pathway or multiple pathways (AV reentry tachycardia) (Fig. 71.1).

Atrioventricular Nodal Reentry Tachycardia and Atrioventricular Reentry Tachycardia

AV nodal reentry tachycardia and AV reentry tachycardia are usually referred to as *paroxysmal supraventricular tachycardias* (SVTs). They are often seen in young patients with little or no structural heart disease, although a congenital heart abnormality giving rise to increased atrial pressure and dilatation (e.g., Ebstein anomaly, atrial septal defect, Fallot tetralogy) can coexist in a small percentage of patients with these arrhythmias.[1] The first presentation is common between age 12 and 30 years, and the prevalence is approximately 2.5 per 1000. Women are twice as likely as men to present with AV nodal reentry tachycardia.

Atrial Flutter and Fibrillation

Atrial fibrillation is the most common supraventricular arrhythmia, affecting 1%–2% of the general population, especially the elderly. It is usually associated with cardiovascular pathologies, among which hypertension and congestive heart failure prevail.[2] About a third of patients, however, present with no underlying heart disease and are considered to have "lone" atrial fibrillation. The incidence of isolated atrial flutter is largely unknown and is believed to be in the range of 0.037%–0.88% per 1000 person-years, but at least half of these patients also have atrial fibrillation as a coexistent arrhythmia.

Atrial Tachycardia

Atrial tachycardia affects 0.34%–0.46% of patients with arrhythmias. It is common in younger individuals after surgical correction of congenital heart disease and in the elderly, in whom it often occurs in association with atrial fibrillation.

Other Supraventricular Tachycardias

Inappropriate sinus tachycardia and sinoatrial reentry tachycardia are less well-defined clinical and electrocardiographic entities, and their prevalence and associated conditions are not well characterized. Sinoatrial reentry tachycardia is found incidentally in 1.8%–16.9% of patients undergoing electrophysiologic studies for other supraventricular tachyarrhythmias.

CLINICAL PRESENTATION

The leading symptom of most supraventricular tachyarrhythmias, particularly AV nodal reentry tachycardia and AV reentry tachycardia, is rapid, regular palpitations, usually with an abrupt onset; they can occur spontaneously or be precipitated by simple movements. A common feature of tachycardias that involve circulation through the AV node is termination by the Valsalva maneuver. In younger individuals with no structural heart disease, the rapid heart rate can be the main pathologic finding. Other symptoms may include anxiety, dizziness, dyspnea, neck pulsation, central chest pain, weakness, and occasionally polyuria caused by the release of atrial natriuretic peptide in response to increased atrial pressures (more common in atrial tachycardia and AV nodal reentry tachycardia). Prominent jugular venous pulsations caused by atrial contractions against closed AV valves may be observed during AV nodal reentry or AV reentry tachycardia.

True syncope is relatively uncommon unless uncontrolled tachycardia over 200 beats per minute is sustained for a long period, especially in patients who remain standing. Syncope has been reported in 10%–15% of patients, usually just after onset of the arrhythmia or in association with a prolonged pause after its termination. However, in older patients with concomitant heart disease such as aortic stenosis, hypertrophic cardiomyopathy, and cerebrovascular disease, significant hypotension and syncope may result from profound hemodynamic collapse associated with only moderately fast ventricular rates.

It is essential to recognize that patients presenting with AV reentry tachycardia may also present with atrial fibrillation. If an accessory pathway has a short antegrade effective refractory period (<250 ms), it may conduct impulses to the ventricles at an extremely high rate and cause ventricular fibrillation. The incidence of sudden death is 0.15%–0.39% per patient-year, and this may be the first manifestation of the disease in younger individuals.

Irregular palpitations may be the result of atrial premature beats, atrial flutter with varying AV conduction block, atrial fibrillation, or multifocal atrial tachycardia. Although highly symptomatic, these arrhythmias usually have a benign hemodynamic prognosis. However, in patients with depressed ventricular function, uncontrolled atrial fibrillation can reduce cardiac output and precipitate hypotension and congestive heart failure. Atrial fibrillation in association with slow AV conduction or complete block (Frederick syndrome) may result in hemodynamic collapse. Inappropriate sinus tachycardia and nonparoxysmal accelerated junctional rhythm are characterized by relatively slow heart rates and gradual onset and termination.

ELECTROCARDIOGRAPHY

Whenever possible, a 12-lead electrocardiogram (ECG) should be taken during the tachycardia. If a patient with an arrhythmia is

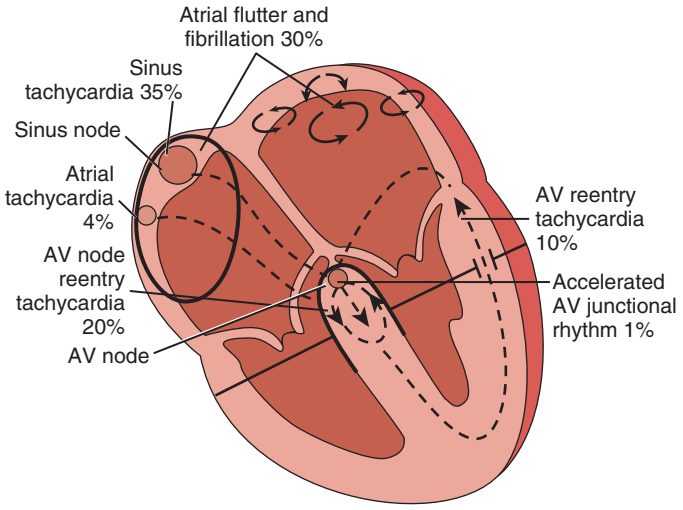

Fig. 71.1 Supraventricular tachyarrhythmias encountered in the emergency setting. *AV,* Atrioventricular.

hemodynamically unstable, a monitor strip should be obtained from the defibrillator before electrical discharge.

Narrow-Complex Tachycardias

The typical ECG feature is narrow QRS complexes less than 120 ms. In this case, the tachycardia is almost always supraventricular, and the differential diagnosis relates to its mechanism (Fig. 71.2).

Wide-Complex Tachycardias

The differential diagnostic features of wide-complex tachycardias favoring a supraventricular origin of the arrhythmia include but are not limited to preexistent bundle branch block; rate-dependent aberrancy; antidromic AV reentry tachycardia, when an accessory pathway conducts and excites the ventricles antegradely; and prominent electrolyte abnormalities (e.g., hypokalemia) or heart muscle disease (cardiomyopathy), all of which may result in QRS widening (Fig. 71.3). If the diagnosis of SVT cannot be proved, the patient should be treated as if ventricular tachycardia is present. Immediate direct current (DC) cardioversion is the treatment for any hemodynamically unstable tachycardia.

ATRIOVENTRICULAR NODAL REENTRY TACHYCARDIA

Mechanism

In AV nodal reentry tachycardia, there are two functionally and anatomically different pathways within the AV node: one is characterized by a short effective refractory period and slow conduction, and the other has a longer effective refractory period and faster conduction. In sinus rhythm, the atrial impulse that depolarizes the ventricles usually conducts through the fast pathway. If the atrial impulse (e.g., an atrial premature beat) occurs early, when the fast pathway is still refractory, the slow pathway takes over in propagating the atrial impulse to the ventricles; the impulse then travels back through the fast pathway, which by then has recovered its excitability, thus initiating the most common "slow-fast," or typical, AV nodal reentry tachycardia.

Electrocardiographic Presentation

In sinus rhythm, the ECG is usually normal unless other unrelated abnormalities are present. During AV nodal reentry tachycardia, the rhythm is regular, with narrow QRS complexes and a rate of 140–250 beats per minute. The atria are activated retrogradely, producing inverted P waves in leads II, III, and aVF. Because atrial and ventricular depolarization occur simultaneously, the P waves are often obscured

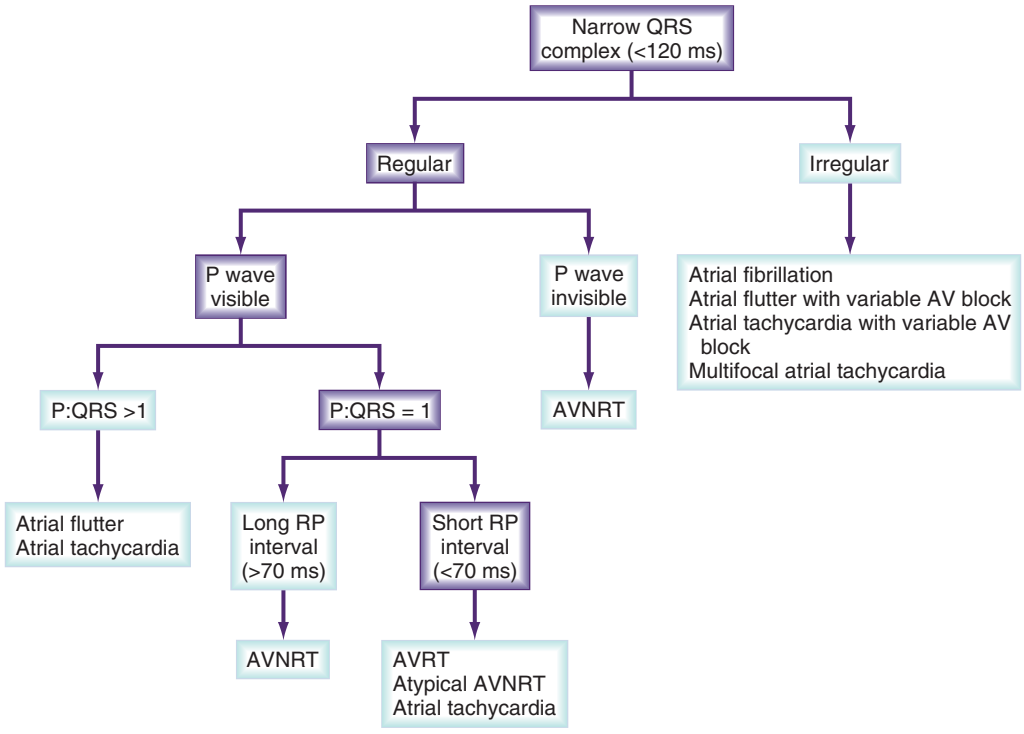

Fig. 71.2 Differential diagnosis for narrow QRS complex (presumably supraventricular) tachycardias. Note that ventricular tachycardia may present with narrow QRS complexes (e.g., fascicular tachycardia). *AV,* Atrioventricular; *AVNRT,* atrioventricular nodal reentry tachycardia; *AVRT,* atrioventricular reentry tachycardia.

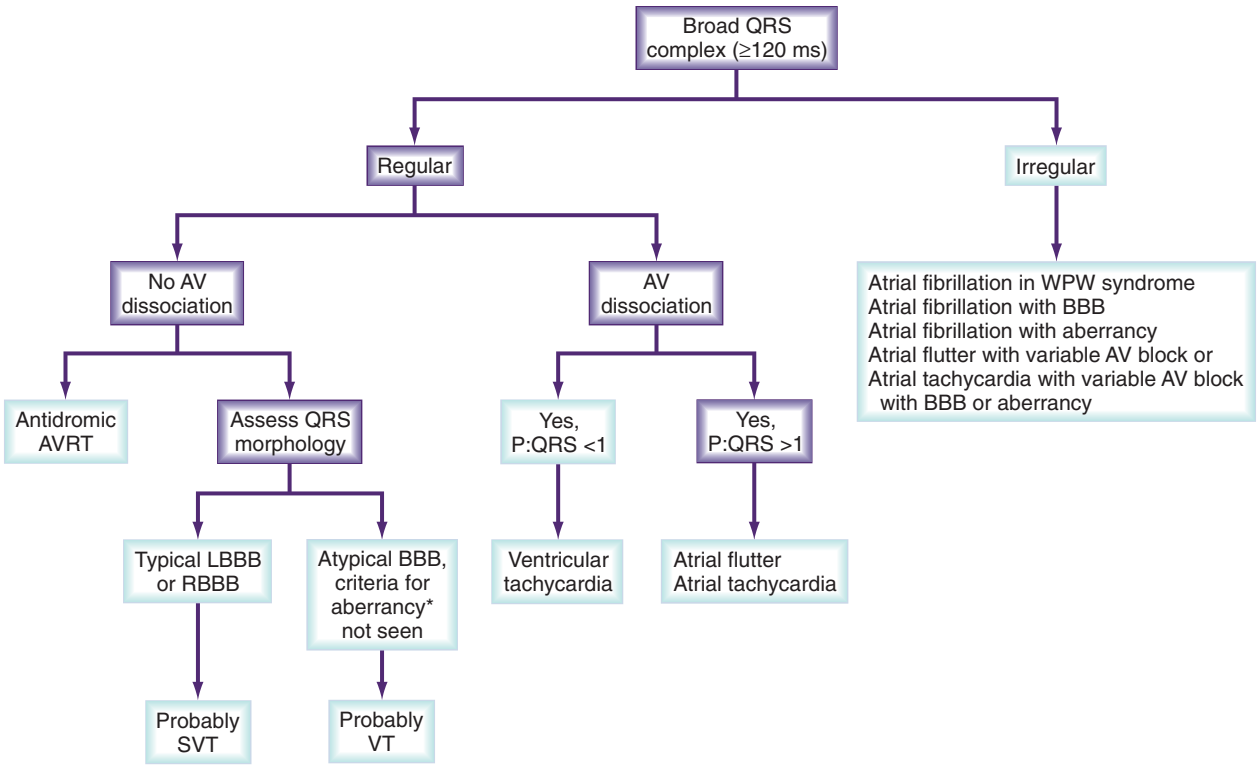

Fig. 71.3 Differential diagnosis for wide QRS complex tachycardias. *AV,* Atrioventricular; *AVRT,* atrioventricular reentry tachycardia; *BBB,* bundle branch block; *LBBB,* left bundle branch block; *RBBB,* right bundle branch block; *SVT,* supraventricular tachycardia; *VT,* ventricular tachycardia; *WPW,* Wolff-Parkinson-White. *Criteria for aberrancy: rate dependency, triphasic QRS complexes, rSR in V_1 with R >, QRS width <140 ms, QRS deflections are discordant in precordial leads, absence of fusion complexes and capture beats.

by the QRS complexes and cannot be detected on the surface ECG (Fig. 71.4A). However, in about one-third of cases of slow-fast AV nodal reentry tachycardia, a terminal positive deflection may be present in lead aVR or V_1 (or both), imitating right bundle branch block, or pseudo-S waves may be noted in the inferiorly oriented leads; these findings reflect retrograde activation of the atria. Tachycardia using these pathways in reverse ("fast-slow," or long RP, tachycardia) is less common, occurring in 5%–10% of cases.

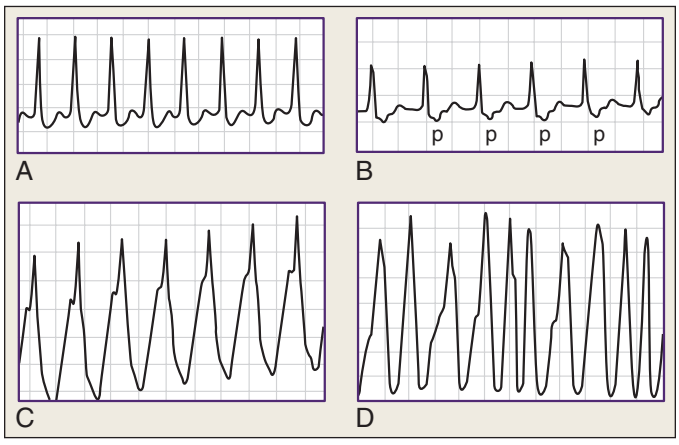

Fig. 71.4 A, Atrioventricular nodal reentry tachycardia, slow-fast type. Note narrow QRS complexes and absence of P waves. **B,** Atrioventricular reentry orthodromic tachycardia. Retrograde inverted P waves follow QRS complexes in leads II, III, and aVF. **C,** Atrioventricular reentry antidromic tachycardia with wide QRS complexes. Electrocardiogram during sinus rhythm with a QRS complex morphology identical to that seen during tachycardia may be helpful in the diagnosis. **D,** Atrial fibrillation in preexcitation syndrome with a fast ventricular rate response.

ATRIOVENTRICULAR REENTRY TACHYCARDIA

Accessory Pathways

AV reentry tachycardia occurs as a result of an anatomically distinct AV connection termed an *accessory pathway,* produced by incomplete separation of the atria and ventricles during fetal development. The most common AV accessory pathway (often called a *Kent bundle*) is located around the mitral or tricuspid annulus. In about 10% of cases, there are multiple pathways.

Accessory pathways are capable of conduction in either or both directions. Accessory pathways that are capable of antegrade conduction are referred to as *manifest,* demonstrating a delta wave during sinus rhythm when the atrial impulses conduct over the accessory pathway without encountering AV delay. The PR interval is short (<120 ms), and the QRS complex is wide; this occurs because the atrial impulse enters nonspecialized ventricular myocardium, and depolarization progresses slowly at first, giving rise to the delta wave before it is overtaken by a depolarization wavefront propagating via the normal conduction tissue. An accessory pathway that is capable of only retrograde conduction is termed *concealed* and does not produce a short PR interval or delta wave during sinus rhythm.

Mechanism and Electrocardiographic Presentation

The reentry circuit of orthodromic AV reentry tachycardia involves the AV node and an accessory pathway, with the impulses conducting from

the atria to the ventricles over the AV node and traveling in the reverse direction through the accessory pathway (see Fig. 71.4B). In antidromic AV reentry tachycardia, the reentrant impulses conduct antegradely from the atria to the ventricles via an accessory pathway and retrogradely via the AV node or a second accessory pathway (see Fig. 71.4C). Antidromic AV reentry tachycardia is uncommon (<10% of cases). Atrial fibrillation is usually encountered in patients with antegradely conducting pathways (see Fig. 71.4D).

Acute Management

In an emergency, distinguishing between AV nodal reentry tachycardia and AV reentry tachycardia may be difficult, but it is usually not critical because both tachycardias respond to the same treatment. If the patient is hemodynamically stable, vagal maneuvers, including carotid sinus massage, the Valsalva maneuver, and facial immersion in cold water (diving reflex), can terminate tachycardia in about 50% of patients (Box 71.1).[3] Commercially available gel packs can be used as cold compresses instead of facial immersion, but the most important elements are wet nostrils and breath-holding.

Pharmacologic Termination

AV blocking agents, such as adenosine, verapamil, diltiazem, and beta-blockers, are effective in terminating both AV nodal reentry and AV reentry tachycardia (Table 71.1).[1]

Adenosine

Intravenous (IV) adenosine is effective in diagnosing, slowing the rate, and often terminating narrow-complex tachycardias. Adenosine usually terminates AV nodal reentry tachycardia and AV reentry tachycardia but rarely interrupts the atrial flutter circuit and does not suppress automatic atrial tachycardia; it can, however, produce high-degree AV block during which the tachycardia persists (Fig. 71.5). It has no effect on most ventricular tachycardias. Adenosine is advantageous compared with verapamil because of its rapid onset and absence of a

BOX 71.1 Vagal Maneuvers to Terminate Tachycardia

Carotid Sinus Massage

Ensure that there is no significant carotid artery disease (carotid bruits).
Monitor the electrocardiogram continuously.
Place the patient in the supine position with the head slightly extended.
Start with right carotid sinus massage.
Apply firm rotatory or steady pressure to the carotid artery at the level of the third cervical vertebra for 5 seconds.
If no response, massage the left carotid sinus.
Generally, right carotid sinus massage decreases sinus node discharge, and left carotid sinus massage slows atrioventricular conduction.
Do not massage both carotids at the same time.
A single application of carotid sinus pressure is effective in about 20%–30% of patients with paroxysmal supraventricular tachycardias; multiple applications terminate tachycardia in about 50% of patients.
Asystole is a potential but rare complication.

Valsalva Maneuver

Valsalva maneuver involves an abrupt voluntary increase in intrathoracic and intraabdominal pressures by straining.
Monitor the electrocardiogram continuously.
Place the patient in the supine position.
The patient should not take a deep inspiration before straining.
Ideally, the patient blows into a mouthpiece of a manometer against a pressure of 30–40 mm Hg for 15 seconds.
Alternatively, the patient strains for 15 seconds while breath-holding.
Transient acceleration of tachycardia usually occurs during the strain phase as a result of sympathetic excess.
On release of strain, the rate of tachycardia slows because of the compensatory increase in vagal tone (baroreceptor reflex); it may terminate in about 50% of patients.
Termination of tachycardia may be followed by pauses and ventricular ectopics.

TABLE 71.1 Acute Pharmacologic Rate Control in Atrial Tachyarrhythmias

Drug	Route of Administration	Dose	Onset	Potential Adverse Effects
Verapamil	Intravenous	5–10 mg (0.075–0.15 mg/kg) over 2 min; if no response, additional 5–10 mg after 15–30 min; 3–10 mg every 4–6 h for rate control	3–5 min	Hypotension, bradycardia, heart block, possible deterioration of ventricular function in the presence of organic heart disease
Diltiazem	Intravenous	0.25 mg/kg over 2 min; if no response, additional 0.35 mg/kg after 15–30 min; followed by 5–15 mg/h infusion for rate control	2–7 min	
Esmolol	Intravenous	0.5 mg/kg over 1 min, followed by 0.05–0.2 mg/kg/min for 4 min; if no response after 5 min, 0.5 mg/kg for 1 min, followed by 0.1 mg/kg for 4 min; infusion 0.05–0.2 mg/kg/min for rate control	2–3 min	Hypotension, bradycardia, heart block, possible deterioration of ventricular function in the presence of organic heart disease
Metoprolol	Intravenous	2.5–5 mg over 2 min followed by repeat doses if necessary (total 10–15 mg)	5 min	
Atenolol	Intravenous	2.5 mg over 2 min, followed by repeat doses if necessary (total 10 mg) or infusion 0.15 mg/kg for 20 min	5–10 min	
Propranolol	Intravenous	1 mg over 1 min (total 10–12 mg; 0.15 mg/kg)	5 min	
Digoxin	Intravenous	0.5–1 mg, followed by 0.25 mg every 2–4 h (maximum, 1.5 mg)	30–60 min	Bradycardia, atrioventricular block, atrial arrhythmias, ventricular tachycardia

Intravenous amiodarone can also be effective for rate control, especially in patients with poor left ventricular function, but there is insufficient evidence to support this recommendation. The rate-slowing effect of amiodarone is usually delayed by 1–2 hours.

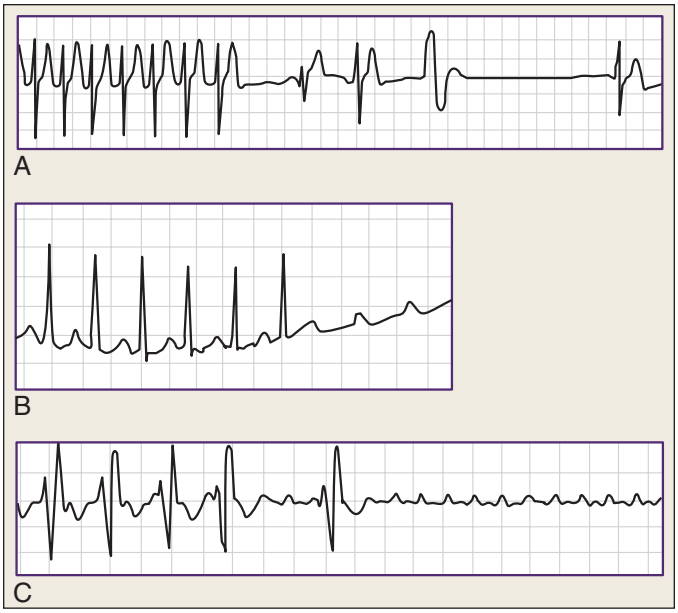

Fig. 71.5 A, Adenosine usually terminates atrioventricular reentry tachycardias. **B** and **C,** It rarely interrupts the atrial flutter circuit or suppresses automatic focal atrial tachycardia, but produces high-degree atrioventricular block during which the tachycardia persists.

negative inotropic effect in patients with poor left ventricular function and those with significant hypotension.

Adenosine is administered as a very rapid 3- to 6-mg IV bolus; if this is ineffective, another 6- to 12-mg bolus can be given 2–5 minutes later. Adenosine is metabolized very quickly, with an effective half-life of 10 seconds. Adverse effects, including dyspnea, facial flushing, and chest tightness, are therefore short-lived, but in about 12% of patients, adenosine may shorten the atrial effective refractory period and provoke atrial flutter or fibrillation or accelerate conduction over the accessory pathway and produce a rapid ventricular response. In a proportion of patients, ventricular premature beats and nonsustained ventricular tachycardia may occur after the successful termination of the SVT.[4] Some individuals, particularly heart transplant recipients, are unusually sensitive to adenosine and require a lower dose (1 mg).

Verapamil and Diltiazem

Verapamil is administered as a 5- to 10-mg IV bolus over 2 minutes, and the effect on the tachycardia should occur in 5–10 minutes. If necessary, a second bolus of 10 mg can be given 30 minutes after the initial dose. Vagal maneuvers can be effective at this stage. Verapamil should not be used for wide-complex tachycardias. IV verapamil is contraindicated in patients with poor left ventricular function or heart failure, and it should not be administered after pretreatment with oral, or especially IV, beta-blockers. It should not be used for atrial fibrillation associated with preexcitation syndrome because it may result in acceleration of conduction over an antegradely conducting accessory pathway (especially with a short effective refractory period), resulting in a rapid ventricular response and ventricular fibrillation. Diltiazem is an alternative to verapamil, but diltiazem has been associated with lower effective rates. Diltiazem has the same contraindications as verapamil.

DC cardioversion or pharmacologic conversion with IV ibutilide, propafenone, or flecainide is appropriate for termination of atrial fibrillation with preexcitation.

Beta-Blockers

Among beta-blockers, esmolol, administered as an IV infusion at a rate of 50–200 μg/kg/min, is the agent of choice because of its rapid onset. More readily available IV metoprolol, atenolol, and propranolol can also be considered (see Table 71.1). Excessive bradycardia caused by AV node–blocking agents can be countered with IV injection of atropine 0.6–2.4 mg in divided doses of 0.6 mg.

Other Antiarrhythmic Agents

Because adenosine, verapamil, diltiazem, and beta-blockers are so highly effective in terminating AV nodal reentry tachycardia and AV reentry tachycardia, specific antiarrhythmic drugs such as propafenone, flecainide, sotalol, ibutilide, and amiodarone are seldom needed in the acute setting. Digoxin is not useful because it is often ineffective and may facilitate conduction over the accessory pathway, shorten the atrial effective refractory period, and promote atrial fibrillation.

Atrial Pacing

In patients with implantable devices, antitachycardia pacing functions can be used to terminate the arrhythmia. However, there is also a risk of inducing atrial fibrillation with a rapid ventricular response in a patient with an antegradely conducting accessory pathway.

Long-Term Management

Patients with AV nodal reentry tachycardia and AV reentry tachycardia should be referred to a cardiologist for electrophysiologic evaluation and long-term management. Both pharmacologic and nonpharmacologic alternatives, including ablation of an accessory pathway, are widely available.

ACCELERATED ATRIOVENTRICULAR RHYTHM

Accelerated AV rhythm is produced by abnormal automaticity in the AV node. It is a narrow QRS complex tachycardia (unless bundle branch block is present), with a ventricular rate ranging from 70 to 250 beats per minute. AV dissociation is also present because the atria are activated normally by the sinus node impulse, whereas the ventricles are depolarized from an accelerated junctional site (Fig. 71.6). This arrhythmia is commonly the result of digitalis toxicity, and drug withdrawal is the usual therapy. If the rate of the AV node pacemaker is not fast, atropine can be given to increase the sinus node discharge rate until the sinus node resumes its dominance.

ATRIAL FIBRILLATION AND ATRIAL FLUTTER

Atrial fibrillation with a fast ventricular response is the most common supraventricular arrhythmia encountered in the emergency department in both younger adults with first-onset arrhythmia and older patients presenting with decompensation. Atrial flutter shares these clinical presentations and requires similar initial therapy. The acute management of both arrhythmias is therefore considered together.

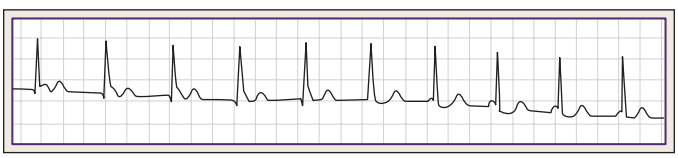

Fig. 71.6 Accelerated junctional rhythm with independent sinus node activity.

Atrial Flutter

Mechanism

Classification of atrial flutter is based on the ECG presentation and electrophysiologic mechanisms. The most common type is typical isthmus-dependent atrial flutter. Incisional reentry atrial flutter occurs after surgical correction for congenital heart disease. There are also various forms of atypical flutters, such as atypical right atrial isthmus-dependent flutter (double-wave and lower loop reentry) and left atrial flutter, in which the circuit contains the pulmonary vein or mitral valve annulus.[5]

Typical, or isthmus-dependent, atrial flutter involves a macroreentrant right atrial circuit around the tricuspid annulus. The wavefront circulates down the lateral wall of the right atrium, through the eustachian ridge between the tricuspid annulus and the inferior vena cava, and up the interatrial septum, giving rise to the most frequent pattern, referred to as *counterclockwise flutter*. Reentry can also occur in the opposite direction (clockwise or reverse flutter).

Electrocardiographic Presentation

Atrial flutter is usually an organized atrial rhythm with an atrial rate typically between 250 and 350 beats per minute. In the more common counterclockwise flutter, F waves are negative in leads II, III, aVF, and $V_{5–6}$ and positive in leads $V_{1–2}$ (Fig. 71.7A). Clockwise atrial flutter is typically characterized by positive F waves in leads II, III, and aVF and negative waves in leads $V_{1–2}$.

Treatment with propafenone, flecainide, and amiodarone to prevent recurrent atrial fibrillation without adding an AV-blocking agent (beta-blocker or nondihydropyridine calcium antagonist) can organize the arrhythmia into typical atrial flutter with AV conduction of 1:1 or 2:1, producing a ventricular rate response of 150 beats per minute or higher (see Fig. 71.7B). The probability of 1:1 conduction is increased in the presence of an accessory pathway with a short effective refractory period.

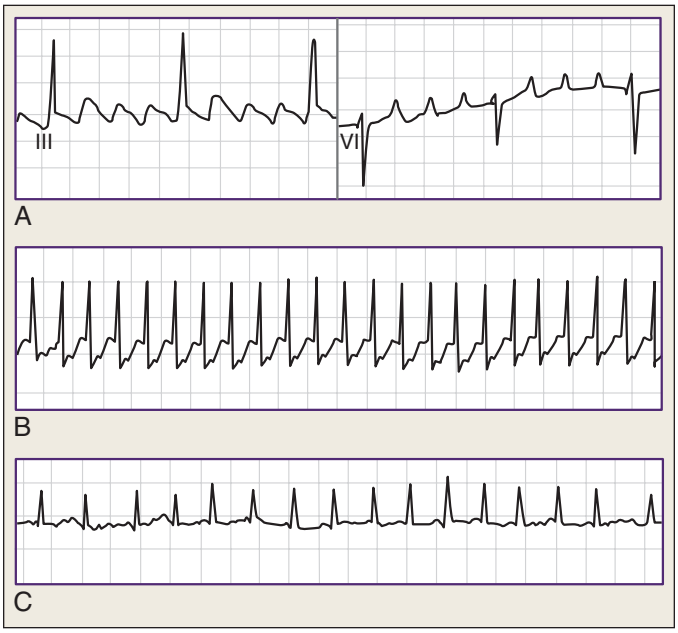

Fig. 71.7 **A,** Typical counterclockwise atrial flutter. F waves are negative in leads II, III, aVF, and $V_{5–6}$ and positive in leads $V_{1–2}$. **B,** Atrial flutter with 1:1 atrioventricular conduction and a ventricular rate of 270 beats per minute in a patient treated with flecainide. **C,** Atrial fibrillation with fast, uncontrolled ventricular rate.

Long-Term Management

The precise mechanism of atrial flutter is important for long-term management (e.g., catheter ablation) but has little influence on the initial approach. Patients with all types of atrial flutter should be referred for electrophysiologic evaluation with a view to ablation. Atrial fibrillation may develop even after successful ablation, and the patient should be followed up carefully.

Atrial Fibrillation

Electrocardiographic Presentation

Atrial fibrillation is defined as rapid oscillations or fibrillatory F waves that vary in size, shape, and timing (see Fig. 71.7C). The ventricular response rate is variable and depends on the rate and regularity of atrial activity, the refractory properties of the AV node itself, and the balance between sympathetic and parasympathetic tone. RR intervals are irregular unless the patient has complete AV block or a paced rhythm.

Classification

The clinical classification of atrial fibrillation includes first detected, paroxysmal (up to 7 days), persistent (more than 7 days), long-standing persistent (>1 year), and permanent (accepted) forms of the arrhythmia. Classification is essential for deciding between rhythm restoration and rate control. First-onset atrial fibrillation, if the duration of the episode is less than 48 hours, is a clear indication to restore sinus rhythm by either electrical or pharmacologic means. Because atrial fibrillation may be asymptomatic, the "first detected episode" should not be regarded as necessarily the true onset of the arrhythmia, in which case formal anticoagulation (see later discussion) and rate control may be preferred. Persistent or permanent atrial fibrillation should be treated initially by rate control and anticoagulation when appropriate.

Long-Term Management

Recognition of the pulmonary veins as the source of atrial premature beats or rapid atrial tachycardia that triggers atrial fibrillation or drives the atria prompted the development of ablation techniques that may "cure" the arrhythmia. In symptomatic permanent or persistent atrial fibrillation, AV node ablation and permanent pacing are effective in rate and symptom control. Any patient with first-onset or recurrent atrial fibrillation should be referred to a cardiologist for long-term management.

Acute Management

Acute therapy for atrial flutter and atrial fibrillation depends on the clinical presentation. Emergency electrical cardioversion is indicated for patients with hemodynamic collapse and progressively deteriorating left ventricular systolic function.

Direct Current Cardioversion

Atrial flutter can be converted with DC shock energy as low as 25–50 J, but because a 100-J shock is virtually always successful, it should be considered as the initial shock strength. In recent-onset atrial fibrillation, sinus rhythm can be restored by a shock of 100 J, but it is generally recommended that cardioversion be started with an initial shock energy level of 200 J or greater. In patients with an arrhythmia of unknown duration, heavier individuals, and those with chronic obstructive lung disease and pulmonary emphysema, an initial setting of 300–360 J is appropriate. Success may occur on the third or subsequent attempt at an intensity that initially proved ineffective.

Rate Control

Rate control is pertinent to all atrial tachyarrhythmias, particularly if restoration of sinus rhythm is deferred. IV verapamil, diltiazem, and

beta-blockers can rapidly control the ventricular response rate in atrial fibrillation[2] (see Table 71.1), but their efficacy may be less in atrial flutter. The decrease in the ventricular rate (approximately 20%–30%), time to maximal effect (20–30 minutes), conversion rate (12%–25%), and adverse reactions (usually hypotension and bradycardia, although left ventricular dysfunction and high-degree heart block may also occur) are reportedly similar with both classes of drugs. Beta-blockers are preferable if thyrotoxicosis is suspected as a cause of the arrhythmia.

IV digoxin is no longer the treatment of choice when rapid rate control is essential because of the delayed onset of its therapeutic effect (>60 minutes). However, because of its positive inotropic action, digoxin may be safer to use in patients with poor ventricular function and moderately fast ventricular rates. Digoxin may convert flutter to fibrillation, in which rate control is easier to accomplish.

There is evidence that IV amiodarone may be effective in rate control when other AV node–blocking agents have no effect on the ventricular response or are contraindicated.

Pharmacologic Cardioversion

If the arrhythmia is hemodynamically stable and of recent onset, pharmacologic cardioversion can be effective.

Flecainide and propafenone. Pharmacologic cardioversion of atrial fibrillation can be accomplished with the IC class of antiarrhythmic drugs—flecainide or propafenone—administered orally as a single dose of 300 or 600 mg, respectively (Table 71.2).[2] Placebo-controlled randomized studies show an efficacy rate of 60%–80% between the third and eighth hour after drug ingestion. Both oral and IV routes of administration are equally effective, although with IV injection, restoration of sinus rhythm can be achieved more quickly.

Flecainide is given as a slow IV injection of 2 mg/kg over 10– 30 minutes, up to the maximum dose of 150 mg. Propafenone is administered as a slow IV injection of 1.5–3 mg/kg, up to 300–600 mg. Because these drugs can significantly slow the atrial rate (from 300–350 beats/min to 200 beats/min), which may result in 1:1 AV conduction, beta-blockers or calcium antagonists with negative dromotropic effects on AV node conduction (verapamil, diltiazem) should be used concomitantly. Other cardiovascular effects include reversible QRS widening and (rarely) left ventricular decompensation. Because of their negative inotropic effects, flecainide and propafenone are contraindicated in patients with severe structural heart disease and a poor ejection fraction.

Class IC drugs are usually ineffective for the conversion of atrial flutter because they slow conduction within the reentrant circuit and prolong the flutter cycle length but rarely interrupt the circuit. These drugs pose the risk of increased (e.g., 2:1 or 1:1) AV conduction. Reported efficacy rates are as low as 13%–40% with IV flecainide and propafenone.

Ibutilide. The class III agent ibutilide is administered intravenously as a 10-minute injection of 1–2 mg and is particularly effective in terminating atrial flutter, with a success rate of about 60%. Its administration may be associated with excessive QT interval prolongation, however, because of rapid delayed rectifier potassium current (I_{Kr}) blockade, which may increase the risk of torsades de pointes. It is less effective in atrial fibrillation. Higher doses of ibutilide administered as two successive infusions of 1 mg are usually required to terminate fibrillation. The advantage of ibutilide is that it may be effective in the conversion of arrhythmias of up to 30 days' duration, but the success rate drops significantly to 20%–30%. The safety of ibutilide in patients with poor left ventricular function is unknown.

Amiodarone. Amiodarone administered intravenously at a dose of 5 mg/kg for 1 hour, followed by an infusion of 20 mg/kg over 24 hours, is effective in converting both atrial fibrillation and flutter, but the effect is significantly delayed.[6,7] However, because of its ability to control the ventricular rate, low likelihood of torsades de pointes, and absence of a negative inotropic effect, amiodarone can be used safely in patients with significant structural heart disease and those who are critically ill.

Procainamide and sotalol. Procainamide administered as a slow IV injection of 1000 mg over 20–30 minutes, followed, if necessary, by an infusion of 2 mg/min over 1 hour, converts atrial flutter or fibrillation of less than 48 hours' duration, but its efficacy is limited in longer-lasting arrhythmias. It is less effective than propafenone, flecainide, and ibutilide.

Sotalol is not indicated for the pharmacologic cardioversion of atrial flutter or fibrillation because its efficacy does not exceed 11%–13%; however, it may satisfactorily control the ventricular rate.

Vernakalant. This drug is given by a short IV infusion (3 mg/kg over 10 minutes). If after a 15-minute waiting period the arrhythmia persists, a second infusion of 2 mg/kg may be given over 10 minutes. In recent-onset (<72 hours) atrial fibrillation, about 50% of cases will terminate on average 12 minutes from the start of the first infusion. Vernakalant may be given to patients with underlying structural heart

TABLE 71.2 Antiarrhythmic Drugs for Pharmacologic Conversion of Atrial Tachyarrhythmias

Drug	Route of Administration	Dose	Potential Adverse Effects
Flecainide	Oral or intravenous	Loading oral dose 200–300 mg or slow injection 1.5–2 mg/kg over 10–20 min; if no response, infusion 1.5 mg/kg for 1 h, then 0.1–0.25 mg/kg over 24 h	Rapidly conducted atrial flutter, possible deterioration of ventricular function in the presence of organic heart disease, monomorphic ventricular tachycardia
Propafenone	Oral or intravenous	Loading oral dose 450–600 mg or 1.5–2 mg/kg over 10–20 min, followed by infusion 5–10 mg/kg if needed	
Ibutilide	Intravenous	1 mg over 10 min; if no response, additional 1 mg	QT prolongation, torsades de pointes, hypotension
Amiodarone	Intravenous (preferably central line)	5–7 mg/kg over 30–60 min, followed by infusion 20 mg/kg for 24 h (total 1200–1800 mg)	Hypotension, bradycardia, QT prolongation, torsades de pointes (?), gastrointestinal upset, constipation, phlebitis
Procainamide	Intravenous	1000 mg over 30 min, followed by 2 mg/min infusion	QRS widening, torsades de pointes, rapid atrial flutter
Vernakalant	Intravenous	3 mg/kg over 10 min; after 15-min break, 2 mg/kg unless arrhythmia terminated	Hypotension, postfibrillation bradycardia

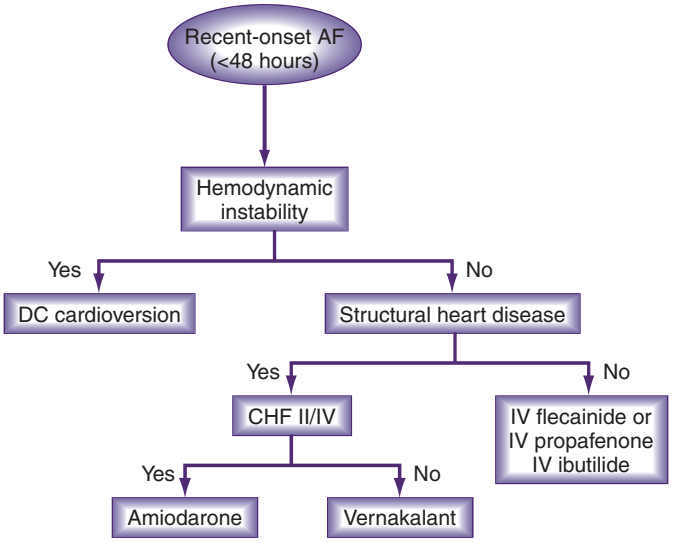

Fig. 71.8 Choice of antiarrhythmic for pharmacologic cardioversion of atrial fibrillation. *AF*, Atrial fibrillation; *CHF*, congestive heart failure; *DC*, direct current; *IV*, intravenous.

disease but not to patients with grades II/IV congestive heart failure. Proarrhythmia effects are uncommon, but hypotension and postermination bradycardia may occur.[8]

The choice of an antiarrhythmic agent for cardioversion is illustrated in Fig. 71.8.

Atrial Pacing

Burst overdrive atrial pacing can terminate atrial flutter in about 80% of cases and is feasible after cardiac surgery, when patients frequently have epicardial atrial pacing wires, or in patients with implantable dual-chamber pacemakers and defibrillators. High-frequency (50 Hz or 3000 beats/min) atrial pacing is available in some of the latest models for the termination of early-onset atrial fibrillation, but its efficacy has not yet been established. Atrial burst overdrive pacing may induce sustained atrial fibrillation, although short periods of fibrillation often precede conversion to sinus rhythm.

Anticoagulation

Anticoagulation is imperative if the arrhythmia persists for more than 24–48 hours or if its duration is unknown. Atrial flutter and atrial fibrillation pose similar risks of thromboembolism, and the same criteria for anticoagulation should be applied in patients with either arrhythmia. In hemodynamically stable arrhythmias of more than 48 hours or of unknown duration, rate control and 3 weeks of anticoagulation with warfarin (international normalized ratio 2.0–3.0) should be considered before any intervention (electrical or pharmacologic cardioversion, catheter ablation).[9]

Transesophageal Echocardiography–Guided Cardioversion

If, for any reason, deferral of cardioversion is not indicated, the transesophageal echocardiography–guided approach, with short-term anticoagulation using low-molecular-weight heparin, is a safe and effective alternative.[10] It may be clinically beneficial in patients with recent-onset arrhythmias or in individuals at high risk of bleeding complications during prolonged anticoagulation therapy.[11] Compared with unfractionated heparin, low-molecular-weight heparin therapy does not involve prolonged IV administration or laboratory monitoring and therefore has the potential to greatly simplify cardioversion-related anticoagulation therapy in low-risk individuals. Postcardioversion anticoagulation should be considered if atrial fibrillation has been present for 48 hours or more, or if thromboembolic risk factors are present.[9,12]

ATRIAL TACHYCARDIA

Mechanism

The mechanism of atrial tachycardia is attributed to enhanced automaticity, triggered activity, or intraatrial reentry. Macroreentrant atrial tachycardia often occurs after surgery for congenital heart disease. Focal atrial tachycardia typically originates along the crista terminalis in the right atrium, in the pulmonary veins entering the left atrium, or around one of the atrial appendages.

Electrocardiographic Presentation

The heart rate varies from 120 to 250 beats per minute, P waves precede the QRS complexes, and PP intervals are regular (see Fig. 71.5B). The PR interval is linked to the rate of the tachycardia and is longer than in sinus rhythm at the same rate. P-wave morphology is usually different from that observed during sinus rhythm and depends on the site of origin. Left atrial tachycardia presents with negative P waves in leads I, aVL, V_5, and V_6. Automatic atrial tachycardia may present as an incessant variety, leading to tachycardia-induced cardiomyopathy.

Atrial Tachycardia With Atrioventricular Block

Tachycardia with AV block occurs commonly in patients with organic heart disease, and in 50%–75% of cases, it results from digitalis toxicity (Fig. 71.9). Digoxin-specific antibody fragments are available for the reversal of life-threatening overdosage.

Multifocal Atrial Tachycardia

This tachycardia presents as rapid, irregular atrial activity with discrete P waves of varying morphology and is considered a transitional rhythm between atrial tachycardia and fibrillation. However, it may occur in patients with chronic severe pulmonary disease as a result of theophylline or beta-agonist overdose. Elimination of the causative factor may reduce the need for antiarrhythmic therapy. IV verapamil can accomplish rate control.

Acute Management

DC cardioversion converts atrial tachycardia based on the reentry mechanism or triggered activity, but it may not terminate automatic tachycardia. Similarly, atrial overdrive pacing may slow the tachycardia rate but seldom suppresses the automatic focus.

It is generally accepted that beta-blockers and calcium antagonists, particularly verapamil, can either terminate the tachycardia or produce rate control. Adenosine can terminate atrial tachycardia, but the most common response to adenosine is to create AV block and thereby reveal the unaffected tachycardia (see Fig. 71.5B and C).

Flecainide, propafenone, sotalol, and amiodarone are effective in converting atrial tachycardia. If the arrhythmia occurs as a result of digitalis intoxication, therapy includes the cessation of digoxin and IV administration of potassium.

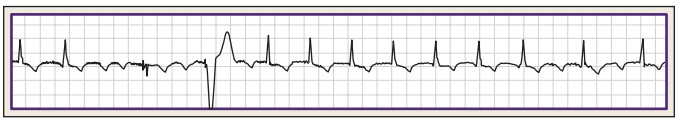

Fig. 71.9 Atrial tachycardia with varying atrioventricular block caused by digitalis toxicity.

Long-Term Management

Patients with atrial tachycardia should be referred to a cardiologist because the arrhythmogenic focus can be found and ablated in up to 86% of cases.

INAPPROPRIATE SINUS TACHYCARDIA

Inappropriate sinus tachycardia is a persistent increase in resting heart rate unrelated or out of proportion to the level of physical or emotional stress. It is found predominantly in women and is not uncommon in health professionals. Sinus tachycardia caused by intrinsic sinus node abnormalities such as enhanced automaticity or abnormal autonomic regulation of the heart, with excess sympathetic and reduced parasympathetic input, is not unusual. The main therapy is beta-blockers, although ivabradine, a drug that blocks the main current responsible for diastolic depolarization in the sinus node, is being increasingly used in Europe.[13] In general, sinus tachycardia is a secondary phenomenon, and the underlying cause should be actively investigated. Depending on the clinical setting, acute causes include fever, hypotension, infection, anemia, thyrotoxicosis, hypovolemia, acute heart failure, acute pulmonary embolism, and shock. Sinus tachycardia may be associated with the abuse of drugs such as amphetamines.

KEY POINTS

- SVT is characterized by narrow QRS complexes, but differentiating SVT from ventricular tachycardia may be necessary when bundle branch block, rate-dependent aberrancy, and antidromic AV reentry tachycardia are present.
- If the diagnosis of SVT cannot be proved, the arrhythmia should be treated as ventricular tachycardia.
- Immediate DC cardioversion is the treatment for any hemodynamically unstable tachycardia.
- In hemodynamically stable paroxysmal junctional tachycardias (AV nodal reentry tachycardia and AV reentry tachycardia), vagotonic maneuvers should be tried first because they may terminate tachycardia in about 50% of patients without the need to resort to pharmacologic therapy.
- IV adenosine, verapamil, and esmolol are first-line drug therapies for paroxysmal junctional tachycardias, but adenosine and verapamil should not be used for wide-complex tachycardias and atrial fibrillation with preexcitation.
- DC cardioversion or pharmacologic conversion with IV ibutilide or flecainide is appropriate for the termination of atrial fibrillation associated with preexcitation syndrome.
- IV verapamil, diltiazem, esmolol, metoprolol, and propranolol can rapidly accomplish rate control in atrial fibrillation but may be less effective in atrial flutter.
- Beta-blockers are preferable in atrial fibrillation associated with thyrotoxicosis.
- Pharmacologic cardioversion of atrial fibrillation in the absence of severe underlying heart disease can be attained using oral or IV flecainide or propafenone, vernakalant, and IV ibutilide, but the last is more effective in atrial flutter.
- Propafenone, flecainide, and vernakalant may result in atrial flutter with slow atrial rates and 2:1 or 1:1 AV conduction; verapamil, diltiazem, or beta-blockers should be available to treat this complication. Ibutilide can significantly prolong the QT interval and cause polymorphic ventricular tachycardia that, if sustained, may require DC cardioversion.
- IV amiodarone should be considered as first-line drug therapy in patients with severely impaired left ventricular function.
- Accelerated AV rhythm and atrial tachycardia with AV block commonly occur as a result of digitalis toxicity; digitalis withdrawal is the usual therapy.
- Anticoagulation is indicated if atrial fibrillation or flutter persists for more than 48 hours or if the duration is unknown; anticoagulation and rate control should be the initial therapy in these patients.
- An alternative approach is transesophageal echocardiography, to exclude the presence of atrial thrombi or dense spontaneous echocontrast, and short-term anticoagulation with low-molecular-weight heparin, followed by DC or pharmacologic cardioversion.
- Patients with paroxysmal junctional tachycardias, atrial tachycardia, atrial flutter, and first-onset or recurrent atrial fibrillation should be referred to a cardiac electrophysiologist/cardiologist for assessment and long-term management planning; effective nonpharmacologic therapies are available for these arrhythmias.

References for this chapter can be found at expertconsult.com.

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Albers GW, Dalen JE, Laupacis A, et al. Antithrombotic therapy in atrial fibrillation. *Chest*. 2001;119:194S–206S.
This paper focuses on the prevention of stroke in nonrheumatic atrial fibrillation and flutter and provides expert recommendations regarding risk stratification, anticoagulation strategies, cardioversion (including transesophageal echocardiography–guided cardioversion), and long-term management of patients at risk of thromboembolism. It contains a complete review of the evidence base for anticoagulation in atrial fibrillation.

Blomström-Lundvist C, Scheiman MM, Aliot EM, et al. ACC/AHA/ESC guidelines for the management of patients with supraventricular arrhythmias—executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to develop guidelines for the management of patients with supraventricular arrhythmias). *J Am Coll Cardiol.* 2003;42:1493–1531.
These practice guidelines describe a range of generally accepted approaches to the diagnosis and management of supraventricular tachyarrhythmias (excluding atrial fibrillation) and provide insight into the multiple mechanisms defined by electrophysiologic studies, with a focus on both acute and long-term therapies.

Camm AJ. Atrial fibrillation: Is there a role for low-molecular-weight heparin? *Clin Cardiol.* 2001;24:I15–I19.
This review paper summarizes evidence emerging from clinical studies that clearly supports both the use of transesophageal echocardiography–based cardioversion protocols and the introduction of low-molecular-weight heparin for anticoagulation in atrial fibrillation. Clinical settings in which low-molecular-weight heparin may offer advantages over unfractionated heparin and warfarin are discussed.

Fuster V, Rydén LE, Asinger RV, et al. Task force report: ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation. *Eur Heart J.* 2001;22:1852–1923.
These guidelines incorporate a comprehensive review of the latest information about the classification, epidemiology, mechanisms, and clinical presentations of atrial fibrillation. Practical approaches to acute and long-term management of this arrhythmia are discussed at length. An extensive list of references covers various aspects of atrial fibrillation.

Mehta D, Wafa S, Ward DE, et al. Relative efficacy of various physical manoeuvres in the termination of junctional tachycardia. *Lancet*. 1988;1:1181–1185.
This paper compares the ability of four vagotonic physical maneuvers to terminate paroxysmal supraventricular tachycardias that involve the AV node as part of their reentrant circuits. It shows that these tachycardias can be terminated without resorting to pharmacologic therapy in more than half of patients. The paper provides a detailed methodologic description and explains the physiologic effects of vagotonic maneuvers.

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Ventricular Arrhythmias

Raúl J. Gazmuri, Cristina Santonocito, Salvatore R. Aiello, and Donghee Kim

Cardiac arrhythmias are common in critically ill patients and a frequent reason for hospital admission to areas with capability for continuous electrocardiographic monitoring and personnel trained in their recognition and management (e.g., intensive care units [ICUs] and telemetry units).

Arrhythmias are supraventricular if they originate above the atrioventricular (AV) node, such as in atrial tissue or pulmonary veins. They may compromise stroke volume and create hemodynamic instability because of excessive heart rate and/or reduced ventricular filling after losing the atrial contribution to preload. However, in the absence of accessory conduction pathways bypassing the AV node (e.g., Wolf-Parkinson-White syndrome), supraventricular arrhythmias are rarely life-threatening and may be managed without immediate urgency by pharmacologic or electrical means. In contrast, arrhythmias such as ventricular tachycardia (VT) and ventricular fibrillation (VF) that originate in the ventricular tissue may be life-threatening and require immediate treatment.

NORMAL ELECTROPHYSIOLOGY

Anatomic Synopsis

The electrical impulse originates in the sinoatrial (SA) node, located high on the right atrium near its junction with the superior vena cava (Fig. 72.1). The impulse propagates through muscle fibers and specialized internodal pathways (composed of Purkinje-type fibers) to converge on the AV node, located in the interatrial septum near the tricuspid valve. The impulse then travels through the bundle of His, its left and right branches, and the Purkinje system to activate both ventricles simultaneously. A ring of fibrous tissue interposed between the atria and the ventricles prevents spread of the impulse through muscle fibers, enabling the AV node to function as a relay and filter, preventing 1:1 conduction under conditions of very rapid atrial activation such as atrial flutter (rate ~300 s^{-1}) or atrial fibrillation (rate ~600 s^{-1}).

Action Potential and Pacemaker Activity

Action Potential

Action potentials, once initiated in pacemaker cells, propagate through both atria and ventricles. The electrical impulse depolarizes cardiac myocytes and opens voltage-dependent Ca^{2+} channels. Influx of Ca^{2+} causes Ca^{2+}-induced Ca^{2+} release via ryanodine receptors located in the sarcoplasmic reticulum to activate contractile proteins and elicit contraction. Each action potential is produced as a result of time- and voltage-dependent opening and closing of different types of plasma membrane ion channels, mainly involving influx of Na^+ and Ca^{2+} (inward currents) and efflux of K^+ (outward currents).[1–3]

Cells from the Purkinje system and muscle tissue have a stable resting potential of approximately −90 mV (negative inside), largely as a result of a background (also called *leak*) K^+ current known as *inward rectifier* (I_{K1}). Because this K^+ channel is open at rest, it "anchors" the membrane potential to a voltage close to the K^+ equilibrium potential. Because of its inward rectification properties, I_{K1} is turned off during depolarization, which is critical for maintaining the action potential duration.

Phase 0 is the initial rapid upstroke of the action potential. Triggering an action potential requires depolarization to a level between −70 and −80 mV, which is the threshold for activation of fast voltage-gated Na^+ channels (I_{Na})[3] and is normally achieved upon arrival of another action potential. The I_{Na} drives the membrane potential toward the Na^+ equilibrium potential, reversing the membrane potential to approximately +20 mV (overshoot). This is *phase 0* of the action potential and is followed by repolarization in four phases (Fig. 72.2).

Phase 1 is the early rapid repolarization period that occurs just after the upstroke (phase 0) of the action potential. *Phase 1* is produced by activation and subsequent inactivation of a "transient" K^+ current (I_{To}) and is composed of "fast" recovering (I_{Tof}) and slowly recovering (I_{Tos}) currents. I_{Tof} is thought to be the predominant contributor to I_{To} in ventricular myocardium.[4] Because K^+ channels that produce I_{To} are expressed at higher levels in the subendocardium and mid-myocardium than in the subendocardium, I_{To} contributes to the repolarization inhomogeneity.[5]

Phase 2, the plateau phase, is produced by Ca^{2+} influx via opening of L-type voltage-gated Ca^{2+} channels ($I_{Ca\text{-}L}$)[6,7] and K^+ efflux via a *delayed rectifier K^+ channel* (I_K). Both I_{Ca} and I_K are activated by the initial depolarization produced by Na^+ influx during *phase 0*. The relatively small inward (I_{Ca}) and outward currents (I_K) produce little net current, resulting in a near-flat *phase 2*. During the plateau phase, Ca^{2+} channels slowly inactivate with time and Ca^{2+} influx decreases, but the K^+ current (I_K) increases with time, producing a net increase in outward current near the end of *phase 2*.

Phase 3 corresponds to the late strong repolarization and is produced by the delayed rectifier K^+ current. The delayed rectifier K^+ current (I_K) has a rapid (I_{Kr}) and a slow (I_{Ks}) component.[8,9] Although both I_{Ks} and I_{Kr} are critical for producing the strong repolarization, they possess quite different activation and inactivation kinetics. The magnitude of I_{Kr} is greater than that of I_{Ks} during the rapid repolarization phase, and therefore I_{Kr} plays an important role in bringing the cell membrane potential back toward the resting state. Both are implicated in acquired and heritable forms of long QT syndrome.[10] Near the end of the repolarization phase, I_{K1} begins to increase as the cell membrane potential returns toward −90 mV and thus partly contributes to the final setting of the resting potential.

Phase 4 is the resting fully repolarized state and is produced by reopening of the inward rectifier background K^+ channels as the cell membrane potential is brought close to −90 mV. During this phase, the ionic balance is restituted by the action of the Na/K pump. This is an important phase that allows diastolic filling of the relaxed ventricle.

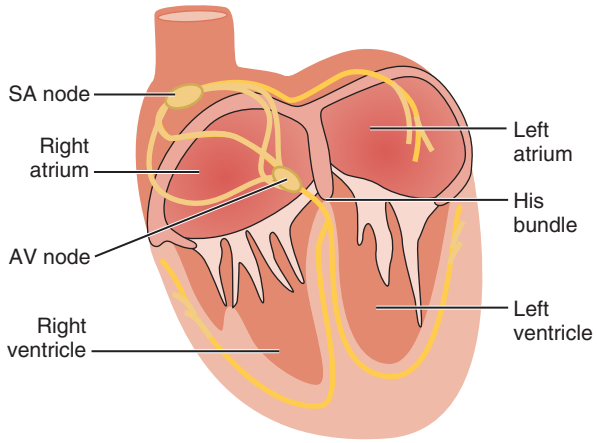


Fig. 72.1 Conduction system of the heart. *AV,* Atrioventricular; *SA,* sinoatrial.

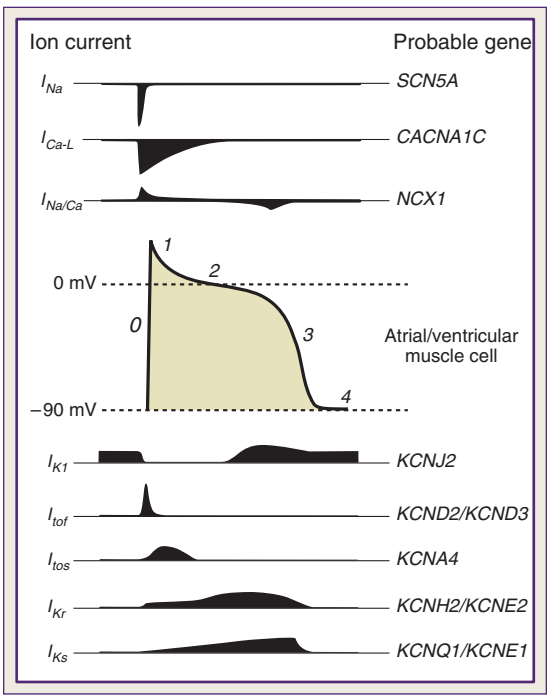


Fig. 72.2 Action potential of a cardiac muscle cell, depicting the main underlying inward and outward currents and respective gene products. Distinctive phases of the action potential are numbered. *Voltage* (mV) refers to the potential on the intracellular side of the plasma membrane relative to an outside reference. Notice that resting potential is negative inside at approximately −90 mV, indicating the cell at rest is polarized (phase 4). Beginning of the action potential is signaled by a rapid reduction in such potential, with inside voltage reaching 0 mV (depolarization) and then becoming transiently positive (overshoot) during phase 0, to be followed by phases 1, 2, and 3 as voltage returns to resting potential on phase 4.

Pacemaker Activity

In cells of the SA and AV nodes, voltage-gated Na^+ channels are in the inactive state, and *phase 0* is produced by $I_{Ca\text{-}L}$.[11] Because the activation kinetics of $I_{Ca\text{-}L}$ are slower than that of I_{Na}, *phase 0* is slanted and in part responsible for the slow SA and AV node conduction velocity (~50 $cm{\cdot}s^{-1}$) relative to that in the His-Purkinje system (~400 $cm{\cdot}s^{-1}$) and muscle cells (~100 $cm{\cdot}s^{-1}$). Pacemaker activity of SA and AV node cells results from slow *phase 4* depolarization (known as prepotential or *pacemaker potential*) to ~−40 mV. Slow depolarization involves opening of the hyperpolarization-activated inward Na^+ current (also known as the "funny current," I_F) and opening of T-type voltage-gated Ca^{2+} channels ($I_{Ca\text{-}T}$). The T-type Ca^{2+} channel is activated at a more negative membrane potential than that of the L-type Ca^{2+} channel and thus contributes to the pacemaker potential. The *phase 3* repolarization produced by activation of the delayed rectifier K^+ current (I_K) is a prerequisite for subsequent activation of I_F. I_K is large at the beginning of *phase 3* but decreases quickly with time as the cell membrane potential becomes negative, and this event helps start the subsequent slowly depolarizing pacemaker potential *(phase 4)*. Cells of the His–Purkinje system have latent prepotential activity and can become active when SA or AV node activity is depressed or their impulses are blocked (i.e., "escape rhythm"). Muscle cells exhibit prepotential activity only under abnormal circumstances.

The preceding paragraphs describe the primary ionic mechanisms that produce *phase 0 through phase 4* of the cardiac action potentials. Other ion channels, antiporters, pumps, and receptor agonists can also modulate the shape of the action potential in response to various stimuli such as high sympathetic tone and hypoxia. For example, a nonselective cationic channel gated at resting potential by intracellular Ca^{2+} is present in cardiac myocytes. This channel produces an inward Na^+ current (I_{NS})[12] that may contribute to delayed afterdepolarizations when Ca^{2+} is released from the sarcoplasmic reticulum. $I_{K(ATP)}$ is a K^+ current carried through channels inhibited by intracellular adenosine triphosphate (ATP) and is opened under conditions of ischemia and hypoxia. $I_{K(ATP)}$ contributes to action potential shortening and the characteristic ST-segment elevation observed during myocardial ischemia.[13,14]

The sarcolemmal Na^+/Ca^{2+} exchanger is another important modulator of the action potential. Because it exchanges one Ca^{2+} for three Na^+, it generates a current ($I_{Na/Ca}$) whose direction depends on Na^+ and Ca^{2+} gradients and the membrane potential.[14,15]

Adrenergic receptor stimulation also modulates the action potential by modifying channel activity.[16–18] For example, beta-1 adrenoceptor stimulation increases $I_{Ca\text{-}L}$ activity and Ca^{2+} influx, enhancing inotropic action. Beta-1 adrenoceptor stimulation also activates K^+ channels, shortening the action potential duration.[19] Alpha-1 adrenoceptor stimulation acting via Gq protein on the Na^+/K^+ pump, K^+ channels, and phospholipase C can alter impulse initiation and repolarization, an effect linked to triggered arrhythmias via early and delayed afterdepolarizations and abnormal automaticity during ischemia and reperfusion.[20,21]

Muscarinic receptors (M_1) coupled to Gi protein are highly expressed in pacemaker and atrial cells. M_1 receptor stimulation by acetylcholine released from the efferent vagus nerve innervating the cells of the SA and AV nodes produces slowing of the heart rate and conduction velocity, which is a parasympathetic response.[22]

Cardiomyocytes can also react to mechanical forces through stretch-activated ion channels and other mechanisms, including mechanical modulation of Ca^{2+} handling and interaction with other mechanosensitive cells.[23,24] These mechanisms are probably involved in commotion cordis,[25] precordial thump,[26] and fist pacing.[27]

MECHANISMS OF VENTRICULAR TACHYARRHYTHMIAS

Abnormalities in impulse generation and conduction are responsible for the genesis and maintenance of ventricular tachyarrhythmias.

Abnormalities in Impulse Generation

Abnormalities in impulse generation are generally the result of automaticity or triggered activity.

Automaticity

Automaticity refers to the emergence of ectopic pacemaker activity resulting from enhanced normal automaticity or development of abnormal automaticity.

Enhanced normal automaticity occurs when cells with intrinsic pacemaker potentials (e.g., cells from the AV node or His–Purkinje system) that are normally suppressed by the SA node fire at rates that escape such suppression. This phenomenon may result from effects on *phase 4* prepotentials yielding earlier development of action potentials (i.e., less maximal polarization, faster depolarization, or lower threshold potential) or from shortening of the action potential duration with earlier return to *phase 4*. Enhanced normal automaticity is usually the result of adrenergic stimulation, which increases the slope of the pacemaker potential by acting on I_F.

Development of abnormal automaticity refers to impulses originating in cells without intrinsic pacemaker potential and typically occurs by generation of depolarizing currents during *phase 4* (e.g., ischemia).[28] Abnormal automaticity can develop in atrial and ventricular muscle cells and in specialized tissues other than the SA and AV node. Examples include accelerated idioventricular rhythms and some VTs developing 24–72 hours after acute myocardial infarction.[29]

Triggered Activity

Triggered activity refers to arrhythmias that arise from afterdepolarizations, defined as alterations in membrane potential that occur during repolarization.[30] Afterdepolarizations are considered early if they develop during *phase 2, phase 3,* or early *phase 4* of the action potential and are characterized by transient retardations in repolarization (Fig. 72.3). If of enough magnitude, they can trigger an "extra" action potential. Early afterdepolarizations are typically associated with conditions that prolong the action potential (e.g., increased sympathetic tone, exogenous catecholamines, hypoxia, acidosis, bradycardia, etc.), enabling increased Ca^{2+} entry through $I_{Ca\text{-}L}$[31] and can trigger torsades de pointes, a form of VT. In the setting of heart failure, Ca^{2+} sparks occurring during *phase 2* or *phase 3* consequent to loss of synchrony in Ca^{2+} release at the start of the action potential can generate enough $I_{Na/Ca}$ current to trigger early afterdepolarizations.[32]

Afterdepolarizations are considered delayed if they develop in late *phase 4* and may also reach the threshold for triggering an action potential (see Fig. 72.3). The main underlying abnormality is intracellular Ca^{2+} overload, triggering Ca^{2+} release from the sarcoplasmic reticulum[31] and depolarizing currents (i.e., inward $I_{Na/Ca}$ currents).[33] Delayed afterdepolarizations are classically associated with digitalis toxicity; however, they can also occur with myocardial stretch, hypertrophy, catecholamines, ischemia, and reperfusion. In heart failure, increased expression of the Na^+-Ca^{2+} exchanger along with abnormalities in the ryanodine receptor predispose to delayed afterdepolarizations.[33]

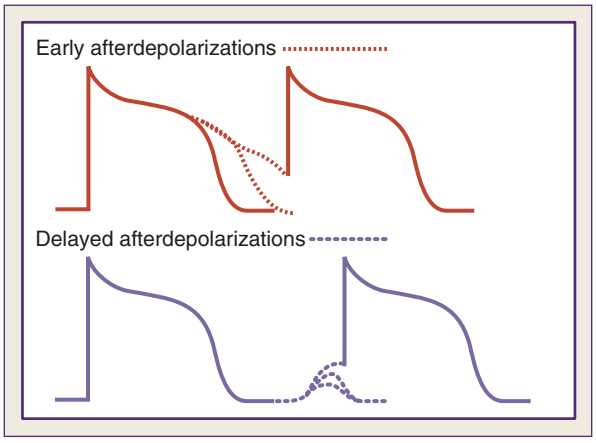


Fig. 72.3 Afterdepolarizations *(dotted lines).* Early afterdepolarizations are retardations in repolarization with prolongation in action potential duration *(upper figure).* Delayed afterdepolarizations represent spontaneous depolarizations that occur after repolarization is over *(lower figure).* Afterdepolarizations that reach a threshold trigger an action potential.

Abnormalities in Impulse Conduction (Reentry)

Abnormalities in impulse conduction leading to reentry account for the vast majority of sustained VTs. Reentry occurs when a propagating impulse reenters and reexcites a region of previously excited tissue after its refractory period is over. Several forms of reentry have been described, including circus movement, *phase 2,* and reflection.[34]

Circus Movement

Circus movement is the most widely studied reentry model and encompasses four distinct models: ring, leading circle, figure of eight, and spiral wave.

The *ring model* is the simplest,[35] and it is useful to illustrate the basic mechanism of reentry (Fig. 72.4). The ring model requires two contiguous paths separated by unexcitable tissue. One path—*b* in Fig. 72.4—has a zone of unidirectional block, whereas the other path—*a* in Fig. 72.4—allows slow but bidirectional conduction. Once the impulse traveling path *a* reaches path *b,* it propagates retrogradely to subsequently reenter path *a.* To establish reentry, the circling impulse wavelength must be shorter than the reentry circuit path length, allowing its leading edge to find tissue in an excitable state. The circling impulse wavelength is the product of conduction velocity and refractory period, and conditions that slow conduction or shorten refractoriness favor reentry. The ring model commonly involves AV accessory pathways and the AV node. Reentry is usually triggered by the arrival of a premature beat. Unidirectional block may result from increased refractoriness caused by anatomic abnormalities (e.g., fibrosis, accessory pathway, bundle branch block) or functional defects (e.g., ischemia, action of drugs).

The *leading circle model* is similar to the ring model but without requiring anatomic obstacles and can develop in structurally uniform myocardium by a properly timed premature impulse.[36]

The *figure-of-eight model* was first described in experimental myocardial infarction. It encompasses two reentry circuits moving alongside a functional conduction block (ischemia or infarct) in opposite directions, forming a pretzel-like configuration.[37]

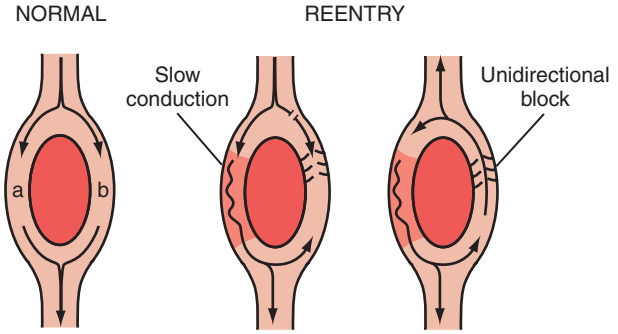


Fig. 72.4 Ring model of reentry.

The *spiral wave model* is a more complex version of the leading circle model and involves a core and filaments and can be described as reentry in two dimensions.[38] It has been used to explain monomorphic and polymorphic VTs and VF. In monomorphic VT, the spiral wave is anchored and unable to drift, whereas in polymorphic VTs—such as torsades de pointes—the spiral is thought to drift. In VF, the spiral wave is thought to break up into multiple rotating spiral waves that continuously extinguish and re-create. Yet some authors have proposed a single rapidly shifting spiral, and others have postulated a stationary rotor whose frequency of excitation is exceedingly high, resulting in multiple areas of intermittent block.[39]

Phase 2

Phase 2 reentry refers to local reexcitation consequent to repolarization heterogeneity with areas of markedly shortened repolarization—essentially obliterating *phase 2* of the action potential—next to areas of normal repolarization. Local reexcitation may precipitate VT during myocardial ischemia.[40] Action potentials of normal duration may alternate with ones of shorter duration during myocardial ischemia, yielding beat-to-beat alternans (temporal dispersion) and site-to-site alternans (spatial dispersion) and promote regions with conduction block and regions with injury current, leading to reentry and VTs. The degree of spatial and temporal dispersion progresses during ischemia, suggesting this mechanism may be an important trigger of VT and VF during acute myocardial ischemia.[41,42] In the surface electrocardiogram (ECG), dispersion of the action potential duration manifests as T-wave alternans, which is a predictor of VF.[43]

Reflection

Reflection refers to a back-and-forth propagation of the impulse over the same functionally unexcitable tissue, with recurrent activation of the proximal region as a result of electrotonic currents.[44] The area of unexcitable tissue could result from ischemia and lead to extrasystolic activity. Reflection differs from classic reentry in that the impulse travels along the same pathway in both directions.

PREEXISTING CONDITIONS PREDISPOSING TO VENTRICULAR ARRHYTHMIAS

Channelopathies

The term *channelopathies* has been coined to identify a group of diseases caused by abnormalities on ion channels.[45,46] These abnormalities distort the action potential, primarily accentuating the inherent instability of repolarization and increase the risk of polymorphic VT of the torsades de pointes type. Channelopathies may be hereditary or acquired.

Hereditary Channelopathies

Most hereditary channelopathies originate from mutations in genes encoding for Na^+, K^+, and Ca^{2+} channels and are largely represented by congenital long QT syndrome (LQTS),[47–51] Brugada syndrome,[52–55] and catecholaminergic polymorphic ventricular tachycardia (CPVT).[56–58] Less common channelopathies include short QT syndrome (SQTS)[59] and early repolarization syndrome (ERS).[60–62] All contribute with varying penetrance to sudden cardiac arrest in young individuals.[63,64]

Long QT Syndrome

LQTS was first described in 1957 by Jervell and Lange-Nielsen in patients with long QT intervals, episodes of torsades de pointes, and deafness.[65] The syndrome is transmitted by autosomal recessive inheritance and is known as *Jervell and Lange-Nielsen syndrome*. In 1963 and 1964, Romano and colleagues[66] and Ward[67] independently reported patients with an almost identical disorder but without deafness. The syndrome is transmitted by autosomal dominant inheritance and is known as *Romano-Ward syndrome*. Of 17 genes reported as being causative for LQTS, only 3 genes (*KCNQ1, KCNH2, SCN5A*) are considered definitive genes for typical LQTS, 9 genes (*ANKB, KCNE1, KCNE2, KCNJ2, CAV3, SCN4β, AKAP9, SNTA1, KCNJ5*) are classified as having limited evidence, and 4 genes (*CALM1, CALM2, CALM3, TRDN*) are found to have strong or definitive evidence as a cause of LQTS with atypical features, including neonatal AV block. The remaining *CACNA1C* gene has moderate evidence for causing LQTS.[68]

Jervell and Lange-Nielsen syndrome and Romano-Ward syndrome are primarily responsible for LQTS1 and account for nearly 50% of all genotyped families. LQTS2 accounts for nearly 40%, and long LQTS3 for about 5%. The remaining types are much less frequent.[69]

The common mechanistic thread is a perturbed balance between I_{Na} and I_K during *phase 2* of the action potential, yielding prolongation of repolarization, slowed $I_{Ca\text{-}L}$ inactivation, late Ca^{2+} influx, and early afterdepolarizations, predisposing to torsades de pointes.[70]

LQTS should be suspected in young individuals who present with syncope or episodes of sudden cardiac arrest precipitated by exercise, emotional distress, or conditions that prolong the QT interval. A family history of unexplained syncope or sudden cardiac arrest should raise suspicion. The diagnosis should be suspected when the corrected QT interval ($QTc = QT_{(ms)} \cdot \sqrt{R - R_{(ms)}}$) exceeds 470 ms in males (normal <422 ms) and 480 ms in females (normal <432 ms). Genetic testing for identifying the various LQTS subtypes is becoming readily available.[69] Genes with limited evidence for disease causation should not be routinely tested in the evaluation of patients and families with LQTS.[68]

The clinical implication is based on the application of precision medicine in clinical care and requires the accurate and appropriate use of genetic testing to optimize the care of patients and families. In addition to LQTS, several studies have shown that even milder prolongation of the QTc in adults (>450 ms in men and >470 ms in women) increases the risk of sudden cardiac arrest.[71]

Recently, mutations in calmodulin genes *CALM1* and *CALM2* have been shown to cause an extremely severe form of LQTS with QT prolongation >600 ms, T-wave alternans, cardiac arrest in infancy, and intermittent 2:1 AV block.[72,73]

A recent study showed that patients with LQTS have a significantly higher incidence of diabetes and higher incidence of neurologic (mostly epilepsy) and psychiatric disorders, suggesting that LQTS may be considered a multiorgan disease.[74]

The management of LQTS starts with discontinuing all drugs known to prolong the QT interval and correcting electrolyte imbalances and metabolic conditions that could trigger torsades de pointes. Restriction of participation in athletic activities is generally recommended along with use of beta-blockers and antiarrhythmic agents (e.g., mexiletine or flecainide). In selected cases an implantable defibrillator, cardiac sympathetic denervation, or both may be necessary.

Catecholaminergic Polymorphic Ventricular Tachycardia

CPVT is a highly malignant arrhythmogenic disorder that may present with sudden cardiac arrest induced by exercise or emotion, typically in children or adolescents without structural heart disease.[58] CPVT is associated with two main mutations that affect Ca^{2+} handling by the sarcoplasmic reticulum. One involves an autosomal dominant mutation on the ryanodine receptor gene *RyR2* (i.e., CPVT type 1). The mutation reduces the affinity of FKBP12.6 for *RyR2,* lowering the threshold for Ca^{2+} release from the sarcoplasmic reticulum.[57] Beta-adrenergic stimulation intensifies Ca^{2+} release and in part explains the effects of exercise and emotion.

The second is an autosomal recessive mutation on the calsequestrin 2 gene *CASQ2* (CPVT type 2). Within the sarcoplasmic reticulum, the CASQ2 protein serves as the major Ca^{2+} reservoir. The mutation causes a negatively charged domain that alters Ca^{2+} binding.[56]

The ECG at rest is typically normal with occasional U waves and bradycardia. Beta-blockers are the cornerstone of therapy, with an implantable cardioverter defibrillator (ICD) indicated in high-risk individuals. Flecainide inhibits the RyR2 receptor and can suppress or terminate the arrhythmias. Familial screening is indicated once the diagnosis is established.

Short QT Syndrome

SQTS is a more recently described syndrome[59] characterized by tall and peaked T waves with QT intervals ≤300 ms insensitive to changes in heart rate in structurally normal hearts. Individuals are at risk of developing atrial fibrillation and VF. A family history may be present, including sudden death at a young age.

The shortened QT interval results from increased outward K^+ currents during *phase 2* and *phase 3* of the action potential associated with autosomal dominant mutations in the *KCNH2*, *KCNJ2,* and *KCNQ1* genes.

ICD implantation is a class I recommendations in survivors of cardiac arrest and in patients with spontaneous sustained VT with or without syncope. Among various drugs, quinidine and sotalol could be effective by prolonging the QT interval.[59]

Brugada Syndrome

Another important hereditary channelopathy is Brugada syndrome, described in 1992 by the Brugada brothers,[52–55] who reported sudden cardiac arrest in individuals with structurally normal hearts but ST-segment elevation in V_1–V_3 and a QRS resembling right bundle branch block.

Brugada syndrome exhibits predominantly an autosomal dominant pattern of inheritance, with an average worldwide prevalence of 5:10,000.[75] Mutations have been identified in 10 genes.[76] Loss of function caused by a mutation in the *SCN5A* gene (encoding for the I_{Na} alpha subunit) accounts for approximately 20% of cases. The other 80% depends on mutations involving *GPD1-L, CACNA1C, CACNB2, SCN1B, KCNE3, SCN3B, MOG1, KCNE5,* and *KCND3*.[76]

The predominant genetic defect of the *SCN5A* gene leads to an accelerated inactivation of I_{Na}, leaving I_{To} unopposed and resulting in rapid repolarization with shortened action potential duration. In addition, the predominant epicardial expression of I_{To} allows normally depolarized endocardium to reexcite, prematurely repolarizing the epicardium and generating reentry, which in turn, can precipitate polymorphic VT.

The ST-segment elevation can adopt various shapes related to the severity of the I_{Na}/I_{To} imbalance. With increasing severity, saddleback, coved, and triangular shapes are recognized.[70] These changes are dynamic and can change in the same affected individual, as shown in Fig. 72.5.

Brugada syndrome exhibits variable expressivity, reduced penetrance, and "mixed phenotypes" where families may include members with Brugada syndrome and members with SQTS, LQTS, atrial fibrillation, disease of the conduction system, and even structural heart disease.[75]

Genetic testing can be useful when there is a personal and family history along with the characteristic electrocardiographic pattern identified at rest or after drug challenge.

Patients with Brugada syndrome may have concealed or intermittent forms, unmasked (or precipitated) by febrile states, vagotonic agents, alpha-adrenergic agonists, beta-adrenergic blockers, tricyclic or tetracyclic antidepressants, a combination of glucose and insulin and hypokalemia, and alcohol and cocaine toxicity.[77] Concealed Brugada syndrome can be unmasked by class IC antiarrhythmic drugs—for example, ajmaline (1 mg/kg intravenous [IV] in 5 minutes), flecainide (2 mg/kg IV in 10 minutes), or procainamide (10 mg/kg IV in 10 minutes). Such testing carries a 0.5% risk of precipitating VF. Ajmaline is favored because of its shorter half-life.[76] The test is considered positive if an additional 1-mm ST-segment elevation (0.08 second after the J point) occurs in leads V_1, V_2, and V_3. The test has high specificity and high sensitivity (94% and 80%, respectively).[78]

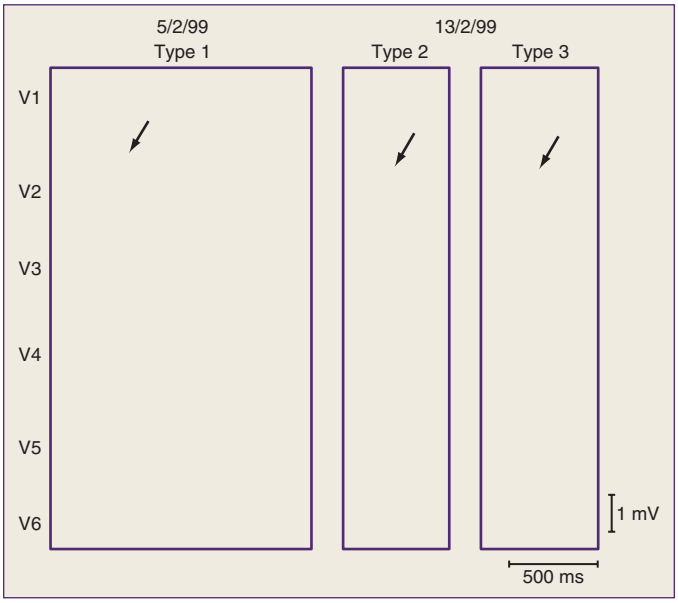


Fig. 72.5 Representative tracings in a patient with Brugada syndrome, demonstrating dynamic changes in V_1–V_2 after resuscitation from cardiac arrest. *Type 1* refers to the coved-type ST-T configuration, whereas *type 2* and *type 3* refer to the saddleback ST-T configuration. (From Wilde AA, Antzelevitch C, Borggrefe M, et al.; Study Group on the Molecular Basis of Arrhythmias of the European Society of Cardiology. Proposed diagnostic criteria for the Brugada syndrome: Consensus report. *Circulation.* 2002;106:2514–2519.)

Patients with suspected Brugada syndrome should be referred to specialized centers on inherited arrhythmias, which focus on counseling in daily life activities (e.g., avoiding excessive alcohol intake, treating fever aggressively, and decreasing exercise activity progressively). A familial screening should be performed to achieve early identification of affected relatives who could be at risk. The second step is a discussion on the therapeutic approach. The preferred management of Brugada syndrome is ICD implantation[54] after risk assessment, with a strong recommendation in symptomatic patients with a spontaneous ECG pattern. Less clear is the indication of ICD implantation in patients with intermediate risk.[79]

Quinidine and hydroquinidine can prevent spontaneous changes in the ECG and reduce the risk of VT and VF, presumably through inhibition of I_{To}.[80–82] However, because of limited data, it cannot be suggested for primary prevention, and the use should be discussed on a case-by-case basis in highly specialized centers.[83] Recently, ablation of the substrate located in the anterior epicardial region of the right ventricular outflow tract has been shown to reduce episodes of VF in patients with an ICD.[84] Determining which patients need pharmacologic treatment and those who would benefit from more aggressive treatment such as sympathectomies and implantable defibrillators is not always clear.

In addition, several diseases, such as myocardial ischemia, acute pericarditis, pulmonary embolism, right ventricular compression, and

metabolic disorder (e.g., hyperkalemia or hypokalemia and hypercalcemia) can exhibit a Brugada-like type 1 ECG pattern.[85,86] These Brugada syndrome phenocopies cannot be differentiated from true Brugada syndrome because of their identical ECG patterns, and a systematic diagnostic approach needs to avoid misdiagnosis.[79]

Early Repolarization and Early Repolarization Syndrome

Early repolarization is generally defined by a J-point elevation on the ECG >0.1 mV in two adjacent leads with a slurred or notched morphology affecting the inferior and/or lateral leads.[87] It is a condition commonly affecting between 1% and 5% of the general population,[60] with a higher incidence up to 13% in certain populations.[88] Early repolarization was previously thought to be a completely benign finding; however, studies and case reports suggest a higher risk of arrhythmias, mainly idiopathic VF in such patients,[61,62,89] and is common in patients who present with idiopathic VF and experience recurrence of VF.[90]

Early repolarization is mainly sporadic; however, genetic inheritance is being noted in the literature, and a wide array of both loss-of-function and gain-of-function genetic mutations have been reported.[91–93] Some studies have stratified the risk of developing arrhythmia based on the patterns of early repolarization on ECG.[87] Type 1 is associated with early repolarization in the lateral leads. This pattern is thought to be largely benign. Type 2 is associated with early repolarization in the inferior or inferolateral leads and is associated with a moderate level of risk. Type 3 is associated with early repolarization in the inferior, lateral, and right precordial leads and appears to be associated with the highest relative risk.[94]

It is important to differentiate between early repolarization in which only the classic ECG findings are found in an asymptomatic individual with ERS, which includes the classic ECG findings of early repolarization in a survivor of sudden cardiac death (SCD) with evidence of VF after an extensive workup has ruled out any other cardiac abnormalities.[95]

A class 1 recommendation for patients with asymptomatic early repolarization on the ECG is to observe. In this patient population in the acute setting of VF requiring defibrillation, isoproterenol was shown to be effective in suppressing the episode.[96] ICD is a class 1 recommendation in patients with ERS who are survivors of SCD.[97]

Acquired Channelopathies

Acquired channelopathies are common, with advanced heart failure being an important cause affecting the expression of ion channels regardless of the primary etiology.[98] There is downregulation of I_{To} and I_{K1} causing QT prolongation, possibly an adaptive response allowing a longer interval for excitation-contraction. Yet it predisposes to inhomogeneous repolarization, early afterdepolarizations, and triggered arrhythmias. There is also upregulation of the Na^+/Ca^{2+} exchanger—responsive in part to downregulation of the sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA2a)[99]—yielding larger $I_{Na/Ca}$, also predisposing to delayed afterdepolarizations and triggered arrhythmias.

An increasingly important mechanism of acquired channelopathies is the use of drugs that prolong the QT interval; most of them are associated with drugs that block I_{Kr}, which is carried by subunits of the human ether-á-go-go *(HERG)* gene.[100] The list is long and includes antiarrhythmic and non-antiarrhythmic drugs. The University of Arizona's Health Sciences Center maintains a list of drugs categorized based on their potential to induce torsades de pointes (available at www.crediblemeds.org) and includes drugs with known risk, drugs with possible risk, drugs with conditional risk, and drugs to avoid in congenital LQTS.

The importance of drug-induced LQTS has mandated pharmaceutical companies to screen early in the process of drug development, mostly for effects on the *HERG* gene product.[100]

Other Conditions

The QT interval may be prolonged by cocaine abuse, organophosphate compounds, subarachnoid hemorrhage, stroke, myocardial ischemia, fasting using liquid protein–modified diets, autonomic neuropathy, and human immunodeficiency virus disease.[101–105] Electrolyte abnormalities can not only prolong but also shorten the QT interval. Some of these conditions and others not associated with channelopathies are discussed next.

Electrolyte Abnormalities

Electrolyte abnormalities rarely precipitate but often contribute to VTs, mostly in relation to abnormalities in serum K^+, Mg^{2+}, and Ca^{2+}.[106]

Hypokalemia (serum K^+ <3.5 mM) makes the resting membrane potential more negative, rendering cells less excitable and reducing the firing rate of pacemaker cells. Hypokalemia also prolongs the QT interval and flattens the T wave,[10] consequent to a dependency of I_{kr} conductivity on the square root of extracellular K^+ and resulting in a prolongation of repolarization at lower serum K^+, an effect more pronounced in the mid-myocardial region (greater I_{Kr}/I_{ks} ratio).

Hyperkalemia (serum K^+ >5.5 mM) makes the resting membrane potential less negative, rendering cells more excitable. By increasing I_{Kr}, hyperkalemia accelerates repolarization and shortens the action potential, explaining the characteristic peaked and tall T waves. With severe hyperkalemia, the rise rate of *phase 0* is reduced, slowing conduction and leading—at very high serum K^+ levels—to widespread blocks (i.e., widened P waves and widened QRS interval). A very rapid serum K^+ rise can precipitate VF, probably by reentry after developing areas of conduction block.

Mg^{2+} is a cofactor of the Na^+/K^+ pump and hence important for maintaining intracellular K^+ and the resting membrane potential. Mg^{2+} also modulates the effects of various K^+ and Ca^{2+} channels. Hypomagnesemia is associated with QT prolongation and increased risk of ventricular arrhythmias. This effect is usually compounded by other electrolyte deficits, including hypokalemia and hypocalcemia.

Serum Ca^{2+} is also important. Hypocalcemia increases the QT interval—predisposing to VT—whereas hypercalcemia exerts the opposite effects, reducing the QT interval. Changes in intracellular calcium contribute to arrhythmias associated with acute ischemia and reperfusion and may be important in the genesis of VT induced by exercise and by digitalis.

Hypothermia

Moderate (32°C–35°C) and severe (<32°C) hypothermia can predispose to VTs by QT prolongation and QT dispersion.[107] Typically, patients with hypothermia develop J waves (also known as *Osborn waves*) in the ECG, which reflect accentuation of the inhomogeneity of repolarization caused by the predominant distribution of I_{To} in subepicardial and mid-myocardial regions.[108]

Hypoglycemia

Acute hypoglycemia can trigger VT and VF in patients with diabetes mellitus.[109] The mechanism involves QT prolongation by direct suppression of repolarizing K^+ currents. In addition, the neuroendocrine stress response to hypoglycemia, via release of catecholamines, favors intracellular Ca^{2+} entry and reduction in serum K^+, further compounding the risk, especially in patients with coronary artery disease, acute myocardial infarction, left ventricular hypertrophy, autonomic neuropathy, congestive heart failure, and those taking medications that prolong the QT interval.

Arrhythmogenic Right Ventricular Cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is characterized by progressive replacement of the right ventricular muscle cells

by fibrous tissue and fat.[110] ARVC may be familial with autosomal dominant inheritance.[111] Patients present with palpitations and syncope, and this is an important cause of sudden cardiac arrest in subjects younger than 35 years, especially when related to exercise.[112]

The ECG is abnormal in 90% of cases, showing T-wave inversions beyond lead V_1 and epsilon waves in leads V_1–V_3. The QRS complex may be widened (>110 ms), with complete or incomplete right bundle branch block morphology. There are ventricular premature beats with left bundle branch configuration.

CLINICAL DIAGNOSIS

The first element to recognize is wide QRS complexes. They may indicate an origin in ventricular tissue; however, supraventricular ectopic activity can produce wide QRS complexes in the presence of preexistent or rate-dependent bundle branch blocks or aberrant pathways. The diagnostic clue is dissociation from atrial activity, which is often difficult to establish, having to rely on other indirect features, as discussed later. Ventricular arrhythmias present in several forms.[113]

Premature Ventricular Contractions

Premature ventricular contractions (PVCs) are isolated ventricular ectopic beats. The QRS is typically wide with opposing T-wave polarity and a full compensatory pause. PVCs may present one after each normal QRS in the form of bigeminy and also as couplets (two consecutive PVCs).

Ventricular Tachycardia

VT is defined as three or more consecutive ventricular ectopic beats with a rate typically greater than 100 bpm, often ranging between 130 and 170 bpm. QRS complexes are 120 ms or longer. However, wide QRS complex tachycardias can also be supraventricular when the impulse originates above the bifurcation of the His bundle but is conducted with aberrancy (see later).[114] VTs are classified as *monomorphic* if all QRS complexes have similar morphology and *polymorphic* if they have variable morphology. VTs are considered *nonsustained* if they last less than 30 seconds and *sustained* if they last 30 seconds or longer.

Nonsustained VTs are rarely symptomatic but are an independent risk factor for sudden cardiac death in patients with severe congestive heart failure.[115] Most sustained VTs present with palpitations, chest discomfort, and weakness or with more severe symptoms such as dizziness, angina, syncope, seizures, and even SCD.

Monomorphic Ventricular Tachycardia

Monomorphic VTs are the most common type of VTs and are usually associated with structural heart disease. The mechanism is commonly reentry operating within or around damaged myocardium. Examination of the jugular veins may show cannon A waves, indicative of AV dissociation.

A standard 12-lead ECG reveals a wide-complex tachycardia with regular complexes of similar morphology. A representative tracing is shown in Fig. 72.6. Establishing the diagnosis requires excluding the possibility of supraventricular tachycardia (SVT) with aberrancy. It is appropriate to assume that a wide-complex tachycardia is VT until proven otherwise in patients with myocardial ischemia, heart failure, and hemodynamic instability. SVT with aberrancy should be suspected if there is a history of previous aberrant rhythms, accessory pathways, and baseline or rate-induced bundle branch block. The ECG should be examined for evidence of AV dissociation (i.e., P waves and QRS complexes at uncoupled rates), which is specific for VT. Use of an esophageal lead could be useful by amplifying atrial potentials.

Some special forms of VT tend to be mistaken for SVT with aberrancy.[116] These include bundle branch reentrant tachycardia, in which the impulse travels down the right bundle branch, across the interventricular septum, and up the left bundle branch.[117] The morphology resembles SVT with left bundle branch block (LBBB) and is common among patients with nonischemic dilated cardiomyopathy.[118] Right ventricular outflow tract tachycardia is another condition caused by triggered activity from delayed afterdepolarizations that most commonly originate in the right ventricular outflow tract.[119] The tachycardia usually presents with LBBB morphology and right axis deviation. Right ventricular outflow tract tachycardias occur in structurally normal hearts, typically in young individuals, and are responsive to verapamil or adenosine.[120] Finally, there are fascicular tachycardias that originate from either fascicle of the left bundle branch. They occur in structurally normal hearts, mimic SVT with aberrancy, and are responsive to beta-blockers and verapamil.[121]

ECG algorithms are available to help differentiate VT from SVT. A widely accepted four-step algorithm was developed by Brugada and colleagues in the early nineties and reported to have 98.7% sensitivity and 96.5% specificity for VT.[122] However, more recent studies found the Brugada criteria to have lower sensitivity and specificity when used by emergency department physicians and cardiologists.[123] Vereckei and

Fig. 72.6 ECG tracing (leads II, III, and V_1) showing couplets followed by an 11-beat episode of nonsustained monomorphic ventricular tachycardia.

colleagues proposed a simpler criteria based on analysis of aVR and reported greater sensitivity and specificity.[124] The aVR lead is useful because in normal sinus rhythm and in SVTs, the ventricular activation wavefront moves away from aVR, typically yielding a QS complex and not an R wave, which is the step 1 criterion in the new algorithm (Fig. 72.7).

Polymorphic Ventricular Tachycardia

Polymorphic VTs have irregular rhythms, usually compromise hemodynamic function, and may quickly degenerate into VF. Variation in QRS morphology represents changes in the electrical axis. One special form of polymorphic VT is torsades de pointes. This is a descriptive term denoting a rotating electrical axis in 180 degrees along an imaginary axis ("twisting points"); it is typically associated with LQTS. Representative tracings are shown in Fig. 72.8.

Accelerated Idioventricular Rhythm

Accelerated idioventricular rhythm (AIVR) is a form of automatic ventricular arrhythmia characterized by regularly wide QRS complexes with a rate between 50 and 120 bpm. It is often slightly faster than the underlying sinus rhythm. AIVR does not produce symptoms, and the treatments for VT do not apply.[125] Its presence may indicate underlying myocardial ischemia.

Ventricular Fibrillation

VF is recognized by the abrupt onset of irregular waveforms of varying contour, duration, and amplitude without identifiable QRS and T waves accompanied by the ability of the heart to generate blood flow precipitating unconsciousness within seconds. VTs or SVTs that conduct through accessory pathways (e.g., Wolff-Parkinson-White syndrome) may be the initiating rhythm. Generalized seizures and agonal breathing may follow.

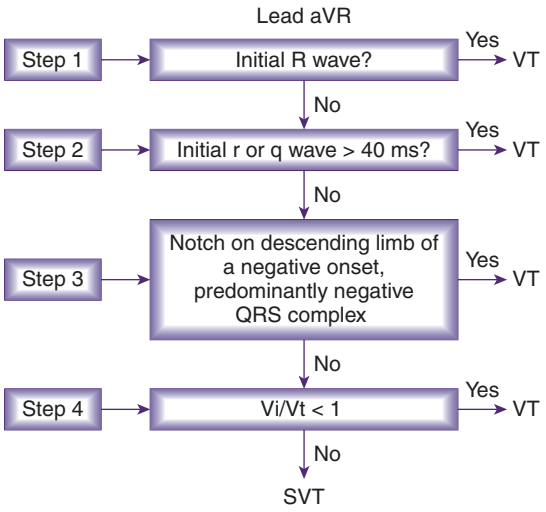
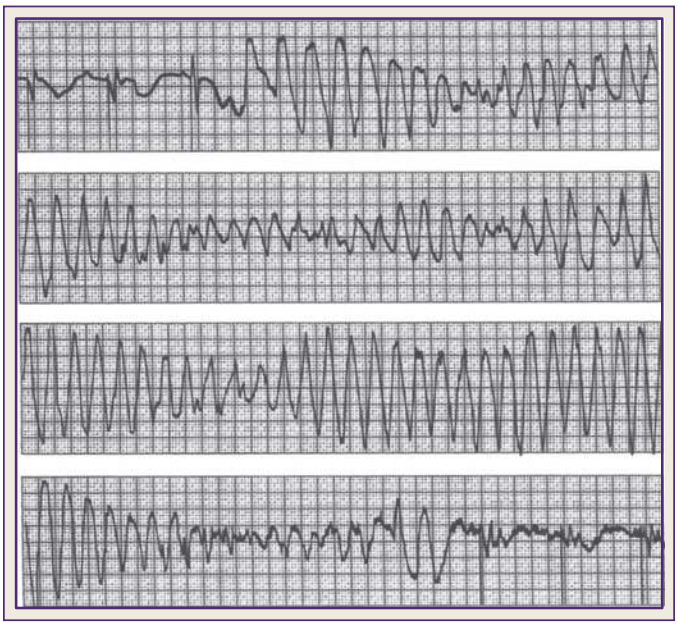


Fig. 72.7 aVR algorithm for distinguishing wide-complex monomorphic ventricular tachycardia (*VT*) from supraventricular tachycardia (SVT). VT is diagnosed whenever the analysis of aVR yields a positive answer to each successive step. In step 4, Vi and Vt refer to ventricular activation velocity measured as the vertical excursion (in millivolts) during the initial (*Vi*) and terminal 40 ms (*Vt*) of the QRS complex. When the initial or terminal 40 ms displays both positive and negative deflections, the sum of their absolute values (disregarding polarity) is used to calculate Vi and Vt, with the ratio Vi/Vt determining whether the rhythm is VT or SVT. (From Vereckei A, Duray G, Szenasi G, et al. Application of a new algorithm in the differential diagnosis of wide QRS complex tachycardia. *Eur Heart J.* 2007;28:589–600.)

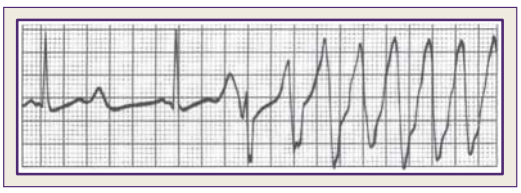
ACUTE MANAGEMENT

PVCs and episodes of nonsustained VT are of little hemodynamic significance in the structurally normal heart and may occur associated with the use of stimulants, electrolyte abnormalities, hypoxemia, catecholamine discharge, and medications, to name a few conditions. The management should focus on removing contributing factors. The risk of progression to sustained VT is low. Even the notorious R-on-T phenomenon has been shown to be of prognostic significance for development of VF only in patients with a predisposing substrate such as Brugada syndrome.[126] Antiarrhythmic drugs are typically not required. Persistence of nonsustained VT after an episode of critical illness should prompt assessment of underlying cardiac substrate and possible triggers.

The management of sustained VTs requires concurrent diagnostic and therapeutic interventions.[83] This is particularly the case in pulseless VT, polymorphic VT, and VF, when delivery of unsynchronized electrical shocks and advanced cardiac life support should be instituted without delay. In less urgent situations, treatment should focus on identifying the



A



B

Fig. 72.8 Torsades de pointes. **A,** Patient with a demand ventricular pacemaker developed QT prolongation (≈640 milliseconds, seen during paced rhythm) after treatment with amiodarone for recurrent ventricular tachycardia (VT). An episode of torsades de pointes developed that spontaneously terminated with resumption of a paced ventricular rhythm. **B,** Tracing from a young boy with congenital long QT syndrome and marked prolongation of the QTU interval (≈600 milliseconds). TU alternans is noted before a late premature complex, occurring on the downslope of the TU wave, which initiates an episode of VT. (From Braunwald E, Zipes D, Libby P, eds. *Heart Disease: A Textbook of Cardiovascular Medicine,* 6th ed. Philadelphia: Saunders; 2001:868.)

substrate and the triggering events. Arrhythmogenic conditions commonly present in critically ill patients include hemodynamic and respiratory abnormalities, endogenous or exogenous adrenergic states, acid-base and electrolyte imbalances, presence of proarrhythmic drugs, prolongation of the QT interval, ongoing myocardial ischemia, and mechanical stimulation of cardiac structures. Often, the treatment of these factors suffices to terminate the arrhythmic episode. Specific antiarrhythmic interventions should take into consideration the type of rhythm and the degree of hemodynamic stability.

Ventricular Arrhythmias With Preserved Blood Flow

Monomorphic Ventricular Tachycardia

Direct-current synchronized cardioversion and IV antiarrhythmic agents are acceptable first-line options. Antiarrhythmic agents have the advantage of having a persistent effect after termination of the event and that anesthetic agents are not required; however, patients may experience adverse effects, including hypotension and increased susceptibility to arrhythmias, given that most agents cause QT prolongation.

The American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) 2017 guidelines for management of patients with ventricular arrhythmias[83] recognize various drugs available in IV formulation for VT, including beta-blockers, sotalol, lidocaine, and amiodarone, with availability contingent on the specific country. Close monitoring is recommended, as IV procainamide can cause transient hypotension,[127] especially in patients with severe left ventricular dysfunction. For patients with sustained monomorphic VT who are hemodynamically unstable, are refractory to electrical shocks, or have recurrent episodes despite procainamide or other agents, IV amiodarone is considered a reasonable choice.[128,129] The initial effect of amiodarone is to slow down AV nodal conduction and block adrenergic stimulation. However, effects on ventricular conduction and refractoriness develop more gradually, achieving the maximal effect only after weeks or months of treatment.[130,131]

When sustained monomorphic VTs are associated with an acute ischemic substrate (i.e., unstable angina or myocardial infarction), lidocaine is considered a reasonable initial choice.[132] Calcium channel blockers such as verapamil and diltiazem should not be used to terminate wide-QRS-complex tachycardia of unknown origin, especially when myocardial dysfunction is present.

Addition of a second antiarrhythmic agent is discouraged to avoid compounding proarrhythmic effects. Thus a single agent should be used and proceed to direct-current synchronized electrical cardioversion if optimal dosing fails.

Direct-current synchronized cardioversion should be considered first-line treatment in patients who are unstable or in those with borderline blood pressure who could experience further deterioration by the vasodilator and antiinotropic effects of antiarrhythmic agents. Monophasic waveform electric shocks at an initial energy of 100 J or higher are effective, with comparable or lower energy levels expected to be effective using biphasic waveform electric shocks. Transvenous pacing with override pacing can terminate monomorphic VT and should be considered in instances of failed cardioversion or frequent recurrence despite antiarrhythmic medication.

Ventricular Arrhythmias With Cessation of Effective Blood Flow

Cessation of blood flow occurs with pulseless VT, VF, and polymorphic VT. The immediate priority is to reestablish an organized electrical activity with mechanically competent pump function, typically requiring the unsynchronized delivery of electric shocks, with cardiopulmonary resuscitation contingent on the duration of the arrhythmia and the response to electrical shocks.

Ventricular Fibrillation and Pulseless Ventricular Tachycardia

Current resuscitation algorithms consider VF and pulseless VT as rhythms requiring delivery of electric shocks upon their recognition through an automated external defibrillator or through manual defibrillators along with quality chest compressions. If VT/VF persists after the third shock, IV amiodarone is recommended.[133] The energy level of the initial electric shock depends on the specific device. For biphasic waveform defibrillators, the energy level typically ranges from 150 to 200 J. The specific energy level should be selected based on the manufacturer's specification. If the available defibrillator uses monophasic waveforms, the energy level should be 360 J. The probability of survival after VF and pulseless VT is inversely related to the time elapsed between the onset of the arrhythmia and the delivery of electric shocks and the quality of cardiopulmonary resusciation.[134]

Electrical storm is a rather uncommon but highly lethal phenomenon defined as recurrent episodes of VF occurring mainly during an acute myocardial infarction, and conventional antiarrhythmic drug therapy—including lidocaine and procainamide—often fails to secure a stable sinus rhythm.

Polymorphic Ventricular Tachycardia

Polymorphic VT with cessation of effective blood flow is treated as VF with unsynchronized shocks at the same energy as for VF. As with all ventricular arrhythmias, substantial effort must be directed at identifying and correcting the causes.

Polymorphic VT with a normal QT interval is most frequently associated with acute myocardial ischemia but also with cardiomyopathies, idiopathic polymorphic VT, and catecholaminergic VT. In this setting, use of IV beta-blockers[135] or IV amiodarone[136] is effective. Coronary angiography should be considered for recurrent polymorphic VT when ischemia is suspected.[137]

Polymorphic VT with prolonged QT interval is usually associated with bradycardia. The management includes discontinuation of drugs that prolong the QT interval, correction of electrolyte abnormalities, and avoidance of catecholamines. In the setting of congenital LQTS, beta-blockers (or sympathetic interruption), pacing, and implantation of an ICD should be considered. In the acquired forms of LQTS, IV magnesium, overdrive pacing, and beta-blockers after pacing are recommended interventions, with recent work suggesting the potential for treatment through gene therapy.[138,139]

CONCLUSION

VTs are important and common manifestations of cardiac and extracardiac abnormalities in critically ill patients. In addition to the traditional assessment based on ECGs and hemodynamic manifestations, understanding and recognizing the processes that affect ion channels, pumps, exchangers, and signaling mechanisms are important for proper management. There is also increased awareness that mutations affecting cardiac channels are prevalent and clinically relevant. The intensivist should be alert and prepared to identify them and provide the necessary initial treatment and referral when appropriate. Initial enthusiasm for antiarrhythmic agents has diminished as the pro-arrhythmic effects of various compounds have become evident. Some drugs are no longer recommended as first-line agents, whereas others have become components of accepted algorithms. More emphasis is currently being placed on understanding arrhythmogenic mechanisms and on correcting the precipitating and maintaining factors.

KEY POINTS

- Hereditary and acquired abnormalities in cardiac ion channels can alter the action potential, mostly by prolonging repolarization, and predispose to VTs, especially torsades de pointes.
- Ventricular arrhythmias are the result of abnormalities in impulse generation (automaticity and triggered activity) and impulse conduction (reentry).
- Proper management of VTs requires assessment of precipitating and sustaining conditions; often, the removal of these conditions is all that is needed.
- A long QT interval in the baseline ECG should prompt a diligent search for possible drugs, metabolic abnormalities, or hereditary channelopathies.
- VTs in critically ill patients are often precipitated by cardiac, metabolic, and respiratory processes.
- AV dissociation is a reliable sign that a wide-complex tachycardia is ventricular; this may be evident on the surface 12-lead ECG or after analyzing an esophageal lead.
- Direct-current synchronized cardioversion should be considered first-line treatment in patients with VT who are hemodynamically unstable or have heart failure.

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Conduction Disturbances and Cardiac Pacemakers

Lorenzo Pitisci, Georgiana Bentea, Ricardo E. Verdiner, and Ruben Casado-Arroyo

CONDUCTION DISTURBANCES

Patients admitted to the intensive care unit (ICU) frequently have conduction disturbances because of their acute medical condition or underlying risk factors. The clinical manifestation varies broadly from asymptomatic to life-threatening events. Locating and understanding the conduction disturbances are vital to stratifying the patient's risk and choosing the best medical or invasive therapy option.

Normal Cardiac Conduction

Depolarization of the myocardium begins spontaneously from a specialized group of cells forming the sinoatrial (SA) node located in the superior and posterior portion of the right atrium (RA). They are regulated by the sympathetic and parasympathetic nervous system. The activity of the cells cannot be seen on a surface electrocardiogram (ECG).

SA depolarization spreads through the right then left atrium, resulting in the P wave seen on the surface ECG. Because the atria and ventricles are electrically isolated, the impulse must travel through the atrioventricular (AV) node, located in the lower part of the atrial septum and regulated by the sympathetic and parasympathetic nervous system as well, to generate the PR interval on ECG.

The impulse is transmitted to the ventricles through the bundle of His, dividing into right and left bundle branches to finally diffusely ramify to form the Purkinje network, resulting in the QRS wave on ECG. The ventricular repolarization can be observed as the T wave on ECG. The atria repolarization is hidden by the ventricular depolarization (QRS).

Bradycardia

Bradycardia is defined as a heart rate (HR) <60 bpm. It can be divided into two categories: sinus node dysfunction (SND), when the rate of impulses arising from the SA node is lower than expected, and AV block, when there is failure to propagate the impulse from the atrium to the ventricle. SND and AV block share common etiologies and may be present at the same time. Nevertheless, their prognosis and treatment are not the same. A high-quality 12-lead surface ECG is mandatory to help differentiate them. Etiologies of bradyarrhythmia are listed in Table 73.1.

Sinus Node Dysfunction

SND refers to a number of conditions causing symptoms and inappropriate atrial rates (bradycardia, sinus pauses, and sinus arrest).[1-4] Symptoms could include weakness, chronotropic incompetence (inability to reach a targeted heart rate), palpitations, and syncope. The mechanism is either an inner pacemaker defect or an SA block (Table 73.2). Degenerative age-related SA fibrosis is the main cause of SND, affecting patients in their seventies and eighties. The fibrotic process, however, is not just limited to the SA. SND is often associated with AV node fibrosis as well. Patients with symptoms attributable to SND have a higher risk of cardiovascular events, including syncope, atrial fibrillation, and heart failure (HF). Moreover, the development of chronotropic incompetence with age is associated with an increased risk of cardiovascular death and overall mortality. Usually, SND is chronic and the result of irreversible causes. Even when clinical presentation is acute and potentially reversible, as in acute myocardial infarction, electrolyte/metabolic disturbances, dysthyroidism, and iatrogenesis (e.g., beta-blocker [BB] use), symptoms are typically mild, stable, and generally do not require therapy apart from correcting the metabolic disturbances and stopping the medication that generated the syndrome. In brady-tachy syndrome (a variant of SND), SND is responsible for pauses after termination of atrial tachyarrhythmia and often needs either invasive ablation of the arrythmia, permanent pacing, or both. Table 73.3 shows a description of the different etiologies of SND.

Atrioventricular Block

AV block encompasses all possible lesions, congenital or acquired, that may interrupt or delay the normal propagation of the sinus node impulse to the ventricles. The most common cause is degenerative. Congenital (Fallot, transposition of the great arteries, etc.) and systemic disorders (amyloidosis, Fabry disease, etc.) are rarer nonreversible etiologies (Table 73.4). As block level and position are associated with different prognoses and therapeutic options, locating block sites helps in understanding the mechanism and stratifying the patient's risk. AV node location (supra-Hisian) is characterized by a slower progression of the disease and a more sustained and reliable junctional escape mechanism with better response to chronotropic drugs (atropine, isoproterenol). On surface ECG, the QRS complex is usually thin. In contrast, intra- and infra-Hisian AV blocks are characterized by a broader QRS complex (>120 ms), poorer prognosis, faster progression, less reliable junctional escape mechanism, and poor or paradoxical response to chronotropic drugs. Some clinical maneuvers can help to identify the level of the disease. Carotid sinus massage, which increases the vagal tone and slows the sinus rate and conduction through the AV node, would further deteriorate nodal block. It may improve the infra-Hisian block by improving the His-Purkinje conduction of slower sinus beats. Atropine, isoproterenol, and exercise would improve a supra-Hisian block but would deteriorate an infra-Hisian block.

AV blocks are also categorized according to a three-degree scale. In first-degree AV block (BAV 1°), every P wave is conducted to the ventricles with an increased conduction delay (PR >200 ms) (Fig. 73.1A). BAV1° is usually asymptomatic and requires no treatment.

TABLE 73.1 Etiologies of Bradyarrhythmias

Intrinsic	Extrinsic
Idiopathic (aging) degeneration	Exaggerated vagal activity: vasovagal, situational, carotid sinus hypersensitivity
Ischemic heart disease	Drug effects: antiarrhythmics, digoxin, clonidine, opioids, lithium, dexmedetomidine
Infiltrative heart disease: sarcoidosis, amyloidosis, hemochromatosis	Electrolyte disturbances: hyperkalemia
Vasculitis because of collagenopathies: rheumatoid arthritis, systemic lupus erythematosus	Hypothyroidism
Infective heart disease: myocarditis, endocarditis, Lyme disease, Chagas disease	Hypothermia
Surgical trauma: catheter ablation procedures, valve replacement (including transcatheter aortic valve implantation)	Hypoxia
Congenital diseases	Increased intracranial pressure
Myopathies (Dannon disease)	

TABLE 73.2 Types of Sinus Node Dysfunction

	Sinus Bradycardia	Sinus Pause/Arrest	Sinus Node Exit Block	Bradycardia-Tachycardia Syndrome
Definition and pathogenesis	SA node discharges at rates inferior to the physiologic needs of the individual.	No spontaneous SA node impulse formation (automaticity) longer than 3 sec (85% of such cases are symptomatic).[5]	First-degree SA exit block reflects a conduction delay of the SA impulse in the perinodal region Second-degree SA exit block is a periodic failure of the sinus impulse to exit the sinus node. Mobitz I (Wenckebach) when the SA node discharges at a constant rate with progressive prolongation of conduction within the perinodal area (hence electrical impulses reach the atrial myocardium with a progressive delay). Mobitz II includes the failure of multiple impulses to exit the sinus node. Third-degree SA exit block reflects a complete conduction block in the SA junction.	Alternating paroxysms of regular or irregular atrial tachyarrhythmias and sinus node dysfunction. The syndrome occurs in more than 50% of individuals with SA node dysfunction.[6]
ECG patterns	Sinus rhythm of less than 60 bpm, 40–50 bpm in athletes and healthy young individuals.[7]	The absence of P waves with sinus pause, which is not equal to the sum of PP intervals.	First-degree SA exit block cannot be identified on a regular ECG. It can be observed during direct electrophysiologic recording by measuring SA conduction time. Second-degree SA exit block: Mobitz I (Wenckebach) is characterized by a progressive shortening of the PP interval until block occurs with a pause of less than two times the shortest PP interval. Mobitz II is characterized by constant PP intervals and a pause that equals the sum of PP intervals. Third-degree SA exit block cannot be accurately distinguished from sinus arrest in the surface ECG.	Alternating sinus pauses with episodes of paroxysmal AF, atrial flutter, or re-entrant atrial tachycardias.

AF, Atrial fibrillation; *ECG,* electrocardiogram; *SA,* sinoatrial.

In second-degree AV blocks (BAV 2°), some P waves are not conducted to the ventricles. BAV 2° are divided into two types:

1. Mobitz I is defined by a progressively longer PR period on consecutive beats, ultimately followed by a blocked P wave. The next PR period is then reset to the shortest duration and it repeats (Wenckebach conduction). The block location is usually nodal (72%) (see Fig. 73.1B).
2. Mobitz II does not follow the same scheme and preserves a certain degree of P-wave conduction (see Fig. 73.1C). The block location is usually intra-Hisian (20%) or infra-Hisian (80%).

The clinical presentation of first-degree AV block is usually benign and only very rarely are symptoms felt to be directly related to first-degree AV block. There are no signs or symptoms that are either sensitive or specific for first-degree AV block.

Most patients with high AV block will present with some degree of symptoms, though the severity of the symptoms can be quite variable. Symptoms in high AV block (Mobitz II) may include fatigue, dyspnea, chest pain, presyncope, syncope, Stokes-Adams attack, and sudden cardiac arrest.

The P:R ratio is used to describe how many P and QRS waves are contained in one repetitive block. The higher the ratio, the more severe the block. A case of 2:1 BAV 2° can be particularly challenging to determine whether it is Mobitz type I or II.

High-degree or high-grade blocks refer to more than two consecutive nonconducted P waves without a complete loss of AV conduction

TABLE 73.3 Etiologies of Sinus Node Dysfunction

Congenital Sinus Node Dysfunction Long QT syndrome, Brugada syndrome, congenital heart disease, noncompaction cardiomyopathy
Acquired Sinus Node Dysfunction Myocardial ischemia
Infective heart disease
Dengue fever, Chagas disease, encephalitis, endocarditis, Legionnaires disease, typhoid, diphtheria, rheumatic carditis
Autoimmune diseases
Systemic lupus erythematosus, systemic sclerosis
Infiltrative diseases
Hemochromatosis, cardiac lipomatosis, amyloidosis
Endocrine disease
Hypothyroidism, hyperthyroidism, hyperparathyroidism, phaeochromocytoma
Autonomic dysfunction
Carotid hypersensitivity syndrome, athletic training, intracranial hypertension
Drugs
Antiarrhythmics, digitalis, ticagrelor, lacosamide, carbamazepine, lithium, ropinirole, ranitidine, clonidine, diphenylhydantoin
Iatrogenic
Cardiac surgery procedures, especially for congenital pathologies
Radiofrequency catheter ablation of arrhythmias
Percutaneous coronary intervention: right coronary artery stent implantation because of iatrogenic occlusion of sinus node artery

TABLE 73.4 Etiologies of Reversible Conduction Disturbances

Electrolyte disturbances	Hyperphosphatemia or hypophosphatemia
	Acidosis
	Hypoglycemia
Hypoxemia/hypercapnia	Sleep apnea, alcohol and/or drug abuse
Ischemia	Acute myocardial infarction
Heart surgery	Maze procedure
	Valve replacement
Infectious	Lyme disease
	Acute rheumatic fever
	Diphtheria, *Legionella*, psittacosis, typhoid fever, *Listeria*, malaria, leptospirosis, dengue fever
	Viral syndrome
Dysthyroidism	Hypothyroidism
Hypervagotonia	Stress, pain, carotid compression, other
Drugs	Beta-blockers
	Non-dihydropyridine calcium channel blockers
	Digoxin and antiarrhythmic drugs
	Lithium, methyldopa, risperidone, cisplatin, interferon
Autoimmune disease	Sarcoidosis, ankylosing spondylitis, rheumatoid arthritis, scleroderma, lupus

(Fig. 73.2). These latter types are more intra- or infra-Hisian and associated with a poorer prognosis.

In cases of acute myocardial infarction, acute AV blocks secondary to right or circumflex coronary artery (responsible for AV and His bundle vascularization in most of the cases) occlusion are usually nodal and associated with a good prognosis and rapid recovery. Those

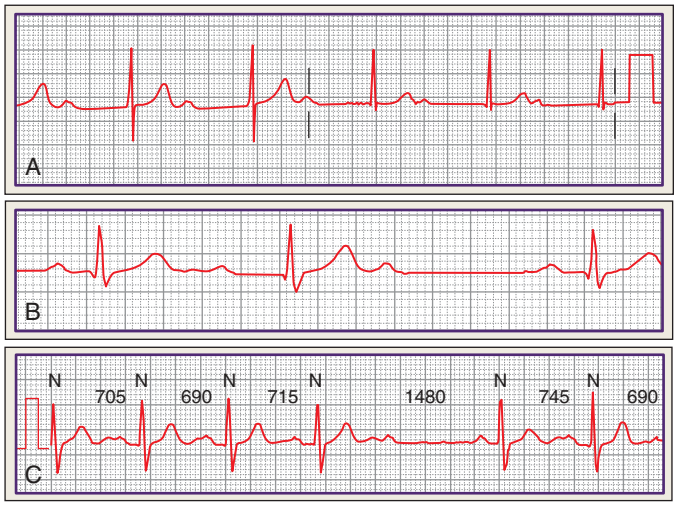

Fig. 73.1 Atrioventricular Block. A, Electrocardiogram from a patient with first-degree atrioventricular block. The PR interval is approximately 290 milliseconds. All P waves are being conducted to the ventricles. The PR interval is constant. **B,** Electrocardiogram rhythm strip from a patient with second-degree atrioventricular block type I. Note progressive prolongation of the PR interval until failure of conduction occurs. The pattern of conduction is 3:2. **C,** Electrocardiogram demonstrating second-degree atrioventricular block type II. The PR interval is constant before and after the blocked P waves. The QRS complex is widened.

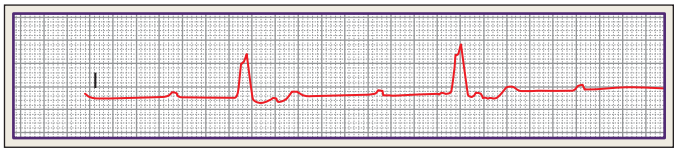

Fig. 73.2 Complete Heart Block. The PR intervals are irregular because the ventricles and atria represent two independent sources of depolarization.

secondary to left anterior descending artery (LAD) occlusion (responsible for right and left anterior bundle brunch vascularization) are associated with a poorer prognosis (infra-Hisian location) and fatal ventricular arrythmia.

Laboratory testing. Measurements of electrolytes, glycemia, pH, renal function, thyroid function, and Lyme serologic testing (if clinical suspicion of Lyme carditis) should be performed in any acute bradyarrhythmia, as they are common and reversible causes that can be treated promptly with possible normalization of conductance disturbances.

Imaging in patients with conduction disorder. Conduction disturbances are encountered in a wide range of cardiovascular and systemic disease with very different prognoses and treatments. Assessment of heart structure and function is highly useful in order to exclude cardiomyopathies, valvular heart diseases, tumors, infections (endocarditis with abscess formation), congenital anomalies, infiltrative processes, great vessel disease, and pericardial diseases. Except for sinus bradycardia and first-degree AV block with no evidence of structural heart disease, it is recommended to perform a transthoracic echocardiography. This is especially true in newly identified left bundle branch block (LBBB; patients with LBBB have a higher prevalence of both noncardiovascular and cardiovascular comorbidities, including structural heart disease),[8] AV block Mobitz II, and high-grade AV block. Magnetic resonance imaging (MRI) can be helpful in diagnosing an infiltrative or dilated cardiomyopathy. Cardiac computed tomography (CT) is helpful for the assessment of valve calcification and coronary artery disease.

Acute medical therapy for bradycardia. The initial management of the patient with AV block depends on the presence and severity of any signs and symptoms related to the ventricular rate (Fig. 73.3). Unstable patients may require pharmacologic therapy and, in some cases, should also receive temporary pacing to increase heart rate and cardiac output. Once the patient is hemodynamically stable, assessment and treatment for any potentially reversible causes should occur, followed by placement of a permanent pacemaker for patients without an identifiable reversible etiology.

Regarding the pharmacologic therapy, atropine should be used in patients with symptomatic bradycardia or hemodynamic (HD) compromise with SND except in patients with heart transplant, in which paradoxical heart block is observed.[9,10] Isoproterenol may be used in symptomatic bradycardia/HD compromise with SND, but there are no data to either support or discourage its use in sinus bradycardia.[7,10,11]Atropine should be used in patients with symptomatic bradycardia or HD compromise with second- or third-degree AV block with caution when the block location is thought to be intranodal or infranodal because of paradoxical worsening of conduction.[7] Isoproterenol may be used in patients with symptomatic bradycardia or HD compromise with second- or third-degree AV block if the likelihood of myocardial ischemia is low.

Calcium channel blocker– or beta-blocker–induced SND and/or AV block. Patients with bradycardia-induced symptoms or hemodynamic instability caused by BBs, calcium channel blocker (CCB) overdose, or high-dose insulin therapy should be given glucagon intravenously to increase heart rate and to improve symptoms. Only if bradycardia is the result of CCB therapy should intravenous (IV) calcium be administrated to improve symptoms. Hypercalcemia is rare, but close monitoring is mandatory and central vein infusion is preferred. Hemodialysis

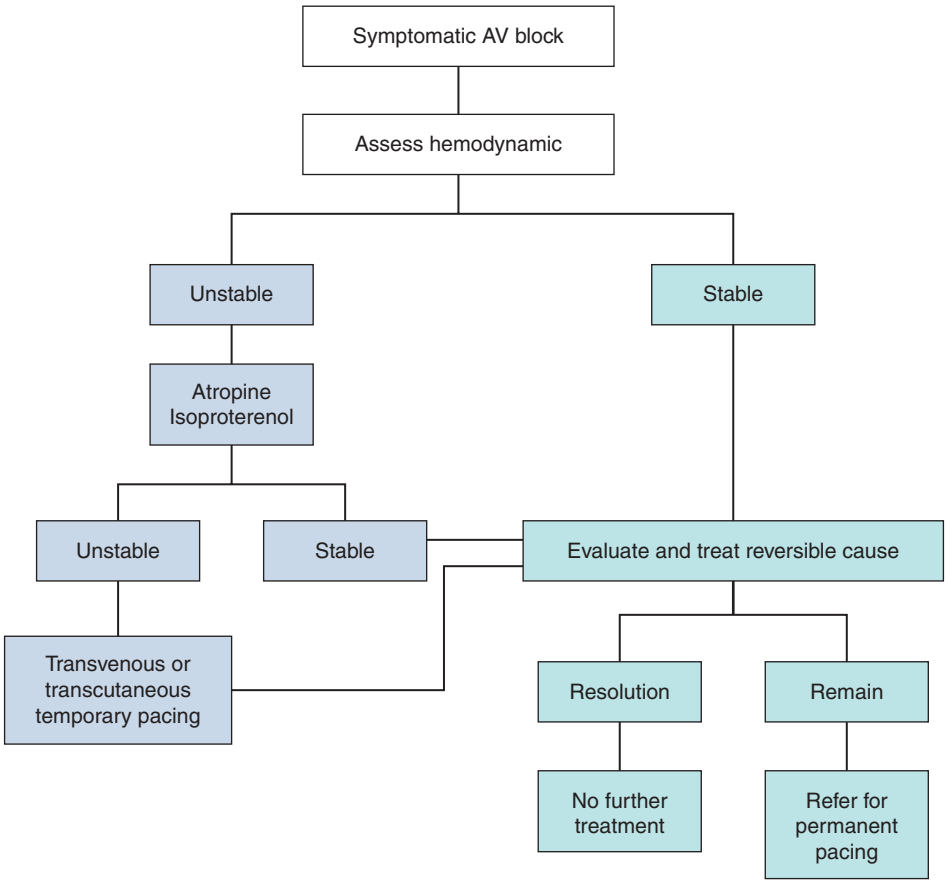

Fig. 73.3 Acute Management of Symptomatic Atrioventricular (*AV*) Block.

may be needed in specific circumstances, although this is uncommon. Given the low toxicity of these antidotes in relation to the severity and the low frequency of BB/CCB overdose, there are no randomized trials to support their use in clinical practice.

Digoxin overdose–induced SND and/or AV block. Bradycardia-induced symptoms or hemodynamic instability by digoxin overdose should be reversed with digoxin Fab antibody fragment. Observational studies have reported a clinical response within 30–45 minutes.[5,6,12] Bradycardia can be treated with atropine and hypotension with IV boluses of isotonic crystalloid in the meantime. Hemodialysis is not recommended. Potassium levels should be monitored. Adverse effects include HF, tachycardia, and hypokalemia; allergic reactions are rare.

Bradycardia in heart transplant and spinal cord injury. SND in the context of denervation after spinal cord injury or after heart transplant is challenging, as atropine may have a paradoxical effect.[9] Administration of oral theophylline was associated in two studies of 15 and 29 patients with increased HR >90 bpm. The evidence concerning aminophylline is less clear.

Patients with bradycardia-induced symptoms or hemodynamic instability with spinal cord injury should be given aminophylline or theophylline orally for 4–6 weeks to improve heart rate and symptoms.

Temporary pacing for bradycardia SND. Temporary pacing should be used for acute treatment of severe symptomatic bradycardia or ventricular arrythmia triggered during bradycardia with hemodynamic instability when medical treatment is failing. It can be delivered transcutaneously until an internal temporary right ventricular (RV) lead is inserted.

Permanent pacing for bradycardia. If all reversible causes of bradycardia are excluded and/or corrected, permanent pacing is considered. A large number of patients are treated with BBs or CCBs, and studies have shown that the withdrawal of these drugs rarely reversed the AV block and only delayed the permanent pacemaker insertion.[13–15] Because AV block secondary to sarcoidosis rarely recovers, many clinicians choose an early strategy to pacemaker implantation in these particular cases (Table 73.5).

Heart surgery and TAVI. Symptomatic and/or hemodynamic instability caused by SND and, most frequently, AV block are not rare after cardiac surgery. The aortic and tricuspid valves are located just next to the AV node and the mitral valve next to the bundle of His. Temporary epicardial leads are recommended during heart valve surgery. Permanent pacing is recommended after 5–7 days of persisting symptoms.

Transcatheter aortic valve implantation (TAVI) procedures are at high risk of periprocedural conduction disturbances requiring permanent pacing (12.6%–17.5% in recent registers).[16,17] The most robust preprocedural predictor is the presence of right bundle branch block (RBBB) (multivariable odds ratio: 2.8–46.7 times).[17] If there is no previous RBBB and no conduction changes peri- or post-procedure, the temporary pacemaker can be removed as early as the first 24 hours. If complete AV block or high-degree AV block occurs, permanent pacing is recommended.[17]

TABLE 73.5 Pacing Modes

Pacing Mode	Indication
VVI(R)	Symptomatic bradycardia and AV asynchrony (atrial tachyarrhythmia)
AAI(R)	Symptomatic sinus node dysfunction if AV node conduction preserved
DDD(R)	Symptomatic bradycardia and AV synchrony (i.e., SND and AV block)
DDI(R)	Idem DDD/DDDR and paroxysmal supraventricular tachycardia
DOO/VOO	Asynchrony mode (i.e., MRI mode)

A, atrial; *AV,* atrioventricular; *D,* A+V; *O,* no response to sensing; *I,* inhibition; *MRI,* magnetic resonance imaging; *SND,* sinus node dysfunction; *R,* responsiveness; *V,* ventricular.

CARDIAC IMPLANTED DEVICES

Permanent Pacing

Many patients have implanted cardiac devices such as pacemakers and defibrillators. These devices are made of one pulse generator containing the battery and one to three leads connected to the RA, RV, or left ventricle (LV) either through the endocardium or epicardium. Every pacemaker patient should have a card containing all information about the device (leads, brand, type, and implantation date). When the information is missing or incomplete, chest x-ray can be helpful to understand how many leads are present, if their integrity is preserved, and if their position is correct. An intracardiac leadless pacemaker can be implanted instead if there are potential hazards with using a conventional device. In a prospective multicenter study evaluating its implantation in 725 patients, 719 devices were deployed with success, with a 96% primary safety endpoint (complication rate was about 4%, with cardiac perforation/tamponade 1.6%, HF 0.9%, and fistula or aneurysm at puncture site 0.7%). No dislodgment was observed.[18] Specific brand controllers are available to modify parameters and retrieve information such as battery life, pacing threshold and sensitivity, and lead impedance.

Temporary Cardiac Pacing

About 20% of patients presenting with bradycardia in the emergency room will need temporary pacing.[10] In general, any patient with bradycardia causing symptoms or hemodynamic instability that is unresponsive to atropine ought to be considered for temporary pacing. These devices (transcutaneous or endocardial) are typically used transiently to compensate for an acute symptomatic bradycardia until it resolves or a permanent pacemaker can be placed.

Transcutaneous pacing was introduced in the 1950s.[19] Pacemakers pads are placed anteriorly (right upper chest and lateral to the apex of the heart) or in an anteroposterior position. The generator unit is typically set to 70 bpm, and the current is increased up to 40–80 mA for adults until the myocardium captures the signal at every beat based on continuous ECG monitoring and arterial pulse check. For safety, the current is then set 10 mA above the upper capture limit.[20,21]

Because of the sedation required and possible AV asynchrony, transcutaneous pacing is only used as a fast bridge to transvenous endocardial pacing. The latter is more stable and much better tolerated by patients. Using the Seldinger wire technique, an electrode catheter is inserted through a sheath in either the femoral, subclavian, or jugular vein. Under fluoroscopy and/or echo guidance,[22] the electrode is connected to a pulse generator pacing at maximum output at 70 bpm and advanced cautiously in the right ventricle. The device is positioned properly when the surface ECG shows 70 bpm paced with LBBB morphology, and the position is confirmed with a chest x-ray, fluoroscopy, or echo.

Adverse complications of endocardial pacing range from 14% to 40% and are linked to the extent of pacing[23,24]: venous thromboses, pulmonary emboli (femoral approach mostly), perforation, life-threatening arrythmia, loss of capture, and death. Because the electrode is passively applied against the endocardium, dislodgment is common (lateral head movement when introduced through the jugular approach as an example). Temporary pacing should be as short of

a duration as possible. Fewer complications were reported with jugular access and fluoroscopic or echo-guided lead placement.[22,25] When durable temporary pacing is needed (i.e., infection), a temporary pacemaker with active fixation leads is more suitable.[26] Importantly, temporary pacing should never delay emergency cardiac reperfusion in the case of ischemia-induced bradycardia.

When establishing temporary pacing, the pacing threshold should be determined, and the pacing energy should then be set at two to three times this minimum output. Thresholds should be checked daily.

Pacing Modes

The North American Society of Pacing and Electrophysiology and the British Pacing and Electrophysiology Group created a code consisting of five letters to describe pacemaker functions known as the *NBG pacemaker* (see Table 73.5). The first letter indicates the cavities that are paced. The second letter indicates the cavities that are sensed. The third letter indicates the response of the device if the programmed event occurs. The fourth letter indicates if a special rate function is activated (i.e., rate responsiveness function using accelerometers inside the pulse generator allowing the basal heart rate to increase in case of physical activity). The fifth describes any anti-tachycardia functions or resynchronization function. Unipolar sensing and pacing use the pulse generator as the anode and the distal lead as the cathode. This arrangement is very sensitive to noise. Bipolar sensing and pacing use the lead's distal part as the anode and cathode, allowing less noise, more robust sensing, and lower energy consumption. The pacemaker and intracardiac device must be controlled by a trained cardiologist.

Complications of Pacing and Management (Table 73.6)

Undersensing: Failure to Sense

Undersensing refers to a situation in which a spontaneous depolarization of the observed cavity occurs and is not recognized by the device and so does not inhibit an impulse generation by the pacemaker (Fig. 73.4). There are multiple causes of undersensing, such as inadequate cardiac signal, pacemaker programmed to a value insufficient to sense intrinsic activity, change in native signal after implantation, ectopic beats, lead maturation, lead failure, pulse generator failure, environmental electrical fields, magnet application, and noise detection. Undersensing can be responsible for asynchrony and precipitating HF.

TABLE 73.6 Management of Pacing System Malfunction

Problem	Solution
Pacing Stimuli Present With Loss of Capture	
Lead dislodgment or malposition (hours and days after implantation)	Reposition of the lead
Inflammation at the electrode interface	Reposition of the lead and/or increasing the output of the pulse generator
Increase in capture threshold (several months after implantation)	Increase output, identify etiology
Subthreshold pacemaker output programming	Increase output
Lead failure	Identify problem (loss of capture, undersensing or oversensing, insulation breach) and provide the specific treatment
Battery depletion	Change battery
Recording system artifact	Identify problem
Pacing Stimulus With Failure to Sense (Undersensing)	Generally, management should implicate programming the sensitivity to a more sensitive value, avoiding inappropriate sensing of noncardiac signals and also:
Inadequate signal	Identify problem (low amplitude of the signal, slew rate or inappropriate frequent content)
Pacemaker programmed to a value insufficient to sense intrinsic activity	Change the programmed sensitivity
Change in native signal since implantation	Identify etiology
Ectopic beats	ECG to confirm the ectopic cardiac activity
Lead maturation	Evaluate the change in sensing
Lead failure, most frequently insulation failure	Replace the lead
Pulse generator failure	Replace the generator, not the leads
Environmental electric fields	Identify the electric field
Magnet application	Remove the magnet
Noise detection	Identify the etiology
Management of undersensing	Evaluate the characteristics of the native signals to determine why they are not being sensed; program the sensitivity
Electromagnetic Interference	
Therapeutic radiation	Evaluation before and after the procedure
External cardioversion	Avoid the delivery of energy to the pulse generator Evaluation before and after the procedure
Magnetic resonance imaging	Evaluation before and after the procedure
Electrocautery	Use bipolar cautery, reprogramming, or magnet application

ECG, Electrocardiogram.

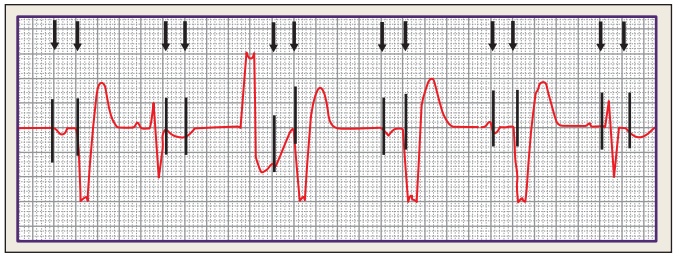

Fig. 73.4 Failure to Sense. Atrial and ventricular pacing spikes are seen around the intrinsic QRS complexes. Pacemaker activity does not lead to capture.

Position and integrity of the lead must be checked by x-ray and the device controlled by a trained cardiologist.

Oversensing

Oversensing refers to a situation in which a signal (noise, far-field) is interpreted as a spontaneous depolarization of the observed cavity, which then inhibits the impulse generation of the device. Pacemaker-dependent patients will have a poor tolerance for this type of event. This was common in the past with unipolar leads but is now quite rare.

Failure to Capture

Failure to capture occurs when a pacing stimulus is generated, but fails to trigger myocardial depolarization the expected cavity (Fig. 73.5). There are various causes of failure to capture, including lead dislodgement or malposition, inflammation and fibrosis at the electrode/myocardial interface, increase in capture threshold, subthreshold pacemaker output programming, lead failure, battery depletion, and recording system artifact. Position and integrity of the lead must be checked by x-ray and the device controlled by a trained cardiologist.

Fusion

Fusion refers to the situation in which the cavity depolarization is triggered by the intrinsic rhythm and pacemaker firing at the same time, resulting in a hybrid QRS.

Pseudo-fusion refers to a similar phenomenon, but the pacemaker firing does not affect the intrinsic QRS shape (Fig. 73.6).

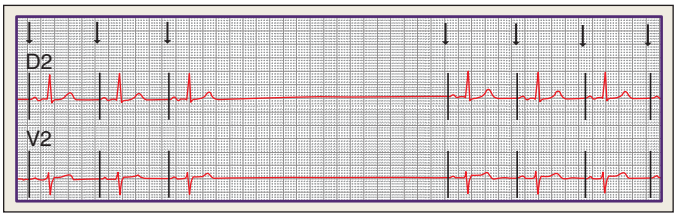

Fig. 73.5 Failure to Pace. An unduly long interval passes after the third QRS complex before another beat occurs. The pacemaker should have fired before this intrinsic beat.

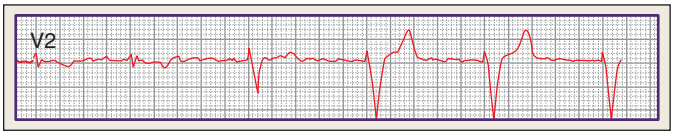

Fig. 73.6 With fusion, the pacemaker fires at the same time as the intrinsic rhythm, resulting in a hybrid QRS.

Cardiac Implanted Devices

- A cardiologist or electrophysiologist should be consulted when cardiac implanted device malfunction is suspected.
- Placing a magnet over a permanent pacemaker temporarily "reprograms" the pacer into an asynchronous mode (causing the pacemaker to fire at its preprogrammed rate regardless of the underlying intrinsic rhythm).
- MRI may be safe in a pacemaker patient if the cardiac implanted device is MRI compatible, is programmed, and is monitored. Verification of the leads and manufacturer-guaranteed MRI compatibility are mandatory.
- Pacemaker failure has three causes:
  a. **Output/capture failure:** Output failure is suspected if the heart rate is below the programmed lower rate and pacing spikes are absent. Capture failure can occur when the generated pacing stimulus does not initiate myocardial depolarization. Output or capture failure can also occur if the appropriate cardiac chamber is not paced.
  b. **Detection:** Problems with detecting intracardiac signals. In undersensing, the pacemaker fails to detect spontaneous myocardial depolarization, which results in asynchronous pacing. In oversensing, the pacemaker senses electrical signals that it should not normally encounter, which results in inappropriate inhibition of the pacing stimulus.
  c. **Pseudo-malfunction**: The pacemaker appears to be malfunctioning when in fact it is actually normal pacemaker behavior (e.g., rate-related).

KEY POINTS

Conduction Disturbances

- Patient history, drug list, and physical examination help make the correct diagnosis and determine choice of therapy.
- AV node block is most often caused by medications, ischemia, or increased parasympathetic tone. In most cases they are reversible. Infranodal blocks, however, are rarely reversible.
- When symptomatic bradyarrhythmia is present, negative chronotropic drugs should be withdrawn unless required for other purposes.
- Locating the site of an AV block helps stratify patient risk and prognosis:
  a. Asymptomatic first-degree and second-degree Mobitz I AV blocks are mostly nodal and do not require treatment.
  b. Symptomatic second-degree Mobitz II AV blocks and third-degree AV blocks are usually infranodal and often require definitive pacing.
- After heart surgery, bradyarrhythmias are frequent, especially after aortic valve surgery or TAVI. In symptomatic patients, temporary pacing is recommended. A decision about permanent pacemaker placement should not be made before 5–7 days after the procedure.

ANNOTATED REFERENCE

Kusumoto FM, Schoenfeld MH, Barrett C, et al. 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, and the Heart Rhythm Society. *Circulation.* 2019;140(8):e333–e381.
These are the latest guidelines available.

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Myocarditis and Acute Myopathies

Fredric Ginsberg and Joseph E. Parrillo

MYOCARDITIS

Myocarditis is defined as inflammation of heart muscle.[1] Many different etiologic agents have been implicated in this disease, but viral infections are the most common cause. Myocarditis can be associated with autoimmune and other systemic diseases and can be caused by adverse drug reactions.[2] The clinical picture of myocarditis varies widely, from asymptomatic patients who fully recover without specific therapy and who suffer no long-term sequelae, to critically ill patients with heart failure and cardiogenic shock. There are no standardized, specific, and widely agreed-upon criteria for making the diagnosis of myocarditis or for determining a specific cause in many patients.[3] Last, there has been controversy regarding the most appropriate medical therapy for this condition.

On pathologic examination of myocardial biopsy specimens or at autopsy, myocarditis is usually apparent as infiltration of myocardium with lymphocytes, macrophages, and fibroblasts, accompanied by myocyte necrosis (myocytolysis).[3] It is this type of myocarditis, termed *lymphocytic myocarditis,* that will be referred to in this chapter unless otherwise specified. Other types of inflammatory reactions are seen less frequently in myocarditis and involve giant cells, eosinophils, or granulomas and can be associated with specific clinical conditions.

The global incidence of myocarditis is estimated at 22 cases/100,000 annually. It is more common in males, and more severe cases tend to occur in women and children.[4] In most patients with myocarditis, a specific cause is not found.[5] It is presumed that in North America and Europe, the most common etiologic agent is viral.[1] Identification of particular viral etiologies may vary by geography and over time. Coxsackie B enterovirus was felt to be the most common cause up to the 1990s, but human herpesvirus 6, cytomegalovirus, and parvovirus B19 have been implicated as causative agents more frequently over the past 20 years.[2] Hepatitis C has also been found to be a common etiology in some populations.[6] Other viral causes include H1N1 influenza A, Epstein-Barr virus (EBV), and herpes simplex 1 and 2. Myocarditis is a common finding in patients infected with human immunodeficiency virus (HIV). However, the causative agent responsible in these cases may be HIV or a secondary viral infection such as cytomegalovirus.[1,6,7] Infectious illnesses such as Lyme disease, acute rheumatic fever, and diphtheria often have myocarditis as a prominent feature. In Central and South America, the most common cause of myocarditis is the protozoan *Trypanosoma cruzi*, the cause of Chagas disease (Table 74.1). Systemic and autoimmune diseases such as systemic lupus erythematosus (SLE), polymyositis, scleroderma, sprue, Whipple disease, and sarcoidosis can be complicated by myocarditis, and myocarditis can be a feature of infiltrative cardiomyopathies seen in hemochromatosis or amyloidosis. Other specific forms of myocarditis include hypersensitivity or eosinophilic myocarditis, which can be caused by allergic reactions to medications, including smallpox vaccination,[8] and giant cell myocarditis (GCM). Lastly, myocarditis can be associated with doxorubicin cardiomyopathy or with peripartum cardiomyopathy (Box 74.1).[9–11]

In 2020 an international pandemic of an acute respiratory illness occurred, called *coronavirus disease 2019 (COVID-19),* caused by infection with a novel coronavirus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The illness is characterized by pneumonia, often progressing to acute respiratory failure. Seven to twenty-eight percent of patients hospitalized with this illness demonstrate acute cardiac injury, defined as a combination of elevated serum troponin, electrocardiogram (ECG) changes consistent with myocardial injury, and/or left ventricular (LV) systolic dysfunction demonstrated on ECG. Myocarditis may be a mechanism of cardiac injury in some of these patients. However, there have only been a very small number of patients with a diagnosis of myocarditis that was confirmed by cardiac magnetic resonance imaging (MRI) or tissue sampling. One report described cardiomegaly, localized ST-segment elevation on ECG, marked troponin elevation, and acute heart failure associated with low left ventricular ejection fraction (LVEF) in a patient with COVID-19 pneumonia. Another report described biventricular heart failure and cardiac MRI findings diagnostic of acute myocarditis. LV function returned to normal within weeks in both cases.[12,13] One report described a patient with cardiogenic shock; impaired LV systolic function; no coronary artery obstruction; and endomyocardial biopsy showing low-grade interstitial and endocardial inflammation with macrophages, myocyte lysis, and viral particles seen in interstitial cells.[14] There have also been reports of a mild mononuclear cell infiltrate on myocardial specimens at autopsy in patients who died from COVID-19 illness.[15] Other causes of myocardial damage are also likely in these patients, including infection-mediated coronary vasculitis, microvascular coronary thrombosis, stress cardiomyopathy, exacerbation of atherosclerotic coronary artery disease, oxygen supply-demand mismatch, and a hyperinflammatory state causing a cardiomyopathy similar to that associated with sepsis.[16]

Unfortunately, it is difficult to make a clinical diagnosis of a specific viral cause of myocarditis. Antiviral antibody titers in acute- and convalescent-phase sera do not aid in the diagnosis, as viruses are highly prevalent in the general population, and antibody levels vary over time and do not correlate well with the onset of symptoms of acute myocarditis.[17,18] Viral cultures of tissue specimens are unreliable.[5] The identification of viral genomes incorporated in myocyte DNA by the use of methods such as polymerase chain reaction (PCR) is highly suggestive but does not specifically prove that the virus is the cause.

PATHOGENESIS

Based on observations of human myocarditis and murine models of the disease caused by coxsackie B3, the pathogenesis of viral myocarditis can be described in three stages.[2,19] The first stage is initiated by

TABLE 74.1 Causes of Myocarditis/Inflammatory Cardiomyopathy

INFECTIOUS MYOCARDITIS	
Bacterial	*Staphylococcus, Streptococcus, pneumococcus, meningococcus, gonococcus, Salmonella, Corynebacterium diphtheriae, Haemophilus influenzae, Mycobacterium tuberculosis, Mycoplasma pneumoniae, Brucella*
Spirochetal	*Borrelia burgdorferi*, (Lyme disease), *Leptospira* (Weil disease)
Fungal	*Aspergillus, Actinomyces, Blastomyces, Candida, Coccidioides, Cryptococcus, Histoplasma, Mucormycoses, Nocardia, Sporothrix*
Protozoal	*Trypanosoma cruzi, Toxoplasma gondii, Entamoeba, Leishmania*
Parasitic	*Trichinella spiralis, Echinococcus granulosus, Taenia solium*
Rickettsial	*Coxiella burnetii* (Q fever), *Rickettsia rickettsii* (Rocky Mountain spotted fever), *R. tsutsugamushi*
Viral	RNA viruses: coxsackieviruses A and B, echoviruses, polioviruses, influenza A and B viruses, respiratory syncytial virus, mumps virus, measles virus, rubella virus, hepatitis C virus, dengue virus, yellow fever virus, Chikungunya virus, Junin virus, Lassa fever virus, rabies virus, human immunodeficiency virus-1
	DNA viruses: adenoviruses, parvovirus B19, cytomegalovirus, human herpes virus-6, Epstein-Barr virus, varicella-zoster virus, herpes simplex virus, variola virus, vaccinia virus
IMMUNE-MEDIATED MYOCARDITIS	
Allergens	Tetanus toxoid, vaccines, serum sickness
	Drugs: penicillin, cefaclor, colchicine, furosemide, isoniazid, lidocaine, tetracycline, sulfonamides, phenytoin, phenylbutazone, methyldopa, thiazide diuretics, amitriptyline
Alloantigens	Heart transplant rejection
Autoantigens	Infection-negative lymphocytic, infection-negative giant cell
	Associated with autoimmune or immune-oriented disorders: systemic lupus erythematosus, rheumatoid arthritis, Churg-Strauss syndrome, Kawasaki disease, inflammatory bowel disease, scleroderma, polymyositis, myasthenia gravis, insulin-dependent diabetes mellitus, thyrotoxicosis, sarcoidosis, Wegener granulomatosis, rheumatic heart disease (rheumatic fever)
TOXIC MYOCARDITIS	
Drugs	Amphetamines, anthracyclines, cocaine, cyclophosphamide, ethanol, fluorouracil, lithium, catecholamines, interleukin-2, trastuzumab, clozapine
Heavy metals	Copper, iron, lead (rare, more commonly causes intramyocyte accumulation)
Miscellaneous	Scorpion sting, snake and spider bites, bee and wasp stings, carbon monoxide, inhalants, phosphorus, arsenic, sodium azide
Hormones	Phaeochromocytoma, vitamins: beriberi
Physical agents	Radiation, electric shock

From Caforio ALP, Pankuweit S, Arbustini E, et al. Current state of knowledge on aetiology, diagnosis, management and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J.* 2013;34: 2636–2648.

BOX 74.1 Distinct Forms of Myocarditis

Active viral
Postviral (lymphocytic): common form of acute myocarditis
Hypersensitivity
Autoimmune
Infectious
Giant cell myocarditis

From Haas G: Etiology, evaluation, and management of acute myocarditis. *Cardiol Rev.* 2001;9:88–95.

viral infection and replication within myocytes. Viral proteases and activation of proinflammatory cytokines initiate myocyte damage.[20] The presence of this viral replication phase is difficult to detect clinically, because patients may be asymptomatic during this phase or may only have nonspecific viremic symptoms. In addition, there is no rapid screening test to confirm most viral infections. Parvovirus B19 may preferentially infect endothelial cells in coronary arteries, venules, and capillaries, and myocardial damage may be a result of impaired blood flow.[21]

The second stage involves host immune activation. Stimulation of cellular immunity and humoral responses attenuates viral proliferation and can result in recovery from the illness. However, unabated immune activation can result in activated T cells targeting myocardial antigens that cross-react with viral peptides. This leads to release of cytokines such as tumor necrosis factor, interleukin-1, and interleukin-6, resulting in further damage to myocytes and the cytoskeleton.[1,20] Activation of CD4 cells and antibody production plays a less important pathogenetic role. This secondary immune response to viral infection may play a greater role in disease pathogenesis than the primary infection and may be genetically influenced. Incomplete clearing of virus or recurrent viral replication may also cause persistence of inflammation and myocardial damage. Evidence supporting these mechanisms includes the following: Myocardial biopsy with recombinant DNA techniques can detect viral genomes in 20%–35% of patients. Tissue-specific autoantibodies have been detected in 25%–73% of patients with evidence of myocarditis on biopsy, with antibodies directed against contractile, structural, and mitochondrial myocyte proteins. Inappropriate expression of the major histocompatibility complex can frequently be demonstrated on biopsy specimens.[1] Elevated levels of inflammatory cytokines are detected in patients with active myocarditis.

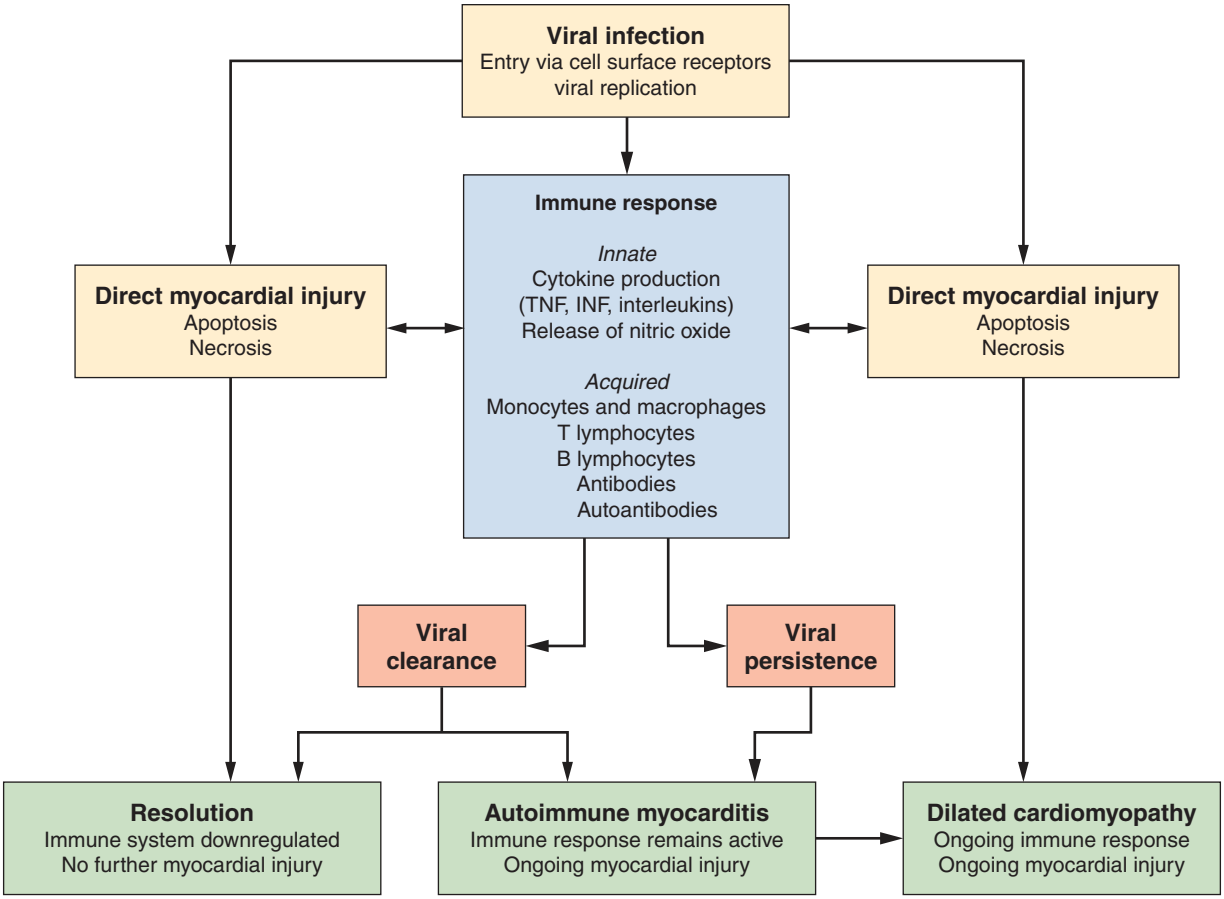


Fig. 74.1 The pathogenesis of viral myocarditis involves direct myocardial injury from viral infection in addition to immunomediated myocyte damage from cytokines, proteases, and autoantibodies. The outcome of these processes can be healing of inflammation and resolution of ongoing active myocarditis or chronic dilated cardiomyopathy. *INF*, Interferon; *TNF*, tumor necrosis factor. (Adapted from Blauwer LA, Cooper LT. Myocarditis. *Prog Cardiovasc Dis*. 2010;52:274–288.)

Either persistent overactivation of cellular immune activity or incomplete clearing with persistent or recurrent viral replication can lead to the third stage, which is marked by cellular apoptosis, ongoing necrosis, and fibrosis. Significant myocardial damage leads to LV dilatation and remodeling, neurohormonal activation, systolic dysfunction, and manifestations of heart failure.[20,22] These processes can then abate, with reduction in LV size and improvement of LV function, or can continue to progress with development of dilated cardiomyopathy, worsening ventricular function, and chronic heart failure. Chronic dilated cardiomyopathy is the major long-term sequela of acute myocarditis (Fig. 74.1).

CLINICAL PRESENTATION AND DIAGNOSIS

The incidence of myocarditis is difficult to determine, as many cases are mild with subclinical disease. Myocarditis is diagnosed on clinical grounds, as there are no specific clinical diagnostic criteria. The presentation of myocarditis varies widely. Patients can be asymptomatic, as myocarditis is found in 1%–10% of autopsy specimens of young adults who had no history of cardiac illness. Myocarditis can be found at autopsy in up to 20% of cases of young, apparently healthy adults who die suddenly and unexpectedly.[1,5,11] It is estimated to be the third most common cause of sudden cardiac death in young athletes.[4]

Patients with myocarditis most commonly present with dyspnea (72%), chest pain (32%), and symptoms of arrhythmia (18%).[23] The presentation may be indistinguishable from acute coronary syndromes caused by coronary artery disease. There may be a preceding viral prodrome with fever, malaise, and arthralgias. Physical examination can show fever, tachycardia, S3 and S4 gallop sounds, and a pericardial rub if pericarditis is present. Signs of heart failure can be present, including pulmonary rales and wheezes, elevated jugular venous pressure, and peripheral edema. Murmurs of mitral regurgitation and tricuspid regurgitation may be heard. Infrequently, the presentation is fulminant and severe, with acute heart failure, pulmonary edema, and cardiogenic shock.[5]

The differential diagnosis includes acute myocardial infarction (AMI), isolated pericarditis, or chest pain from pulmonary causes, including pulmonary embolism or pneumonia. Generalized sepsis is also a consideration. Myocarditis involving the right ventricle may mimic findings in right ventricular (RV) cardiomyopathy.

Laboratory findings can include leukocytosis, eosinophilia, and an elevated erythrocyte sedimentation rate. The cardiac biomarkers creatine phosphokinase (CPK), troponin T, and troponin I may be elevated, with sensitivity of troponin I reported at 34%–53% and specificity of 89%.[18,24] Rheumatologic serologic markers and HIV status should be evaluated in selected cases.

The 12-lead ECG is an insensitive test for the diagnosis of myocarditis. ECG findings are nonspecific and include sinus tachycardia and nonspecific ST-segment depression and T-wave inversion most often. Patients may present with chest pain and ST-segment elevation with a

BOX 74.2 Results of ECG, Laboratory Testing, and Imaging in Acute Myocarditis

ECG, Holter, or Stress Test
AV block I–III, bundle branch block, sinus arrest
Extrasystoles
Supraventricular tachycardia, atrial fibrillation
Ventricular tachycardia, ventricular fibrillation, asystole
ST-segment and T-wave changes (ST-segment elevation, T-wave inversion)
Intraventricular conduction delay
New Q waves
Low voltage

Seromarkers for Myocardial Necrosis
Troponin elevation
Creatine kinase elevation

Cardiac Imaging
Echocardiography/angiography
Regional or global systolic or diastolic dysfunction, with or without LV dilatation
Increased wall thickness
Pericardial effusion
Intracavitary thrombi
CMR
Edema
Hyperemia or capillary leak (early gadolinium enhancement)
Irreversible injury (necrosis, scar; late gadolinium enhancement)
Regional or global systolic or diastolic dysfunction, with or without LV dilatation
Increased wall thickness
Pericardial effusion
Intracavitary thrombi

Modified with permission from Caforio AL, Pankuweit S, Arbustini E, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J.* 2013;34:2636–2648.
AV, Atrioventricular; *CMR,* cardiovascular magnetic resonance; *ECG,* electrocardiogram; *LV,* left ventricular.

picture mimicking AMI or acute pericarditis. More severe cases can be associated with supraventricular or ventricular arrhythmias, conduction disturbances, and heart block.[1] QTc prolongation over 440 msec, QRS duration over 120 msec, and abnormal QRS axis have been associated with a poorer prognosis.[25]

Echocardiography is essential to diagnose and quantitate regional and global LV wall motion abnormalities, LV and RV size and function, the presence of pericardial effusion, and valvular regurgitation. RV involvement may be seen in 25% of patients.[18] Fulminant myocarditis is characterized by a nondilated left ventricle with severe systolic dysfunction and increased wall thickness reflecting myocardial edema.[26] Pericardial effusion may be present. Cardiac catheterization and coronary angiography are often necessary to exclude acute ischemia resulting from coronary artery disease as the cause of chest pain or acute heart failure (Box 74.2).

Cardiac Magnetic Resonance Imaging

There is increasing use of cardiac MRI with contrast enhancement as a noninvasive method to diagnose myocarditis.[27–30] Diagnostic criteria were published in 2009 called the "Lake Louise criteria."[31] These include (1) focal or diffuse myocardial edema in T2-weighted images, (2) early gadolinium enhancement (EGE) on T1 imaging indicating myocardial hyperemia, and (3) late gadolinium enhancement (LGE) indicating necrosis and fibrosis specifically located in subepicardial or mid-myocardial regions.[32] Myocardial edema may be localized or global and is not always associated with EGE. LGE may be diffuse or patchy, and is most often seen in basal and mid-inferolateral segments of the left ventricle or the base of the interventricular septum (see Box 74.2 and Fig. 74.2). Diagnostic sensitivity is improved when all three techniques are assessed. In a meta-analysis of reported studies, diagnostic accuracy of these criteria are 83%, with a sensitivity of 80% and specificity of 87%. Diagnostic accuracy is 68% when only LGE is present. Novel cardiac MRI T1 and T2 mapping procedures are being investigated and are proposed to supplement the Lake Louise criteria to improve diagnostic accuracy. These techniques offer quantitative tissue characterization and may correct for technical limitations of standard cardiac MRI techniques.[33] Cardiac MRI is more likely to be abnormal when performed more than 7 days after onset of symptoms. It may also detect pericardial inflammation and effusion (seen in 32%–57% of patients) and gives information regarding LV function. Cardiac MRI can also be used to direct myocardial biopsy in patients with patchy uptake.[31,34,35]

Advantages of cardiac MRI include that it is noninvasive and low risk, sampling error is avoided (a problem with endomyocardial biopsy, see later), and it can be used serially over time to assess a patient's course. However, cardiac MRI may be normal in patients with milder forms of myocarditis, and it does not distinguish between viral and other etiologies of the disease. It is also more difficult to apply in critically ill patients with cardiogenic shock.

The value of cardiac MRI in estimating prognosis is unclear. Prognosis is better in patients with edema and hyperemia but without LGE.[32] However, in a series of 203 consecutive patients with a diagnosis of myocarditis, all of whom had LGE and 70% of whom presented with chest pain, 10.8% experienced a major cardiac event (sudden death, heart failure, serious ventricular arrhythmia, or cardiac transplant). A multivariate analysis concluded that only reduced LVEF was an independent predictor of major events. Extent, pattern, and location of LGE were not significant predictors.[36] It is important to realize that cardiac MRI may provide diagnostic information regarding myocarditis; however, it does not predict clinical outcomes.

ENDOMYOCARDIAL BIOPSY

Percutaneous endomyocardial biopsy (EMB) is used to aid in the diagnosis of myocarditis and is considered the definitive diagnostic technique. The Dallas criteria have been accepted as the standard for histopathologic diagnosis, but the utility of the Dallas criteria is strongly debated (see later). These criteria define "active myocarditis" as the presence of an inflammatory myocardial infiltrate (more than five lymphocytes per high-power field) accompanied by myocyte necrosis. "Borderline myocarditis" is defined as inflammation without myocyte necrosis. However, there is no difference in prognosis in patients with either of these biopsy results. Thus lymphocyte infiltration (with or without myocyte necrosis) is the most important diagnostic criterion. A more recent pathologic definition of myocarditis is the presence on EMB of a focal or diffuse mononuclear cell infiltrate of lymphocytes and macrophages, with >14 cells/mm^2, with <4 monocytes/mm^2 and CD-3–positive lymphocytes >7/mm^2,[4] which emphasizes that immunohistochemistry to identify upregulated human leukocyte antigen (HLA) proteins and examining specimens for viral genomes using PCR should also be performed.[25,37,38] Viral myocarditis is considered to be present when there is evidence for active inflammation with a positive molecular test for virus on EMB, and autoreactive or autoimmune myocarditis is diagnosed when inflammation is present without viral markers.[39] Findings in eosinophilic myocarditis

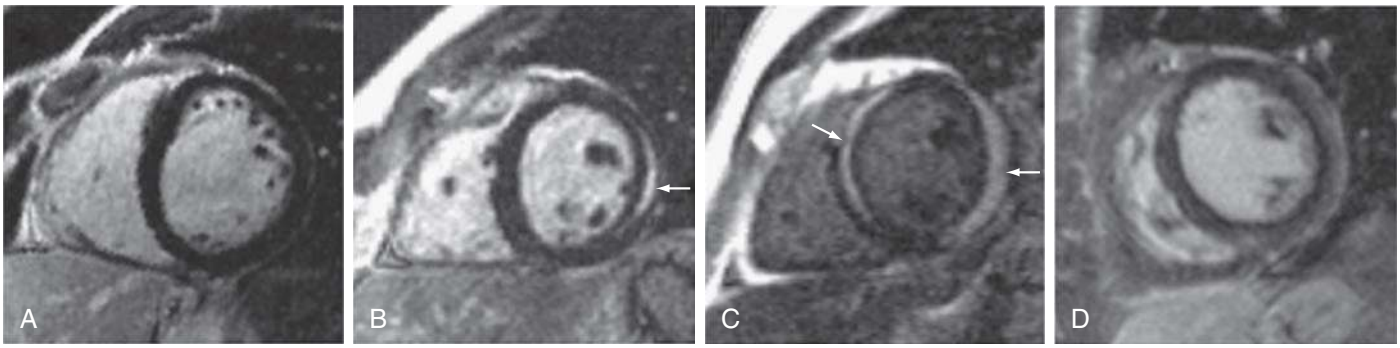


Fig. 74.2 Cardiac magnetic resonance imaging with late gadolinium enhancement (LGE): normal and abnormal findings in myocarditis. **A,** Normal myocardium with no evidence of LGE. **B,** Regional subepicardial enhancement of the lateral wall *(arrow).* **C,** Subepicardial enhancement of lateral and midwall enhancement of the septum *(arrows).* **D,** Diffuse subepicardial enhancement. (From Friedrich MG, Sechtem U, Schulz-Menger J, et al. Cardiovascular magnetic resonance in myocarditis: a JACC white paper. *J Am Coll Cardiol.* 2009;53[17]:1475–1487.)

include intense eosinophilic infiltrate with histiocytes, lymphocytes, and plasma cells. Pathology of GCM shows infiltration with giant cells, with lymphocytes and myonecrosis but without granulomas.

A positive EMB has a high positive predictive value, but there are a number of significant limitations. A high frequency of interobserver variation has been noted among pathologists in applying the Dallas criteria. Biopsies are not sensitive in diagnosing myocarditis, as various series have reported positive RV biopsy results in only 10%–67% of patients with myocarditis suspected on clinical grounds or with recent-onset idiopathic dilated cardiomyopathy. This variability may relate to the timing of biopsies in respect to the stage or chronicity of the patient's illness. In addition, sampling error is possible when myocardial inflammation is patchy and not global or may predominantly involve the LV free wall.[37] Thus diagnostic yield is improved by performing a biopsy earlier in a patient's clinical course, taking more than six biopsy specimens, and performing LV biopsies. In addition, immunohistochemical staining for HLAs can improve diagnostic sensitivity. EMB may also be useful to diagnose persistence of viral activity. Novel analyses assess viral transcription activity and messenger RNA (mRNA) expression.[19,40,41] EMB should be performed in centers with a high-volume experience and with proven safety and availability of appropriate pathologic techniques.[42] Recent reports indicate a very low rate of serious complications related to EMB in experienced centers, <0.1%.[39] It is important to emphasize that a negative biopsy finding does not preclude the diagnosis of myocarditis.

In the majority of patients, diagnosis is made on clinical grounds combined with cardiac MRI findings, and the clinical course is one of steady improvement. EMB is not necessary in these patients. EMB should be strongly considered in cases of suspected myocarditis when pathology results will affect management decisions. An American Heart Association/American College of Cardiology/European Society of Cardiology (AHA/ACC/ESC) scientific statement offered recommendations concerning the appropriate use of EMB based on patients' clinical presentations.[43] EMB was deemed useful, beneficial, and effective (class I indication) in patients with acute heart failure with hemodynamic compromise after causes such as coronary artery disease are excluded. EMB in this setting is necessary to diagnose GCM and eosinophilic myocarditis, which most often present with severe heart failure or arrhythmias, as immunosuppressive therapy is mandated in these conditions. A class I indication for EMB was also recommended for patients with new-onset, subacute heart failure or duration of illness of 2 weeks to 3 months and who fail to improve with medical therapy for heart failure or who demonstrate severe ventricular arrhythmia or advanced heart block. EMB should be considered if causes such as sarcoidosis or autoimmune disease are suspected.[44] EMB should always be performed before initiating immunosuppressive therapy (Box 74.3).

BOX 74.3 Indications for Endomyocardial Biopsy

- Exclusion of potential common etiologies of dilated cardiomyopathy (familial, ischemic, alcohol, postpartum, cardiotoxic exposures) and the following:
- Subacute or acute symptoms of heart failure refractory to standard management
- Substantial worsening of left ventricular (LV) systolic function despite optimal pharmacologic therapy
- Suspicion for giant cell myocarditis: younger patient, severe acute heart failure, hemodynamically significant ventricular arrhythmia, advanced heart block
- Suspicion of eosinophilic myocarditis: severe heart failure with rash, fever, peripheral eosinophilia
- Suspicion or diagnosis of systemic autoimmune disease such as systemic lupus erythematosus, scleroderma, or polyarteritis nodosum
- New-onset cardiomyopathy in the presence of suspected sarcoidosis or amyloidosis

An algorithm has been proposed outlining the steps in the evaluation of patients suspected of having acute myocarditis (Fig. 74.3).

CLINICAL COURSE

The clinical course of acute myocarditis is variable. The majority of patients diagnosed with myocarditis will improve, and those with mild symptoms most often recover without complications. Eight to twelve percent of young, apparently healthy adults who die suddenly from a cardiac cause are found to have myocarditis at autopsy, suggesting that patients even with apparently mild illness can suffer fatal arrhythmias.[19] In over 50% of patients, clinically recognized myocarditis will resolve in 4 weeks. However, 25% will develop persistent abnormalities of ventricular function, and roughly 10% to 20% may develop dilated cardiomyopathy with chronic, severe heart failure.[3,38] Fifteen to twenty-five percent of patients who present with new-onset dilated cardiomyopathy have evidence of antecedent myocarditis.[3] Patients with heart failure

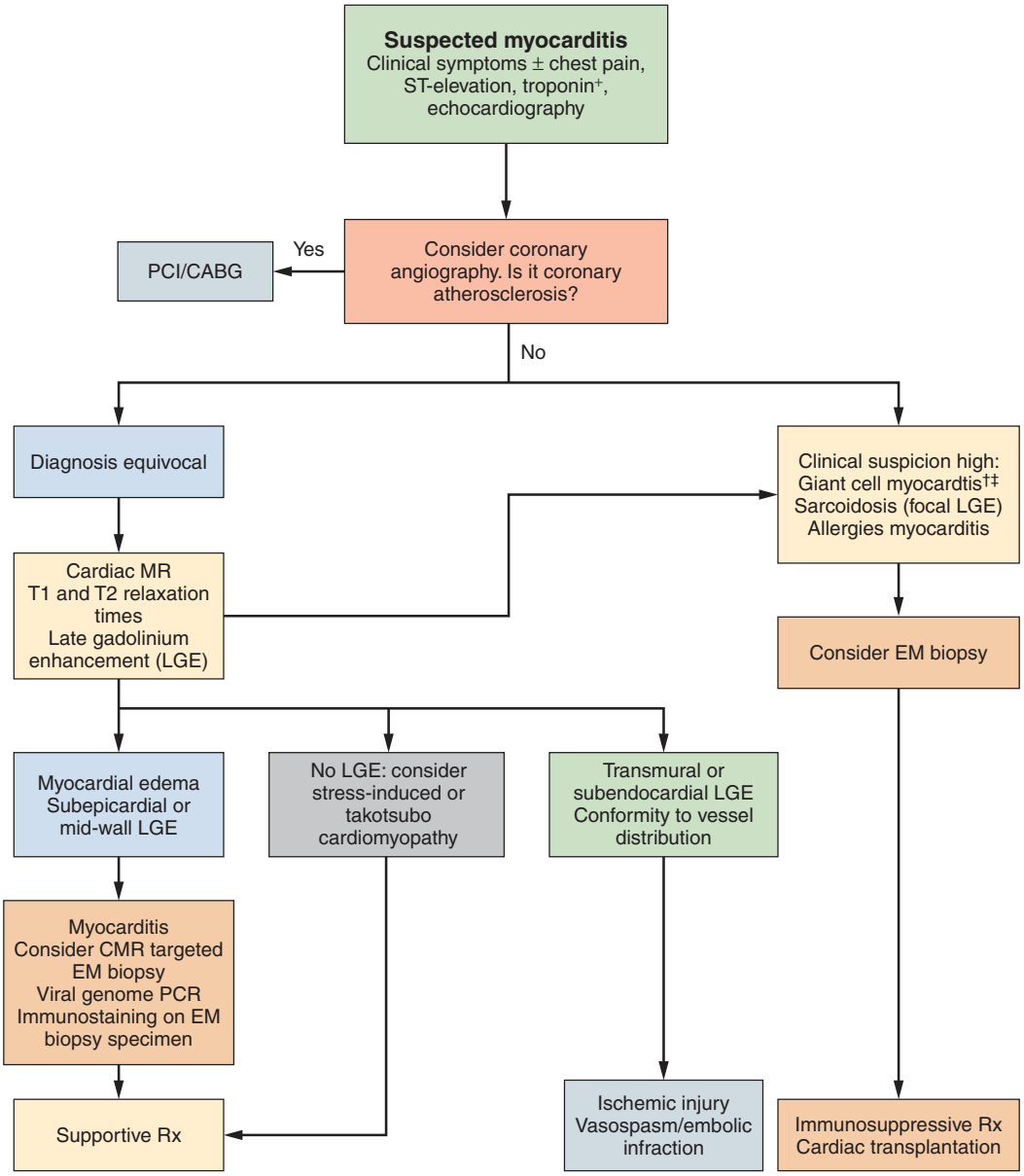


Fig. 74.3 Diagnostic Algorithm for Suspected Acute Myocarditis. *CABG*, coronary artery bypass grafting; *CMR*, cardiac magnetic resonance; *EM*, endomyocardial; *PCI*, percutaneous coronary intervention; *PCR*, polymerase chain reaction; *Rx*, treatment. (Adapted from Nelson KH, Li T, Afonso L. Diagnostic approach and role of MRI in the assessment of acute myocarditis. *Cardiol Rev.* 2009;17:24–30.)

and LV dysfunction will experience spontaneous resolution of their illness within 12 months in up to 40% of cases, without long-term sequelae. Roughly one-quarter of patients with acute myocarditis and ejection fraction below 35% will improve, one-half will develop chronic cardiomyopathy and heart failure, and one-quarter will deteriorate and may be candidates for cardiac transplantation.[45]

A minority of patients with acute myocarditis present critically ill with acute severe heart failure and cardiogenic shock. This presentation is termed *fulminant myocarditis* (FM). Most often these patients give a history of symptoms of a viral illness during the previous weeks, with a distinct time of onset of heart failure symptoms. These patients require hemodynamic support, including inotropes, vasopressors, and possibly mechanical circulatory support. This presentation is contrasted with that of patients with myocarditis who have chest pain and may have heart failure but not cardiogenic shock, termed *nonfulminant myocarditis* (NFM). These patients demonstrate a less distinct time of onset of heart failure symptoms and do not require vasoactive support. Direct cytolysis of myocytes caused by viral infection and replication is felt to be particularly important in FM. Early and extensive loss of myocytes and myocardial tissue leads to the rapid development of severe heart failure.

An early study comparing FM with NFM included 147 patients with heart failure caused by biopsy-positive active myocarditis, with ejection fraction less than 40%. Ten percent of patients were diagnosed with FM and 90% had NFM.[9] With aggressive treatment, patients with FM actually had better long-term survival rates: 93% at 1 year and 93% at 11 years. Patients with NFM had an 85% 1-year survival rate and a 45% survival rate at 11 years.[10] However, this early reported experience has not been confirmed in more contemporary studies (see later).

PROGNOSIS

It is important to examine the patient population under study and the criteria used for diagnosing myocarditis in any series assessing prognosis and mortality. No clinical markers reliably predict which patients with myocarditis will recover or worsen.[10] Early trials reported a 1-year mortality rate of 20% and 5-year mortality of 56% in patients with biopsy-confirmed lymphocytic myocarditis.[46] Another earlier trial reported 181 patients with myocarditis confirmed by EMB using the Dallas criteria, immunohistochemical staining, and PCR. LV biopsy was performed in 90% of patients. Patients were followed for an average of 59 months, and 22% died or received cardiac transplantation. Multivariate analysis concluded that functional class III and IV heart failure and a positive immunohistochemical result were the only predictors of a poor outcome, and treatment with beta-blockers was associated with better outcomes[40] (Fig. 74.4).

In more contemporary reports, the prognosis for patients who present with chest pain and other features similar to acute coronary syndrome, without heart failure or reduced LVEF, is favorable. In a series of 203 consecutive cases of acute myocarditis confirmed with LGE on CMR, 70% presented with chest pain without hemodynamic compromise, and none of these patients suffered cardiac arrest or required heart transplantation.[36] More recent series have shown that patients with FM have worse outcomes compared with NFM. In a report of 187 consecutive patients with acute myocarditis with symptoms <30 days, 80% underwent cardiac MRI and 27% had EMB. A reported 25.5% of FM patients died in hospital or required cardiac transplantation, and 18.2% died in hospital. Serious ventricular dysrhythmia and complete heart block occurred more often. Nine-year survival was 64%. In contrast, none of the NFM patients died or required transplant, and 9-year survival was 100%. LVEF was significantly lower in the FM group, and a lower LVEF correlated with a poorer prognosis. Females had a lower incidence of myocarditis, but their disease was more severe. Women comprised 57% of the FM group and only 12% of NFM. In FM, LVEF did tend to improve during the first few weeks of follow-up, but few recovered to normal, and LVEF was more likely to be abnormal at long-term follow-up than in NFM.[47] In another retrospective series of 220 patients with duration of illness <30 days and abnormal EMB, 165 patients had FM. Sixty-day mortality in this group was 27.8%, and 1-year mortality was 43%, compared with 1.8% and 9%, respectively, in 55 patients with NFM. GCM was associated with the worst prognosis. In patients with lymphocytic myocarditis, 60-day mortality was 19.5% in FM and 0% in NFM. Average LVEF was 22% in FM and 32% in NFM. Life-threatening ventricular arrhythmia occurred in 46.9% of FM and 16.7% of NFM. Mechanical circulatory support was used in 69% of FM and was not used in NFM. In patients with FM and eosinophilic myocarditis, 60-day mortality was 21%[48] (Figs. 74.5 and 74.6).

Thus contrary to early reports, the short- and long-term prognosis of FM is worse than NFM. The presence of early and severe hemodynamic compromise is the major determinant of a poorer outcome.

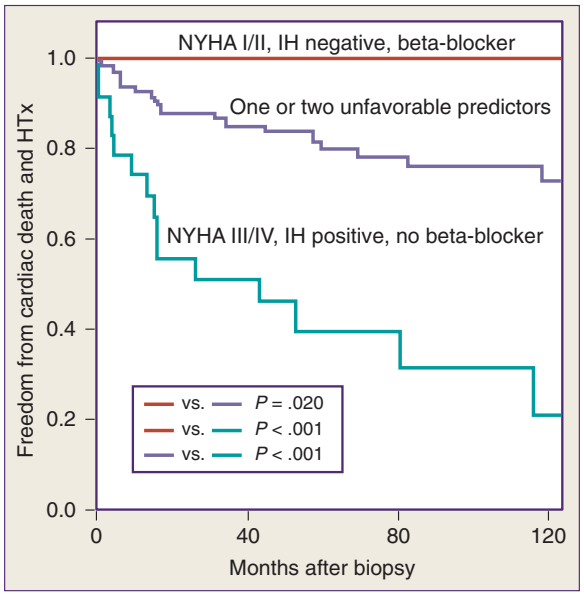


Fig. 74.4 Prognosis for patients with acute myocarditis was predicted by three factors: NYHA functional class, positive immunohistology for myocarditis at EMB, and therapy with beta-blockers. *EMB,* Endomyocardial biopsy; *NYHA,* New York Heart Association. (From Kindermann I, Kindermann M, Kandolf R, et al. Predictors of outcome in patients with suspected myocarditis. *Circulation.* 2008;118:639–648.)

GIANT CELL MYOCARDITIS

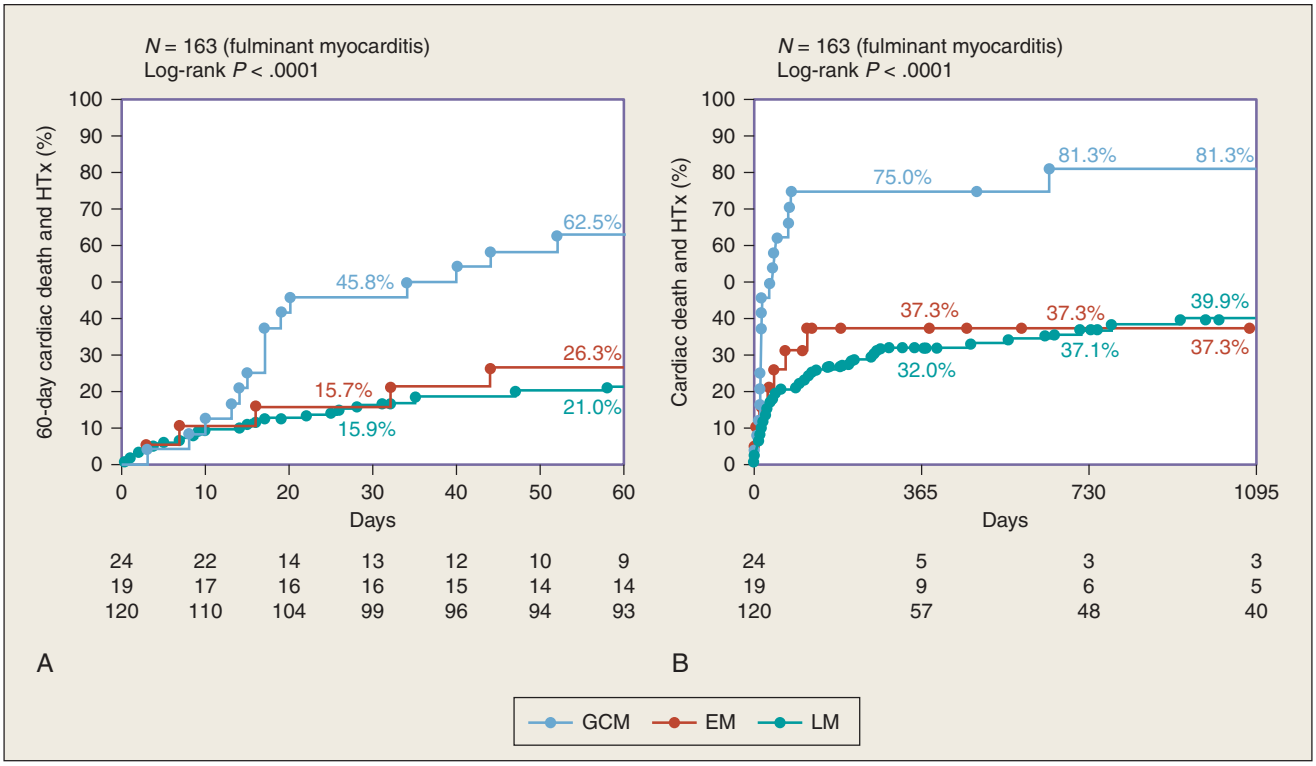
GCM is a distinct form of myocarditis, characterized by severe heart failure, life-threatening ventricular arrhythmias, and high-grade heart block. The pathogenesis is not clearly defined, although autoimmune mechanisms involving CD4 T lymphocytes are believed to play an important role. Usually the heart alone is affected without multisystem illness, but occasionally it is associated with an autoimmune disease such as inflammatory bowel disease, celiac disease, or rheumatoid arthritis or with neoplasm such as thymoma or lymphoma.[49] It has a rapidly progressive course, without significant likelihood of spontaneous resolution. On EMB, a diffuse or multifocal infiltration with inflammatory giant cells and lymphocytes is seen with myonecrosis. Eosinophils and plasma cells may be seen. Granulomas and fibrosis are not present. This differs from the myocarditis occurring with sarcoidosis in that patients with GCM have a more acute and severe illness, patients tend to be younger, and granulomas are not present on EMB as they are in sarcoidosis.

One retrospective study reported on 63 patients with biopsy-confirmed GCM.[50] Seventy-five percent presented with heart failure; 14% presented with severe ventricular arrhythmias; and 11% with chest pain, an abnormal ECG, or heart block. Other series report a presentation mimicking AMI in 6%–19% with complete heart block in 5%–8%.[51]

The prognosis of untreated GCM is poor, with median survival of 5.5 months and 89% dying or undergoing heart transplant. EMB is essential to make this diagnosis in order to initiate immunosuppressive therapy early in the course of the disease. In uncontrolled series, immunosuppressive therapy was associated with improved survival from 3 months in 30 patients not given immunosuppressive drugs to 11.5 months in patients given prednisone plus azathioprine and 12.6 months in patients in whom cyclosporine was added. More recent reports describe 5-year survival without cardiac transplant of 52%–75% with multidrug immunosuppression. Implantable cardioverter defibrillator (ICD) therapy is often used. Initial experience indicated that the prognosis after heart transplant was worse compared with other forms of heart disease, although more recent results describe similar posttransplant survival.[51]

EOSINOPHILIC MYOCARDITIS

Eosinophilic myocarditis, also termed *hypersensitivity myocarditis,* is a rare form of myocarditis characterized by eosinophilic infiltration and degranulation on endomyocardial biopsy. It is believed that



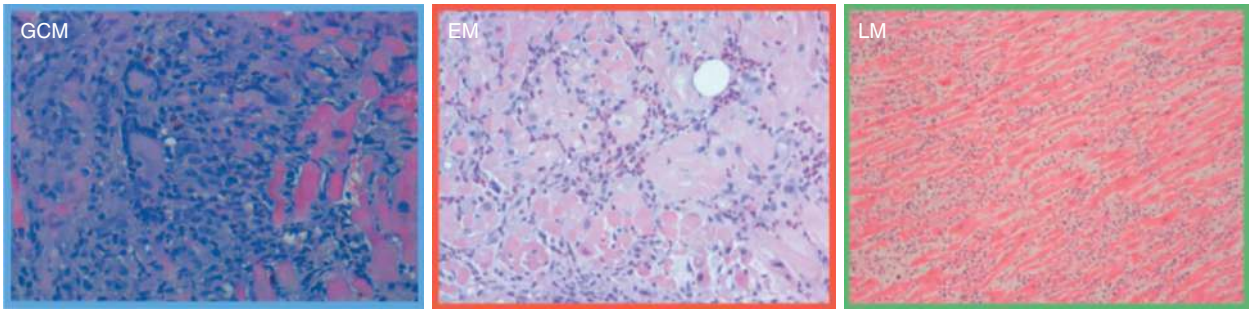


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Fig. 74.5 Prognosis in Fulminant Myocarditis According to Histologic Type of Myocarditis. Giant cell myocarditis (*GCM*) vs. eosinophilic myocarditis (*EM*) vs. lymphocytic myocarditis (*LM*). (From Ammirati E, Veronese G, Brambatti M, et al. Fulminant versus acute nonfulminant myocarditis in patients with left ventricular systolic dysfunction. *J Am Coll Cardiol.* 2019;74:299–311.)

pathogenesis involves a direct role of eosinophil-mediated myocyte damage. There can be associated arteritis. This entity is distinct from eosinophilic endocarditis (Loffler endocarditis). The clinical manifestations are not specific, aside from a high incidence of eosinophilia in peripheral blood. Patients usually present with heart failure caused by LV systolic dysfunction. Fever and rash may be present. Untreated, the disease is often rapidly fatal.[8]

The cause is believed to be a hypersensitivity reaction, usually to medication or, rarely, in association with parasitic infections. Drugs most often implicated are sulfonamides, diuretics, angiotensin-converting enzyme (ACE) inhibitors, cephalosporins, digoxin, or dobutamine. Eosinophilic myocarditis has been reported to occur weeks after smallpox vaccination, with an incidence of 1 in 16,000 vaccinated.[52] Untreated, the clinical course is unfavorable, often with rapidly worsening heart failure and sudden death caused by ventricular arrhythmia. Treatment involves discontinuing all potentially offending medication and the use of high-dose corticosteroids with azathioprine.[44] Excellent responses to immunosuppressives, in addition to some spontaneously resolving illness, have been reported.[53,54]

Eosinophilic myocardial infiltration has been reported in 2%–7% of myocardial biopsy specimens of patients awaiting cardiac transplantation or in the explanted heart after transplant. The cause is unclear, but dobutamine therapy, sodium bisulfite used as a preservative in dobutamine solutions, and the use of LV assist devices have been implicated. The presence of eosinophilic myocarditis in this setting did not have an adverse affect on posttransplant survival and did not recur in the transplanted heart.[55,56]

Immune Checkpoint Inhibitor–Associated Myocarditis

Immune checkpoint inhibitors (ICIs) are a new class of medication effectively used to treat certain cancers, including melanoma, lung cancers, and lymphoma. These drugs are monoclonal antibodies that

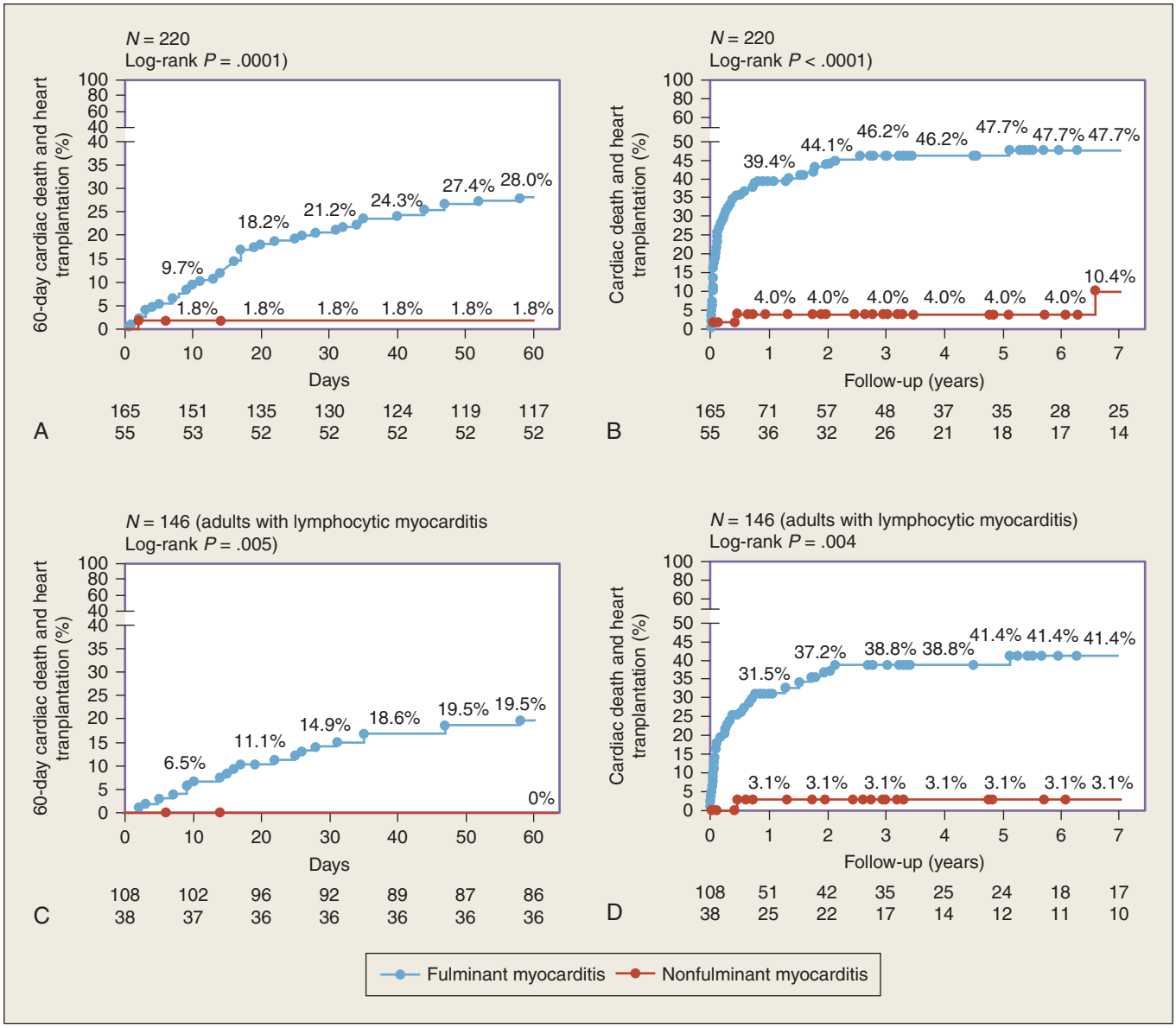

Fig. 74.6 Survival curves in all patients with fulminant myocarditis (FM) vs. nonfulminant myocarditis (NFM) and in patients with lymphocytic myocarditis and FM vs. NFM. (From Ammirati E, Veronese G, Brambatti M, et al. Fulminant versus acute nonfulminant myocarditis in patients with left ventricular systolic dysfunction. *J Am Coll Cardiol.* 2019;74:299–311.)

block the regulatory checkpoints on T cells that maintain self-tolerance, resulting in activation and increased function of T cells. After these drugs were approved for use as cancer chemotherapy, an adverse effect, acute lymphocytic myocarditis, was reported.[57] Although this complication is uncommon, it is the most severe adverse effect of these drugs and has a high fatality rate. Current incidence is estimated at 0.06%–2.4% of patients treated with these drugs. Patients with this complication most often present with new-onset heart failure. Other presentations include chest pain, cardiac arrhythmia, cardiogenic shock, pericardial effusion, and cardiac tamponade. Other organ systems may also be affected, including skeletal muscle myositis and hepatitis, although half of patients with myocarditis do not demonstrate other organ involvement. These drugs can block one of three different checkpoints, and drugs that block cytotoxic T-lymphocyte antigen 4 (CTLA-4) are reported to have a higher incidence of myocarditis. Combining two of these drugs is also associated with increased risk. Endomyocardial biopsy reveals inflammatory infiltrates with T lymphocytes and, less commonly, macrophages and giant cells, with variable fibrosis. Inflammation involving the conduction system and sinus node is also reported. Seventy-five percent of cases present within 6 months of beginning treatment and often present within the first few weeks after the initial dose.[58,59]

A review of 88 reported cases with ICI-associated myocarditis described that in addition to symptoms of heart failure, patients presented with weakness, chest pain, syncope, and fever. More than 90% of patients had significant elevation of serum troponin, and 91% had ECG abnormalities such as ST-segment changes, including pathologic ST-segment elevation, bundle branch block, and heart block including complete heart block. Seventy-seven percent had LVEF <50% on ECG. Sustained ventricular tachycardia (VT) and low cardiac output syndrome/cardiogenic shock were frequent. The mortality rate of ICI-associated myocarditis was 50%, three-quarters of these the result of

cardiac causes.[60] Another series reported similar characteristics, and 46% of these patients died or suffered cardiogenic shock, complete heart block, or cardiac arrest.[61] In both series, initial LVEF at diagnosis was not predictive of prognosis. At present there is no specific screening methodology recommended that can result in early recognition of this condition.

Treatment of ICI-associated myocarditis involves cessation of chemotherapy and urgent administration of high-dose corticosteroids, such as 1000 mg methylprednisolone daily. Additional immunosuppressive agents such as mycophenolate and tacrolimus may also be considered. Supportive care is also recommended, including therapies for heart failure, pacemakers, antiarrhythmic drugs, and mechanical support as appropriate. If the patient improves, ICI therapy should not be resumed.[62]

THERAPY

General Management of Heart Failure

The treatment of myocarditis is based on the clinical presentation. Patients with mild disease can be treated expectantly, with avoidance of strenuous exercise for several weeks.[3] Animal models indicate that strenuous exercise can worsen myocarditis. Elimination of unnecessary medications is important in patients with eosinophilia. Nonsteroidal antiinflammatory drugs should be avoided because they may worsen myocarditis.[5] The routine use of anticoagulants for prophylaxis of systemic emboli is not recommended. Patients who present with symptoms of arrhythmia or heart failure should be hospitalized, with continuous cardiac rhythm monitoring performed for evaluation of potential life-threatening arrhythmias or conduction abnormalities. If these are diagnosed, they are treated in a similar matter as in patients with other causes of heart disease, using antiarrhythmic drugs or pacemakers. However, a period of observation is recommended to assess for improvement of cardiac function before implantation of an ICD.

There are data in murine models of myocarditis supporting the use of ACE inhibitors, angiotensin blockers, and beta-blockers. These drugs reduce inflammation and lessen necrosis and fibrosis.[2,3,19,34] There are convincing data in humans supporting the use of these medications in addition to aldosterone antagonists in patients with dilated cardiomyopathy. Therefore in patients with myocarditis and heart failure, the use of standard multidrug medical therapy for heart failure and LV systolic dysfunction is indicated.[3,11] These medications have been shown to improve symptoms, prolong life, and regress the adverse LV remodeling in patients with dilated cardiomyopathy of various causes.[63–65]

Treatment with ACE inhibitors should be initiated at low doses, with upward titration to maximally tolerated doses. Potential side effects include renal insufficiency, hyperkalemia, and angioedema. Relative contraindications to the use of ACE inhibitors include renal failure, hyperkalemia, bilateral renal artery stenosis, and hepatic failure. Patients with hypotension should be treated with parenteral vasopressors or circulatory assist devices before initiation of low-dose ACE inhibitor therapy.

In one study, beta-adrenergic blockade was associated with improved survival in a multivariate analysis of patients with acute myocarditis.[40] Large randomized controlled clinical trials of patients with chronic heart failure with reduced LVEF, including patients with idiopathic dilated cardiomyopathy, have unequivocally shown benefit from beta-blockers in patients with LV systolic dysfunction,[66–68] and these agents should also be used in patients with heart failure caused by myocarditis. Beta-blockers should be initiated after patients are on a stable dose of ACE inhibitors and when signs of fluid overload have resolved. Contraindications to beta-blocker therapy include bronchospastic disease or severe chronic obstructive lung disease, heart block, or significant underlying bradycardia. Hypotension should be corrected before initiating beta-blocker therapy.

Digoxin has been shown in animal models to decrease levels of cytokines, but digoxin was associated with adverse outcomes in one murine model of myocarditis. Digoxin can be used to control rapid ventricular rates in patients with atrial fibrillation. The use of digoxin should be considered in patients with significant LV systolic dysfunction, after ACE inhibitors and beta-blockers have been initiated. However, no survival benefit for digoxin has ever been shown in patients with heart failure resulting from dilated cardiomyopathy.[69] Contraindications to the use of digoxin include renal failure or heart block.

Lastly, the use of the aldosterone antagonist spironolactone has been shown to have symptomatic and survival benefit in patients with chronic systolic heart failure.[70] In experimental models, these agents can reverse the progressive myocardial fibrosis that occurs in the remodeling process of dilated cardiomyopathy. These agents have not been studied in patients with myocarditis, but their use should be strongly considered in patients with severe LV dysfunction (ejection fraction $<35\%$) and symptomatic heart failure.[2] Contraindications to the use of aldosterone antagonists include renal insufficiency with serum creatinine levels above 2.0 mg%, or hyperkalemia. Serum potassium levels needs to be carefully monitored during initiation and dose titration.

In critically ill patients with severe heart failure and low cardiac index without serious hypotension, parenteral vasodilators should be used. Intravenous nitroprusside reduces systemic vascular resistance, mean systemic arterial pressure, and pulmonary capillary wedge pressure and can improve the cardiac index. It is used with invasive hemodynamic monitoring with a pulmonary artery catheter to best gauge the appropriate dose of medication and to accurately assess response to therapy. Prolonged use of nitroprusside is associated with accumulation of the toxic metabolites. Intravenous nitroglycerin is also an effective venodilator and coronary vasodilator with a less arterial dilating property than nitroprusside. The use of nitroglycerin in cases of myocarditis has not been studied. Patients often develop tolerance to this drug.

Patients with severe myocarditis may develop cardiogenic shock, respiratory failure, and end-organ hypoperfusion. In these instances, treatment with inotropic agents or vasopressors is indicated. Dobutamine is a potent $beta_1$-agonist with less $beta_2$- and alpha-agonist properties. Dobutamine has favorable short-term hemodynamic effects, increasing myocardial contractility, reducing systemic vascular resistance, and reducing pulmonary capillary wedge pressure. However, dobutamine can be proarrhythmic, and patients can develop tolerance to the drug. Milrinone is a parenteral inotropic agent that works by inhibiting phosphodiesterase. This drug leads to increased inotropy and decreased systemic vascular resistance and pulmonary capillary wedge pressure, with resultant increased stroke volume and cardiac index. Milrinone may cause hypotension. It is less proarrhythmic than dobutamine, and it does not induce tolerance.[71,72] Arterial vasoconstrictors such as norepinephrine and dopamine can be used in patients with refractory hypotension and poor end-organ perfusion.

In patients with fulminant myocarditis and cardiogenic shock not responding to pharmacologic therapy, mechanical circulatory support with intraaortic balloon counterpulsation (IABP), percutaneous mechanical ventricular assist devices (p-VADs), or extracorporeal membrane oxygenation (ECMO) should be used. ECMO is often used in children with fulminant myocarditis. Mechanical circulatory support improves hemodynamics, end-organ perfusion, and coronary flow and may allow for beneficial reverse remodeling

TABLE 74.2 Medical Therapy for Heart Failure in Acute Myocarditis and Advanced Supportive Therapies

Heart failure with left ventricular (LV) systolic dysfunction	Loop diuretics Beta-blockers (metoprolol succinate, carvedilol, bisoprolol) Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers Aldosterone blockers Digoxin
Severe heart failure with reduced cardiac output	Intravenous vasodilators (nitroprusside, nitroglycerin) Intravenous inotropes (milrinone, dobutamine), vasopressors (norepinephrine)
Cardiogenic shock not responding to medical therapy	Intraaortic balloon counterpulsation Extracorporeal membrane oxygenation (ECMO) Mechanical circulatory support: percutaneous or implanted ventricular assist device (VAD) Cardiac transplantation

and spontaneous resolution of LV dysfunction to occur. Patients with fulminant myocarditis should be given a reasonable time to recover ventricular function before cardiac transplantation is performed. Cardiac transplantation is the final option for treating critically ill patients with myocarditis (Table 74.2).

Immunosuppressive Therapy

Because autoimmune mechanisms are responsible for myocardial injury and the clinical manifestations of myocarditis, therapy with immunosuppressive drugs has been studied. Given the high rate of spontaneous recovery of LV function, placebo-controlled trials are essential to properly evaluate the effects of therapy. In addition, heterogeneous patient populations, consisting of patients with acute myocarditis and chronic dilated cardiomyopathy, have been included in older immunosuppressive trials, confounding the interpretation of results.

High-dose daily prednisone therapy was used for a 3-month course in 102 patients with dilated cardiomyopathy, 59% of whom were classified as having "reactive" myocarditis on endomyocardial biopsy.[73] The authors found a significant improvement in LVEF at 3 months in treated patients with reactive myocarditis, but this improvement was not sustained at 9 months. Improvement did not occur in patients with nonreactive biopsies treated with prednisone. No significant mortality benefit from immunosuppressive treatment was noted, although this was not a prespecified primary endpoint.

The Myocarditis Treatment Trial enrolled 111 patients with a positive endomyocardial biopsy finding and LVEF <45%. These patients had a protracted clinical course, with a duration of illness of less than 2 years.[46] Three treatment groups were compared: daily prednisone plus azathioprine, prednisone plus cyclosporine, and placebo. Mortality was 20% at 1 year and 56% at 3 years. These investigators found no difference in ejection fraction at week 28 or week 52, no change in LV size at week 28, and no difference in 1-year mortality between treated and untreated groups. Their conclusion was that these immunosuppressive strategies were not beneficial. Significant limitations of this study include a 30% dropout rate and significant interobserver variability among pathologists' diagnoses of biopsy specimens despite using the Dallas criteria.

In view of the limitations of histopathologic diagnosis using the Dallas criteria, another group of investigators used immunohistologic markers of inflammation, upregulation of HLA, to diagnose active myocarditis as an indication for immunosuppressive therapy.[74] These criteria have the advantage of indicating that autoimmunity is playing a role in pathogenesis. Also, because HLA is distributed throughout the entire myocardium, biopsy sampling error is eliminated as a confounding variable in assessing response to therapy. These patients also had a more chronic course of disease. Eighty-four of 202 patients with idiopathic dilated cardiomyopathy with duration >6 months and ejection fraction under 40% were found to have strong expression of HLA in biopsy specimens and were randomized to receive placebo or prednisone plus azathioprine for 3 months. At 3 months follow-up, a significant improvement in the prespecified secondary endpoints of LVEF, LV volumes, and functional capacity was seen in the treated group, and this improvement was maintained at 2 years (71.8% improvement in the treated group vs. 30.8% in the untreated group). However, there was no improvement in the prespecified composite primary endpoints of death, cardiac transplant, or hospital readmission. This study was limited by a 31% dropout rate.

In another study, patients with positive EMB specimens and progressive heart failure who responded to 6 months of therapy with prednisone and azathioprine were more likely to have circulating cardiac autoantibodies and no viral genome in their myocardium as compared with nonresponders.[75] Another randomized, placebo controlled trial of prednisone plus azathioprine was performed in 85 patients with chronic heart failure (>6 months illness) with active lymphocytic myocarditis on EMB and absence of viral genome on PCR. There was significant improvement in LVEF in the treated group (average ejection fraction increased from 26.5% to 45.6%) and no improvement in controls (average ejection fraction 27.7%–21.3%). In addition, there was significant improvement in LV dimensions and patients' functional status in the group receiving immunosuppression. This study suggests that this therapy may have favorable effects in patients who persist with active myocardial inflammation after the virus has been cleared[76] (Fig. 74.7).

Studies have suggested that in patients with heart failure and low ejection fraction, intravenous immunoglobulin (IVIg) has a pronounced antiinflammatory effect as measured by circulating levels of inflammatory markers.[77] Uncontrolled studies suggested benefit in patients with myocarditis from treatment with IVIg.[78,79] However, a placebo-controlled double-blind trial of IVIg in patients with myocarditis or idiopathic dilated cardiomyopathy of less than 6 months' duration showed no significant improvement with therapy as assessed by ejection fraction or functional capacity at 6 and 12 months.[80] In this study, average LVEF improved from 25 ± 8% at baseline to 41 ± 17% at 6 months in both treated and untreated groups. The 1-year event-free survival rate was 91.9% in both groups, indicating a favorable prognosis. Therefore the use of IVIg is not supported by any randomized trial.[81]

In summary, there is no evidence that patients with lymphocytic myocarditis or idiopathic dilated cardiomyopathy benefit from the *routine* use of immunosuppressive therapy. This treatment should be considered in patients with myocarditis who develop early signs of severe heart failure or who experience progressive worsening of LV function. EMB should be performed before initiating immunosuppression, and active inflammation should be seen, preferentially without viral genome detected on immunohistology. Immunosuppressive therapy should be used in patients with myocarditis associated with autoimmune diseases such as SLE, eosinophilic or granulomatous forms of the disease, and in GCM (Box 74.4).

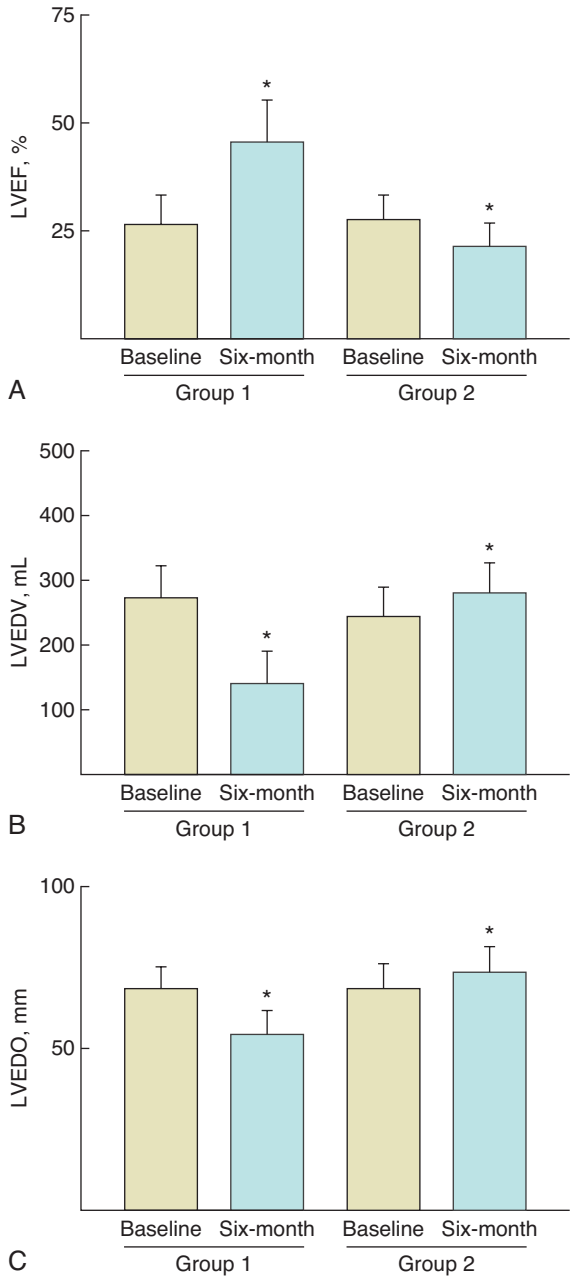

Fig. 74.7 Left ventricular function and size at baseline *(pink bars)* and at 6 months *(blue bars)* in patients with myocarditis. Group 1 was treated with immunosuppressive therapy and group 2 with placebo. (From Frustaci A, Russo MA, Chimenti C. Randomized study on the efficacy of immunosuppressive therapy in patients with virus-negative inflammatory cardiomyopathy: The TIMIC trial. *Eur Heart J.* 2009;30:1999.)

SUMMARY

The most common cause of myocarditis is viral infection, and autoimmune mechanisms are involved in the pathogenesis. Patients with myocarditis can present with acute chest pain, mimicking acute ischemic heart disease or other cardiopulmonary illnesses, or can present with heart failure. A smaller percentage of patients present with acute severe heart failure and cardiogenic shock. Oral and parenteral pharmacologic therapies that are used in patients with heart failure not caused by myocarditis are also used in these patients. FM is characterized by severe heart failure and cardiogenic shock. These patients need intensive, aggressive pharmacologic therapy and may require mechanical circulatory support. Cardiac MRI is an important tool in the diagnosis of myocarditis and may help with prognostication. EMB is a safe technique used to diagnose myocarditis in sicker patients and to decide on immunosuppressive therapy, although it is limited by sampling error and by current histopathologic techniques for assessing disease activity. Newer immunohistologic methods may better define those patients who will respond to immunosuppressive therapy. Patients with myocarditis and progressive myocardial failure despite conventional heart failure therapy should be considered for immunosuppressive therapy on a case-by-case basis.

BOX 74.4 Indications for Immunosuppressive Therapy in Myocarditis

Inflammation present on endomyocardial biopsy and:

1. Continued severe heart failure symptoms despite good medical therapy
2. Progressive worsening of heart failure symptoms or LV systolic function despite good medical therapy
3. Fulminant myocarditis
4. Presence of giant cell myocarditis
5. Presence of eosinophilic myocarditis
6. Presence of myocarditis in association with a systemic autoimmune disease (e.g., SLE, inflammatory bowel disease, polymyositis).

LV, Left ventricular; *SLE,* systemic lupus erythematosus.

STRESS CARDIOMYPATHY

A distinctive cardiomyopathy with acute onset, frequently precipitated by emotional or physical stress, is termed *stress cardiomyopathy.* This cardiomyopathy was first described in patients in Japan in 1991[82] and has subsequently been described elsewhere.[83,84] It is characterized by the sudden onset of chest pain and/or dyspnea, ECG changes mimicking AMI, and mild elevation of serum troponin. The syndrome is precipitated by extreme emotional or physical stress in >70% of cases.[85] The characteristic LV wall motion abnormality, seen in 75%–80% of cases, is akinesis or dyskinesis of a large area of the LV apex (Figs. 74.8 and 74.9). Coronary artery stenosis is not present or does not contribute to the cause. Other names for the cardiomyopathy are transient apical ballooning syndrome (TABS), describing the distinctive LV wall motion abnormality, or takotsubo, so named because the takotsubo pot used by Japanese fishermen to trap octopus has a shape similar to the left ventricle in this condition ("short neck, round flask").[84–87] Particular diagnostic criteria have been proposed (Box 74.5).

Precipitators of stress cardiomyopathy include arguments with family members, the death of loved ones, or sudden financial setbacks. Physical stresses include medical procedures such as thoracentesis or biopsy, institution of cancer chemotherapy or hemodialysis, and hip fracture and noncardiac surgeries. Stress cardiomyopathy in younger males can be associated with substance abuse disorders or withdrawal. A similar acute cardiomyopathy can occur as a complication of acute central nervous system illnesses, including subarachnoid hemorrhage, ischemia or hemorrhagic stroke, head trauma, and encephalitis. This is termed *neurogenic stunned myocardium*. The pathophysiology is felt to be similar to stress cardiomyopathy (see later).

Stress cardiomyopathy has been reported to occur in approximately 1.7%–2.2% of admissions for acute coronary syndrome in Japan and the United States,[88,89] with an annual incidence of 15–30 per 100,000 in the United States. It may be more common than currently recognized. There is a marked preponderance for postmenopausal females to be affected by this condition, 86%–100% in reported series,

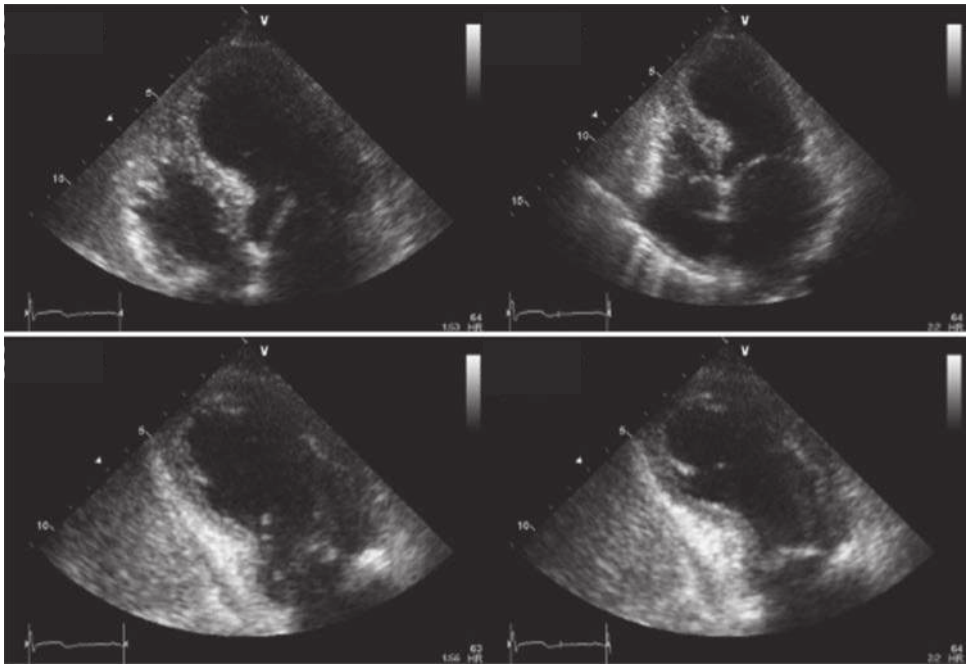

Fig. 74.8 End-diastolic and end-systolic apical four- and two-chamber echocardiographic views demonstrating the typical apical and mid-ventricular wall motion abnormalities seen in stress cardiomyopathy. (From Gianni M, Dentali F, Grandi AM, et al. Apical ballooning syndrome or takotsubo cardiomyopathy: a systematic review. *Eur Heart J.* 2006;27:1523–1529.)

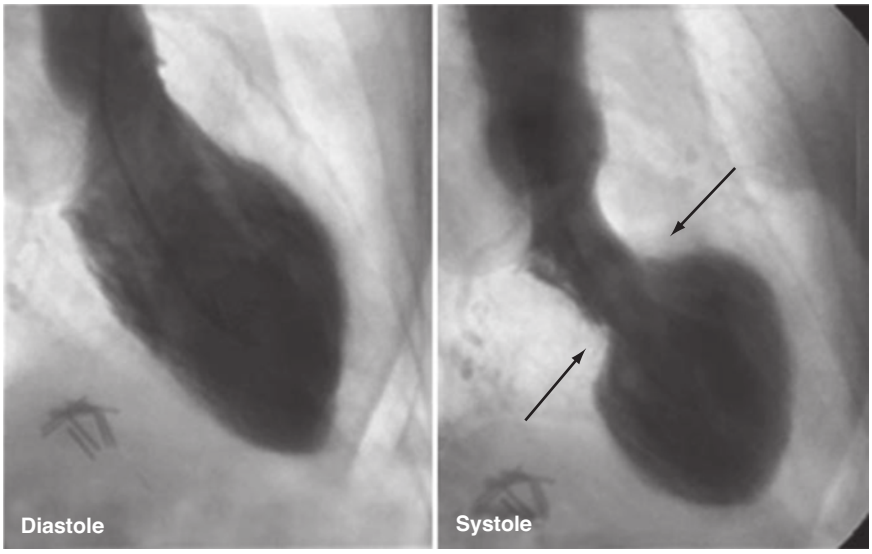

Fig. 74.9 Left ventriculogram showing typical wall motion abnormalities in stress cardiomyopathy. *Arrows* in systole indicate hyperkinesis of basal inferior and anterior segments, with dyskinesia of remaining wall segments. (From Sharkey SW, Lesser JR, Zenovich AG, et al. Acute and reversible cardiomyopathy provoked by stress in women from the United States. *Circulation.* 2005;111:472–479.)

with a mean age of 63–67 years. Many subsequent reports have described this condition in younger patients, including a subset of patients with cannabis use disorder. Sixty-six to ninety percent of patients will present with chest pain, and 15%–20% will present with dyspnea, pulmonary edema, or shock. ECG is abnormal in 95% of cases. The most common abnormalities seen are ST-segment elevation in precordial leads (40%) or in lead aVR or marked T-wave inversions in the precordial leads. ST-segment depression is uncommon. These findings are indistinguishable from acute coronary syndromes caused by coronary artery disease. Elevation of creatine kinase-MB (CK-MB) and troponin is seen in the majority of patients, but the enzyme rise is typically lower than would be expected, given the marked ECG and LV wall motion abnormalities. Serum brain natriuretic peptide (BNP) levels tend to be markedly elevated.[90]

Correct diagnosis involves emergency coronary angiography to exclude acute coronary syndrome resulting from obstructive coronary artery disease. Echocardiography and left ventriculography show moderate-to-severe LV dysfunction in these patients, with characteristic

BOX 74.5 Diagnostic Criteria for Stress Cardiomyopathy According to the Heart Failure Association of the European Society of Cardiology

1. Transient regional wall motion abnormalities of left ventricle or right ventricle myocardium, which are frequently, but not always, preceded by a stressful trigger (emotional or physical).
2. The regional wall motion abnormalities usually extend beyond a single epicardial vascular distribution and often result in circumferential dysfunction of the ventricular segments involved.
3. The absence of culprit atherosclerotic coronary artery disease, including acute plaque rupture, thrombus formation, and coronary dissection or other pathologic conditions, to explain the pattern of temporary LV dysfunction observed (e.g., hypertrophic cardiomyopathy, viral myocarditis).
4. New and reversible electrocardiography abnormalities (ST-segment elevation, ST-segment depression, LBBB, T-wave inversion, and/or QTc prolongation) during the acute phase (3 months).
5. Significantly elevated serum natriuretic peptide (BNP or NT-proBNP) during the acute phase.
6. Positive but relatively small elevation in cardiac troponin measured with conventional assay (i.e., disparity between the troponin level and the amount of dysfunctional myocardium present).
7. Recovery of ventricular systolic function on cardiac imaging at follow-up (3–6 months).

BNP, Brain natriuretic peptide; *LBBB,* left bundle branch block; *LV,* left ventricular; *NT-proBNP,* N-terminal-pro hormone BNP.
Adapted from de Chazal H, Del Buono M, Keyser-Marcus, L, et al. Stress cardiomyopathy diagnosis and treatment. *J Am Coll Cardiol.* 2018;72:1955–1971.

hyperkinesis of inferior-basal and basal-septal segments, with severe hypokinesis or dyskinesis involving mid-anteroseptal, apical, and inferior-apical wall segments. A small percentage of patients will demonstrate different contraction abnormalities, with akinesis involving the mid-anterior and mid-inferior walls, with normal motion or hypercontractility of the apex and basal segments, or akinesis localized to basal segments or particular regions of the left ventricle. The right ventricle is affected rarely. Thrombus in the left ventricle is not uncommon. Acutely, LVEF is reduced to 20%–40%.[85,86] Up to 20% of patients may demonstrate an LV outflow tract gradient resulting from basal septal hyperkinesis and transient systolic anterior motion of the anterior leaflet of the mitral valve.[83,84]

Patients with stress cardiomyopathy often present critically ill, with pulmonary edema (15%–45%), hypotension, and shock. Cardiogenic shock can develop because of marked LV systolic dysfunction and decreased stroke volume. Shock can also be exacerbated by the development of an LV outflow tract gradient. Cardiogenic shock has been reported in 5% of patients at presentation and has occurred during the course of the illness in 6%–46% of patients in different series.[83,85–88] Ventricular arrhythmia, including torsades de pointes, is seen in 5%–10% of patients, and atrial fibrillation may occur in 5%–15%.

Suspicion of stress cardiomyopathy and urgent diagnosis are important, as therapy and prognosis differ substantially from acute coronary syndromes caused by coronary artery disease. Stress cardiomyopathy should not be treated with thrombolytic therapy, as coronary occlusion is not involved in the pathogenesis. Beta-blocker therapy is recommended, although registries have not shown improved in-hospital outcomes with this medication. Anticoagulation is recommended if LV thrombus is diagnosed. If cardiogenic shock develops, treatment with IABP is advised. Inotropic therapy should be used judiciously or not at all. Dobutamine and other beta-agonists may worsen cardiogenic shock by increasing hyperkinesis of the basal portion of the heart and causing or aggravating an LV outflow tract gradient. There have been case reports of patients with stress cardiomyopathy whose hypotension progressed to frank cardiogenic shock after initiation of inotropic therapy. Because a hyperadrenergic state has been proposed to be the major pathogenic mechanism, empiric use of beta-blockers while patients are being supported with IABP has been used successfully. Echocardiography can be useful to guide therapy. For those with extensive wall motion abnormalities but no outflow obstruction, IABP support without beta-blockers is recommended. Administration of the alpha-agonist phenylephrine can also be considered in cases with a high LV outflow tract gradient, as this drug increases afterload, causing LV dilatation and a decrease in mitral valve systolic anterior motion and lowering of intraventricular gradients. The initial course may be complicated by severe ventricular arrhythmia.

Stress cardiomyopathy has a prognosis that approximates that of acute coronary syndromes, with an in-hospital mortality rate of 4%.[91] Aggressive therapy of hemodynamic compromise and cardiogenic shock is indicated. In almost all patients, the marked apical wall motion abnormalities begin to improve within days, and LV function can be expected to recover to normal during the ensuing 1–6 months. However, in a small percentage of patients wall motion abnormalities may persist for up to 1 year. Follow-up in various series has shown recovery of LVEF to normal in most instances. The large majority of survivors will recover completely with normal functional status. The long-term prognosis is good. In one series, only 2 out of 72 patients had recurrence of TABS within 13 months. In another series, the recurrence of TABS was calculated at 2.9% per year. Over a 4-year follow-up, long-term survival of patients who recovered from TABS was equivalent to sex- and age-matched control groups without a history of TABS.[85,92]

The pathogenesis of TABS is unknown. A hyperadrenergic state, precipitated by acute stress and causing myocardial stunning, is proposed, with activation of noradrenergic neurons and release of systemic catecholamines and norepinephrine and neuropeptides in the myocardium, which can be toxic to myocytes and can cause vascular dysfunction. One study documented supraphysiologic levels of serum catecholamines and stress neuropeptides in patients during the acute phase of the illness, likely caused by adrenal and sympathoneuronal hyperactivity. The apex of the left ventricle may be more sensitive to the deleterious effects of adrenergic hyperstimulation than other LV wall segments.[86] Transient multivessel coronary spasm has also been proposed, but this has not been demonstrated at the time of acute coronary angiography in the vast majority of patients. Additionally, in most patients the extent of LV wall motion abnormality is larger than the distribution of a single coronary artery. Cardiac MRI has not shown evidence of infarction or myocarditis.[89]

In summary, stress cardiomyopathy should be suspected in patients who present with symptoms and ECG findings consistent with AMI, who have the typical large apical wall motion abnormality seen on echocardiography or left ventriculography, and whose symptoms are precipitated by severe emotional or physical stress. Diagnosis is confirmed when urgent cardiac catheterization and coronary angiography demonstrate no significant coronary artery occlusion or stenosis.

TACHYCARDIA-INDUCED CARDIOMYOPATHY

A sustained rapid heart rate can lead to the acute development of LV dilation and systolic dysfunction, with symptoms of heart failure. This is termed *tachycardia-induced cardiomyopathy* (TICMP). The definition includes sustained heart rate over 100/min, exclusion of other causes of LV dysfunction, and complete recovery to baseline after adequate control of heart rate.[93] This can occur in otherwise normal hearts, or tachycardia may exacerbate heart failure in patients with

preexisting cardiomyopathy. Supraventricular or ventricular arrhythmias of any type can lead to this syndrome. Arrhythmias that may be responsible for TICMP include atrial fibrillation, atrial flutter, automatic atrial tachycardia, atrioventricular (AV) node re-entry tachycardia, supraventricular tachycardia (SVT) involving accessory pathways, accelerated junctional tachycardia, VT (from RV and LV sites), sustained rapid cardiac pacing, and even very frequent premature ventricular contractions or prolonged, sustained ventricular bigeminy. The development of TICMP is related to the rate of the tachycardia and the duration of the arrhythmia, and in TICMP caused by ventricular arrhythmia, the frequency, site of origin, and coupling intervals are important.[93,94] It is not known how long the tachycardia needs to be present in order to cause LV dysfunction, but sustained arrhythmia for days to weeks is likely necessary. The presence of an underlying predisposing substrate has been postulated, as not all patients with sustained tachycardia will develop cardiomyopathy.[95]

Animal models of TICMP have been established and studied to elucidate pathophysiologic mechanisms and clinical correlates. In these models, sustained, rapid atrial or ventricular pacing leads to severe biventricular systolic and diastolic dysfunction with four-chamber dilation and change in LV geometry to a more spherical shape. Within 24 hours of initiating rapid pacing, there is a fall in cardiac output and blood pressure. During the first week, pulmonary artery pressure rises, and there is an increase in left and right ventricular filling pressures. Neurohormonal activation occurs typical for dilated cardiomyopathy. Cardiac output and ejection fraction fall and ventricular volume increases over 3–5 weeks. When pacing is discontinued, cardiac output improves to near normal in 48 hours, and hemodynamics are normal within 4 weeks. Ejection fraction recovers to normal in 1–2 weeks, although end-diastolic volume remains high at 12 weeks, suggesting persistent remodeling. Structural cardiac changes seen include myocyte hypertrophy, apoptosis, and altered extracellular matrix. Proposed pathophysiologic mechanisms include myocardial energy depletion, ischemia, matrix remodeling with fibrosis, and altered myocyte handling of calcium.[95–98]

One study described EMB results in 19 patients diagnosed with TICMP. Compared with biopsy specimens in patients with inflammatory cardiomyopathy and dilated cardiomyopathy from other nonischemic causes, there was less fibrosis in TICMP (63% "mild," 37% "moderate"), more frequent infiltration with macrophages, and less prominent T lymphocytes. Electron microscopy revealed severely disturbed mitochondrial distribution.[93]

TICMP can occur at any age, from infants to the elderly. It has been reported to occur in fetuses with sustained SVT, which resolved with correction of the arrhythmia.[96] The incidence and prevalence of TICMP are not known. One study analyzed patients who were hospitalized for treatment of heart failure who had rapid atrial fibrillation and no prior diagnosis of cardiac illness. One-third of this group were determined to have TICMP. These patients had smaller ventricles initially and had better long-term prognosis, with lower rehospitalization and mortality rates.[99] In other observations, males were more frequently affected than females, the mean heart rate was 122/min, 84% of patients had atrial fibrillation as the inducing arrhythmia, and the average LVEF was 30%, with improvement by 15% at follow-up.[93] Patients with rapid atrial fibrillation and cardiomyopathy treated with AV node ablation also show improved cardiac function over time, indicating that tachycardia was more important in the pathophysiology than the lack of atrial-ventricular synchrony.

The diagnosis of TICMP should be suspected in any patient with impaired ventricular function in the setting of sustained SVT or VT. The diagnosis is clear when LV function before the onset of tachycardia was demonstrated to be normal and no intercurrent illness other than the arrhythmia has occurred. The diagnosis is confirmed when LV function rapidly improves with correction of the arrhythmia.

Treatment of TICMP is to rapidly restore normal heart rate. This can be done with parenteral rate-slowing medication, including beta-blockers such as esmolol or metoprolol, or calcium channel blockers such as diltiazem. Verapamil may aggravate hypotension and LV dysfunction and should be avoided. Adenosine can rapidly convert AV nodal re-entry tachycardia to sinus rhythm. Intravenous digoxin can also be considered, although its onset of action is delayed. Type I drugs such as procainamide can be prescribed for SVT associated with accessory pathways. Electrical cardioversion and ablation techniques can rapidly terminate supraventricular and ventricular arrhythmias and restore sinus rhythm. In patients with atrial flutter or atrial fibrillation, reliable control of the heart rate to a range of 60–90 per minute is a reasonable alternative to conversion of the arrhythmia to sinus rhythm.

In patients with TICMP who have received appropriate arrhythmia therapy, heart failure symptoms improve rapidly. LV systolic function will generally recover to normal within 4 weeks if there is no other underlying heart disease. Twenty-four to forty-eight hour cardiac rhythm monitoring is often necessary to ensure that heart rate is controlled during activity and at rest.[96] In a report of 11 patients with atrial flutter and abnormal systolic function who underwent atrial flutter ablation, ejection fraction improved from an average of 31% at baseline to 41% within 7 months of ablation. Lack of resolution of cardiomyopathy was predicted by a lower baseline ejection fraction.[100] A series of 24 patients with TICMP was reported whose cardiomyopathy initially resolved with arrhythmia control but who experienced repeated rapid decline in LV function and recurrent heart failure when their arrhythmias recurred. These patients again had improvement or normalization of ejection fraction after repeated arrhythmia control within 6 months. However, three of the patients died suddenly and unexpectedly, emphasizing that structural and electrical abnormalities may persist on a chronic basis.[101]

KEY POINTS

- Myocarditis is most often caused by a viral infection. Myocardial damage is mediated through activation of cellular immune mechanisms.
- The clinical course of myocarditis can be benign, with complete resolution, or the illness can be more severe, with the development of dilated cardiomyopathy and congestive heart failure. Cardiogenic shock and fatal arrhythmias can occur.
- The pharmacologic therapy of heart failure associated with myocarditis is similar to therapy used in other forms of dilated cardiomyopathy Severe cases may require the use of mechanical circulatory support.
- FM is an infrequent but severe form of myocarditis marked by severe heart failure and cardiogenic shock, requiring treatment with vasopressors, inotropes, and at times mechanical circulatory support. The prognosis is worse than in NFM. Significant improvement in LV function often occurs.
- Cardiac MRI is useful for the diagnosis of myocarditis. EMB can also be used for diagnosis and to decide on immunosuppressive therapy in severe cases.
- Immunosuppressive therapy based on the EMB results should not be used routinely in the treatment of myocarditis but should be strongly considered in patients who have severe heart failure early in the course of the illness, who have clinical characteristics of a treatable form of myocarditis, or whose condition deteriorates despite the use of conventional heart failure treatment.
- Stress cardiomyopathy, also called TABS, is an acute, severe cardiomyopathy often precipitated by emotional or physical stress, with a presentation similar to AMI. Patients will usually make a full recovery after intensive care during the acute phase of the illness.

References for this chapter can be found at expertconsult.com.

ANNOTATED REFERENCES

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Pericardial Diseases

Bernhard Maisch and Arsen D. Ristic

ETIOLOGY AND CLASSIFICATION OF PERICARDIAL DISEASE

The spectrum of pericardial diseases consists of congenital defects, pericarditis (dry, effusive, effusive-constrictive, or constrictive), neoplasms, and cysts. The etiologic classification comprises infectious pericarditis, pericarditis in systemic autoimmune diseases, type 2 (auto) immune process, postmyocardial infarction syndrome, and autoreactive (chronic) pericarditis.[1,2]

PERICARDIAL SYNDROMES

Congenital Defects of the Pericardium

Congenital defects of the pericardium are found in 1 in 10,000 autopsies. Pericardial absence can be partial left (70%), partial right (17%), or total bilateral (rare). Additional congenital abnormalities occur in approximately 30% of patients. Most patients with total pericardial absence are asymptomatic. Homolateral cardiac displacement and augmented heart mobility impose an increased risk for traumatic aortic dissection.[3] Partial left-side defects can be complicated by herniation and strangulation of the heart through the defect (causing chest pain, shortness of breath, syncope, or sudden death). Surgical pericardioplasty (Dacron, Gore-Tex, or bovine pericardium) is indicated for imminent strangulation.

Acute Pericarditis

Acute pericarditis is dry, fibrinous, or effusive, independent of its etiology. The major symptoms are retrosternal or left precordial chest pain (which radiates to the trapezius ridge, can be pleuritic or simulate ischemia, and varies with posture) and shortness of breath. A prodrome of fever, malaise, and myalgia is common, but elderly patients may not be febrile. A pericardial friction rub can be transient and monophasic, biphasic, or triphasic. A pleural effusion may be present. The heart rate is usually rapid and regular. Echocardiography is essential to detect effusion and concomitant heart or paracardial disease (Table 75.1).[4–11]

Hospitalization and symptomatic treatment are warranted. Nonsteroidal antiinflammatory drugs (NSAIDs) are the mainstay. Indomethacin should be avoided in elderly patients owing to its effect on reducing flow in the coronaries. Ibuprofen (300–800 mg TID) is preferred for its rare side effects, favorable impact on coronary blood flow, and large dose range.[4] Colchicine 0.5 mg at least twice daily for 3 months added to aspirin or another NSAID reduced the recurrence rate impressively in the COPE trial,[12] even at the first episode of pericarditis or even as monotherapy in "idiopathic" effusions. Colchicine is well tolerated, with fewer side effects than NSAIDs. Systemic corticosteroids should be restricted to connective tissue diseases and autoreactive or uremic pericarditis. Intrapericardial steroid application, as long-acting crystalloid triamcinolone, is effective for autoreactive effusions and avoids systemic side effects.[2]

Chronic Pericarditis

Chronic (>3 months) pericarditis includes effusive (inflammatory or hydropericardium in heart failure), adhesive, and constrictive forms.[4] Symptoms (chest pain, palpitations, and fatigue) are usually mild and related to the degree of cardiac compression and pericardial inflammation. The detection of curable causes (e.g., tuberculosis; toxoplasmosis; myxedema; or viral, autoimmune, and systemic diseases) allows successful specific therapy. Symptomatic treatment and pericardiocentesis should be applied, if indicated. For recurrences, the etiology should be investigated intensely, and if no specific therapy is effective, balloon pericardiotomy or pericardiectomy may be considered.

Recurrent Pericarditis

The term *recurrent pericarditis* encompasses (1) the intermittent type (symptom-free intervals without therapy) and (2) the incessant type (discontinuation of antiinflammatory therapy precipitates a relapse). Massive pericardial effusion, overt tamponade, or constriction is rare. Symptomatic management relies on exercise restriction and regimens used for acute pericarditis. Colchicine may be effective when NSAIDs and corticosteroids fail to prevent relapses.[12,13] It should be considered the first-choice treatment for recurrent pericarditis according to the CORE trial. Corticosteroids should be used only in patients with a poor general condition or in frequent crises.[4] A common mistake could be to use a dose too low to be effective or to taper the dose too rapidly. The recommended regimen is prednisone 1–1.5 mg/kg for at least 1 month. If patients do not respond adequately, azathioprine (75–100 mg/day) or cyclophosphamide can be added.[14]

Corticosteroids should be tapered over a 3-month period. Toward the end of the taper, introduce antiinflammatory treatment with colchicine (0.5 mg BID or TID) or an NSAID. Renewed treatment should continue for 3–6 months. Recently, it has been demonstrated in "idiopathic" pericarditis that previous corticosteroid treatment was a risk factor for recurrence or chronicity. Therefore corticosteroids should be administered after the definite exclusion of viral or bacterial infection of the pericardium. Pericardiectomy is indicated only for frequent and highly symptomatic recurrences resistant to medical treatment.[15]

Pericardial Effusion and Cardiac Tamponade

Pericardial effusion may appear as transudate (hydropericardium), exudate, pyopericardium, or hemopericardium. Large effusions are common with neoplastic, tuberculous, cholesterol, and uremic pericarditis and with myxedema and parasitoses. Loculated effusions are more common when scarring has supervened (e.g., postsurgical,

TABLE 75.1 Diagnostic Pathway and Sequence of Performance in Acute Pericarditis

Diagnostic Measure	Characteristic Findings
Obligatory	
Auscultation	Pericardial rub (monophasic, biphasic, or triphasic)
ECG*	*Stage I:* anterior and inferior concave ST-segment elevation. PR-segment deviations opposite to P-wave polarity.
	Early stage II: all ST junctions return to the baseline. PR segments deviated.
	Late stage II: T waves progressively flatten and invert.
	Stage III: generalized T-wave inversions in most or all leads.
	Stage IV: ECG returns to prepericarditis state.
Echocardiography	Effusion types B to D (Horowitz).
	Signs of tamponade.
Blood analyses	Erythrocyte sedimentation rate, C-reactive protein, lactate dehydrogenase, leukocytes (inflammation markers).
	Troponin I,† CK-MB (markers of myocardial involvement).
Chest radiograph	Ranging from normal to "water bottle" shape of the heart shadow.
	Performed primarily to reveal pulmonary or mediastinal pathology.
Mandatory in Tamponade, Optional in Large/Recurrent Effusions or if Previous Tests Inconclusive in Small Effusions	
Pericardiocentesis/drainage	Polymerase chain reaction and histochemistry for etiopathogenetic classification of infection or neoplasia.
Optional or if Previous Tests Inconclusive	
CT	Effusions, pericardium, and epicardium.
MRI	Effusions, pericardium, and epicardium.
Pericardioscopy, pericardial/epicardial biopsy	Establishing the specific etiology.

Data from Refs. 2, 3, and 7–19.
CK-MB, Creatine kinase-MB; *CT,* computed tomography; *ECG,* electrocardiogram; *MRI,* magnetic resonance imaging.
*Typical lead involvement: I, II, aVL, aVF, and V_3–V_6. The ST segment is always depressed in aVR, frequently in V_1, and occasionally in V_2. Stage IV may not occur, and there are permanent T-wave inversions and flattenings. If an ECG is first recorded in stage III, pericarditis cannot be differentiated by ECG from diffuse myocardial injury, "biventricular strain," or myocarditis. ECG in early repolarization is very similar to stage I. Unlike stage I, this ECG does not acutely evolve, and J-point elevations are usually accompanied by a slur, oscillation, or notch at the end of the QRS just before and including the J point (best seen with tall R and T waves—large in an early repolarization pattern). Pericarditis is likely if, in lead V_6, the J point is greater than 25% of the height of the T-wave apex (using the PR segment as a baseline).
†A rise in cardiac muscle troponin I (cTnI) was detected in 38/118 patients (32.2%); more frequently in younger, male patients; and with ST-segment elevation and pericardial effusion at presentation. An increase beyond 1.5 ng/mL was rare (7.6%) and associated with CK-MB elevation. cTnI increase was not a negative prognostic marker for the incidence of recurrences, constrictive pericarditis, cardiac tamponade, or residual left ventricular dysfunction.

posttraumatic, or purulent pericarditis). Effusions that develop slowly can be remarkably asymptomatic, whereas rapidly accumulating smaller effusions can present as tamponade. Cardiac tamponade is the decompensated phase of cardiac compression caused by effusion accumulation, leading to increased intrapericardial pressure. Heart sounds are distant. Orthopnea, cough, and dysphagia, occasionally with episodes of unconsciousness, can be observed. Insidiously developing tamponade may present as signs of its complications (renal failure, abdominal plethora, shock liver, worsening of glaucoma,[16] and mesenteric ischemia). Tamponade without two or more inflammatory signs (typical pain, pericardial friction rub, fever, or diffuse ST-segment elevation) is usually associated with a malignant effusion (likelihood ratio, 2.9).[17]

Electrocardiography demonstrates low QRS and T-wave voltages, PR-segment depression (Fig. 75.1), ST-segment/T-wave changes, bundle branch block, and electrical alternans (rarely seen in the absence of tamponade).[4] Microvoltage and electrical alternans are reversible after the drainage of the effusion and resolution of the inflammatory process.[11] In chest radiography, large effusions are depicted as globular cardiomegaly with sharp margins ("water bottle" silhouette) (Fig. 75.2). The size of effusions noted during echocardiography can be graded as (1) small (echo-free space in diastole <10 mm), (2) moderate (10–20 mm; Fig. 75.3), (3) large (≥20 mm), or (4) very large (≥20 mm and

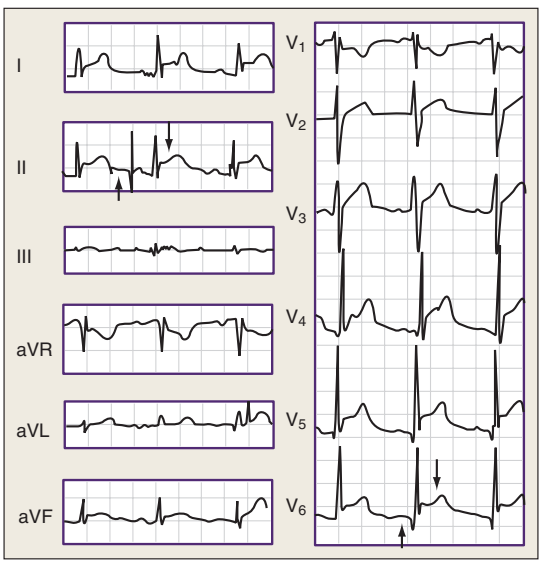

Fig. 75.1 Typical electrocardiographic changes in acute pericarditis: PR depression *(small arrow)* and concave ST-segment elevation *(large arrow)*.

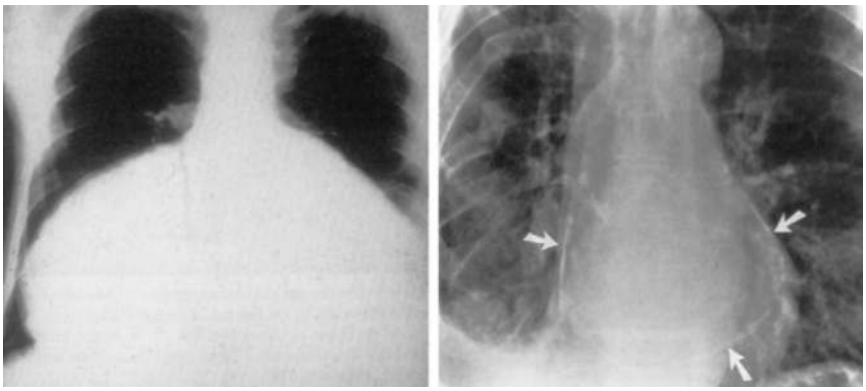

Fig. 75.2 Chest radiographs in a patient with a very large pericardial effusion—"water bottle" sign *(left)*—and in a patient with constrictive pericarditis and pericardial calcifications *(white arrows, right).*

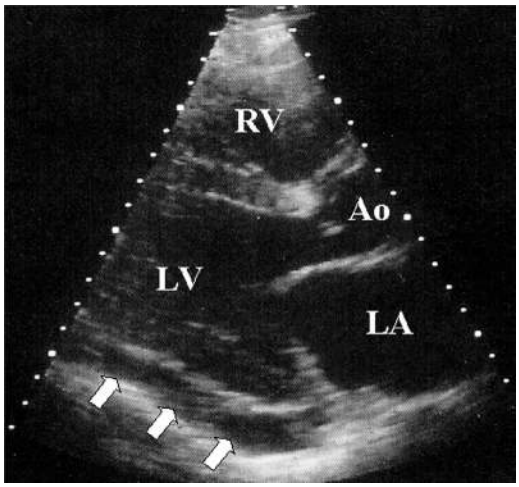

Fig. 75.3 Echocardiographic findings in a small to moderate pericardial effusion *(white arrows).* Long-axis parasternal view. *Ao,* Aortic root; *LA,* left atrium; *LV,* left ventricle; *RV,* right ventricle.

compression of the heart). In large pericardial effusions, the heart may move freely within the pericardial cavity ("swinging heart"), inducing pseudoprolapse and pseudosystolic anterior motion of the mitral valve, paradoxical motion of the interventricular septum, and midsystolic aortic valve closure (Table 75.2).[18–20] Up to one-third of patients with an asymptomatic large pericardial chronic effusion develop unexpected cardiac tamponade. Triggers for tamponade include hypovolemia, paroxysmal tachyarrhythmia, and intercurrent acute pericarditis.

Constrictive Pericarditis

Constrictive pericarditis is a rare, but severely disabling, consequence of chronic inflammation of the pericardium, leading to impaired filling of the ventricles and reduced ventricular function. Until recently, increased pericardial thickness has been considered an essential diagnostic feature of constrictive pericarditis. However, in a large surgical series from the Mayo Clinic, constriction was present in 18% of patients with normal pericardial thickness.[21] Tuberculosis, mediastinal irradiation, and previous surgical procedures are frequent. Constrictive pericarditis may rarely develop only in the epicardial layer in patients with a previously removed parietal pericardium.[22] Transient constrictive pericarditis is an uncommon but important entity because pericardiectomy is not indicated in these patients.[23]

Patients complain of fatigue, peripheral edema, breathlessness, and abdominal swelling, which may be aggravated by a protein-losing enteropathy. In decompensated patients, venous congestion, hepatomegaly, pleural effusions, and ascites may occur. Hemodynamic impairment can be additionally aggravated by systolic dysfunction caused by myocardial fibrosis or atrophy. Differential diagnosis has to include acute dilatation of the heart, pulmonary embolism, right ventricular infarction, pleural effusion, chronic obstructive lung disease, and restrictive cardiomyopathy. The best way to distinguish constrictive pericarditis from restrictive cardiomyopathy is by Doppler and/or tissue Doppler echocardiographic analysis of respiratory changes with or without changes in preload.[24] However, physical findings, an electrocardiogram (ECG), chest radiography (see Fig. 75.2, right), computed tomography (CT) (Fig. 75.4, left), magnetic resonance imaging (MRI) (see Fig. 75.4, right), hemodynamics, and endomyocardial biopsy may be helpful as well.[4]

Pericardiectomy is the only treatment for permanent constriction. The indications are based on clinical symptoms, echocardiographic findings, CT/MRI, and heart catheterization. A primary installation of cardiopulmonary bypass (CPB) is not recommended, as diffuse bleeding can occur after systemic heparinization. Pericardiectomy for constrictive pericarditis has a mortality rate of 6%–12%,[25] and complete normalization of cardiac hemodynamics is reported in only 60% of patients. Major complications include acute perioperative cardiac insufficiency and ventricular wall rupture. Cardiac mortality and morbidity with pericardiectomy are mainly caused by the presence of myocardial atrophy or myocardial fibrosis that was not recognized before surgery. The exclusion of patients with extensive myocardial fibrosis and/or atrophy has reduced the mortality rate of pericardiectomy to 5%. Postoperative low cardiac output should be treated by fluid substitution and catecholamines, high doses of digitalis, and intraaortic balloon pump in the most severe cases. If indications for surgery are established early, long-term survival after pericardiectomy corresponds to that of the general population. However, if severe clinical symptoms are present for a longer period before surgery, even complete pericardiectomy may not achieve total restitution.

Pericardial Cysts

Congenital pericardial cysts are uncommon; they may be unilocular or multilocular, with a diameter ranging from 1 to 5 cm. Inflammatory cysts comprise pseudocysts, in addition to encapsulated and loculated pericardial effusions, caused by rheumatic pericarditis, bacterial infection (particularly tuberculosis), trauma, and cardiac surgery. Most patients are asymptomatic, and cysts are detected incidentally on chest

TABLE 75.2 Diagnosis of Cardiac Tamponade

Clinical presentation	Elevated systemic venous pressure,* hypotension,† pulsus paradoxus,‡ tachycardia,§ dyspnea, or tachypnea with clear lungs
Precipitating factors	Drugs (cyclosporine, anticoagulants, thrombolytics), recent cardiac surgery, indwelling instrumentation, blunt chest trauma, malignancies, connective tissue disease, renal failure, septicemia‖
ECG	Can be normal or nonspecifically changed (ST-T wave), electrical alternans (QRS, rarely T), bradycardia (end stage), electromechanical dissociation (agonal phase)
Chest radiograph	Enlarged cardiac silhouette with clear lungs
M-mode/two-dimensional echocardiogram	Diastolic collapse of the anterior RV free wall,¶ RA collapse, LA and rarely LV collapse, increased LV diastolic wall thickness "pseudohypertrophy," IVC dilatation (no collapse in inspiration), "swinging heart"
Doppler	Tricuspid flow increases and mitral flow decreases during inspiration (reverse in expiration)
	Systolic and diastolic flows are reduced in systemic veins in expiration, and reverse flow with atrial contraction is increased
M-mode color Doppler	Large respiratory fluctuations in mitral/tricuspid flows
Cardiac catheterization	Confirmation of the diagnosis and quantification of the hemodynamic compromise
	RA pressure is elevated (preserved systolic × descent and absent or diminished diastolic and descent)
	Intrapericardial pressure is also elevated and virtually identical to RA pressure (both pressures fall in inspiration)
	RV mid-diastolic pressure is elevated and equal to the RA and pericardial pressures (no dip-and-plateau configuration)
	Pulmonary artery diastolic pressure is slightly elevated and may correspond to the RV pressure
	Pulmonary capillary wedge pressure is also elevated and nearly equal to intrapericardial and RA pressure
	LV systolic and aortic pressures may be normal or reduced
	Documenting that pericardial aspiration is followed by hemodynamic improvement**
	Detection of coexisting hemodynamic abnormalities (LV failure, constriction, pulmonary hypertension)
	Detection of associated cardiovascular diseases (cardiomyopathy, coronary artery disease)
RV/LV angiography	Atrial collapse and small hyperactive ventricular chambers
Coronary angiography	Coronary compression in diastole

Data from Refs. 31–41.
ECG, Electrocardiogram; *IVC,* inferior vena cava; *LA,* left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle.
*Jugular venous distention is less notable in hypovolemic patients or in "surgical tamponade." An inspiratory increase or lack of fall of pressure in the neck veins (Kussmaul sign), when verified by tamponade or after pericardial drainage, indicates effusive-constrictive disease.
†Heart rate is usually greater than 100 beats per minute but may be lower in patients with hypothyroidism or uremia.
‡Pulsus paradoxus is defined as a drop in systolic blood pressure greater than 10 mm Hg during inspiration, while diastolic blood pressure remains unchanged. It is easily detected by simply feeling the pulse, which diminishes significantly during inspiration. Clinically significant pulsus paradoxus is apparent when the patient is breathing normally. When this sign is present only in deep inspiration, it should be interpreted with caution. The magnitude of pulsus paradoxus is evaluated by sphygmomanometry. If pulsus paradoxus is present, the first Korotkoff sound is not heard equally well throughout the respiratory cycle, but only during expiration at a given blood pressure. The blood pressure cuff is therefore inflated above the patient's systolic pressure. Then it is slowly deflated, while the clinician observes the phase of respiration. During deflation, the first Korotkoff sound is intermittent. Correlation with the patient's respiratory cycle identifies a point at which the sound is audible during expiration but disappears when the patient breathes in. As the cuff pressure drops further, another point is reached when the first blood pressure sound is audible throughout the respiratory cycle. The difference in systolic pressure between these two points is the clinical measure of pulsus paradoxus. Pulsus paradoxus is absent in tamponade complicating an atrial septal defect and in patients with significant aortic regurgitation.
§Occasional patients are hypertensive, especially if they have preexisting hypertension.
‖Febrile tamponade may be misdiagnosed as septic shock.
¶Right ventricular collapse can be absent in elevated right ventricular pressure and right ventricular hypertrophy or in right ventricular infarction.
**If after drainage of the pericardial effusion, the intrapericardial pressure does not fall below atrial pressure, effusive-constrictive disease should be considered.

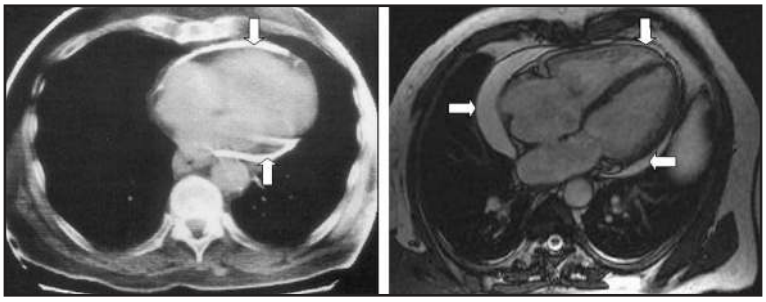

Fig. 75.4 Computed tomography findings in constrictive pericarditis *(left). White vertical arrows* are depicting thickened pericardium and pericardial calcification. The magnetic resonance imaging results of a patient with effusive-constrictive pericarditis are shown in the *right image. Horizontal arrows* show a loculated pericardial effusion, and the *vertical arrow* shows thickened pericardium.

radiographs as an oval, homogeneous radiodense lesion, usually at the right cardiophrenic angle. However, patients can also present with chest discomfort, dyspnea, cough, or palpitations, owing to compression of the heart. Echocardiography is useful, but additional imaging by CT (density readings) or MRI is often needed.[26] Treatment of congenital and inflammatory cysts involves percutaneous aspiration and ethanol sclerosis.[27] If this is not feasible, video-assisted thoracotomy or surgical resection may be necessary. Echinococcal cysts usually originate from ruptured hydatid cysts in the liver and lungs. Their surgical excision is not recommended; percutaneous aspiration and instillation of ethanol or silver nitrate after pretreatment with albendazole (800 mg/day for 4 weeks) is recommended instead.[27]

SPECIFIC FORMS OF PERICARDITIS

Viral Pericarditis

Viral pericarditis is the most common infection of the pericardium. Inflammatory abnormalities are the result of direct viral attack, the immune response (antiviral or anticardiac), or both. Early viral replication in pericardial and epimyocardial tissue elicits cellular and humoral immune responses against the virus and/or cardiac tissue. Deposits of immunoglobulin (Ig) M, IgG, and occasionally IgA can be found in the pericardium and myocardium for years. Various viruses can cause pericarditis, including enteroviruses, echoviruses, adenoviruses, cytomegaloviruses, Epstein-Barr virus, herpes simplex, herpes human virus 6 (HHV6), influenza viruses, parvovirus B19 (PVB19), hepatitis C, and human immunodeficiency virus (HIV). In the past few years, PVB19 and HHV6 have been increasing and enteroviruses, echoviruses, and adenoviruses have been decreasing as causes; these trends have also been observed in myocarditis. Attacks of enteroviral pericarditis follow the seasonal epidemics of coxsackievirus A and B and echovirus infections. Cytomegalovirus (CMV) pericarditis has an increased incidence in immunocompromised and HIV-infected hosts. Infectious mononucleosis may also present as pericarditis.

Diagnosing viral pericarditis is not possible without evaluating pericardial effusion and/or pericardial/epicardial tissue, preferably by polymerase chain reaction (PCR) or in situ hybridization. A fourfold rise in serum antibody levels is suggestive, but not diagnostic, of viral pericarditis.

Treatment of viral pericarditis is directed toward resolving symptoms (see "Acute Pericarditis"), preventing complications, and eradicating the virus. In patients with chronic or recurrent symptomatic pericardial effusion and confirmed viral infection, the following specific treatments are under investigation[28]:

1. CMV pericarditis: hyperimmune globulin once per day 4 mL/kg on days 0, 4, and 8 and 2 mL/kg on days 12 and 16
2. Coxsackievirus B pericarditis: interferon alfa or interferon beta 2.5×10^6 IU/m^2 subcutaneously three times per week
3. Adenovirus, PVB19, and HHV6 perimyocarditis: immunoglobulin treatment with 20 g or more intravenously on days 1 and 3 for 6 to 8 hours, which may be repeated and combined with ganciclovir to become effective for virus elimination

Pericardial manifestations of HIV infection can result from infective, noninfective, and neoplastic (Kaposi sarcoma and/or lymphoma) diseases. Infective (myo)pericarditis results from local HIV infection and/or from other viral, bacterial (e.g., *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Mycobacterium avium*, *M. tuberculosis*), and fungal coinfections (*Cryptococcus neoformans*). In progressive disease, the incidence of echocardiographically detected pericardial effusion may be up to 40%. Cardiac tamponade is rare. During treatment with retroviral compounds, lipodystrophy can develop (best demonstrated by MRI), with intense paracardial fat deposition leading to heart failure. Treatment is generally symptomatic, whereas in large effusions and cardiac tamponade, pericardiocentesis is necessary. The use of corticosteroid therapy is contraindicated except in patients with secondary tuberculous pericarditis, as an adjunct to tuberculostatic treatment.[29]

Bacterial Pericarditis

Purulent pericarditis in adults is rare but always fatal if not treated.[30,31] The mortality rate in treated patients is 40%, mostly because of cardiac tamponade, toxicity, and constriction. It is usually a complication of an infection originating elsewhere in the body, arising by contiguous spread or hematogenous dissemination.[32] Predisposing conditions are pericardial effusion, immunosuppression, chronic diseases (e.g., alcohol abuse, rheumatoid arthritis), cardiac surgery, and chest trauma. The disease appears as an acute, fulminant infectious illness of short duration. Percutaneous pericardiocentesis must be promptly performed, and the obtained pericardial fluid should undergo Gram staining, acid-fast staining, and fungal staining, followed by cultures of the pericardial and body fluids. Rinsing of the pericardial cavity, combined with effective systemic antibiotic therapy, is mandatory (antistaphylococcal antibiotic plus aminoglycoside, followed by tailored antibiotic therapy according to the pericardial fluid and blood culture results).[30] Intrapericardial instillation of antibiotics (e.g., gentamicin) is useful but not sufficient. Frequent irrigation of the pericardial cavity with urokinase or streptokinase using large catheters may liquefy the purulent exudate,[31] but open surgical drainage through a subxiphoid pericardiotomy is preferable. Pericardiectomy is required in patients with dense adhesions, a loculated and thick purulent effusion, recurrence of tamponade, persistent infection, and progression to constriction.[30] Surgical mortality is up to 8%.

Tuberculous Pericarditis

In the past decade, tuberculous pericarditis in developed countries has been primarily seen in immunocompromised patients, such as those with acquired immunodeficiency syndrome (AIDS). The mortality rate in untreated effusive tuberculous pericarditis approaches 85%. Pericardial constriction occurs in 30%–50% of patients.

The clinical presentation is variable: acute pericarditis with or without effusion; cardiac tamponade; silent, often large, pericardial effusion with a relapsing course; toxic symptoms with persistent fever; acute constrictive pericarditis; subacute constriction; effusive-constrictive or chronic constrictive pericarditis; and pericardial calcifications. The diagnosis is made by identification of *M. tuberculosis* in the pericardial fluid or tissue and/or the presence of caseous granulomas in the pericardium. Importantly, PCR can identify the DNA of *M. tuberculosis* rapidly from only 1 μL of pericardial fluid. Increased adenosine deaminase activity and interferon gamma concentration in pericardial effusion are also diagnostic, with a high sensitivity and specificity. Both pericardioscopy and pericardial biopsy have also improved the diagnostic accuracy for tuberculous pericarditis (Fig. 75.5). Pericardial biopsy enables rapid diagnosis with better sensitivity than pericardiocentesis (100% vs. 33%).

Pericarditis in a patient with proven extracardiac tuberculosis is strongly suggestive of a tuberculous etiology (several sputum cultures should be taken). The tuberculin skin test may be falsely negative in 25%–33% of tests and falsely positive in 30%–40% of patients. The more accurate enzyme-linked ImmunoSpot test detects T cells specific for *M. tuberculosis* antigen.[33] Perimyocardial tuberculous involvement is also associated with high serum titers of antimyolemmal and antimyosin antibodies. The diagnostic yield of pericardiocentesis in tuberculous pericarditis ranges from 30% to 76% according to methods used for analyzing pericardial effusions. Pericardial fluid demonstrates high specific gravity, high protein levels, and a high white blood cell count (from 0.7 to 54×10^9/L).

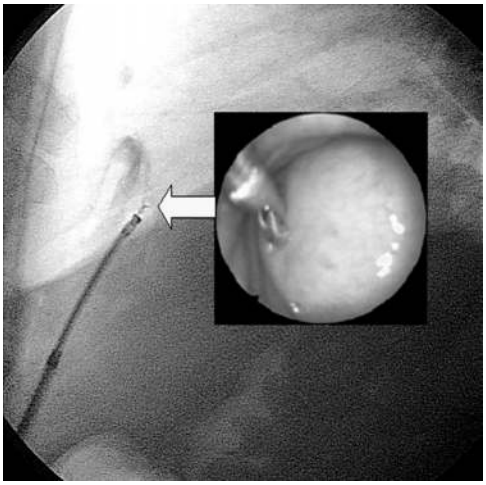

Fig. 75.5 Flexible percutaneous pericardioscopy and epicardial biopsy *(arrow).*

Various antituberculous drug combinations of different durations (6, 9, or 12 months) have been used.[34,35] Prevention of constriction in chronic pericardial effusion of undetermined etiology by "ex iuvantibus" antitubercular treatment was not successful. The use of corticosteroids remains controversial.[34,35] A meta-analysis of patients with effusive and constrictive tuberculous pericarditis[34,35] suggested that tuberculostatic treatment combined with corticosteroids might be associated with fewer deaths and less frequent need for pericardiocentesis or pericardiectomy. If given, prednisone should be administered in relatively high doses (1–2 mg/kg/day) because rifampicin induces its liver metabolism.[4] This dose is maintained for 5–7 days and progressively reduced in 6–8 weeks. If constriction develops despite combination therapy, pericardiectomy is indicated.

Pericarditis in Renal Failure

Renal failure is a common cause of pericardial disease, producing large pericardial effusions in up to 20% of patients. Two forms have been described:

1. Uremic pericarditis: this occurs in 6%–10% of patients with advanced renal failure (acute or chronic) before dialysis has been instituted or shortly thereafter. It results from inflammation of the visceral and parietal pericardium and correlates with the degree of azotemia (blood urea nitrogen >60 mg/dL).
2. Dialysis-associated pericarditis: this occurs in up to 13% of patients on maintenance hemodialysis and occasionally with chronic peritoneal dialysis. It is the result of inadequate dialysis and/or fluid overload. Pathologic examination of the pericardium shows adhesions between the thickened pericardial membranes ("bread and butter" appearance). The clinical features may include transient pericardial rubs, fever, and pleuritic chest pain, but many patients are asymptomatic. Because of autonomic impairment in uremic patients, the heart rate may remain slow (60–80 beats/min) during tamponade, despite fever and hypotension. Anemia, caused by induced resistance to erythropoietin, may worsen the clinical picture. The ECG may not show the typical diffuse ST-segment/T-wave elevations observed with other causes of acute pericarditis, owing to a lack of myocardial inflammation.[36] If the ECG is typical of acute pericarditis, intercurrent infection must be suspected.

Most patients with uremic pericarditis respond rapidly to hemodialysis or peritoneal dialysis with resolution of chest pain and the pericardial effusion. To avoid hemopericardium, heparin-free hemodialysis should be used. Hypokalemia and hypophosphatemia should be prevented by supplementing the dialysis solution when appropriate. Intensified dialysis usually leads to resolution of the pericarditis within 1–2 weeks.[37] Peritoneal dialysis, which does not require heparinization, may be therapeutic in pericarditis resistant to hemodialysis or if heparin-free hemodialysis cannot be performed. NSAIDs and systemic corticosteroids have limited success when intensive dialysis is ineffective.[38] Cardiac tamponade and large chronic effusions resistant to dialysis must be treated with pericardiocentesis. Large, nonresolving symptomatic effusions should be treated with intrapericardial instillation of corticosteroids after pericardiocentesis or subxiphoid pericardiotomy (triamcinolone hexacetonide 50 mg every 6 hours for 2–3 days).[38] Pericardiectomy is indicated only in severely symptomatic patients refractory to other treatment owing to its potential morbidity and mortality. After renal transplantation, pericarditis has also been reported in 2.4% of patients. Uremia or infection (CMV) may be the causes.

Autoreactive Pericarditis and Pericarditis in Systemic Autoimmune Diseases

The diagnosis of autoreactive pericarditis is established using the following criteria[2]:

1. Pericardial fluid containing increased number of lymphocytes, in addition to mononuclear cells greater than 5000/mm^3 (autoreactive lymphocytic) or antibodies (e.g., antisarcolemmal) against heart muscle tissue (autoreactive antibody mediated)
2. Inflammation in epicardial/endomyocardial biopsy samples of more than 14 cells/mm^2
3. Exclusion of active viral infection both in the pericardial effusion and endomyocardial/epimyocardial biopsy samples (no virus isolation, no IgM titer against cardiotropic viruses in the pericardial effusion, and PCR negative for major cardiotropic viruses)
4. Tuberculosis, *Borrelia burgdorferi, Chlamydia pneumoniae,* and other bacterial infections excluded by PCR and/or cultures
5. Neoplastic infiltration absent in the pericardial effusion and biopsy samples
6. Exclusion of systemic metabolic disorders and uremia

For autoreactive pericarditis, intrapericardial treatment with triamcinolone is effective, with rare side effects.

Pericarditis occurs in many systemic autoimmune diseases: rheumatoid arthritis, systemic lupus erythematosus, progressive systemic sclerosis, polymyositis/dermatomyositis, mixed connective tissue disease, seronegative spondyloarthropathies, systemic and hypersensitivity vasculitides, Behçet syndrome, granulomatosis with polyangiitis, and sarcoidosis.[4] Intensified treatment of the underlying disease and symptomatic management are indicated.

The Postcardiac Injury Syndrome: Postpericardiotomy Syndrome

Postcardiac injury syndrome develops within days to months after cardiac injury, pericardial injury, or both.[4,39,40] It resembles postmyocardial infarction syndrome, with both conditions appearing to be variants of a common immunopathologic process. Pericardial effusion also occurs after orthotopic heart transplantation (21% of patients). It is more frequent in patients receiving aminocaproic acid during the operation.[41] Cardiac tamponade after open heart surgery is more common after valve surgery than after coronary artery bypass grafting and may be related to the preoperative use of anticoagulants.[42]

Warfarin administration in patients with early postoperative pericardial effusion imposes the greatest risk, particularly in those who did not undergo pericardiocentesis and drainage of the effusion.[43] Symptomatic treatment is generally the same as in acute pericarditis (NSAIDs

or colchicine for several weeks or months), but this has been questioned recently.[44] In patients undergoing cardiac surgery, perioperative use of colchicine compared with placebo reduced the incidence of postpericardiotomy syndrome but with an increased rate of gastrointestinal adverse effects.[45] Long-term (3–6 months) oral corticosteroids, or preferably pericardiocentesis and intrapericardial instillation of triamcinolone (300 mg/m^2), are therapeutic options in refractory forms. Redo surgery is rarely needed.

Postinfarction Pericarditis

Two forms of postinfarction pericarditis can be distinguished: an "early" form (pericarditis epistenocardiaca) and a "delayed" form (Dressler syndrome). Epistenocardiac pericarditis, caused by direct exudation, occurs in 5%–20% of transmural myocardial infarctions but is rarely discovered clinically. Dressler syndrome occurs from 1 week to several months after myocardial infarction and has symptoms and manifestations similar to those of postcardiac injury syndrome. It does not require a transmural infarction, and it can also appear as an extension of epistenocardiaca pericarditis. Its incidence is 0.5%–5% and is lower still in patients treated with thrombolytics (<0.5%) but more frequent in cases of pericardial bleeding after antithrombotic treatment. Of note, ECG changes are often overshadowed by myocardial infarction changes. Stage I ECG changes are uncommon and suggest "early" postmyocardial infarction syndrome, whereas failure to evolve or "resurrection" of previously inverted T waves strongly suggests myocardial infarction pericarditis. Postinfarction pericardial effusion greater than 10 mm is most frequently associated with hemopericardium, and two-thirds of these patients may develop tamponade/free wall rupture.[46] Urgent surgical treatment is lifesaving. If immediate surgery is not available or contraindicated, pericardiocentesis and intrapericardial fibrin glue instillation could be an alternative in subacute tamponade.[46,47] Ibuprofen, which increases coronary flow, is the agent of choice. Aspirin, up to 650 mg every 4 hours for 2–5 days, has also been successfully applied. Corticosteroids can be used for refractory symptoms but may delay healing after the infarction.[4]

Traumatic Pericardial Effusion and Hemopericardium in Aortic Dissection

Direct pericardial injury can be induced by accidents or iatrogenic wounds. Iatrogenic tamponade occurs most frequently in percutaneous mitral valvuloplasty, during or after transseptal puncture, particularly if no biplane catheterization laboratory is available and a small left atrium is present. Whereas puncture of the interatrial septum is asymptomatic, passage through the free wall induces immediate chest pain. If high-pressure–containing structures are punctured, rapid deterioration occurs. However, if only the atrial wall is perforated, tamponade may be delayed for 4–6 hours. Rescue pericardiocentesis is successful in 95%–100% of cases, with less than 1% mortality.

Transection of the coronary artery and acute or subacute cardiac tamponade occur very rarely during percutaneous coronary interventions.[48] A breakthrough in the treatment of coronary perforation has been the development of membrane-covered graft stents.

During right ventricular endomyocardial biopsy, the catheter may pass through the myocardium, particularly when the bioptome has not been opened before reaching the endocardial border or has been directed toward the right ventricular free wall instead of toward the septum. Frank cardiac perforations are accompanied by sudden bradycardia and hypotension. Perforation rates of 0.3%–5% have been reported, leading to tamponade and circulatory collapse in less than half of cases.[49] The incidence of pericardial hemorrhage with left ventricular endomyocardial biopsy is lower (0.1%–3.3%). Severe complications, leading to procedure-related mortality, were reported in only 0.05% of more than 6000 cases in a worldwide survey and in none of the 2537 patients at our center.[49]

Pacemaker leads penetrating the right ventricle or epicardial electrodes may cause pericarditis with tamponade, adhesions, or constriction.[50,51] A right bundle branch block instead of the usual left bundle branch block is a clue that this has occurred.

Blunt chest trauma is a major risk of motor vehicle accidents. The deceleration force can lead to myocardial contusion with intrapericardial hemorrhage, cardiac rupture, pericardial rupture, or herniation. Transesophageal echocardiography or immediate CT should be performed. Pericardial laceration and partial extrusion of the heart into the mediastinum and pleural space may also occur after injury.

In dissection of the ascending aorta, pericardial effusion can be found in 17%–45% of patients and 48% of autopsy cases. In a clinical series of aortic dissection, pericardial tamponade was found by CT, MRI, or echocardiography in 17%–33% of patients with type I dissection, 18%–45% with type II dissection, and 6% with type III dissection. Pericardiocentesis is contraindicated, owing to the risk of intensified bleeding and extension of the dissection.[52] Surgery should be performed immediately.

Neoplastic Pericarditis

Primary tumors of the pericardium are 40 times less common than metastatic ones.[4] Mesothelioma, the most common primary tumor, is almost always incurable. The most common secondary malignant tumors are lung cancer, breast cancer, malignant melanoma, lymphoma, and leukemia. Effusions may be small or large with imminent tamponade (frequent recurrences) or constriction. Tamponade may even be the initial sign of malignant disease. With small effusions, most patients are asymptomatic. The onset of dyspnea, cough, chest pain, tachycardia, and jugular venous distention is observed when the volume of fluid exceeds 500 mL. Pulsus paradoxus, hypotension, cardiogenic shock, and paradoxical movement of the jugular venous pulse are important signs of cardiac tamponade. The diagnosis is based on confirmation by cytology or biopsy of malignant infiltration within the pericardium. Of note, in almost two-thirds of patients with documented malignancy, pericardial effusion is caused by nonmalignant diseases (e.g., radiation pericarditis, opportunistic infections). The chest radiograph, CT, and MRI may reveal mediastinal widening, a hilar mass, or pleural effusion.[4] The analysis of pericardial fluid and pericardial or epicardial biopsy is essential for the confirmation of malignant pericardial disease.

Cardiac tamponade is an absolute indication for pericardiocentesis. In suspected neoplastic pericardial effusion without tamponade, systemic antineoplastic treatment as baseline therapy can prevent recurrences in up to 67% of cases. However, pericardial drainage is recommended in all patients with large effusions because of the high recurrence rate (40%–70%).[46–55] Prevention of recurrences may be achieved by intrapericardial instillation of sclerosing agents, cytotoxic agents, or immunomodulators. Intrapericardial treatment tailored to the type of the tumor indicates that administration of cisplatin is effective in secondary lung cancer, and intrapericardial instillation of thiotepa appears to be highly effective in breast cancer pericardial metastases.[56–58] No patient in these studies showed signs of constrictive pericarditis. Tetracyclines as sclerosing agents also control malignant pericardial effusions in around 85% of cases, but side effects and complications are quite frequent: fever (19%), chest pain (20%), and atrial arrhythmias (10%).[55] Although intrapericardial administration of radionuclides has yielded very good results, it is not widely accepted because of the logistic problems connected with radioactivity. Radiation therapy is very effective (93%) in controlling malignant pericardial effusions in patients with radiosensitive tumors, such as lymphoma and leukemia.

However, radiotherapy of the heart itself can cause myocarditis and pericarditis.

RARE FORMS OF PERICARDIAL DISEASE

Fungal pericarditis occurs mainly in immunocompromised patients or in the course of endemic, acquired fungal infections. It is caused by endemic *(Histoplasma, Coccidioides)* or opportunistic fungi *(Candida, Aspergillus, Blastomyces)* and semifungi *(Nocardia, Actinomyces)*. Diagnosis is obtained by staining and culturing pericardial fluid or tissue. Antifungal antibodies in serum are also helpful in establishing the diagnosis. Treatment with fluconazole, ketoconazole, itraconazole, amphotericin B, liposomal amphotericin B, or amphotericin B lipid complex is indicated. NSAIDs can support the treatment with antifungal drugs. Patients with histoplasmosis pericarditis do not need antifungal therapy but respond to NSAIDs given for 2–12 weeks. Sulfonamides are the drugs of choice for nocardiosis. A combination of three antibiotics, including penicillin, should be given for actinomycosis. Pericardiocentesis or surgical treatment is indicated for hemodynamic impairment. Pericardiectomy is indicated in fungal constrictive pericarditis.

Radiation pericarditis may begin during exposure (very rare) or months to years later, with a latency of up to 15–20 years. Its occurrence is influenced by the applied source, dose, fractionation, duration, radiation-exposed volume, form of mantle field therapy, and age of the patient. The effusion may be serous or hemorrhagic, later on with fibrinous adhesions or constriction; it is typically without tissue calcification. The symptoms may be masked by the underlying disease or chemotherapy. Imaging should start with echocardiography, followed by cardiac CT or MRI, if necessary. Pericarditis without tamponade may be treated conservatively, but effusions respond favorably to intrapericardial triamcinolone instillation. Pericardiocentesis and fluid analysis can rule out neoplastic progression to the pericardium.[59] Pericardial constriction occurs in up to 20% of patients, requiring pericardiectomy. Operative mortality is high (21%) and postoperative 5-year survival is poor (1%), mostly because of myocardial fibrosis.

Chylopericardium refers to a communication between the pericardium and thoracic duct. It may be the result of trauma, congenital anomalies, complications of open heart surgery, mediastinal lymphangiomas, lymphangiomatous hamartomas, lymphangiectasis, and obstruction or anomalies of the thoracic duct. Infection, tamponade, or constriction may aggravate the prognosis. The pericardial fluid is sterile, odorless, and opalescent, with a milky white appearance and the microscopic finding of fat droplets. The chylous nature of the fluid is confirmed by its alkaline reaction, specific gravity between 1010 and 1021, Sudan III stain for fat, and high concentrations of triglycerides (5–50 g/L) and protein (22–60 g/L). Enhanced CT, alone or combined with lymphography, can identify not only the location of the thoracic duct but also its lymphatic connection to the pericardium.

Treatment depends on the etiology and amount of chylous accumulation. Chylopericardium after thoracic or cardiac operations is preferably treated by pericardiocentesis and diet (medium-chain triglycerides).[60] If further production of chylous effusion continues, surgical treatment is mandatory. When conservative treatment and pericardiocentesis fail, creation of a pericardioperitoneal window is a reasonable option.[61] Alternatively, when the course of the thoracic duct is precisely identified, its ligation and resection just above the diaphragm is the most effective treatment.

Drug- and toxin-related pericarditis, tamponade, adhesions, fibrosis, or constriction may be induced by several drugs.[4] Mechanisms include drug-induced lupus reactions, idiosyncrasy, "serum sickness," foreign substance reactions, and immunopathy. Management is based on discontinuation of the causative agent and symptomatic treatment.

Pericardial effusion in hypothyroidism occurs in 5%–30% of patients.[4] Fluid accumulates slowly, and tamponade occurs rarely. In some cases, cholesterol pericarditis may be observed. The diagnosis is based on serum levels of thyroxine and thyroid-stimulating hormone. Bradycardia, low QRS voltage and T-wave inversion or flattening on the ECG, cardiomegaly on a chest radiograph, and pericardial effusion on echocardiography, in addition to a history of radiation-induced thyroid dysfunction, myopathy, ascites, pleural effusion, and uveal edema may be observed.[62] Therapy with thyroid hormone decreases the pericardial effusion.

Pericardial effusion and constriction in pregnancy may manifest as a minimal to moderate, clinically silent hydropericardium by the third trimester. Cardiac compression is rare. ECG changes of acute pericar-

KEY POINTS

- The diagnosis of acute pericarditis is based on clinical presentation (chest pain, pericardial friction rub) and typical four-stage ECG changes. For etiologic diagnosis, pericardiocentesis, pericardioscopy, and pericardial/epicardial biopsy may be necessary.
- Echocardiography is essential in all patients with pericarditis to detect pericardial effusion and determine its physiologic significance and to check for signs of constriction, concomitant heart disease, or paracardial pathology.
- A large proportion of patients usually classified as having "idiopathic" pericarditis actually have viral and autoreactive pericarditis. The diagnosis of viral pericarditis is not possible without the evaluation of pericardial effusion and/or pericardial/epicardial tissue, preferably by PCR or in situ hybridization.
- PCR identification of *M. tuberculosis,* high adenosine deaminase activity, and interferon gamma concentration in pericardial effusion are diagnostic with a high sensitivity and specificity for tuberculous pericarditis.
- Pericardiocentesis is indicated for cardiac tamponade; for a high suspicion of purulent, tuberculous, or neoplastic pericarditis; or in patients with a very large effusion without signs of tamponade (>20 mm in echocardiography in diastole). Electrical alternans and pulsus paradoxus are clinically important signs of the advanced stages of cardiac tamponade and indicate the need for prompt pericardial drainage.
- Aortic dissection is a major contraindication to pericardiocentesis. Relative contraindications include uncorrected coagulopathy; anticoagulant therapy; thrombocytopenia less than 50,000/mm^3; and small, posterior, and loculated effusions.
- In cardiac wounds, postinfarction myocardial rupture, or dissecting aortic hematoma, emergency cardiac surgery is lifesaving. Loculated effusions may require open surgery or thoracoscopic drainage.
- Postinfarction pericardial effusions larger than 10 mm in diastole are frequently associated with cardiac rupture. Urgent surgical treatment is indicated.
- Intrapericardial instillation of antineoplastic (e.g., cisplatin, thiotepa) and/or sclerosing agents (e.g., gentamicin) can prevent recurrences of neoplastic pericardial effusions. Intrapericardial instillation of triamcinolone is highly effective in preventing recurrences in patients with autoreactive pericardial effusion and avoids the adverse effects of systemic corticosteroid therapy.
- Pericardiectomy is the only treatment for permanent constrictive pericarditis. However, surgery should not be performed too early to avoid operating on patients with transient constriction. Even more important is not to perform surgery too late or in patients with myocardial fibrosis and/or atrophy. If indications for surgery are established early enough, long-term survival after pericardiectomy corresponds to that of the general population.

ditis in pregnancy should be distinguished from the slight ST-segment depression and T-wave changes seen in normal pregnancy. Occult constriction becomes manifest in pregnancy because of the increased blood volume. Most pericardial disorders are managed as in nonpregnant women.[63,64] However, caution is necessary because high-dose aspirin may prematurely close the ductus arteriosus, and colchicine is contraindicated in pregnancy. Pericardiotomy and pericardiectomy can be safely performed if necessary and do not impose a risk for subsequent pregnancies.[64,65]

Fetal pericardial fluid can be detected by echocardiography after 20 weeks' gestation and is normally 2 mm or less in depth. A greater amount of fluid should raise questions about the possibility of Rh disease (hydrops fetalis), neoplasia, hypoalbuminemia, immunopathy, or maternally transmitted mycoplasmal or other infections.

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76

Emergency Heart Valve Disorders

Jason P. Linefsky and Catherine M. Otto

Key concepts in the management of a critically ill patient with valvular heart disease are the use of echocardiography to provide an accurate diagnosis of disease severity and the appropriate use of invasive hemodynamic monitoring to optimize loading conditions. Physical examination is not reliable for diagnosing the presence or severity of valvular heart disease, particularly in patients with acute hemodynamic compensation. Handheld echocardiography may provide clues to the presence of valve disease but does not replace the need for a complete diagnostic study when this diagnosis is suspected. With acute valve regurgitation or prosthetic valve thrombosis, urgent surgical intervention may be necessary. In critically ill patients who are poor surgical candidates, rapid relief of valve obstruction can be lifesaving, including transcatheter balloon valvotomy for rheumatic mitral stenosis or transcatheter aortic valve implantation for calcific aortic stenosis (Fig. 76.1).

MITRAL REGURGITATION

Etiology

Mitral regurgitation may be caused by disease or the distortion of any component of the mitral valve apparatus—the mitral annulus, leaflets, chordae, and papillary muscles—and by alterations in left ventricular (LV) geometry or systolic function (Fig. 76.2).[1] Primary causes of acute mitral regurgitation include endocarditis and myxomatous valve disease (mitral valve prolapse) with spontaneous chordal rupture [2] Bacterial endocarditis results in acute mitral regurgitation because of the destruction of valve tissue, often with leaflet perforation.[3]

Acute secondary mitral regurgitation may be the result of an acute cardiomyopathy (e.g., takotsubo cardiomyopathy) or coronary disease with acute myocardial infarction or papillary muscle rupture Moderate to severe mitral regurgitation caused by papillary muscle involvement or regional myocardial dysfunction complicates 12% of acute myocardial infarctions and is associated with an increased risk of heart failure or death.[4,5]

Iatrogenic acute mitral regurgitation is a rare complication of balloon mitral valvotomy.[6] Acute mitral regurgitation also may complicate the use of transaortic axial flow ventricular assist devices if the catheter interferes with normal mitral valve closure or disrupts the valve apparatus when the device is removed.[7]

The management of acute mitral regurgitation differs depending on the cause, making the identification of the correct etiology essential during evaluation.

Clinical Presentation

Acute mitral regurgitation presents with acute pulmonary edema and is a surgical emergency (Figs. 76.3 and 76.4).[8] Mitral chordal rupture results in the acute presentation of heart failure, often in patients unaware of the diagnosis of mitral valve prolapse. Patients with mitral valve perforation caused by endocarditis present with pulmonary edema superimposed on the signs and symptoms of endocarditis. Papillary muscle rupture or dysfunction after myocardial infarction (MI) usually presents several days after acute MI; in some cases, the initial presentation is of acute pulmonary edema, with the MI being clinically silent.

Chronic mitral regurgitation is usually well tolerated even when there is a superimposed hemodynamic load such as systemic infection, pregnancy, or trauma. However, mitral regurgitant severity may acutely worsen by at least two mechanisms. An increase in afterload, for example, with a hypertensive crisis, may increase regurgitant severity caused by an increased driving pressure from the left ventricle to the left atrium. An alteration in the LV geometry, for example, with ventricular dilation caused by decompensated heart failure may change the orientation of the papillary muscles such that leaflet closure is impaired, resulting in a larger regurgitant orifice area.[9] In this situation, a vicious cycle may ensue where LV dilation worsens mitral regurgitant severity, which increases LV dilation.

Diagnosis

A high level of clinical suspicion is needed to make a diagnosis of acute mitral regurgitation (Table 76.1).[8] Acute pulmonary edema often obscures the signs and symptoms of the underlying disease process. The classical finding is a holosystolic murmur at the apex, radiating to the axilla. Although there is some correlation between murmur loudness and regurgitant severity with chronic regurgitation, the murmur may be soft with acute severe mitral regurgitation. In patients with severe mitral regurgitation after MI, a murmur cannot be appreciated in up to 50% of patients.

Thus in patients presenting with acute pulmonary edema or cardiogenic shock, prompt echocardiography is essential. Transthoracic images are often diagnostic, allowing the identification of the etiology of valve dysfunction, quantitation of regurgitant severity, estimation of pulmonary pressures, and measurement of ventricular size and systolic function. If transthoracic images are nondiagnostic, transesophageal echocardiography (TEE) can be performed at the bedside in the intensive care unit (ICU). TEE provides excellent images of valve anatomy and the Doppler evaluation of valve function.

Other diagnostic tests are based on the clinical presentation. Multiple blood cultures should be obtained in febrile patients with systemic or pulmonary edema to exclude the possibility of endocarditis. In patients with an abnormal electrocardiogram (ECG), chest pain, or a history of coronary artery disease, coronary angiography may be needed.

In patients with acute pulmonary edema or cardiogenic shock after MI, the differential diagnosis includes acute mitral regurgitation, a ventricular septal defect, or a contained rupture of the ventricular free

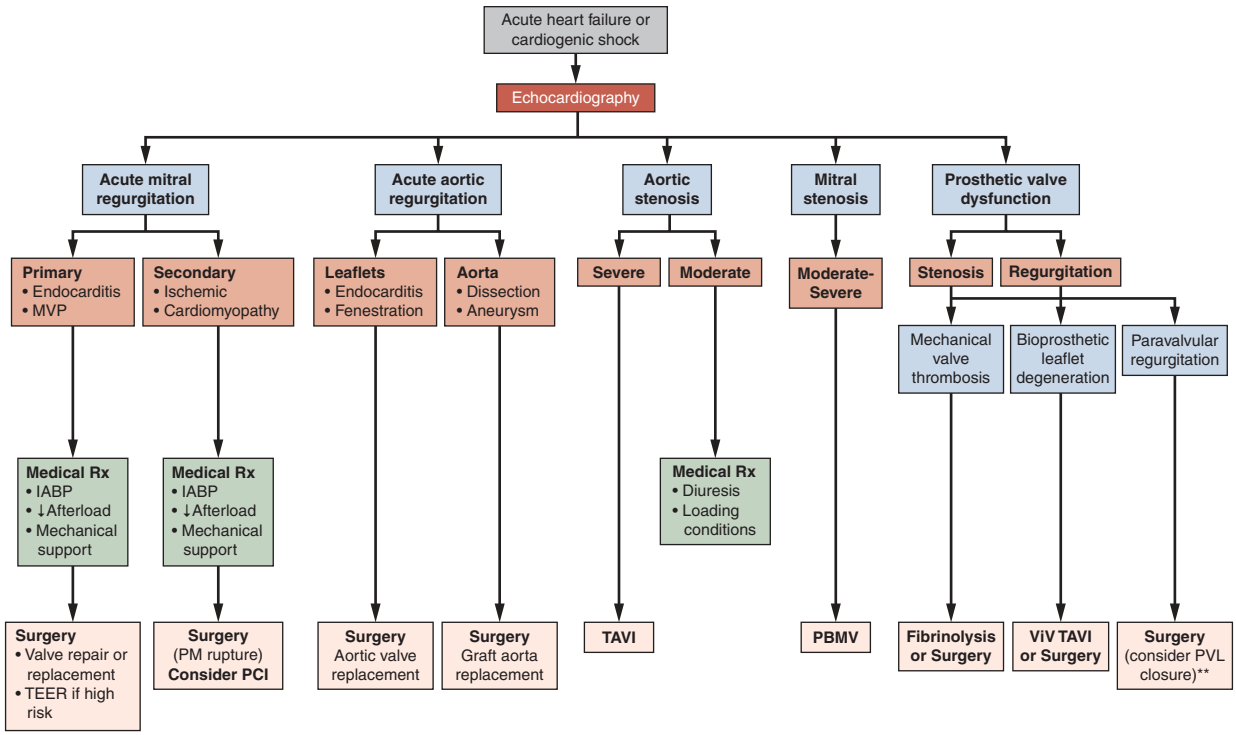

Fig. 76.1 Flowchart for the Diagnosis and Management of Acute Valvular Heart Disease. Echocardiography is recommended in all acutely ill patients with heart failure or cardiogenic shock because physical examination is not reliable to exclude significant valvular heart disease. Management depends on both valve hemodynamics (stenosis or regurgitation) and the etiology of valve dysfunction. *IABP,* intraaortic balloon pump; *MVP,* mitral valve prolapse; *PBMV,* percutaneous mitral balloon valvotomy; *PCI,* percutaneous coronary intervention; *PM,* papillary muscle; *PVL,* paravalvular leak; *TAVI,* transcatheter aortic valve implantation; *TEER,* transcatheter edge-to-edge repair; *ViV,* valve in valve.

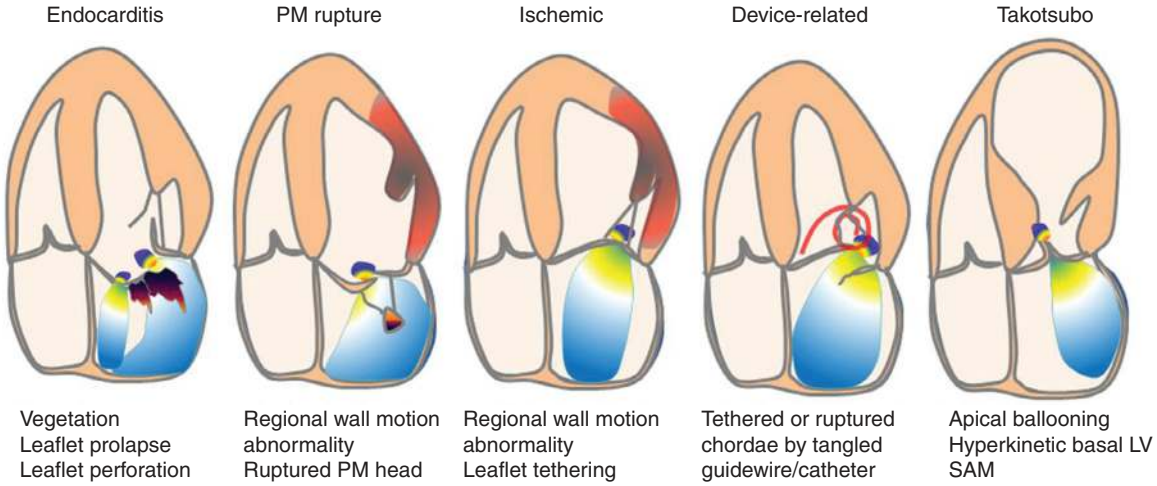

Fig. 76.2 Schematic Examples of the Cause of Acute Mitral Regurgitation. *LV,* Left ventricle; *PM,* papillary muscle; *SAM,* systolic anterior motion. (From Watanabe N. Acute mitral regurgitation. *Heart.* 2019;105:671–677.)

wall. All these possibilities can be diagnosed by echocardiography in an experienced center.

When imaging is nondiagnostic or discrepant with clinical findings, invasive hemodynamic monitoring with a Swan-Ganz catheter for the measurement of pulmonary pressure and cardiac output may be considered in patients with suspected acute mitral regurgitation. At the time of placement, oxygen saturations in the right atrium, right ventricle, and pulmonary artery should be measured. A ventricular septal defect results in a "step-up" in oxygen saturation between the right atrium and ventricle secondary to oxygenated blood from the left ventricle entering the right ventricle. The pulmonary artery balloon-occluded (wedge) pressure tracing should be examined for the presence of a giant "v-wave," which supports the diagnosis of acute mitral regurgitation but is not always present.

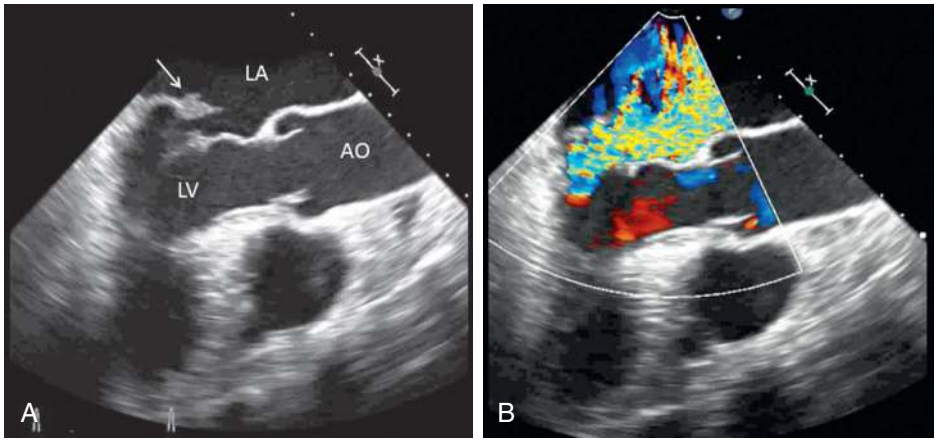

Fig. 76.3 Two-dimensional transesophageal echocardiogram **(A)** in a 72-year-old male with known mitral valve prolapse; ruptured chordae resulted in flail of the mitral posterior leaflet (*arrow*) and acute worsening of symptoms. Color Doppler **(B)** shows severe eccentric mitral regurgitation with a mosaic pattern through the noncoapting mitral valve. *AO,* Aorta; *LA,* left atrium; *LV,* left ventricle.

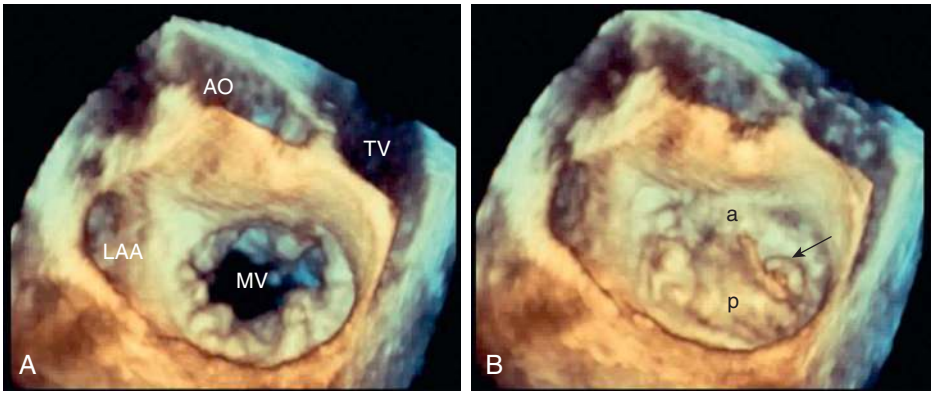

Fig. 76.4 Three-dimensional (3D) echocardiography of the same patient as in Fig. 76.3 in both diastole **(A)** and systole **(B)**. 3D imaging provided a "surgeon's view," allowing instant viewing of the mitral valve en face to assist operative planning for potential repair. In systole, the posterior leaflet (*p*) can be seen to prolapse above the anterior (*a*) leaflet, and ruptured chordae with flail segments can be seen *(arrow)*. *AO,* Aorta; *LAA,* left atrial appendage; *MV,* mitral valve; *TV,* tricuspid valve.

TABLE 76.1 Diagnostic Approach to Acute Valve Dysfunction

Physical examination	Unreliable Consider valve dysfunction in all patients with pulmonary edema
Echocardiography (transthoracic)	Accurate diagnosis of etiology of disease Quantitation of severity of stenosis or regurgitation Measurement of ventricular ejection fraction Estimation of pulmonary pressures
Transesophageal echocardiography	Sensitive for detection of valvular vegetations Detection of paravalvular abscess Essential for prosthetic mitral valve dysfunction Useful for prosthetic aortic valve dysfunction
Right heart catheterization	Not reliable for the diagnosis of valve disease May be helpful for optimizing loading conditions
Chest computed tomography	Sensitive and specific for diagnosis of aortic dissection
Angiography	Used when coronary angiography is needed

BOX 76.1 Therapeutic Approach to Acute Valve Dysfunction

1. Accurate diagnosis with echocardiography; differentiates acute valve dysfunction from acute decompensation with chronic valve disease.
2. Treat the underlying disease process associated with decompensation (endocarditis, acute myocardial infarction, anemia, etc.).
3. Optimize loading conditions using diuretics, vasodilators, and other agents with invasive hemodynamic monitoring.
4. Consult the cardiac surgery team as soon as the diagnosis is made.
5. Intraaortic balloon pump for acute mitral regurgitation.
6. Consider surgical or percutaneous intervention.

Management

In patients with acute heart failure associated with chronic mitral regurgitation, management is directed at treating the process leading to decompensation and optimizing loading conditions (Box 76.1). For example, in a patient with a systemic infection, treating the infection, controlling fever and tachycardia, and invasive monitoring to optimize

preload and afterload are used. Medical therapy typically includes afterload reduction with nitroprusside or other vasodilators and preload reduction with diuretics.[10] The goal is to support the patient through the period of decompensation. Typically, hemodynamics returns to the baseline-compensated state after the acute illness.

In contrast, acute severe mitral regurgitation is a medical and surgical emergency. Mortality is extremely high without the restoration of valve competence; even with prompt valve surgery, the 30-day mortality is 23%.[11] Medical stabilization should occur concurrently with consultation by a cardiac surgeon. Acutely, the placement of an intraaortic balloon pump (IABP) provides optimal afterload reduction while improving diastolic coronary blood flow. Advanced circulatory support with extracorporeal membrane oxygenation (ECMO) or a ventricular assist device also has been used successfully for patient stabilization in some cases.[12,13] However, valve replacement or repair is the definitive therapy for acute severe mitral regurgitation, with the timing and type of intervention dependent on mitral regurgitation etiology and patient factors.

Spontaneous chordal rupture can usually be treated early with mitral valve repair. Some high-risk patients may be candidates for mitral transcatheter edge-to-edge repair (TEER) with placement of a clip that attaches to both the anterior and posterior leaflet, reducing mitral regurgitation severity while creating a double-orifice valve in diastole.[14]

In patients with endocarditis, acute severe mitral regurgitation is an indication for early surgical intervention (during the initial hospitalization), without waiting for completion of antibiotic therapy. Other indications for early surgical intervention in patients with endocarditis include any valve dysfunction causing heart failure, paravalvular abscess formation, infection caused by highly resistant organisms, or persistent infection despite appropriate antibiotic therapy.[15–17] In a large prospective multicenter study, early surgery was associated with a lower mortality than medical therapy (12% vs. 21%).[18] Valve repair is preferred but may not be possible, depending on the extent of tissue destruction.

In patients with acute ischemic mitral regurgitation, treatment depends on the exact etiology of valve dysfunction.[19] In patients with acute mitral regurgitation caused by a regional wall-motion abnormality, myocardial function and mitral regurgitation may improve after percutaneous revascularization.[20] In these patients, the use of an IABP and medical therapy may be advantageous during the acute episode, with weaning of therapy as myocardial function improves.

Mitral regurgitation caused by partial or complete papillary muscle rupture requires surgical intervention. Although the risk of surgery is high, with an operative mortality rate of about 50%, the outcome is worse with medical therapy, with a mortality of 75% at 24 hours and 95% within 2 weeks after complete papillary muscle rupture. With the use of echocardiography, partial papillary muscle rupture can be recognized; prognosis in these patients depends on the extent of myocardial damage and severity of mitral regurgitation. With partial papillary muscle rupture, some surgeons prefer to stabilize the patient and delay surgery for 6–8 weeks after MI to avoid operating on the necrotic myocardial tissue. However, many patients cannot be stabilized, so acute intervention must be considered. Risk factors for adverse outcomes with surgery include older age, female gender, and poor LV systolic function.

Given the high risk of surgical intervention in many patients with acute severe mitral regurgitation, other options also should be considered (Table 76.2). Mitral TEER reduces mitral regurgitation by clipping together the two leaflets of the mitral valve, both reducing mitral regurgitation severity and creating a double-orifice valve in diastole with some degree of stenosis. TEER is currently recommended for the treatment of symptomatic severe primary mitral regurgitation when surgical risk is high or prohibitive, active infection has been excluded, and valve anatomy is amenable to this approach.[17,21] In patients with acute ischemic mitral regurgitation caused by papillary muscle rupture, prompt surgical intervention continues to be recommended,[22] although TEER might be considered in decompensated patients with a high surgical risk.[23]

TABLE 76.2 Catheter-Based Techniques for Valve Interventions

Commonly accepted	Mitral balloon valvotomy for rheumatic mitral stenosis Edge-to-edge mitral valve repair with MitraClip Aortic balloon valvuloplasty Transcatheter aortic valve replacement Transcatheter pulmonary valve replacement in congenital heart disease
Investigational	Transcatheter mitral valve implantation Transcatheter mitral annuloplasty repair techniques Paravalvular leak closures Transcatheter valve placement within surgical bioprosthetic valve ("valve-in-valve")

AORTIC REGURGITATION

Etiology

The most common causes of acute aortic regurgitation are endocarditis, rupture of a congenital aortic leaflet fenestration, blunt trauma, and acute aortic dissection.[24,25] Endocarditis results in aortic regurgitation by the destruction of the valve leaflet tissue, with a high percentage of cases also having paravalvular abscess formation.[26,27]Aortic dissection results in acute aortic regurgitation either because of the enlargement of the aortic annulus, resulting in inadequate central closure of the leaflets, or extension of dissection into the valve region, resulting in a flail aortic valve leaflet.

Clinical Presentation

The acute backflow of blood from the aorta to the left ventricle in diastole results in an acute elevation in LV end-diastolic pressure, with consequent pulmonary edema. Because there is no time for compensatory LV dilation, forward cardiac output falls abruptly owing to the regurgitant flow across the valve in diastole, so patients with acute aortic regurgitation also may be in cardiogenic shock. Decreased coronary perfusion pressure results in diffuse subendocardial ischemia, further impairing ventricular function.

Diagnosis

The clinical diagnosis of acute aortic regurgitation differs markedly from that of chronic aortic regurgitation (Fig. 76.5).[24,25] In contrast to the high-pitched diastolic decrescendo murmur of chronic aortic regurgitation, there is a "to-and-fro" murmur across the aortic valve that many clinicians fail to recognize as an indication of aortic regurgitation. The pulse pressure is narrow because of the low forward stroke volume, and peripheral signs of aortic regurgitation are not seen. As with acute mitral regurgitation, physical examination findings are often subtle, so a high index of suspicion and prompt echocardiography are needed to make this diagnosis.

Acute aortic regurgitation should be considered in patients with signs or symptoms of endocarditis, with a personal or family history of aortic root disease, and with a presentation consistent with acute aortic

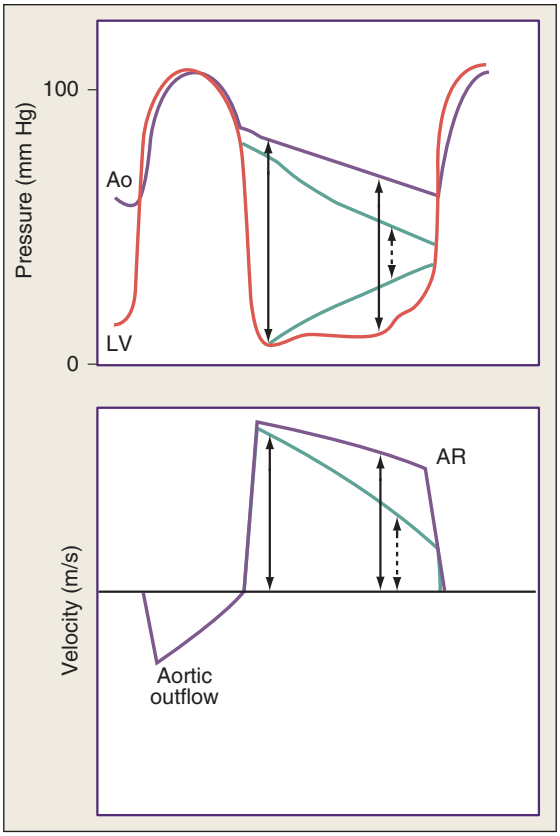

Fig. 76.5 Left ventricular (*LV*) and central aortic (*Ao*) pressures and corresponding Doppler velocity curves are shown for chronic *(purple lines)* and acute *(green lines)* aortic regurgitation. The shape of the velocity curve is related to the instantaneous pressure differences across the valve over the cardiac cycle, as stated in the Bernoulli equation. With acute aortic regurgitation (*AR*), aortic pressures fall more rapidly and ventricular diastolic pressure rises more rapidly, resulting in a steeper deceleration slope on the Doppler curve. (From Otto CM. *Textbook of Clinical Echocardiography*. 5th ed. Philadelphia: Saunders; 2013:316.)

dissection.[28] Endocarditis causing acute aortic regurgitation may be the first presentation of a congenital bicuspid aortic valve but increasingly is seen on normal trileaflet valves, often associated with drug use.[29]

Echocardiography allows the imaging of the aortic valve and root and determination of the severity of aortic regurgitation based on a combination of two-dimensional (2D) imaging and pulsed, continuous-wave, and color Doppler modalities (Figs. 76.6 and 76.7).[30] The continuous-wave Doppler curve shows a steep diastolic slope corresponding to the rapid equalization of diastolic pressure in the aorta and left ventricle. With severe acute regurgitation, there is no pressure gradient at end diastole, so cuff diastolic blood pressure is equal to LV end-diastolic pressure. Echocardiography also allows the accurate assessment of LV size and systolic function. When the differential diagnosis includes aortic dissection, transthoracic echocardiography (TTE) is inadequate to exclude this possibility. Instead, TEE or computed tomography (CT) images should be obtained.

Management

Acute aortic regurgitation is a surgical emergency.[24] Preoperative management is supportive, with ventilatory support and invasive hemodynamic monitoring. While the diagnosis is being made, therapy may include the use of diuretics, inotropic agents, and nitroprusside or other vasodilators in an attempt to stabilize hemodynamics.[24] However, an IABP is contraindicated, as inflation of the balloon in the descending thoracic aorta in diastole will increase the amount of backflow across the aortic valve.[31]

If acute aortic regurgitation is the result of aortic dissection, acute surgical intervention is needed. The surgical approach may be the replacement of the ascending aorta and valve with a combined prosthetic valve and aortic graft. When the valve leaflets are normal, some centers will preserve the native valve by reimplanting the native valve (and coronary arteries) in the prosthetic conduit (called the *David procedure*).

When acute aortic regurgitation is the result of endocarditis, surgical options include a mechanical valve, a heterograft tissue valve such as a porcine aortic valve or bovine pericardial valve, or a cryopreserved homograft aortic valve. Rarely, the patient may undergo valve repair if

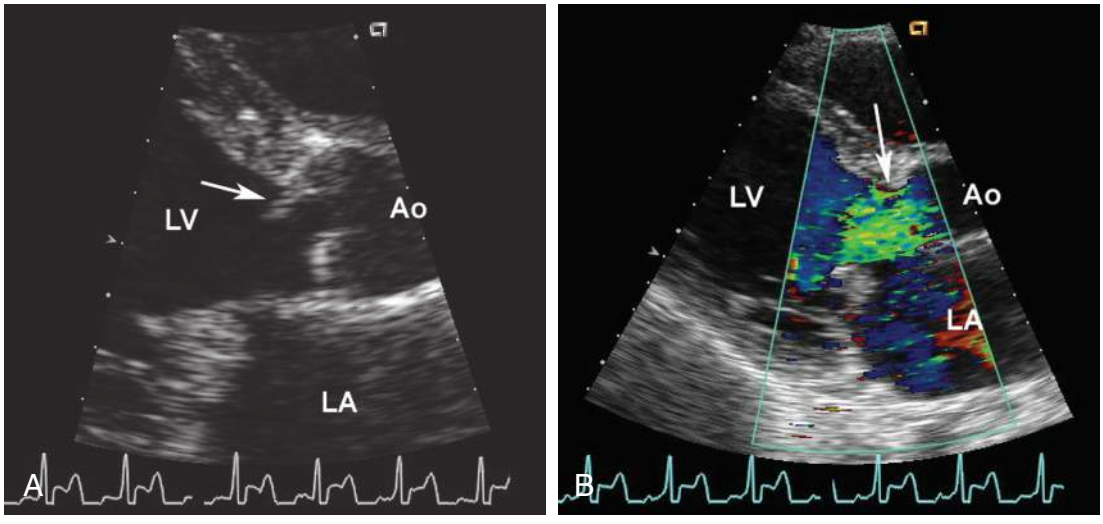

Fig. 76.6 Endocarditis Resulting in Acute Severe Aortic Regurgitation. In a long-axis view of the aortic valve **(A)**, a flail aortic valve leaflet is seen *(arrow),* with the leaflet *(arrow)* prolapsing into the left ventricular outflow tract in diastole. Color-flow Doppler imaging **(B)** in the same view shows a broad jet of diastolic flow filling the outflow tract, consistent with severe regurgitation. *Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle.

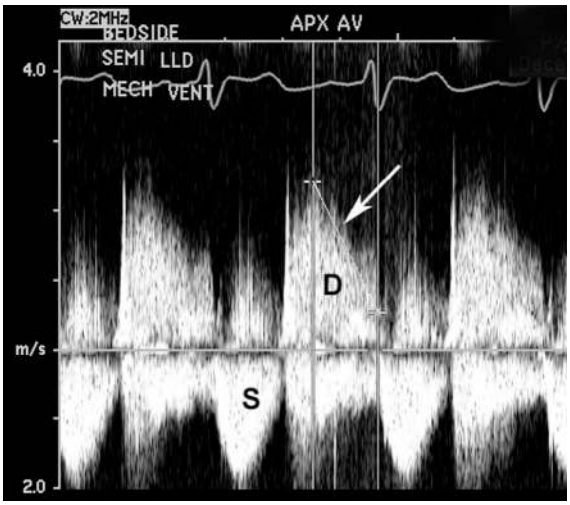

Fig. 76.7 Same patient as Fig. 76.6. Continuous-wave Doppler recording of flow across the aortic valve shows an increased antegrade velocity in systole (*S*) consistent with a high transaortic stroke volume. In diastole (*D*), a dense signal of retrograde flow is seen, with a steep deceleration slope *(arrow)* consistent with rapid equalization of pressures between the aorta and left ventricle in diastole from acute regurgitation.

there is a simple perforation with adjacent normal leaflet tissue and no evidence of active infection.

MITRAL STENOSIS

Etiology and Clinical Presentation

Mitral stenosis is almost always the result of rheumatic disease, with only rare cases of calcific mitral stenosis seen in the elderly. Rheumatic mitral stenosis is a slowly progressive disease with an insidious decline in exercise tolerance and symptom onset over many years.[32] However, in an asymptomatic patient with compensated moderate or severe mitral stenosis, acute decompensation can occur in the setting of increased systemic hemodynamic demands. Because mitral stenosis is more common in women (80% of cases) and occurs during the reproductive years, the most common emergency presentation of mitral stenosis is a pregnant woman with heart failure. Many of these patients are unaware of the underlying valve disease and are initially diagnosed during pregnancy. The clinical presentation may also be caused by or exacerbated by the onset of atrial fibrillation.

A large atrial myxoma may mimic the clinical presentation of mitral stenosis, presenting with acute hemodynamic compromise caused by obstruction of the mitral valve orifice by the tumor mass.

Diagnosis

The apical diastolic rumble and opening snap of mitral stenosis is challenging to appreciate even in a quiet room with optimal patient positioning and is frequently inaudible in the ICU setting. However, the diagnosis is easily made by TTE, with the mitral leaflet showing the characteristic findings of rheumatic disease: commissural fusion, chordal shortening and fusion, and restriction of the diastolic opening of the leaflets (Fig. 76.8).[33] The mitral valve area can be quantitated by 2D or three-dimensional planimetry or the Doppler pressure half-time method, with severe stenosis defined as a valve area of less than 1.5 cm^2. TTE also provides information on LV size and systolic function, left atrial size, pulmonary pressure, and any associated valve lesions. If evaluation for left atrial thrombus is needed, TTE has a sensitivity of only 60% compared with that of nearly 100% of the transesophageal approach.

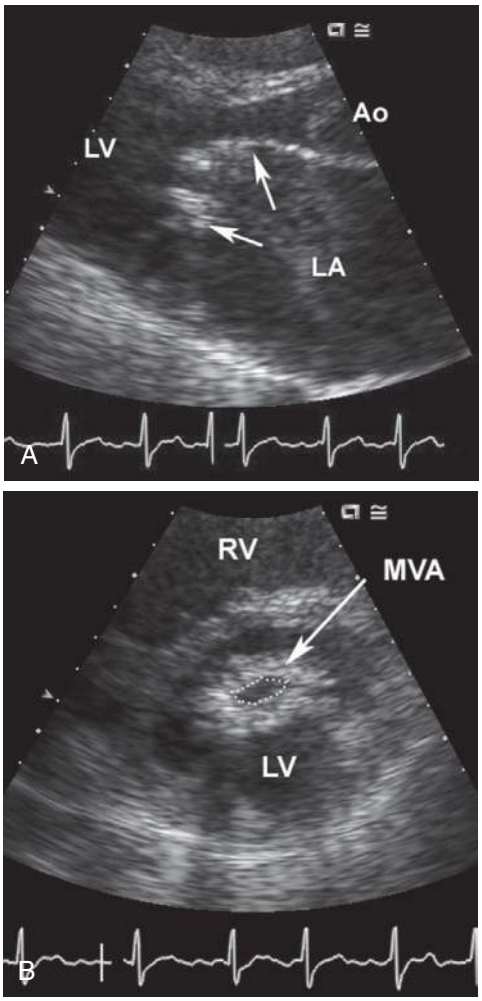

Fig. 76.8 In a patient with mitral stenosis, the long-axis view **(A)** demonstrates the classic findings of the diastolic doming of leaflets *(arrows)* caused by commissural fusion, with thickening predominantly at the leaflet tips. In the short-axis view **(B)**, the restricted mitral orifice with fusion of the commissures is visualized, providing accurate measurement of the valve area by direct planimetry. In this case, the valve area of 0.7 cm^2 indicates severe valve obstruction. *Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle; *MVA,* mitral valve area; *RV,* right ventricle.

Management

Most patients with mitral stenosis and acute decompensation can be managed conservatively with the treatment of the superimposed illness. Efforts should be directed toward decreasing overall metabolic demand and increasing oxygen delivery by controlling fever, maintaining a normal hemoglobin level, and providing supplemental oxygen. If atrial fibrillation is present, rate control is essential, preferably with conversion back to sinus rhythm. Even when sinus rhythm is present, beta-blockers may improve ventricular diastolic filling by prolonging the duration of diastole as the heart rate is decreased.[34] Invasive hemodynamic monitoring and ventilatory support may be needed when severe heart failure is present.

In patients who do not respond to conservative therapy, emergency intervention should be considered. The optimal intervention is percutaneous balloon mitral valvotomy (PBMV), which typically results in an increase in mitral valve area to more than 1.5 cm^2 (Fig. 76.9).[35] PBMV can be safely performed even during pregnancy.[36–38] Patients with a left atrial thrombus, coexisting moderate to severe mitral regurgitation, or

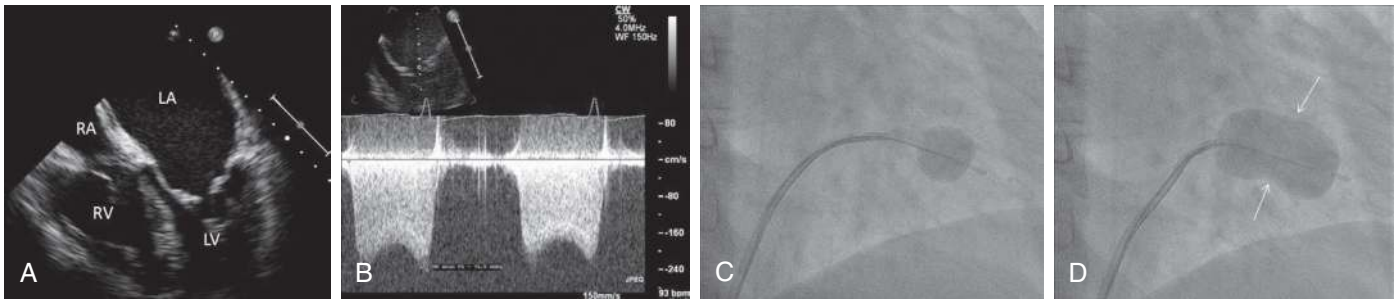

Fig. 76.9 This 48-year-old female underwent percutaneous balloon mitral valvotomy (PBMV) for severe symptomatic rheumatic mitral stenosis and acute pulmonary edema. The transesophageal echocardiogram four-chamber view demonstrates restricted diastolic mitral valve opening with hockey-stick deformation and severely enlarged left atrium **(A)**. Continuous-wave Doppler before PBMV measures a severely elevated mean gradient of 15 mm Hg **(B)**. Fluoroscopic images show the use of an Inoue balloon distally inflated across the mitral valve via a transseptal catheter **(C)**. The initial distal inflation stabilizes the position of the balloon, allowing for full inflation to split the mitral valve commissures; a waist *(white arrows)* in the balloon is seen from the resistance of the mitral valve **(D)**. Successful PBMV reduced the mean gradient to 6 mm Hg and relieved the patient's symptoms. *LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle.

heavily calcified and deformed mitral valves are not candidates for PBMV; in these patients, surgical mitral valve replacement may be needed.

AORTIC STENOSIS

Etiology and Clinical Presentation

Valvular aortic stenosis in adults most often is the result of calcification of a normal trileaflet or congenital bicuspid valve (Fig. 76.10A). Rheumatic aortic stenosis is less common and is invariably accompanied by mitral valve involvement. In younger adults, congenital aortic stenosis may be encountered; some of these patients have restenosis after prior commissurotomy in childhood.

Like mitral stenosis, aortic valve stenosis is a chronic, slowly progressive disease that presents acutely only in patients who have not been receiving regular medical care or with previously asymptomatic moderate to severe stenosis who present with acute decompensation caused by a superimposed systemic condition.[39–41] Young women with congenital aortic stenosis may present with angina or heart failure during pregnancy. In older adults, asymptomatic patients with moderate to severe valve obstruction may present with heart failure in the setting of pneumonia, anemia, or other conditions with increased metabolic demands.

Diagnosis

Classic physical examination findings for aortic stenosis include a delayed and decreased carotid upstroke, a narrow pulse pressure, a single second heart sound (S2), and a systolic ejection murmur at the aortic region that radiates to the carotids. However, although a grade 4 murmur (palpable thrill) with a single S2 and diminished carotids is specific for severe stenosis, these findings are very insensitive for the diagnosis. In particular, when a patient is decompensated, the murmur may be soft, and carotid upstrokes may be altered by coexisting vascular disease or loading conditions.[42]

Echocardiography provides reliable evaluation of aortic stenosis severity based on the maximum velocity through the narrowed orifice, mean pressure gradient, and valve area, calculated with the continuity equation (see Fig. 76.10B). Disease severity is a continuum, and velocities may be relatively low despite severe stenosis when stroke volume is reduced. In general, stenosis can be graded as severe (jet velocity >4 m/sec

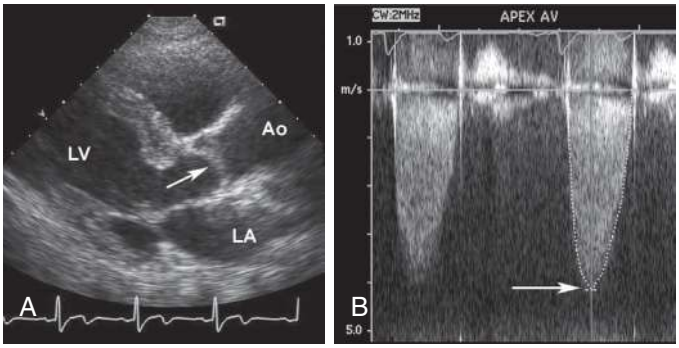

Fig. 76.10 A, In this 26-year-old pregnant woman with a loud systolic murmur, the long-axis view shows doming of the aortic valve in systole *(arrow).* Short-axis images confirmed a unicuspid aortic valve. **B,** Continuous-wave Doppler examination of the aortic valve demonstrates a high-velocity signal consistent with severe aortic stenosis. The maximum velocity of 4.2 m/sec corresponds to a maximum transaortic pressure gradient of 69 mm Hg and a mean gradient of 41 mm Hg. Valve area, calculated by the continuity equation, was 0.8 cm^2. *Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle.

or a valve area <1.0 cm^2 with a lower jet velocity), moderate (jet velocity, 3–4 m/sec), or mild (jet velocity <3 m/sec). Echocardiography also allows the evaluation of ventricular systolic and diastolic function and any associated valve disease.[31]

Management

Most patients with decompensated aortic stenosis can be managed conservatively by (1) treating the underlying disease process that led to decompensation and (2) restoring the patient's normal loading conditions. However, in patients who have denied symptoms or have not been receiving medical care, the first presentation of severe aortic stenosis may be syncope or pulmonary edema. In these patients, aortic stenosis is the cause of decompensation, as evidenced by very severe valve obstruction, often with a low ejection fraction. Treatment is urgent aortic valve replacement, with transcatheter aortic valve implantation now replacing surgical intervention for most patients with acute decompensation. Although patients undergoing emergency transcatheter valve implantation have a higher 30-day (8.7% vs. 4.3%) and

1-year mortality (29.1% vs. 17.5%) than patients undergoing a nonemergent procedure, these adverse outcomes primarily are related to baseline patient characteristics, with data strongly supporting the benefit of relief of valve obstruction when severe stenosis is the cause of clinical decompensation.[43–46]

If there is any delay in availability of valve replacement, the cautious use of nitroprusside may improve hemodynamics if the mean arterial pressure is above 60 mm Hg.[47,48] If aortic valve replacement is temporarily contraindicated, primarily because of an active infection, balloon aortic valvuloplasty might be considered.

RIGHT-SIDED VALVE DISEASE

Pulmonic valve disease is almost always congenital in origin, with a chronic disease course. Tricuspid valve stenosis is rare and usually accompanies rheumatic mitral valve disease. Tricuspid valve endocarditis often results in acute severe regurgitation; pulmonic valve endocarditis is rare. Cases of acute traumatic disruption of the tricuspid valve with blunt chest trauma have been described, although myocardial contusion or thoracic aorta disruption is more common.[49] Acute severe tricuspid regurgitation results in a low forward cardiac output and signs of an elevated right atrial pressure.[17,50] Numerous studies show that significant tricuspid regurgitation is associated with adverse cardiovascular outcomes. The role of transcatheter procedures for reduction of tricuspid regurgitant severity is currently under investigation.

PROSTHETIC VALVES

Mechanical Valves

Prosthetic mechanical heart valves are highly durable, with complications most often the result of valve thrombosis or paravalvular regurgitation. Valve thrombosis occurs in the setting of inadequate anticoagulation and may result in functional valve stenosis if movement of the valve occluder is restricted or valve regurgitation if the clot prevents full closure of the valve. The clinical presentation of valve thrombosis is similar to that of native valve stenosis or regurgitation. Echocardiography provides key information on the presence and severity of valve dysfunction. TEE is especially important with mitral prosthetic valves (Fig. 76.11); the valve itself blocks ultrasound penetration from a transthoracic approach.

The treatment of prosthetic valve thrombosis depends on the severity of valve obstruction. Evaluation includes TTE and TEE to detect a thrombus and evaluate valve hemodynamics, plus either fluoroscopy or cine-computed tomographic imaging to evaluate valve occluder motion. When only a small thrombus and mild hemodynamic compromise are present, conservative therapy with full-dose intravenous anticoagulation for several days may be adequate. When severe stenosis is present, either repeat surgical intervention or slow-infusion, low-dose fibrinolytic therapy is recommended.[17] Fibrinolytic therapy success rates are >90%, with rates of embolic events and major bleeding both <2%. Surgical intervention has a 30-day mortality as high as 10%–15%. The decision between surgery and systemic fibrinolysis should be made by a heart valve team with consideration of multiple factors, including availability of surgical expertise, clinical symptoms, thrombus burden, and patient choice. Fibrinolytic therapy is reasonable with left-sided thrombosis, with mild symptoms of recent onset or a small clot burden and patients who are high-to-prohibitive-risk surgical candidates.[17,51–53]

Paravalvular regurgitation early after valve replacement may be related to suture dehiscence at a site of annular calcification. Paravalvular regurgitation may be associated with hemolytic anemia, which can be treated conservatively if mild, but may require reoperation if severe recurrent anemia is present. The new onset of paravalvular regurgitation should prompt careful evaluation for endocarditis (see Chapter 117). Paravalvular regurgitation has been successfully treated with percutaneous techniques in high-risk surgical candidates with refractory heart failure and hemolytic anemia (Fig. 76.12).[23,54,55]

Tissue Valves

Tissue valves are subject to the degeneration of the leaflets, with superimposed calcification that may result in stenosis or regurgitation. Usually, this is a slowly progressive process with presentation 10–15 years after valve implantation.[56] As with native valve disease, acute decompensation may occur in patients with chronic prosthetic valve dysfunction if there is a superimposed hemodynamic stress. Valve thrombosis also is a concern with bioprosthetic valves, particularly after transcatheter aortic valve implantation.[57]

Acute regurgitation of a tissue valve can result from endocarditis or a leaflet tear caused by tissue degeneration. Tears in the valve leaflet typically occur adjacent to an area of calcification secondary to the increased stress on the normal leaflet tissue. As with mechanical valves, both transthoracic and transesophageal imaging are needed for the full evaluation of suspected prosthetic tissue valve dysfunction. Treatment is similar to that for native valves, with medical stabilization followed by surgery for repeat valve replacement. However,

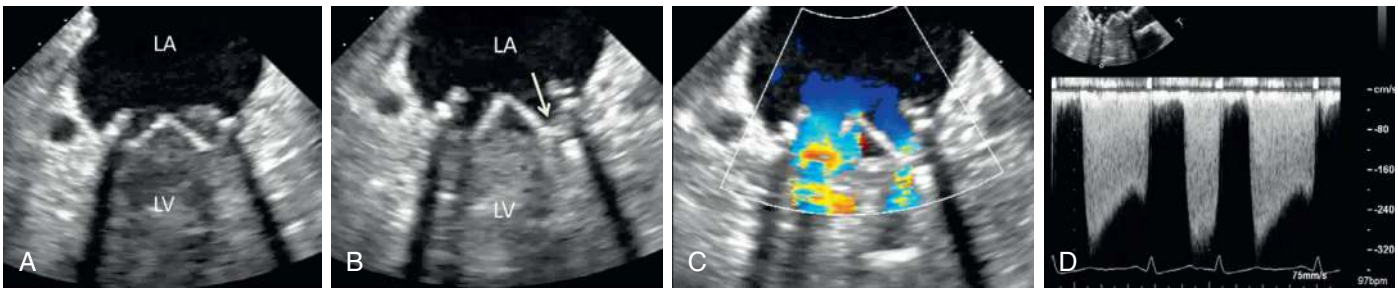

Fig. 76.11 Transesophageal echocardiogram of a thrombosed bileaflet mechanical mitral valve in a 43-year-old female who stopped anticoagulation for a dental procedure with inadequate bridging. In systole **(A)**, the bright occluder can be seen in a closed position, causing reverberation artifact into the left ventricle (*LV*). During diastole **(B)**, there is a minimal opening of the occluder *(white arrow)* from the acute thrombus. Color-flow Doppler **(C)** shows flow primarily through only one side of the valve, whereas there is only a very narrow jet at the site of the stuck leaflet. Continuous-wave Doppler **(D)** estimated a severely elevated mean gradient of 24 mm Hg, and the patient required emergent surgical valve replacement with a bioprosthesis. *LA*, Left atrium.

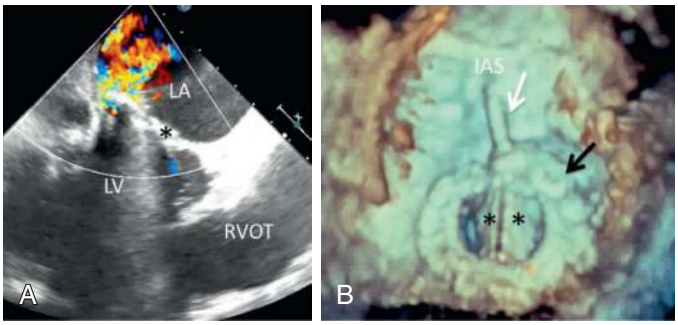

Fig. 76.12 Severe paravalvular leak in a 72-year-old male with a history of multiple mitral valve (MV) replacements because of previous endocarditis presenting with symptomatic heart failure and hemolytic anemia. Two-dimensional transesophageal color Doppler **(A)** shows eccentric regurgitation around the closed prosthetic MV occluder (*) during systole. Three-dimensional echocardiography **(B)** assists with paravalvular closure of the defect using an Amplatzer plug *(black arrow)*. A second plug is required in this case and can be seen being deployed via a transseptal catheter *(white arrow)* during diastole with an open MV occluder. *IAS,* Interatrial septum; *LA,* left atrium; *LV,* left ventricle; *RVOT,* right ventricular outflow tract.

many patients are at a very high surgical risk because of advanced age, comorbidities, and repeated sternotomy; in these patients, a transcatheter bioprosthetic "valve-in-valve" implantation may be performed at experienced centers.[58,59]

KEY POINTS

- Echocardiography is the first step in the diagnosis of acute valve disease; physical examination is not reliable, and valve disease should be considered in all patients with acute heart failure.
- Acute mitral regurgitation may be the result of primary diseases of the valve apparatus, such as spontaneous chordal rupture or endocarditis, or secondary to an acute cardiomyopathy or acute ischemic heart disease.
- Treatment of acute mitral regurgitation depends on the cause of valve dysfunction, ranging from coronary revascularization for acute ischemia to emergency surgery for a flail leaflet or ruptured papillary muscle. Medical therapy, an IABP, or an LV support device may be needed for stabilization before intervention.
- Acute aortic valve regurgitation may be primary diseases of the valve leaflets, such as endocarditis, or because of aortic dissection with distortion of normal aortic valve anatomy.
- Endocarditis causes destruction of valve tissue with acute regurgitation and heart failure. Early surgery, before completion of antibiotic therapy, improves clinical outcomes.
- In critically ill patients who are poor surgical candidates, rapid relief of valve obstruction can be lifesaving, including transcatheter balloon valvotomy for rheumatic mitral stenosis or transcatheter aortic valve implantation for calcific aortic stenosis.
- Prosthetic valve thrombosis may require acute surgical intervention, with selected patients responding to increased anticoagulation or fibrinolytic therapy.

References for this chapter can be found at expertconsult.com.

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Of the 40,042 patients who underwent transcatheter aortic valve implantation (TAVI) in the Society of Thoracic Surgeons and the American College of Cardiology Transcatheter Valve Therapy (STS/ACC TVT) Registry, about 10% were considered an emergency procedure. Successful placement of the device and procedural complication rates were similar for patients undergoing an emergency procedure compared with the rest of the patients; however, there were higher rates of acute kidney injury and/or new dialysis (8.2% vs. 4.2%; P <.001), 30-day mortality (8.7% vs. 4.3%, adjusted hazard ratio: 1.28, 95% confidence interval: 1.10–1.48), and 1-year mortality (29.1% vs. 17.5%, adjusted hazard ratio: 1.20, 95% confidence interval: 1.10–1.31).

Lalani T, Cabell CH, Benjamin DK, et al. Analysis of the impact of early surgery on in-hospital mortality of native valve endocarditis: use of propensity score and instrumental variable methods to adjust for treatment-selection bias. *Circulation.* 2010;121(8):1005–1013.
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Maheshwari V, Barr B, Srivastava M. Acute valvular heart disease. *Cardiol Clin*. 2018;36(1):115–127.
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Watanabe N. Acute mitral regurgitation. *Heart*. 2019;105:671–677.
State-of-the-art review article that highlights the key differences between acute and chronic mitral regurgitation, discusses iatrogenic causes of acute mitral regurgitation, and presents current surgical and transcatheter options for treatment.

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Pulmonary Hypertension and Right Ventricular Failure

Lewis J. Rubin and John Selickman

Pulmonary hypertension (PH) is defined by an elevated mean pulmonary artery pressure (mPAP) of >20 mm Hg and may be precapillary or postcapillary in etiology.[1] Precapillary PH is further characterized by an elevated pulmonary vascular resistance (PVR) of ≥3 Wood units and a pulmonary arterial wedge pressure of ≤15 mm Hg. Management of postcapillary PH, which is caused by left-sided heart dysfunction, typically involves treating the underlying process. Medications used to treat precapillary PH are often not only ineffective for postcapillary PH but may in fact be harmful, potentially leading to the development of pulmonary edema or systemic hypotension.

The World Health Organization (WHO) categorizes PH into five groups based on their underlying pathophysiology: (1) pulmonary arterial hypertension (PAH), (2) PH caused by left heart disease, (3) PH caused by lung diseases and/or hypoxia, (4) PH caused by pulmonary artery obstructions, and (5) PH with unclear and/or multifactorial mechanisms. PAH can be idiopathic (IPAH, previously known as *primary PH* [PPH]) or may occur in association with a variety of underlying disease processes, such as collagen vascular disease, portal hypertension, congenital systemic-to-pulmonary shunts, drug or toxin exposure, or human immunodeficiency virus (HIV) infection.[2] IPAH is principally a disease of young women, but it can affect all age groups and both sexes. A genetic predisposition may underlie a substantial proportion of these cases and is referred to as *heritable pulmonary arterial hypertension* (HPAH).[3–9]

Initial therapy may be directed at an underlying cause or contributing factors, such as using continuous positive airway pressure (CPAP) and supplemental oxygen for PH associated with obstructive sleep apnea. After the identification and treatment of underlying associated disorders and contributing factors, specific therapy for PAH should be considered. IPAH carried a very poor prognosis (median survival rate of approximately 2.8 years from the time of diagnosis) through the mid-1980s. Subsequently, a number of therapeutic options have been developed, and 14 have been approved by the U.S. Food and Drug Administration (FDA), falling into three classes of drugs: (1) prostanoids, including epoprostenol (intravenous), treprostinil (subcutaneous, intravenous, inhaled, or oral), iloprost (inhaled), and selexipag (oral); (2) endothelin receptor antagonists (ERAs), including bosentan, ambrisentan, and macitentan (all oral); and (3) drugs acting on the nitric oxide pathway, including the phosphodiesterase (PDE) type-5 inhibitors, sildenafil and tadalafil (both oral), and the guanylate cyclase activator, riociguat (oral).

DIAGNOSIS

Symptoms, Signs, and Clinical History

As a result of the insidious onset of symptoms, PAH is often advanced at the time of diagnosis. Dyspnea upon exertion is the most common presenting symptom, but it is sometimes attributed to deconditioning or another cardiorespiratory ailment. Chest pain mimicking angina pectoris may also occur. Patients with advanced disease may present with syncope or signs and symptoms of right-sided heart failure, including lower extremity edema, jugular venous distention, and ascites.

The clinical history should focus initially on the exclusion of underlying causes of PH. Important clues to an underlying condition might include a previous history of a heart murmur, deep venous thrombosis (DVT) or pulmonary embolism, Raynaud phenomenon, arthritis, arthralgias, rash, heavy alcohol consumption, hepatitis, heavy snoring, daytime hypersomnolence, morning headache, and morbid obesity. A careful family history should be obtained. Medication exposure, particularly to appetite suppressants and amphetamines, should be noted. Cocaine is a powerful vasoconstrictor that may contribute to the development of PH, and intravenous drug use has also been associated with the development of PAH.

Physical Examination

Signs of PAH may not become apparent until late in the disease. Findings such as an accentuated second heart sound, a systolic murmur over the left sternal border, jugular venous distention, peripheral edema, and ascites might suggest the presence of PH and right ventricular (RV) dysfunction. Associated systemic diseases, such as collagen vascular disease or liver disease, may also become apparent during routine examination.

Laboratory Evaluation

Laboratory evaluation can provide important information in detecting associated disorders and contributing factors. A collagen vascular screen including antinuclear antibodies, rheumatoid factor, and erythrocyte sedimentation rate is often helpful in detecting autoimmune disease, although some patients with IPAH will have a low-titer positive antinuclear antibody test.[10] The scleroderma spectrum of disease, particularly limited scleroderma, or the CREST syndrome (i.e., calcinosis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasias), has been associated with an increased risk of the development of PAH.[11,12] Liver function tests (aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase) may be elevated in patients with RV failure and passive hepatic congestion but may also be associated with underlying liver disease. Liver disease with portal hypertension has been associated with the development of PH. Thyroid disease may occur with increased frequency in patients with IPAH and should be excluded with thyroid function testing.[13] HIV testing and hepatitis serologic studies should be performed. Routine laboratory studies, such as complete blood cell count, complete metabolic panel, prothrombin time, and partial thromboplastin time, are recommended during the initial evaluation and as indicated to monitor the patient's long-term clinical status.

Echocardiography

Transthoracic echocardiography (TTE) is the initial test of choice in assessing the severity of PH and detecting left-sided heart disease. Findings may include elevated peak tricuspid regurgitant jet velocity, elevated estimated pulmonary artery systolic pressure, RV enlargement, flattening of the interventricular septum, and compression of the left ventricle.[14] Bubble contrast echocardiography may detect a right-to-left shunt, but exclusion of a left-to-right intracardiac shunt may require cardiac catheterization with an oximetry series. Echocardiography may be useful as part of a long-term follow-up,[15,16] although not all patients have suitable echocardiographic windows.

Radiographic Evaluation and Exclusion of Thromboembolic Disease

Chest radiography may reveal an enlargement of the central pulmonary vessels and evidence of RV enlargement. Evidence of parenchymal lung disease may also be apparent. When parenchymal lung disease is suspected, pulmonary function testing and high-resolution computed tomography (CT) of the chest may be indicated. Because of its high sensitivity, ventilation/perfusion (V/Q) scanning is the imaging modality of choice to exclude chronic thromboembolic disease–related PH (CTEPH), which is among the most preventable and treatable causes of PH. Diffuse mottled perfusion can be seen in IPAH, whereas larger segmental and subsegmental mismatch defects are suggestive of CTEPH. Because any process that leads to decreased perfusion without an associated decrease in ventilation will result in a mismatch, V/Q scanning lacks specificity for CTEPH. CT pulmonary angiography (CTPA) is thus an important adjunct to V/Q scanning, not only to exclude other disease processes in which similar mismatch defects can be seen but also to define the extent and location of thromboembolic disease before surgical evaluation. Although CTPA remains the imaging modality of choice for acute pulmonary embolism, it lacks the sensitivity of V/Q scanning for CTEPH, particularly at the subsegmental level, and caution should be exercised when using it to exclude CTEPH.[17]

Pulmonary Function Testing

Pulmonary function testing is indicated to detect underlying parenchymal lung disease. The diffusing capacity is often reduced in pulmonary vascular disease, consistent with impaired gas exchange.

Right-Sided Heart Catheterization and Vasoreactivity Testing

Right-sided heart catheterization remains an important part of the evaluation. Left-sided heart dysfunction and intracardiac shunts can be excluded, the degree of PH can be accurately quantified, cardiac output can be measured, and PVR can be calculated. Acute pulmonary vasoreactivity can be assessed using a short-acting agent, such as prostacyclin (epoprostenol), inhaled nitric oxide, or intravenous adenosine. The consensus definition of a positive acute vasodilator response in a patient with PAH is a decrease in mPAP by $\geq$10 mm Hg to $\leq$40 mm Hg with increased or unchanged cardiac output. The primary objective of acute vasodilator testing in patients with PAH is to identify the subset of patients who might be effectively treated with oral calcium channel blockers; response to a short-acting pulmonary vasodilator has been shown to be predictive of a response to calcium channel blockers.[18] Unstable patients or those in severe right-sided heart failure who would not be candidates for treatment with calcium channel blockers need not undergo vasodilator testing.

TREATMENT

General Care

Warfarin, Oxygen, Diuretics, Digoxin, and Vaccination

Although earlier studies suggested improved survival with oral anticoagulation in PAH,[19] the benefits were primarily seen in patients with IPAH and not present in those with other forms of PAH. More recent studies have not only failed to demonstrate a survival advantage in patients with IPAH treated with anticoagulation, but they have demonstrated an increased mortality in patients with PAH secondary to most other causes.[20] Generally, patients with PAH who are treated with chronic intravenous epoprostenol are anticoagulated in the absence of contraindications, owing in part to the additional risk of catheter-associated thrombosis. All patients with CTEPH should receive lifelong anticoagulation.

Hypoxemia is a pulmonary vasoconstrictor and can contribute to the development or progression of PAH. It is generally considered important to maintain oxygen saturations greater than 90% at all times, although data supporting the role of supplemental oxygen in PH are largely based on expert opinion or extrapolated from clinical trials that evaluated its use in patients with chronic obstructive pulmonary disease (COPD). Although no randomized controlled trials have yet addressed the role of supplemental oxygen in PH, a post hoc analysis of data from a large, observational study demonstrated improved survival among patients with PAH and severely reduced diffusing capacity who were treated with supplemental oxygen.[21]

Diuretics are indicated in patients with evidence of RV failure and volume overload. Careful dietary restriction of sodium and fluid intake is important in the management of patients with PAH and right-sided heart failure. Rapid and excessive diuresis may produce systemic hypotension, renal insufficiency, and syncope. Serum electrolytes and measures of renal function should be followed closely in patients receiving diuretic therapy.

Although not extensively studied in PAH, digitalis is sometimes used in refractory RV failure or atrial dysrhythmias. Drug levels should be followed closely, particularly in patients with impaired renal function.

Because of the potentially devastating effects of respiratory infections in patients with PH, immunization against influenza, coronavirus disease 2019 (COVID-19), and pneumococcal pneumonia is recommended.

Calcium Channel Blockers

Patients with IPAH who respond to vasodilators and calcium channel blockers generally have improved survival.[18] Unfortunately, this tends to represent a relatively small proportion of patients, comprising less than 20% of patients with IPAH and even fewer patients with other causes of PAH.

Prostacyclin Receptor Agonists

Prostacyclin, a metabolite of arachidonic acid produced primarily in the vascular endothelium, is a potent systemic and pulmonary vasodilator that also has antiplatelet aggregatory effects. A relative deficiency of endogenous prostacyclin may contribute to the pathogenesis of PAH.[22]

Epoprostenol. Epoprostenol therapy is complicated by the need for continuous intravenous infusion. The drug is unstable at room temperature and is generally best kept cold before and during infusion. It has a very short half-life in the bloodstream (<6 minutes), is unstable in an acidic pH, and cannot be taken orally. Because of the short half-life, the risk of rebound worsening with abrupt or inadvertent interruption of

the infusion, and its effects on peripheral veins, it should be administered through an indwelling central venous catheter. Common side effects of epoprostenol therapy include headache, flushing, jaw pain with initial mastication, diarrhea, nausea, a blotchy erythematous rash, and musculoskeletal aches and pain (predominantly involving the legs and feet). These tend to be dose dependent and often respond to a cautious reduction in dose. Severe side effects can occur with an overdose of the drug. Acutely, overdosage can lead to systemic hypotension. Chronic overdosage can lead to the development of a hyperdynamic state and high-output cardiac failure.[23] Abrupt or inadvertent interruption of the epoprostenol infusion should be avoided because this may lead to a rebound worsening of PH, with symptomatic deterioration and even death. Other complications of chronic intravenous therapy with epoprostenol include line-related infections, catheter-associated venous thrombosis, systemic hypotension, thrombocytopenia, and ascites.

Treprostinil. Treprostinil, a prostacyclin analog with a half-life of 3 hours, is stable at room temperature. A placebo-controlled, randomized trial demonstrated that continuous subcutaneous treprostinil improved exercise tolerance, although the 16-meter median difference between treatment groups in 6-minute walking distance was relatively modest.[24] Treprostinil also improved hemodynamic parameters. Common side effects included headache, diarrhea, nausea, rash, and jaw pain. Side effects related to the infusion site were common (85% of patients complained of infusion-site pain, and 83% had erythema or induration at the infusion site). Treprostinil is also approved for both intravenous delivery based on bioequivalence with the subcutaneous route and as an inhaled preparation administered in doses of 18–54 μg, four times daily.[25]

A multicenter, randomized, double-blind, placebo-controlled trial evaluating the use of inhaled treprostinil in patients with PH secondary to interstitial lung disease demonstrated a small improvement in exercise capacity and 15% reduction in N-terminal pro-B-type natriuretic peptide (a biomarker of cardiac overload) after 16 weeks, without any increase in serious adverse events, thus making it one of the only medications to demonstrate clinical efficacy in this population.[26]

Inhaled iloprost. Iloprost is a chemically stable prostacyclin analog with a serum half-life of 20–25 minutes[27] and is a potent pulmonary vasodilator. In uncontrolled and controlled studies of iloprost for various forms of PAH,[28,29] inhaled iloprost at a total daily dose of 15–45 μg divided in 6–9 inhalations improved functional class, exercise capacity, and pulmonary hemodynamics for periods up to 1 year of follow-up. The treatment was generally well tolerated except for mild coughing, minor headache, and jaw pain in some patients. The most important drawback of inhaled iloprost is the relatively short duration of action, requiring the use of six to nine inhalations per day.

Beraprost. Beraprost sodium is an orally active prostacyclin analog[30] that is absorbed rapidly under fasting conditions. It has been evaluated in patients with intermittent claudication,[31] Raynaud phenomenon, and digital necrosis from systemic sclerosis,[32] with variable results. Although several small, open, uncontrolled studies reported beneficial hemodynamic effects with beraprost in patients with IPAH, two randomized double-blind, placebo-controlled trials have shown only modest improvement and suggest that beneficial effects of beraprost may diminish with time.[33,34]

Selexipag. Selexipag is a selective *nonprostanoid* prostacyclin receptor agonist that is administered orally. Its efficacy in patients with PAH was demonstrated in a randomized, double-blind, placebo-controlled trial.[35] The primary endpoint was a composite of death from any cause or complication related to PAH (disease progression, hospitalization, initiation of parenteral prostanoid or long-term oxygen, need for lung transplantation, or need for balloon atrial septostomy). The primary endpoint occurred in significantly fewer patients randomized to the selexipag group, primarily because of a decrease in disease progression and decreased hospitalizations. Approximately 80% of patients enrolled were already on PH therapy (either ERAs, PDEs, or both) at the time of enrollment, but an additional benefit of selexipag was still present in a subgroup analysis of these patients. Headache, diarrhea, nausea, and jaw pain were the most common adverse events.

Endothelin Receptor Antagonists

Endothelin-1 is a vasoconstrictor and a smooth muscle mitogen that may contribute to the pathogenesis of PAH. Endothelin-1 expression, production, and concentration in plasma[36,37] and lung tissue[38] are elevated in patients with PAH, and these levels are correlated with disease severity. The main adverse effects associated with ERAs are peripheral edema, hepatotoxicity, and potent teratogenicity.

Bosentan. Bosentan is a dual ERA that has been shown to improve pulmonary hemodynamics and exercise tolerance and delay the time to clinical worsening in patients with PAH.[39] The most frequent and potentially serious side effect with bosentan is dose-dependent abnormal hepatic function (as indicated by elevated levels of alanine aminotransferase and aspartate aminotransferase). Because of the risk of potential hepatotoxicity, the FDA requires that liver function tests be performed at least monthly in patients receiving this drug. Bosentan may also be associated with the development of anemia, which is typically mild. Hemoglobin and hematocrit should also be checked regularly.

Ambrisentan. Ambrisentan is a selective ERA that has shown efficacy in PAH. In a double-blind, placebo-controlled, randomized, multicenter study, patients with PAH were randomized to one of three doses of ambrisentan ranging from 2.5 to 10 mg once daily for 12 weeks. Patients receiving ambrisentan had statistically significant improvements in exercise capacity, time to clinical worsening, quality of life, and dyspnea.[40]

Macitentan. Macitentan is a dual ERA that reduces disease progression in PAH and is associated with a low incidence of liver function abnormality and peripheral edema. In a double-blind, placebo-controlled, randomized, multicenter study, patients with PAH were randomized to a once-daily dose of either 3 mg macitentan, 10 mg macitentan, or placebo for a median duration of 85 weeks.[41] The primary endpoint (composite of death, atrial septostomy, lung transplantation, initiation of prostanoid, or worsening of PAH) was significantly lower in both macitentan groups compared with placebo. Patients receiving macitentan also had improved exercise capacity and cardiac hemodynamics (decreased PVR and increased cardiac output). The incidence of peripheral edema and elevation of serum aminotransferases was similar in all three groups, although a higher incidence of nasopharyngitis, headache, and anemia was seen with macitentan.

Cyclic Guanosine Monophosphate Pathway Enhancers

Nitric oxide (NO) is a potent vasodilator and one of the principal mediators of pulmonary vascular tone. It is synthesized from L-arginine by NO synthases and exerts its effects on vascular smooth muscle through activation of soluble guanylate cyclase (sGC), leading to increased production of cyclic guanosine monophosphate (cGMP). cGMP acts directly on vascular smooth muscle and leads to vasodilation and decreased cellular proliferation. PAH is associated with both decreased production of endogenous NO and increased production of phosphodiesterase type 5 (PDE5), an enzyme that hydrolyzes cGMP and limits intracellular signaling.[42,43] Drugs that selectively inhibit cGMP-specific PDEs (or PDE5 inhibitors) augment the pulmonary vascular response to endogenous or inhaled NO in models of PH.[44,45]

Sildenafil. Sildenafil, an oral medication initially approved for erectile dysfunction, is a potent specific PDE5 inhibitor that blocks acute

hypoxic pulmonary vasoconstriction in healthy adult volunteers and acutely reduces mPAP in patients with PAH.[46] Several randomized studies have demonstrated sildenafil's efficacy in PAH, both as monotherapy and in combination with other agents.[47,48] Sildenafil treatment in animal models with experimental lung injury reduced PAP, but gas exchange worsened owing to impaired V/Q mismatch.[49,50] Accordingly, caution is advised when using sildenafil to treat PH in patients with severe lung disease. Side effects commonly observed include headache, dyspepsia, and flushing.

Tadalafil. Tadalafil, another oral PDE5 inhibitor previously approved for erectile dysfunction, is approved for the treatment of PAH based on a randomized clinical trial demonstrating increased exercise capacity and decreased time to clinical worsening.[51] Unlike sildenafil, it has the advantage of once-daily administration, although side effects appear to be similar.

Riociguat. Riociguat is a novel agent that increases production of cGMP through stimulation of sGC. In a randomized placebo-controlled trial, patients treated with oral riociguat for 12 weeks had improved exercise capacity, pulmonary hemodynamics, and decreased time to clinical worsening.[52] Riociguat is the only drug approved for the treatment of inoperable CTEPH, and it has been shown to both improve exercise capacity and decrease vascular resistance in this population.[53] Common side effects include headache, dyspepsia, and dizziness. It should not be used in combination with PDE inhibitors because of the risk of systemic hypotension, and its use is contraindicated in pregnancy because of teratogenicity.

Combination Therapy

The AMBITION trial demonstrated that treatment-naïve PAH patients treated with the initial combination therapy of ambrisentan and tadalafil had a significant reduction in the relative risk of disease progression.[54] Additionally, greater reductions in N-terminal pro-brain natriuretic peptide and greater improvements in exercise capacity were observed in patients who were treated with monotherapy compared with those using either agent alone. Based on these findings, many experienced clinicians have begun initiating PAH treatment with the combination of an ERA and a PDE5 inhibitor.

Nitric Oxide

NO contributes to the maintenance of normal vascular function and structure. It is particularly important in the normal adaptation of the lung circulation at birth, and impaired NO production may contribute to the development of neonatal PH.

Inhaled nitric oxide. Inhaled NO has been shown to have potent and selective pulmonary vasodilator effects during brief treatment of adults with IPAH.[55] It is an effective pulmonary vasodilator in newborns with PH (persistent PH of the newborn [PPHN]); children with congenital heart disease; and patients with postoperative PH, acute respiratory distress syndrome, or those undergoing lung transplantation.[56] It is of substantial benefit in PPHN, decreasing the need for support with extracorporeal membrane oxygenation (ECMO).[57] Although inhaled NO has been used in diverse clinical settings, especially in intensive care medicine, FDA approval for this therapy is limited to newborns with hypoxemic respiratory failure at this time.

In chronic PAH, the use of inhaled NO has been primarily for acute testing of pulmonary vasoreactivity during cardiac catheterization or for acute stabilization of patients during deterioration.

Lung Transplantation

PAH accounts for only 2.7% of adult lung transplants[58] and is generally reserved for those who are failing despite the best available medical therapy. Lung transplantation in general is challenging, but it is even more so in patients whose primary indication for transplant is PAH.[59] Patients transplanted for PAH have a higher 3-month mortality rate (23%) than those transplanted for any other indication.[58] However, patients with PAH who survive to 1 year posttransplant have a higher median long-term survival (10.0 years) than groups transplanted for most other indications, including both COPD (7.0 years) and interstitial lung disease (ILD) (6.9 years).[58]

The higher early mortality in PAH patients may be related to higher anesthetic and operative risks, the need for cardiopulmonary bypass,[60] and the increased occurrence of postoperative reperfusion pulmonary edema in patients with PAH undergoing single-lung transplantation. In this situation, reperfusion pulmonary edema may be aggravated by the increased blood flow to the newly engrafted lung. In addition, V/Q mismatching can be particularly severe.[61] Most centers therefore seem to prefer bilateral lung transplantation for patients with PAH.[62] The International Society for Heart and Lung Transplantation (ISHLT) recommends early referral for patients with PAH to ensure there is adequate time to both complete the transplant evaluation and find a suitable graft. Referral should be considered for all patients with significant RV dysfunction or progressive disease despite appropriate therapy, need for parenteral prostacyclin, high-risk variants (e.g., pulmonary veno-occlusive disease), signs of hepatic or renal dysfunction secondary to PAH, or life-threatening complications such as hemoptysis.[63]

Special Situations in the Intensive Care Unit

DVT Prophylaxis

Patients with PAH are likely at increased risk for DVT and are certainly at increased risk for poor outcomes as the result of DVT. Patients with PAH are prone to a more sedentary lifestyle and to chronic venous congestion of the lower extremities owing to increased right-sided cardiac filling pressures. Hospitalization in the intensive care unit (ICU), often with discontinuation of anticoagulation in anticipation of invasive procedures, likely places these patients at even higher risk for DVT. For these reasons, meticulous attention must be paid to DVT prophylaxis.

Procedures and Surgery

Procedures and surgery in patients with PAH can be associated with substantially increased operative and perioperative risks. In addition, appropriate precautions should be undertaken to optimize outcomes. As always, careful consideration should be given to whether an invasive procedure is absolutely necessary.

Vasovagal Events

Patients with severe PAH are prone to vasovagal events. Pain, nausea, vomiting, or even defecation can lead to a vasovagal event in patients with severe PAH, as cardiac output may be disproportionately dependent on heart rate. Moreover, the bradycardia and systemic vasodilatation that accompany a vasovagal event can result in an abrupt decrease in systemic arterial pressure, leading to syncope or even cardiopulmonary arrest. Therefore patients should be closely monitored for their heart rate during invasive procedures, with readily available atropine or a similar agent.

Avoidance of Hypoxemia and Hypercarbia

Hypoxemia and hypercarbia are both pulmonary vasoconstrictors and can contribute to the worsening of PH. Oversedation can lead to ventilatory insufficiency and precipitate clinical deterioration. Caution should be used in laparoscopic procedures in which carbon dioxide is used for abdominal insufflation, because absorption can lead to hypercarbia. The induction of anesthesia and intubation for surgical

procedures can be a particularly high-risk period for patients with PAH because of the increased risk for vagal events, hypoxemia, hypercarbia, and shifts in intrathoracic pressure with associated changes in cardiac filling pressures.

Pregnancy

The hemodynamic changes in pregnancy are substantial, and volume shifts occur immediately postpartum, with cardiac filling pressures increasing as a result of decompression of the vena cava and the return of uterine blood into the systemic circulation. The changes induced by pregnancy impose a significant hemodynamic stress in women with IPAH, leading to an estimated 30%–50% mortality rate.[64,65] Because of high maternal and fetal morbidity and mortality rates, most experts recommend effective contraception and early fetal termination in the event of pregnancy.[66] There have been case reports of successful treatment of pregnant IPAH patients with chronic intravenous epoprostenol,[67–69] inhaled NO,[70–72] and oral calcium channel blockers.[73] ERAs and guanylate cyclase stimulants (riociguat) are classified as teratogenic and should be avoided in this setting. In general, management includes early hospitalization for monitoring, supportive therapy with cautious fluid management, supplemental oxygen, diuretics, and dobutamine, as needed. The use of a pulmonary artery catheter for close hemodynamic monitoring and titration of vasodilator and cardiotonic therapy also has been recommended. Recommendations regarding the mode of delivery remain controversial.

Portopulmonary Hypertension

Patients with chronic liver disease have an increased prevalence of pulmonary vascular disease.[74,75] Two forms of pulmonary vascular disease can complicate chronic liver disease: (1) hepatopulmonary syndrome (HPS) and (2) portopulmonary hypertension (PPHTN). Both tend to occur in patients with chronic, late-stage liver disease, and each may increase the risk associated with liver transplantation.

Hypoxemia and intrapulmonary shunting characterize HPS. Shunting manifests echocardiographically as the late appearance (after three to five cardiac cycles) of bubble contrast in the left side of the heart. Treatment is generally supportive with supplemental oxygen, although patients with HPS and severe hypoxemia should be evaluated for liver transplant, which remains the only definitive treatment. Hypoxemia improves or resolves altogether in the majority of patients with HPS posttransplant.

PPHTN occurs in patients with chronic, late-stage liver disease and portal hypertension.[76] It often differs hemodynamically from IPAH, and these differences may affect the approach to therapy. Patients with PPHTN have lower pulmonary arterial diastolic and mean pressures, higher cardiac outputs, and lower pulmonary and systemic resistances.[77] Later-stage patients may develop hemodynamic findings similar to those of patients with IPAH, and this group may have a poorer prognosis and be at higher risk with attempted liver transplantation. It is occasionally possible to turn a patient who is an otherwise marginal candidate for liver transplant resulting from PPHTN into an acceptable one through aggressive treatment of the PAH. Supplemental oxygen should be used as needed to maintain saturations ≥90% at all times, and diuretic therapy should be used to control edema and ascites. There have been a number of case reports and small case series describing the use of intravenous epoprostenol for treatment of PPHTN,[78–82] although management of PAH in PPHTN is largely extrapolated from studies that evaluated PAH secondary to other causes.

Unlike HPS, transplant is not a treatment for PPHTN; although patients may demonstrate an improvement in PH after liver transplantation,[83] others may worsen. It may be possible to wean a select few patients off PAH medications after liver transplantation, but this should probably be done very gradually and under close observation. Because of the potential for hepatoxicity, caution is advised when using ERAs in this population.

KEY POINTS

- The evaluation of patients with PH is directed at the detection of underlying contributing factors and associated conditions, such as left-sided cardiac dysfunction, congenital heart disease, pulmonary thromboembolic disease, collagen vascular disease, parenchymal lung disease, obstructive sleep apnea, liver disease, amphetamine or appetite suppressant use, intravenous drug use, or HIV infection.
- Patients with severe PH are particularly prone to vasovagal events, and when these occur they can lead to severe consequences, including syncope, cardiopulmonary arrest, and death.
- Hypoxemia and hypercarbia are both pulmonary vasoconstrictors and can contribute to the worsening of PH.
- The induction of anesthesia and intubation for surgical procedures can be a particularly high-risk time for patients with PAH, as they are at risk for vagal events, hypoxemia, hypercarbia, and shifts in intrathoracic pressure with associated changes in cardiac filling pressures.

References for this chapter can be found at expertconsult.com.

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Hypertensive Crisis: Emergency and Urgency

Shweta Bansal and Stuart L. Linas

Hypertension is a common problem, and population data suggest its incidence is increasing globally. One billion individuals worldwide now have hypertension.[1] Nearly one in three US adults has hypertension. Compared with two-thirds in the past decade, currently half of these individuals do not have their blood pressure under control. One-third of those in whom it is not controlled are unaware of their diagnosis.[2,3] The exact risk of hypertensive crisis is not clear, but most authors estimate it to be less than 1%. A carefully conducted descriptive analysis from the Nationwide Emergency Department (ED) Sample's ED visits report hypertensive emergencies in fewer than 2 in 1000 adult ED visits and 6 in 1000 visits carrying any diagnosis of hypertension in 2013. These data reveal a prevalence much lower than previously thought.[4–6]

Hypertensive emergency is defined as an elevated blood pressure associated with evidence of acute end-organ damage. With acute damage to vital organs such as the kidney, heart, and brain, there is a significant risk of morbidity in hours without therapeutic intervention. Both the absolute level of blood pressure and the time course of the elevation determine the development of an emergency. In general with hypertensive emergency, the diastolic blood pressure is above 120 mm Hg. However, in children, gravid females, and previously normotensive individuals, hypertensive emergencies may occur with relatively minor increases in blood pressure. It is very important to identify this syndrome early to prevent end-organ damage and institute appropriate therapy as soon as the diagnosis is made. Malignant hypertension is a specific syndrome in which a markedly elevated blood pressure is associated with hypertensive neuroretinopathy.

Individuals with *hypertensive urgency* have an elevated blood pressure (systolic blood pressure [SBP] often >180 mm Hg and diastolic pressure often >115 mm Hg) without evidence of acute end-organ damage. Hypertensive urgency may be associated with chronic, stable complications such as stable angina, previous myocardial infarction, chronic congestive heart failure, chronic renal failure, previous transient ischemic attacks, or previous cerebrovascular accident with no threat of an acute insult. The focus of this chapter is on both types of hypertensive crises, with the emphasis on hypertensive emergency.

PATHOPHYSIOLOGY OF HYPERTENSIVE EMERGENCY

The precise pathophysiology of hypertensive emergency is unknown. An abrupt increase in blood pressure is one of the initiating events in the transition from simple hypertension or normotension to hypertensive emergency. The product of cardiac output and peripheral vascular resistance determines blood pressure. The initial blood pressure increase is likely secondary to an increase in vascular resistance. Considerable evidence suggests that mechanical stress in the arteriolar wall leads to vascular myogenic responses and disruption of endothelial integrity.[7] With disruption of vascular integrity, diffuse microvascular lesions develop.[8,9] Fibrinoid necrosis of the arterioles and myointimal proliferation are seen in vulnerable organs and are considered the histologic hallmark of hypertensive emergency.[8,9] Endothelial damage also causes impaired production of nitric oxide. These maladaptive responses result in increases in peripheral resistance and set up a vicious cycle, where relative hypoperfusion from vasoconstriction causes a further increase in vasoactive hormones. For example, hypoperfusion causes activation of the renin–angiotensin–aldosterone system, and evidence suggests angiotensin II may directly injure the vascular wall by activation of genes for proinflammatory cytokines (e.g., interleukin-6) and also of nuclear factor κB.[10,11] Other vascular-toxic influences may contribute to increased peripheral vascular resistance, including hyperviscosity; immunologic factors; and other hormones, including catecholamines, vasopressin, and endothelin.[12–14] The end result of these changes is a significant increase in peripheral vascular resistance, with ischemia of heart, brain, and kidneys.

In considering hypertensive emergencies and their treatment, the impact of blood pressure on cerebrovascular physiology is important. For example, hypertensive encephalopathy is a distinct clinical syndrome that occurs when rapidly rising central perfusion pressures (CPPs) exceed the ability of the central nervous system (CNS) to autoregulate. *Autoregulation* of cerebral blood flow (CBF) refers to the ability of the brain to maintain a constant CBF as the CPP varies between 60 and 150 mm Hg. In the setting of chronic hypertension, the range of autoregulation is increased to a range of 80–160 mm Hg. Autoregulation of CBF is a function of CPP (derived from the mean arterial pressure [MAP] minus the venous pressure) and cerebral vascular resistance (CVR), according to the following equation:

$$CBF = CPP/CVR$$

Under normal physiologic conditions, the backflow in the cerebral venous system or venous pressure is near zero, and the arterial pressure determines the CPP. With acute brain injury, as seen with subarachnoid hemorrhage, stroke, and intracranial hemorrhage, the ability of the brain to autoregulate and maintain CBF is impaired. Inability to autoregulate CBF is also seen in hypertensive emergency when the MAP is greater than 140 mm Hg. Failure of autoregulation leads to transmission of elevated blood pressure resulting in endothelial damage, with blood–brain barrier disruption leading to fluid and protein transudation, vasogenic edema, and further cerebral vasoconstriction causing infarcts in the brain.

DIAGNOSIS OF HYPERTENSIVE EMERGENCIES

Medical History, Physical Examination, and Laboratory Evaluation

From 40% to 50% of hypertensive emergencies arise in patients with preexisting hypertension without identifiable secondary causes.[15,16] Essential hypertension is the underlying disorder in the majority of Black individuals.[17–19] In contrast, from 50% to 60% of white patients with malignant hypertension have an identifiable cause (Box 78.1). Renovascular hypertension secondary to either fibromuscular dysplasia or atherosclerosis is not uncommon. Hypertensive emergency can occur in individuals with no hypertensive history, as in preeclampsia, pheochromocytoma, drug withdrawal, and acute glomerulonephritis. A medication history, including over-the-counter medications and illegal drug use, should be ascertained from every patient. Malignant hypertension is a unique clinical and pathologic syndrome where increases in blood pressure and target-organ damage are caused by changes in the vasculature characterized by fibrinoid necrosis and a proliferative endarteritis. Risk factors associated with the development of malignant hypertension include age between 30 and 50 years,[20] male gender,[7] Black background,[16] and smoking (increases the risk by 2.5- to 5-fold).[21]

The clinical presentation of hypertensive emergency may include headache that is generally located occipitally or anteriorly, with a steady quality. Other symptoms include visual complaints (scotoma, diplopia, hemianopsia, blindness), neurologic symptoms (focal deficits, stroke, transient ischemic attacks, seizures, confusion, somnolence), ischemic chest pain, renal symptoms (nocturia, polyuria, hematuria), back pain (aortic aneurysm), and gastrointestinal complaints (nausea, vomiting). Weight loss occurs as the high levels of circulating renin and angiotensin induce a diuresis.[22] These patients often present with intravascular volume depletion, which has strong implications for treatment.

The blood pressure is measured in both arms with the patient lying and standing. Pathologic processes such as atherosclerosis, Monckeberg medial calcification, and metastatic calcification as experienced in end-stage renal disease (ESRD), cause stiffening of the vascular wall, which can prevent vessel compression by external compression with a blood pressure cuff. This results in an artificial and at times extreme increase in the systolic and diastolic blood pressures, or "pseudohypertension." Clues to pseudohypertension include a markedly elevated blood pressure in an individual without evidence of end-organ damage. The diagnosis is suggested by a palpable radial artery despite proximal compression with a sphygmomanometer (Osler maneuver).[23]

A dilated funduscopic examination should be performed on all individuals. Arteriolar thickening reflects chronic hypertension and is manifested by increased light reflex, vascular tortuosity, and arteriovenous nicking where the arterioles cross the venules. These changes have no prognostic significance with regard to hypertensive emergency. However, as hypertension increases in severity, there are additional findings caused by the breakdown of the blood–retina barrier, leading to retinal hemorrhage and leakage of lipids, causing hard exudates or cotton-wool spots as a result of nerve ischemia and swelling of the optic nerve with papilledema.[24]

A complete cardiovascular examination should include a careful evaluation for evidence of left ventricular hypertrophy and heart failure and peripheral pulse examination for absence or delay suggestive of aortic dissection. Chest x-ray or point-of-care ultrasonography can be used to discriminate cardiac from noncardiac dyspnea.[25,26] Examination of the abdomen should include evaluation for enlarged kidneys, as seen with polycystic kidney disease, and for evidence of aortic aneurysm. Last, a careful neurologic examination should be done to rule out any evidence of a cerebrovascular accident. Alterations in mental status may indicate a stroke or hypertensive encephalopathy. The initial laboratory evaluation should include a serum sodium, chloride, potassium, bicarbonate, creatinine and blood urea nitrogen, complete blood count (with a peripheral smear to identify schistocytes), prothrombin time, activated partial thromboplastin time, serum and urine toxicology screen, pregnancy test when appropriate, an electrocardiogram, and a urinalysis (Box 78.2). Evidence of intravascular hemolysis is common and may make it difficult to differentiate hypertensive emergency from primary vasculitis with secondary hypertension.[27,28] The renin–angiotensin–aldosterone axis is markedly activated, as evidenced by hypokalemia and metabolic alkalosis.[4,29] The blood urea nitrogen and creatinine are often

BOX 78.1 Syndromes of Hypertensive Crisis

- Malignant hypertension
- Nonmalignant hypertension with target-organ disorders
  - Patient requiring emergency surgery with poorly controlled hypertension
  - Hyperviscosity syndrome
  - Postoperative patient
  - Renal transplant patient: acute rejection, transplant renal artery stenosis
  - Quadriplegic patient with autonomic hyperreflexia
  - Severe burns
  - Acute aortic dissection
  - Intracranial hemorrhage, ischemic stroke, or subarachnoid hemorrhage
  - Hypertensive encephalopathy
  - Myocardial ischemia/acute left ventricular failure
  - Preeclampsia/eclampsia
  - Antiphospholipid antibody syndrome
  - Acute renal failure
    - Scleroderma renal crisis
    - Chronic glomerulonephritis
    - Reflux nephropathy
    - Analgesic nephropathy
    - Acute glomerulonephritis
    - Radiation nephritis
    - Ask-Upmark kidney
    - Chronic lead intoxication
  - Renovascular hypertension
    - Fibromuscular dysplasia
    - Atherosclerosis
  - Endocrine hypertension
    - Congenital adrenal hyperplasia
    - Pheochromocytoma
    - Oral contraceptives
    - Aldosteronism
    - Cushing disease/syndrome
  - Systemic vasculitis
  - Atheroembolic renal crisis
  - Drugs
    - Oral contraceptives
    - Nonsteroidal antiinflammatory agents
    - Atropine
    - Corticosteroids
    - Sympathomimetics
    - Erythropoietin
    - Lead intoxication
    - Cyclosporine
  - Catecholamine excess states
    - Pheochromocytoma
    - MAO/tyramine interaction
    - Antihypertensive withdrawal
    - Cocaine intoxication, sympathomimetic overdose

MAO, Monoamine oxidase.

BOX 78.2 Proposed Diagnostic Studies in Patients With Suspected Hypertensive Emergency

Laboratory Analysis
- Hemoglobin, platelet count
- Serum creatinine, sodium, potassium, bicarbonate, lactic dehydrogenase (LDH), haptoglobin, prothrombin time, activated partial thromboplastin time
- Serum and urine toxicology screen
- Quantitative urinalysis for protein, urine sediment for erythrocytes, leukocytes, cylinders, and casts

Diagnostic Examination
- ECG (ischemia, arrhythmias, left ventricular hypertrophy)
- Fundoscopy

On Indication
- Troponin-T, creatine kinase (CK) and its isoenzyme MB (CK-MB)
- Pregnancy test
- Peripheral blood smear (for assessment of schistocytes)
- Plasma renin activity and plasma aldosterone levels, serum metanephrines
- Connective tissue disorders serology
- Chest x-ray (fluid overload)
- Transthoracic echocardiography (cardiac structure and function) or point-of-care cardiac and lung ultrasound (cardiac pulmonary edema)
- CT (or MRI) brain (intracranial hemorrhage)
- CT angiography of thorax and abdomen (acute aortic disease)
- Renal ultrasound (postrenal obstruction, kidney size, left-to-right difference)

CT, Computed tomography; *ECG,* electrocardiogram; *MRI,* magnetic resonance imaging.

BOX 78.3 Differential Diagnosis of Hypertensive Encephalopathy

Cerebral infarction
Subarachnoid hemorrhage
Intracerebral hemorrhage
Subdural or epidural hematoma
Brain tumor or other mass lesion
Seizure disorder
Central nervous system vasculitis
Encephalitis/meningitis
Drug ingestion
Drug withdrawal

elevated. The urinalysis may show small amounts of proteinuria and hematuria with occasional erythrocyte casts.[7] Marked increases in proteinuria suggest a primary glomerular process such as glomerulonephritis as the etiology of the elevated blood pressure.

If hypertensive encephalopathy is suspected, magnetic resonance imaging (MRI) of the brain should be performed. Edema seen posteriorly, particularly in the parieto-occipital regions (a finding earlier called *posterior leukoencephalopathy* and now the widely accepted term *posterior reversible encephalopathy syndrome [PRES]*) and rarely in the brainstem, is a manifestation of hypertensive encephalopathy.[30,31] It is important to consider and eliminate other conditions with a similar clinical presentation (Box 78.3). Several important diagnostic considerations help exclude other causes of altered mental status: (1) symptoms of generalized brain dysfunction tend to develop over time (12–24 hours) with hypertensive encephalopathy, as compared with acutely in ischemic stroke or cerebral hemorrhage; (2) focal neurologic findings are unusual with hypertensive encephalopathy unless there is an associated bleed; (3) papilledema is almost always noted with hypertensive encephalopathy and, if absent, should raise suspicion of another etiology; and (4) in comparison with an acute CNS bleed, mental status with hypertensive encephalopathy improves within 24–48 hours of treatment.

TREATMENT OF HYPERTENSIVE EMERGENCY

Patients with hypertensive emergency are best treated parenterally with intensive care monitoring by arterial cannulation or automated blood pressure cuff measurement. In general, the need to lower the blood pressure and the rate at which this should occur are dictated by the clinical setting. Excessive falls in pressure should be avoided, given the potential for resulting in renal, cerebral, and coronary ischemia.

In most but not all settings, blood pressure can be reduced acutely by 20%–25% within minutes to hours.[4] Although the autoregulatory range of CBF is reset upward in chronic hypertension, the lower limit of the autoregulation remains approximately 25% below the resting MAP in patients with both normotension and chronic hypertension.[32] When the arterial blood pressure falls below this lower limit, CBF progressively decreases and symptoms of low CBF, including nausea, yawning, hyperventilation, clamminess, and syncope, develop. To protect cerebral function, after an initial reduction of blood pressure by 20% within the first hour, blood pressure is further reduced over the next 2–6 hours to the 160/110 mm Hg range as long as the patient remains stable.[4] Assuming continued stability, the blood pressure may then be decreased to 140/90 mm Hg over the next 24–48 hours.[4] With these decreases in blood pressure, CBF autoregulation is usually maintained. There are several clinical settings where additional issues and alternative approaches to reducing blood pressure should be considered. In ischemic stroke, immediate reduction of blood pressure is usually not indicated except when the blood pressure is over 220/120 mm Hg or the patient requires thrombolytic therapy. Recent data indicate that acute blood pressure reduction is of no benefit (CATIS trial) or even harmful (SCAST trial).[33,34] In intracerebral hemorrhage (ICH), acute lowering of SBP to 140 mm Hg is recommended based on weak evidence. Results of the INTERACT2 study support this recommendation, although further lowering to 126 mm Hg did not result in any additional benefit in the ATACH2 trial.[35,36] In acute aortic dissection, if the patient tolerates it, a rapid blood pressure reduction in 15–30 minutes to a SBP under 100 mm Hg is clinically warranted. Finally, more rapid reduction in blood pressure is also recommended in patients with active unstable angina or congestive heart failure with pulmonary edema.

Exceptions to rapid blood pressure reduction may include older patients with carotid stenosis, given that these individuals are particularly susceptible to CNS hypoperfusion. Significant reduction of blood pressure in the setting of ischemic stroke may not be beneficial (discussed later). Overall, blood pressure management in patients with stroke or intracranial bleeding is controversial, because the loss of CBF autoregulation and the presence of brain edema require high systemic pressures to provide adequate cerebral perfusion.

SPECIFIC TREATMENT RECOMMENDATIONS FOR HYPERTENSIVE EMERGENCY BASED ON ETIOLOGY

General Comments on Medications Used to Treat Hypertensive Emergency

The classes of parenteral antihypertensive agents available to treat hypertensive emergency include direct vasodilators (sodium nitroprusside, nitroglycerin), alpha- and beta-adrenergic blockers (labetalol), alpha-adrenergic blockade (phentolamine), angiotensin-converting enzyme (ACE) inhibitors (enalaprilat), calcium channel blockers (nicardipine and clevidipine), and dopamine agonists (fenoldopam). Some of the advantages and disadvantages of these medications are detailed in Table 78.1. There is

TABLE 78.1 Treatment of Hypertensive Crisis: Intravenous Medications

Drug Name and Mechanism of Action	Indications/Advantages/Dose	Disadvantages/Adverse Effects/ Metabolism Cautions
Sodium Nitroprusside Nitric oxide compound; vasodilation of arteriolar and venous smooth muscle Increases cardiac output by decreasing afterload	Useful in most hypertensive emergencies Onset of action immediate, duration of action 1–2 minutes Dose: 0.25 μg/kg/min Maximum dose: 8–10 μg/kg/min	Contraindicated in high-output cardiac failure, congenital optic atrophy. Anemia and liver disease at risk of cyanide toxicity: acidosis, tachycardia, change in mental status, almond smell on breath. Risk of thiocyanate toxicity with renal disease: psychosis, hyperreflexia, seizure, tinnitus. Cautious use with increased intracranial pressure. Do not use maximum dose for more than 10 minutes. Crosses the placenta.
Nitroglycerin Directly interacts with nitrate receptors on vascular smooth muscle Primarily dilates venous bed Decreases preload	Use with symptoms of cardiac ischemia, perioperative hypertension in cardiac surgery Initial dose: 5 μg/min Maximum dose: 100 μg/min	Contraindicated in angle-closure glaucoma, increased intracranial pressure. Blood pressure decreased secondary to decreased preload, cardiac output—avoid when cerebral or renal perfusion compromised. Caution with right ventricular infarct.
Labetalol Beta- and alpha-adrenergic blockade Alpha:beta-blocking ratio is 1:7	Onset of action 2–5 minutes, duration 3–6 hours Bolus 20 mg, then 20–80 mg every 10 minutes for maximum dose 300 mg Infuse at 0.5–2 mg/min	Avoid in bronchospasm, bradycardia, congestive heart failure, greater than first-degree heart block, second/third trimester pregnancy. Use caution with hepatic dysfunction, inhalational anesthetics (myocardial depression). Enters breast milk.
Esmolol Cardioselective beta-1-adrenergic blocking agent	Use with aortic dissection Use during intubation, intraoperative, and postoperative hypertension Onset of action 60 seconds, duration 10–20 minutes 200–500 μg/kg/min for 4 minutes, then infuse 50–300 μg/kg/min	See labetalol. Not dependent on renal or hepatic function for metabolism (metabolized by hydrolysis in red blood cells).
Fenoldopam Postsynaptic dopamine-1 agonist; decreases peripheral vascular resistance; ten times more potent than dopamine as vasodilator	May be advantageous in kidney disease, increases renal blood flow, increases sodium excretion, no toxic metabolites Initial dose: 0.1 μg/kg/min, with titration every 15 minutes No bolus	Contraindicated in glaucoma (may increase intraocular pressure) or allergy to sulfites; hypotension, especially with concurrent beta-blocker. Check serum potassium every 6 hours. Concurrent acetaminophen may significantly increase blood levels. Dose-related tachycardia.
Hydralazine Primarily dilates arteriolar vasculature	Primarily used in pregnancy/eclampsia Dose: 10 mg every 20–130 minutes; maximum dose 20 mg Decreases blood pressure in 10–20 minutes Duration of action 2–4 hours	Reflex tachycardia; give beta-blocker concurrently. May exacerbate angina. Half-life 3 hours, affects blood pressure for 100 hours. Depends on hepatic acetylation for inactivation.
Phentolamine Alpha-adrenergic blockade	Used primarily to treat hypertension from excessive catecholamine excess (e.g., pheochromocytoma) Dose: 5–15 mg Onset of action 1–2 minutes, duration 3–10 minutes	Beta-blockade is generally added to control tachycardia or arrhythmias. As in all catecholamine excess states, beta-blockers should never be given first, as the loss of beta-adrenergically mediated vasodilatation will leave alpha-adrenergically mediated vasoconstriction unopposed and result in increased pressure.
Nicardipine Dihydropyridine calcium channel blocker; inhibits transmembrane influx of calcium ions into cardiac and smooth muscle	Onset of action 10–20 minutes, duration 1–4 hours Initial dose: 5 mg/h to maximum of 15 mg/h	Avoid with congestive heart failure, cardiac ischemia. Adverse effects include tachycardia, flushing, headache.
Clevidipine Short-acting dihydropyridine calcium channel antagonist[47]	Initial dose: 1 mg/h; can be increased to 21 mg/h	Reduces blood pressure without affecting cardiac filling pressures or causing reflex tachycardia. It has been endorsed as first-line treatment option for acute ischemic stroke
Enalaprilat Angiotensin-converting enzyme inhibitor	Onset of action 15–20 minutes, duration 12–24 hours Dose: 1.25–5 mg every 6 hours	Response not predictable, with high renin states may see acute hypotension. Hyperkalemia in setting of reduced glomerular filtration rate. Avoid in pregnancy.
Trimethaphan Nondepolarizing ganglionic blocking agent; competes with acetylcholine for postsynaptic receptors	Used in aortic dissection Dose: 0.5–5 mg/min	Does not increase cardiac output. No inotropic cardiac effect. Disadvantages include parasympathetic blockade, resulting in paralytic ileus and bladder atony and development of tachyphylaxis after 24–96 hours of use.

no consensus on the most effective antihypertensive medications in the setting of a CNS insult and no large randomized trials demonstrating the superiority of a given agent. Rather, the choice of antihypertensive therapy should be individualized to the patient and clinical setting. With the availability of newer agents such as nicardipine, clevidipine, and fenoldopam, most authors now caution against the use of nitroprusside, which can increase intracranial pressure (ICP) and has a low safety margin. Vasodilators increase blood volume and therefore have the potential to increase ICP. Animal and human studies in the setting of a normal ICP show no effect of nitroprusside on ICP.[27–29] However, in studies on animals and humans with preexisting increased ICP, nitroprusside further increased the ICP, likely reflecting vasodilatation on the background of decreased cranial compliance.[37–41] When sodium nitroprusside is contraindicated, other treatment options include labetalol and nicardipine. Fenoldopam, which is an agonist of the vasodilator dopamine-1 receptor, shares with nitroprusside a rapid onset and short duration of action. In addition, in contrast to nitroprusside, fenoldopam increases renal blood flow, induces natriuresis, and produces no toxic metabolites.[42–46]

Malignant Hypertension

As noted earlier, malignant hypertension is a specific syndrome characterized by markedly elevated pressures in conjunction with hypertensive neuroretinopathy. Funduscopic examination often reveals flame-shaped hemorrhages, cotton-wool spots, or papilledema. Malignant hypertension is also associated with nephropathy, encephalopathy, microangiopathic hemolytic anemia, and cardiac ischemia. Untreated malignant hypertension is a rapidly fatal disorder, with a mortality of more than 90% within 1 year, as reported in a classic series by Kincaid-Smith and colleagues.[8] In this series, deaths were the result of renal failure (19%), congestive heart failure (13%), renal failure plus congestive heart failure (48%), stroke (20%), and myocardial infarction (1%). More contemporary studies report 7%–15% mortality over 5 years in patients with treated malignant hypertension compared with 2.5% in matched hypertensive controls.[48,49] In these cohorts, patients with malignant hypertension had a more favorable cardiovascular risk profile compared with hypertensive controls but a higher prevalence of renal insufficiency.[48,49]

Aggressive therapy to prevent progressive ischemic injury in malignant hypertension is critical. Nitroprusside had been the preferred agent; however, because of concerns related to increased ICP, cyanide toxicity in the setting of anemia or liver disease, thiocyanate toxicity in the setting of renal failure, and the availability of the newer agents, its utility has decreased over the years. A number of parenteral agents, including fenoldopam and nicardipine, have been used as successful alternatives to nitroprusside. If nitroprusside is used, thiocyanate levels should be monitored and the duration of therapy kept to less than 72 hours whenever possible. Fenoldopam has no toxic metabolites and may protect renal function.[42–46] Premature discontinuation of parenteral therapy may cause rebound hypertension. Oral therapy is usually started after the pressure has been stabilized on parenteral therapy, and the latter is then slowly weaned.

Renal failure is common with malignant hypertension, and, in a vicious cycle, the renal failure exacerbates the hypertension. Aggressive treatment can arrest and reverse renal damage. Because the arteriolopathy of malignant hypertension includes fixed anatomic lesions, initial lowering of blood pressure may worsen renal function. Dialysis may be required in patients presenting with a creatinine greater than 4.5 mg/dL.[50] In the majority of patients, renal function begins to improve after 2 weeks of therapy. Of the patients who require dialysis, 50% will regain sufficient function to discontinue dialysis.[51] Recovery of renal function is predicted when the combined length of both kidneys is 20.2 cm or more but is felt to be unlikely when the length is 14.2 cm or less.[52] The mean time to recovery is approximately 2–3 months, but recovery after up to 26 months has been reported.[53] In patients with malignant hypertension secondary to glomerulonephritis, eventual deterioration to ESRD may occur despite blood pressure control.[54] In contrast, renal function tends to remain well preserved in patients without underlying glomerulonephritis if the blood pressure is well controlled.

Hypertensive Encephalopathy

In hypertensive encephalopathy, the MAP exceeds the limits of autoregulation, and brain edema develops from extravasation of plasma proteins. If hypertensive encephalopathy is untreated, coma and death may follow.[55] The challenge of hypertensive encephalopathy is appropriate lowering of blood pressure in the setting of CNS ischemia and edema. The hallmark of hypertensive encephalopathy is improvement within 12–24 hours of adequate blood pressure reduction. The MAP should be cautiously reduced by no more than 15% over 2–3 hours. Neurologic complications have been reported from reductions in MAP of 40% or more.[56]

Hypertensive encephalopathy is one of the medical conditions believed to cause reversible posterior leukoencephalopathy, a condition that results from reversible vasogenic subcortical edema without infarction.[30,31] This syndrome is characterized by headache, decreased alertness, changes in behavior including confusion and diminished speech, seizures, and alterations in visual perceptions. It is rapidly reversible with lowering of the blood pressure.[30,31] An MRI examination shows characteristic findings, including white matter edema in the posterior cerebral hemispheres.[30]

There is a growing literature supporting a shared pathologic process between hypertensive encephalopathy and eclampsia. Both syndromes have the same clinical features and imaging findings. Eclampsia during pregnancy, in addition to postpartum eclampsia, has also been associated with reversible posterior leukoencephalopathy.[30,31]

In previously normotensive patients, including those with eclampsia, blood pressure should be normalized. If the mental status worsens with treatment, the pressure should be allowed to increase until neurologic symptoms resolve and then be reduced to within the normal range over several days to allow restoration of autoregulation.

Ischemic Cerebral Infarction

When the CPP decreases below the level of autoregulation, ischemia develops. In response, there may be a marked elevation in arterial blood pressure to maintain perfusion, which tends to spontaneously return to baseline 24–48 hours after the acute event. Thus treatment of acutely increased blood pressure may not be required. After an ischemic cerebrovascular accident, it is also important to consider other causes that may contribute to an increase in blood pressure, including a full bladder, nausea, pain, preexisting hypertension, hypoxia, or increased ICP. Oftentimes, simply calming the patient, treating the pain, and relieving a full bladder may reduce the blood pressure.

Data from animal studies show that in the area surrounding the ischemic infarct, there are "neurons at risk" that rely on collateral circulation to maintain perfusion.[57] These neurons are nonfunctional but not dead, a phenomenon referred to as *ischemic penumbra,* and they can potentially be rescued by reperfusion.[58] The degree to which this occurs in humans is not known. In addition, in acute stroke, autoregulation is impaired, and CBF is therefore not preserved in a predictable manner. As a result of these changes, acute reductions in blood pressure could potentially increase the area of infarct, resulting in severe clinical consequences.

Comprehensive guidelines for the treatment of stroke recommend that for patients determined to be candidates for administration of

intravenous recombinant tissue plasminogen activator, the blood pressure must be reduced if the SBP is >185 mm Hg or the diastolic blood pressure is >110 mm Hg, and the patient must be carefully monitored before, during, and after administration of this compound. The same blood pressure criteria have been used in recent trials examining the effect of thrombectomy with or without prior thrombolysis.[59–61] Thrombolytic therapy is contraindicated if the blood pressure is >185/100 mm Hg.[62]

Questions remain as to how to manage individuals with ischemic stroke who are not candidates for thrombolysis. There are no good data from randomized controlled trials to guide blood pressure management. A prospective observational study analyzing the impact of blood pressure lowering in the setting of ischemic stroke in 1092 patients suggested an improved outcome at 3 months with modest reductions in SBP between 10 and 27 mm Hg. However, the authors noted that the benefit of blood pressure reduction waned with age. If the systolic pressure was lowered by more than 27 mm Hg, the odds ratio for a poor outcome at 3 months increased more than 5-fold at age 70–76 years, nearly 10-fold for 76–80 years, and nearly 15-fold in patients older than 80 years.[63] Moreover, recently published randomized controlled studies, where patients were enrolled as long as 30–48 hours after stroke onset, do not show any significant difference in mortality and functional outcome with aggressive hypertension treatment.[33,34] In the absence of any definitive data, the current recommendation is that if there is no indication for acute lowering of the blood pressure (e.g., acute ischemic damage to vital organs such as cardiac ischemia or aortic dissection), then the threshold for treatment should be a SBP over 220 mm Hg or a diastolic blood pressure over 120 mm Hg, with the aim to lower the blood pressure 15%–25% over the first 24 hours in the acute phase of ischemic stroke.[62]

Subarachnoid Hemorrhage

Approximately 10% of cerebrovascular accidents are caused by subarachnoid hemorrhage, which remains a devastating entity with a mortality rate of 50%–60% at 30 days and a 50% dependency rate in survivors.[64] Subarachnoid hemorrhage increases ICP and decreases cerebral perfusion, causing global ischemia. Complications include an ICH or the development of hydrocephalus. Management of these patients is significantly different from those with ischemic stroke. In contrast to ischemia, intracranial bleeding induces intense vasospasm in neighboring vessels 4–12 days after the initial bleed, increasing the risk for significant cerebral ischemia. The mental status evaluation may be used to guide therapy, with an intact mental status implying adequate cerebral perfusion.

Markedly elevated pressures increase the risk of rebleeding. The goal is a 20%–25% reduction in blood pressure over 6–12 hours, but not to less than 160–180/100 mm Hg.[65] Labetalol and nicardipine are the preferred agents, as they have no significant adverse effects on ICP or CPP.[4] There are clinical data to show that treatment with oral nimodipine within 4 days of the acute event decreases vasospasm and cerebral ischemia.[46] Nimodipine may also directly protect against ischemic damage to nerve cells by blocking calcium uptake into cells.

Intracerebral Hemorrhage

ICH accounts for 10%–20% of all strokes and affects more than 1 million people worldwide annually.[66,67] Hypertension is a major risk factor; 75% of affected individuals have preexisting hypertension.[68] Although patients with ICH may present with nausea, vomiting, change in mental status, hypertension, headache, and a focal neurologic examination, the definitive diagnosis must be made by neuroimaging. Unlike ischemic stroke, where blood pressure generally returns to normal within 24–48 hours, in ICH, the most rapid decline in blood pressure occurs in the first 24 hours, but it may remain elevated for 7–10 days.[58] The hematoma compresses normal tissue, creating an area of ischemia, increasing ICP, and further decreasing CPP. Autoregulation is altered, making cerebral perfusion critically dependent on systemic blood pressure.[69]

There is no clear consensus on the appropriate treatment of hypertension in the setting of acute ICH. The central issue is whether aggressive lowering of blood pressure reduces the risk of intracerebral bleeding without disrupting blood flow to collateral areas. Some argue that decreasing blood pressure lowers the risk of hemorrhage extension, edema, and associated systemic complications, particularly when SBP exceeds 200 mm Hg, a level associated with hematoma growth in some studies.[66,68,69] A retrospective analysis of 76 patients with ICH and hypertension showed that maximum SBP was significantly associated with hematoma enlargement, particularly if the SBP was ≥160 mm Hg.[70] The greatest risk of hematoma extension is in the first few hours after the initial result and can occur in up to a third of affected individuals.[71,72] Others argue that not treating hypertension allows continued perfusion of areas at risk from low blood flow.[69] Taking these factors into account, two recent randomized controlled trials, INTERACT2 and ATACH2, evaluated the impact of rapid lowering of elevated blood pressure within 6 hours or 4.5 hours of symptom onset, achieved over 1 hour, on death and disability in patients with ICH and SBP between 150 and 220 mm Hg or more than 180 mm Hg, respectively.[35,36] The mean minimal achieved SBP was 150 mm Hg and 126 mm Hg, respectively, in the INTERACT2 and ATACH2 trials. Although there was no significant reduction in death and disability in the two trials, patients assigned to intensive treatment had improved functional outcomes at 3 months in INTERACT2 and worse renal adverse events in ATACH2.[35,36]

The recommendation is as follows for treatment of hypertension in ICH[73]: (1) If there is no suspected elevation of the ICP and the SBP is 150–180 mm Hg, consider aggressive lowering of SBP to 140 mm Hg. (2) In the setting of suspected ICH, ICP should be monitored and consideration given to aggressive lowering of the blood pressure with continuous or intermittent intravenous medication when the SBP is over 180 mm Hg or the MAP is over 130 mm Hg, keeping the CPP above 60–80 mm Hg. (3) Aggressive lowering of blood pressure using intravenous medication and blood pressure monitoring every 5 minutes should be considered when the SBP is over 220 mm Hg or the MAP is over 150 mm Hg. The optimal goal blood pressure is uncertain, but an SBP of 140–160 mm Hg is a reasonable target.

There is no consensus on the agent of choice. Concern revolves around the impact of different antihypertensives on ICP. Common to all agents is a decrease in MAP and a decrease in CPP. Vasodilating agents may increase CBF and in the setting of decreased cranial compliance may potentially increase ICP, further decreasing CPP.[40,69] The combination of decreased cerebral compliance, decreased CBF, and altered autoregulation—as occurs in chronic hypertension—makes the administration of any antihypertensive agent potentially dangerous. No large randomized studies are available to guide therapy. Combination alpha- and beta-blockers are recommended when antihypertensive treatment is indicated in ICH. Risks of this therapy include worsening of bradycardia associated with the Cushing response. However, in the setting of normal cranial compliance and an increased ICP, vasodilators are probably safe. Because of the very high levels of circulating catecholamines with an intracerebral bleed, beta-blockade is added when vasodilator therapy alone is ineffective.

Head Trauma

Head trauma complications include skull fractures, epidural hematomas, subdural hematomas, intracerebral hematomas, and diffuse axonal damage. With trauma, there is often edema. Acute increases in ICP

are initially prevented by flow of blood and cerebrospinal fluid (CSF) from the cranial vault. However, with increasing edema, ICP eventually increases. In most trauma centers, ICP monitoring has become the standard of care.[74] Anywhere from 31% to 61% of patients with a closed head injury may have defective autoregulation.[75] If autoregulation is intact, increasing the MAP will cause vasoconstriction and produce no change in ICP. With altered autoregulation, increasing the MAP may cause vasodilatation, increasing blood volume and leading to edema and increased ICP. The goal is to maintain a minimum CPP of 70 mm Hg and an MAP above 90 mm Hg. If an antihypertensive agent is needed, a major consideration is its impact on ICP. A combination alpha- and beta-blocker or nicardipine may be preferred when there is decreased intracranial compliance and increased ICP.[76,77] In the absence of ICH, vasodilators may be preferred.

Aortic Dissection

Aortic dissection begins with a tear in the intima of the aorta that is propagated by the aortic pulse wave. Myocardial contractility, heart rate, and blood pressure contribute to the aortic pulse wave. There are two types of aortic dissections: type A and type B. Type A dissections are often associated with a tear in the intima of the proximal aorta next to a coronary artery and may extend to the aortic arch.[78] Type B dissections occur in the descending aortic arch and usually begin with an intimal tear next to the subclavian artery.[79] Risk factors for dissection include advanced atherosclerosis, Marfan syndrome, Ehlers-Danlos syndrome, and coarctation of the aorta.[80] Symptoms occur as the expanding hematoma causes pressure on the vasculature. This may cause myocardial infarction, stroke, spinal cord or bowel infarction, and acute renal failure. Kidney ischemia may develop, leading to refractory hypertension.[81] Dissection to the aortic root can precipitate acute aortic insufficiency, and rupture of the ascending aorta leads to hemopericardium and tamponade.[82]

Both types of dissections may present with severe, often tearing pain in the chest, back, or abdomen, accompanied by diaphoresis, nausea, or vomiting. Dissection is often, but not always, associated with hypertension.[83] Discrepancies in peripheral pulses may be observed. Chest pain is reportedly present in only half of individuals with type B dissections.[84] The diagnosis may be confirmed with computed tomography (CT) or MRI. Multiplane transesophageal echocardiography is also used. Type A dissections usually require surgery to prevent the catastrophic consequences of great vessel occlusion, aortic insufficiency, or tamponade. Type B dissections may usually be treated medically[85,86] unless there is rupture, in which case open or endovascular repair is indicated. A recent meta-analysis suggested that endovascular repair may be preferred.[85]

Treatment for both type A and type B dissections is initiated based on clinical suspicion alone, given the high mortality associated with this entity. The first goal of treatment is to decrease myocardial contractility and heart rate with a beta-blocking agent. Reasonable initial targets are a heart rate less than 60 beats per minute and an SBP between 100 and 120 mm Hg. Esmolol has advantages in the acute setting because of its short half-life and ability to titrate to effect. Next, the blood pressure is reduced to the lowest tolerable level until pain is relieved. Relief of pain suggests arrest of ongoing aortic dissection. In addition to beta-blockade, vasodilators may be required to control blood pressure. The most established agent has been nitroprusside; however, nicardipine, nitroglycerin, and fenoldopam are appropriate for this situation.[87] Prior treatment with beta-blockade prevents reflex cardiac stimulation and a potential increase in the aortic pulse wave seen with nitroprusside. Even normotensive individuals should be treated with antihypertensive medications to keep the heart rate and shear forces low.

Pulmonary Edema

Many patients who present with pulmonary edema have long-standing antecedent hypertension with concentric left ventricular hypertrophy and well-preserved systolic contraction.[88,89] They develop acute diastolic dysfunction in response to abrupt increases in cardiac afterload because of increased systemic blood pressure.[90] With poor diastolic relaxation, the left ventricle requires markedly elevated filling pressures, leading to pulmonary venous hypertension and edema. The therapeutic goal is to decrease afterload, improve diastolic relaxation, and decrease pulmonary pressure. Vasodilators are the agents of choice, as they improve diastolic relaxation and lower pulmonary venous pressure.[91] A beta-blocker may also be used. Nitroprusside is often used because it reduces preload and afterload, improving left ventricular function and reducing myocardial oxygen demand. Modest decreases in pressure improve symptoms markedly. In less emergent settings, ACE inhibitors or calcium channel antagonists have been shown to improve diastolic function and cause regression of concentric ventricular hypertrophy.[92]

In patients with left ventricular failure secondary to poor systolic function, vasodilators are the agents of choice. Nitroglycerin is preferred with cardiac ischemia. Nitroprusside may be used in patients refractory to nitrites. Whereas nitroglycerin dilates intercoronary collateral vessels more than small resistance arterioles and improves perfusion of ischemic myocardium, nitroprusside dilates resistance arterioles predominantly, thereby resulting in a potential steal of blood flow away from ischemic areas. Diuretics are used to reduce left ventricular end-diastolic volume.

In the setting of acute myocardial infarction, acute catecholamine release and sympathetic outflow contribute to hypertension. The hypertension usually resolves in a few hours with sedation and pain control alone. Diastolic blood pressures over 100 mm Hg should be treated with nitroglycerin. The pressure is rapidly, but cautiously, reduced to near-normotensive levels; overshoot hypotension can worsen coronary perfusion. Therapy can usually be stopped within 24 hours. There is considerable evidence that early use of beta-blocking agents may reduce ultimate infarct size independent of blood pressure control.[93]

Perioperative Hypertension

Perioperative hypertension is a major risk factor for the development of postoperative hypertension.[94] Whenever possible, it is preferred to postpone elective surgery until the blood pressure has been well controlled over days to weeks. However, when waiting is not an option, lowering the blood pressure to below 180/110 mm Hg before noncardiac surgery is recommended.[94] In patients with chronic hypertension on adequate treatment, oral medications should be taken the morning of surgery. Adequate blood pressure control reduces the risk of bleeding from suture lines, premature graft closure, and ischemic damage to organs at risk.

Induction of anesthesia and surgical stimuli increase sympathetic activity, causing elevated blood pressure both intraoperatively and postoperatively. This response may be exaggerated in uncontrolled hypertension, with decreased use of deep anesthesia and absence of prolonged sedation. As anesthesia continues, there is generally a fall in blood pressure. Rapid and wide fluctuations in blood pressure leading to intraoperative hypotension, stroke, myocardial ischemia, or acute renal failure are more common in individuals with a hypertensive history.

Patients taking hypertensive therapy before surgery should continue treatment after surgery, changing to an equivalent intravenous medication if they are unable to take oral medications. If patients have been on a beta-blocker or clonidine, this medication should be continued postoperatively to prevent rebound hypertension. Effective pain control and avoidance of hypoxia may be sufficient to treat the hypertension. If intravenous medication is necessary, nitroglycerin is preferred for the

post–coronary bypass patient. Fenoldopam, with its impact on increasing renal blood flow, is also recommended, especially in clinical settings where renal ischemia is a risk. Clevidipine has been gaining popularity in this setting because of its rapid onset and short duration of action with limited effect on cardiac preload and output. However, there is limited experience with this drug, and cost is an issue.[95]

Catecholamine-Associated Hypertension

Hypertensive emergency related to excess catecholamine secretion can result from the ingestion of sympathomimetic agents such as cocaine; amphetamines; phencyclidine, phenylpropanolamine (diet pills); decongestants such as ephedrine and pseudoephedrine; and other agents, including atropine, ergot alkaloids, and tricyclic antidepressants. It may also be caused by tyramine ingestion in conjunction with monoamine oxidase (MAO) inhibitor therapy, autonomic dysfunction, withdrawal from certain antihypertensive medications, and pheochromocytoma (Box 78.4). Critically elevated pressures can result and cause myocardial infarction, aortic dissection, and stroke.

Pheochromocytoma is a rare cause of hypertension.[96] Excess catecholamine secretion by the tumor results in a sustained elevation of blood pressure in the majority of cases, and peripheral catecholamine uptake and storage lead to paroxysmal symptoms when the catecholamines are released in response to stimuli. Symptoms of pheochromocytoma include headache, palpitations, hypertension, anxiety, abdominal pain, and diaphoresis. Patients may present with orthostatic changes in blood pressure, a clue to the diagnosis.[97] For the patient with hypertensive emergency, the treatment of choice is the short-acting parenteral alpha-antagonist phentolamine. After blood pressure reduction, beta-blockade is generally added to control tachycardia or arrhythmias. As in all catecholamine excess states, beta-blockers should not be used as initial therapy. Loss of beta-adrenergically mediated vasodilatation leaves alpha-adrenergically mediated vasoconstriction unopposed and results in increased pressure. An oral regimen of the nonselective alpha-antagonist phenoxybenzamine can be used in less critical situations. Labetalol has been effective in treating hypertension related to pheochromocytoma in selected patients. However, as its beta-blockade exceeds its alpha-blocking effect, severe hypertension has been reported.[98]

Gestational Hypertension, Preeclampsia, and Eclampsia

Gestational hypertension is defined as an SBP of at least 140 mm Hg and a diastolic blood pressure of at least 90 mm Hg on two separate blood pressure measurements done 6 hours apart. It occurs after 20 weeks of pregnancy in patients known to previously be normotensive.[99] Up to 50% of these women develop preeclampsia if gestational hypertension develops before 30 weeks of gestation. *Preeclampsia* is defined as gestational hypertension with 300 mg or more of protein on a 24-hour urine (urine dipstick 1+). A 24-hour urine is necessary because dipstick urine protein correlates poorly with 24-hour urine protein in gestational hypertension.[100] Preeclampsia should also be suspected in patients with hypertension developing after 20 weeks' gestation and is associated with nausea, vomiting, cerebral symptoms, abnormal liver function tests, and thrombocytopenia, even in the absence of proteinuria. Preeclampsia develops in 5% of all pregnancies and occurs twice as often in primigravid versus multigravid women.[101] Preeclampsia also appears in women with a history of multiple pregnancies but with a new partner.[101] In the setting of molar pregnancy, it is seen in up to 70% of individuals.[102] During normal pregnancy, blood pressure is initially decreased and then slowly rises toward the normal range during the third trimester. In preeclampsia, intravascular volume is low despite peripheral edema, and the renin–angiotensin system is activated. Progression to seizures defines eclampsia and may occur with diastolic pressures of as low as 100 mm Hg. Clinical treatment includes bedrest and parenteral magnesium.

With regard to hypertensive treatment in pregnancy, the optimal blood pressure has not been defined; however, emerging evidence is suggesting to individualize treatment target decisions taking other risk factors into account.[101a] The goal is to prolong the pregnancy until the fetus can be delivered and reduce maternal complications. In the case of mild preeclampsia, there are no large studies to guide therapy.[101] With more severe preeclampsia, treatment is given to prevent cerebral hemorrhage. The recommendation is to initiate antihypertensive therapy when the SBP is above 160 mm Hg or the diastolic blood pressure is above 110 mm Hg. Intravenous labetalol and nicardipine have been shown to be a safe and effective treatment to keep the SBP 140–155 mm Hg and the diastolic blood pressure 90–105 mm Hg.[101] Treatment with hydralazine is no longer recommended, as it has been associated with adverse perinatal outcomes.[103] A good blood pressure control has been reported with the use of oral nifedipine. Fewer doses were required and less time needed to achieve control, and the adverse-effect profile was similar to intravenous labetolol.[104] In an updated opinion, the American College of Obstetricians and Gynecologists Committee added oral nifedipine as a first-line therapy.[105] Concern for neuromuscular blockade and severe hypotension with the contemporaneous use of nifedipine and magnesium sulfate were not substantiated in a large retrospective review.[106] However, because both drugs are calcium antagonists, careful monitoring is advisable. Nitroprusside should be avoided because of the risk of cyanide toxicity in the fetus. ACE inhibitors should also be avoided because of their potential impact on the fetal kidney.

BOX 78.4 Tyramine-Containing Foods

Chianti wine
Chicken liver
Soy sauce
Yeast
Avocados
Fermented sausage
Bananas
Canned figs
Coffee
Certain beers

Other Hypertensive Situations

The renal crisis of scleroderma is an aggressive form of malignant hypertension in which proliferative endarteritis precedes hypertension. Ischemic-induced activation of the renin–angiotensin system causes the hypertension. The incidence of this condition among patients with scleroderma ranges from 8% to 13%, and it is more common among Blacks.[107] Progression to ESRD occurs in 1–2 months without treatment. Aggressive pressure control with ACE inhibitors leads to a long-term survival of about 50%–70%.[108]

Hypertension is a feature of both primary and secondary antiphospholipid antibody syndromes, occurring in up to 93% of patients.[109] Malignant hypertension occurs in this syndrome secondary to both microvasculopathy and emboli to the renal artery. Antihypertensive treatment is similar to that for malignant hypertension. Successful treatment outcomes have been reported with anticoagulation.[109]

One-fourth of patients with extensive second- or third-degree burns develop severe hypertension in the first few days, likely the result of high levels of circulating catecholamines and renin. Nitroprusside

and phentolamine (in countries where it is still available) are other treatments.

Drugs that inhibit the vascular endothelial growth factor pathway have been approved for use in several malignancies. Its increased use has shown an increased incidence in proteinuria and hypertension, which can be severe and associated with acute end-organ damage.[110,111] There is some evidence that renin–angiotensin system blockade and a low-sodium diet were helpful in controlling blood pressure.[112]

Patients with transverse spinal cord lesions at the T6 level or higher, including patients with Guillain-Barré syndrome, have dysreflexia in which noxious stimuli in dermatomes below the level of the lesion trigger a massive sympathetic discharge. This leads to severe hypertension, bradycardia, diaphoresis, and headache. In 90% of patients, distention of the bladder or bowel causes the dysreflexia, and prompt decompression leads to resolution of hypertension.[113] Drugs that have been used successfully in treating this condition include nitroprusside, phentolamine, and labetalol.

HYPERTENSIVE URGENCY

Hypertensive urgency refers to patients in whom blood pressure is severely elevated, but based on detailed history, physical examination, and laboratory evaluation, there is no evidence of acute end-organ damage related to the current episode of hypertension, although there may be evidence of previous hypertension-induced end-organ damage. Although long-term control of blood pressure in this setting can prevent complications resulting from stroke, myocardial infarction, or congestive heart failure, there is no evidence that acute reduction of blood pressure results in any improvement in short- or long-term prognosis. Unfortunately, the term *urgency* is a misnomer and has led to overly aggressive management of many patients. Aggressive treatment with intravenous drugs or even oral agents, such as clonidine or nifedipine, to rapidly lower blood pressure can lead to cumulative effects causing hypotension, sometimes after discharge from the emergency room. A recent retrospective cohort analysis reported prevalence of hypertensive urgency in 4.6% of office visits. Referrals to the emergency department compared with home management were associated with more hospitalization but no difference in major adverse cardiovascular events at 7 days, 1 month, or 6 months.[114] A more appropriate clinical term to describe this condition is *severe uncomplicated hypertension,* because there is no need for urgent reduction of blood pressure, as would be required in patients with true hypertensive emergencies (Box 78.5).

The treatment of choice is gradual pressure reduction over a few days in the outpatient setting. The choice of antihypertensive agent is based on ease of administration and side-effect profile rather than on rapid blood pressure reductions. Frequently, restarting a previously effective regimen is all that is necessary. It is critically important to follow these patients over the next 24–48 hours to ensure the blood pressure is appropriately reduced. Although medicolegal issues may pressure physicians into loading these patients with medication to observe on-the-spot control of their blood pressure, this practice has been questioned as having no clear rational scientific basis.

BOX 78.5 Severe Uncomplicated Hypertension

Severe hypertension (diastolic blood pressure >115 mm Hg) in association with one or more of the following:
Chronic renal failure
Chronic congestive heart failure
Stable angina
Previous myocardial infarction
Transient ischemic attacks
Previous cerebrovascular accident

KEY POINTS

- Hypertension crisis is defined as new or progressive end-organ damage associated with high blood pressure and requires immediate blood pressure control over the course of minutes to hours.
- Hypertensive urgency defines a very high blood pressure in the absence of end-organ damage, is a misnomer, and does not require acute reduction of blood pressure; rather, acute aggressive reduction could be harmful.
- The pathophysiology of hypertensive emergency is not clear but is proposed to involve a sudden rise in blood pressure causing vascular myogenic response and endothelium damage resulting in an increase in vasoactive hormones and vessel damage (fibrinoid necrosis and myointimal proliferation). This sets up a vicious cycle of an increase in peripheral vascular resistance and worsening of hypertension.
- Management of hypertension emergencies begins with careful assessment of blood pressure, end-organ damage (most of the time brain, heart, and kidney), identification of reversible insults, and institution of parenteral antihypertensives in most circumstances.
- The choice of antihypertensives and level of blood pressure reduction depend on the etiology and type of hypertensive organ damage.

References for this chapter can be found at expertconsult.com.

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Pathophysiology and Classification of Shock States

Mark E. Astiz

PATHOPHYSIOLOGY OF SHOCK

Circulatory shock represents a final common pathway of cardiovascular failure. Septic shock is the most common cause of shock followed by cardiogenic and hypovolemic shock.[1] Mortality remains high, particularly for patients with septic and cardiogenic shock, where it approaches 40%.[2,3] From a physiologic perspective, circulatory shock is defined as a syndrome in which blood flow is inadequate to meet cellular metabolic requirements.[4] Clinically, shock is manifested by organ hypoperfusion, which is most evident in the skin and peripheries, kidneys, and brain. The principal signs of circulatory shock are as follows: cool, clammy, and cyanotic extremities; decreased pulses; oliguria with a urine output <0.5 mL/kg/h; and confusion, disorientation, and obtundation.

Mechanisms Underlying Impaired Cardiovascular Performance

The development of shock is related to alterations in the components of the circulatory system that regulate cardiovascular performance. The first component is intravascular volume, which regulates mean circulatory pressures and venous return to the heart. Decreases in intravascular volume limit venous return to the heart and cardiac output. The heart is the second component. Cardiac output is determined by heart rate, contractility, and loading conditions. Abnormalities in rhythm and heart rate may limit cardiac output. Impaired cardiac contractility decreases effective ventricular ejection and compromises stroke volume. Abnormalities in valvular function may also limit cardiac output. The third component is the resistance circuit; it consists of the arteriolar bed, where the major decreases in vascular resistance occur. Arteriolar tone plays an important role in ventricular loading conditions, arterial pressure, and distribution of systemic blood flow. Excessive decreases in arteriolar tone lead to hypotension and limit effective organ perfusion, whereas excessive increases in arteriolar tone impede cardiac ejection by increasing ventricular afterload. Differences in arteriolar tone between organs can result in maldistribution of blood flow and mismatching of blood supply with tissue metabolic demands. The capillaries are the fourth component. They are the site of nutrient exchange and fluid flux between the intravascular and extravascular spaces. Increases in capillary permeability result in tissue edema and loss of intravascular volume. Decreases in capillary cross-sectional area, secondary to either obstruction or impairment in endothelial cell function, compromise nutrient blood flow. The opening of arteriovenous connections, which bypass the capillary network, may play a role in tissue hypoperfusion. The venules are the fifth component. They are the site of the lowest shear stress in the circulatory system and are thus the site most prone to occlusion from alterations in cell rheology. Venular resistance contributes 10%–15% of total vascular resistance. Increases in venular tone increase capillary hydrostatic pressures, thereby promoting the extravascular movement of fluid. The sixth component is the venous capacitance circuit. More than 80% of the total blood volume resides in large-capacitance vessels. Increases in venous tone decrease venous capacitance, redistributing blood volume centrally and thereby increasing venous return to the heart. Decreases in venous tone increase venous capacitance and decrease effective arterial blood volume and venous return. The seventh component is mainstream patency. Obstruction of the systemic or pulmonary circuit impedes ventricular ejection, and venous obstruction limits venous return to the ventricles.

Hemodynamic Assessment

Circulatory performance can be assessed from hemodynamic parameters. A low heart rate may limit cardiac output, whereas an increased heart rate can compromise stroke volumes by limiting ventricular filling times. Bradyarrhythmias indicate structural abnormalities, effects of drugs, hypoxia, or other metabolic stimuli. Severe bradyarrhythmias can also represent reflex-mediated responses, as occurs in cases of severe hemorrhagic shock and acute inferior wall myocardial infarction. Tachyarrhythmias may be the result of underlying cardiac disease or pharmacologic or environmental stimuli. Alternatively, increases in the heart rate may reflect compensatory responses to maintain cardiac output.

In patients with circulatory shock, blood pressure should be monitored using intravascular measurements.[4] Vasoconstriction related to compensatory mechanisms to maintain arterial pressure and the use of pharmacologic agents limits the accuracy of noninvasive measurements. This is particularly true in hypodynamic forms of circulatory failure.

For most vital organs, autoregulatory and neuronal mechanisms maintain blood flow independent of blood pressure at a mean arterial pressure of 60–130 mm Hg. At either higher or lower levels of pressure, blood flow becomes linearly dependent on blood pressure. Diseases such as hypertension can shift this relationship and increase the critical level of arterial pressure required for organ perfusion. Similarly, impaired autoregulatory mechanisms present in a variety of pathologic states expand the range of pressure-dependent blood flow.

The level of arterial pressure is not a reliable indicator of circulatory performance and tissue perfusion.[5,6] In states of hypodynamic circulatory shock such as traumatic injury, cardiac failure, and obstructive shock, hypotension is a late marker of critical hypoperfusion. As cardiac output falls, blood pressure is initially maintained by increases in peripheral vascular resistance largely mediated by the sympathoadrenal system. It is only after these mechanisms have been exhausted that hypotension develops. Accordingly, tissue hypoperfusion may be present despite normal levels of blood pressure as blood flow

is redirected toward more vital organs. Conversely, hypotension may exist without evidence of organ hypoperfusion. In some vasodilated states, increases in cardiac output maintain vital organ blood flow despite decreased levels of arterial pressure.

Filling pressures have traditionally been used as measures of ventricular preload and to guide fluid resuscitation. However these measurements correlate poorly with blood volume, end-diastolic volumes, and fluid responsiveness.[7] Echocardiographic techniques can provide an alternative assessment of chamber size and end-diastolic volumes, whereas fluid responsiveness is best assessed with dynamic measurements that reflect the response of stroke volume to changes in loading conditions. Examples include respiratory variations in pulse pressure, velocity time integral, and stroke volume on mechanical ventilation. Alternatively, changes in stroke volume may be assessed during passive leg raising or after volume challenge.

Cardiac output can be measured by multiple techniques.[4,8] Pulmonary artery thermodilution has been supplanted by less-invasive techniques, including lithium dilution, bioreactance, echocardiography, esophageal Doppler, and arterial pulse contour analysis. Echocardiographic measurements and esophageal Doppler can be used to assess ventricular ejection and provide diagnostic information regarding the presence of pericardial tamponade and valvular function. The response of stroke volume to changes in ventricular loading during fluid infusion is also useful to assess cardiac function. A good response indicates preserved cardiac function, whereas lack of response may be related to either cardiac dysfunction or inadequate fluid volumes. However, the adequacy of cardiac output in meeting tissue metabolic demands must be assessed independently by monitoring indices of tissue perfusion and oxygen metabolism. A low cardiac output may be adequate when metabolic requirements are decreased—for example, in deep sedation or hypothermia. In contrast, an increased cardiac output may not be adequate when metabolic requirements are increased or maldistribution of blood flow exists, such as in septic shock.

Systemic vascular resistance is an indicator of arterial tone; it is calculated from cardiac output and arterial pressure. Increases in systemic vascular resistance are the result of vasoconstriction and represent compensatory mechanisms directed at maintaining blood pressure in the setting of a decreased cardiac output. Excessive increases in vascular resistance increase ventricular afterload and the impedance to ejection. Decreases in vascular resistance are the result of vasodilation, decreases in blood viscosity, or presence of arteriovenous connections. Vasodilation may be pathologic, as occurs in septic shock and liver disease, or it may be adaptive, as occurs in hyperdynamic stress after major surgery and traumatic injury. Venous tone is much harder to assess clinically. In most cases, changes in venous tone parallel changes in arterial tone. Modest increases in central venous pressures in the setting of large-volume infusion and the absence of intravascular volume loss suggest decreased venous tone.

CLASSIFICATION OF SHOCK

Hinshaw and Cox proposed a classification of circulatory shock involving four subsets: hypovolemic, cardiogenic, distributive, and obstructive.[9] This classification can be simplified into two categories with typical hemodynamic profiles (Table 79.1). The first category, hypodynamic shock, includes the hypovolemic, cardiogenic, and obstructive shock subsets. The second category, hyperdynamic shock, includes the distributive shock subset.

The central features of hypodynamic shock are a low cardiac index and a high-resistance vasoconstricted state. Increased oxygen extraction and lactic acidosis usually parallel the decrease in cardiac output. In cases of hypodynamic shock, the development of organ dysfunction is directly related to inadequate global blood flow. Common causes of hypovolemic shock are hemorrhage, dehydration, and massive capillary leak. Acute decreases in blood volume of 25% result in tachycardia and orthostatic hypotension. The loss of 40% of blood volume is associated with severe hypotension and clinical shock. Decreased filling pressures are the hallmark of hypovolemic shock, in contrast to cardiogenic shock in which filling pressures are elevated. Acute myocardial infarction involving 40% or more of ventricular mass is the most common cause of cardiogenic shock. Cardiomyopathies and severe valvular lesions are other important causes of cardiogenic shock. Severe stress may also induce severe reversible cardiac dysfunction. Finally, obstructive shock is most commonly caused by pericardial tamponade, acute pulmonary embolism, and tension pneumothorax. Dynamic obstruction to left ventricular output may also lead to circulatory shock. Because filling pressures are usually increased in these settings (owing to outflow obstruction, impaired ventricular filling, and decreased ventricular compliance), distinguishing between obstructive shock and cardiogenic shock can be difficult.

Hyperdynamic circulatory shock is characterized by a high cardiac index and a low-resistance vasodilated state. Filling pressures may be increased or normal, depending on volume status and myocardial competence. Common causes of hyperdynamic shock include sepsis, anaphylaxis, drug intoxications, spinal shock, and adrenal insufficiency. The underlying hemodynamic defect is maldistribution of blood flow and/or blood volume such that effective nutrient blood flow is compromised. In contrast to hypodynamic shock, oxygen extraction may be normal or decreased despite evidence of hypoperfusion.[10] Direct mediator-related effects coupled with tissue hypoperfusion lead to cellular injury and organ dysfunction in patients with septic shock.

A considerable overlap may exist between these different syndromes. Early in septic and anaphylactic shock, before fluid infusion, a significant hypovolemic component usually exists. Hypovolemia may also be present in a small group of patients presenting with shock secondary to acute myocardial infarction. In the presence of severe

TABLE 79.1 Circulatory Shock Hemodynamic Profiles

	MAP	PAWP, LVEDV	CO	SVR	SvO_2	Lactate
Hypodynamic						
Hypovolemic hemorrhage, dehydration	↓	↓	↓	↑	↓	↑
Cardiogenic myocardial infarction	↓	↑	↓	↑	↓	↑
Obstructive pulmonary embolism, pericardial tamponade, tension pneumothorax	↓	↔↑	↓	↑	↓	↑
Hyperdynamic						
Distributive sepsis, adrenal insufficiency, anaphylaxis	↓	↔↓	↔↑	↓	↔↑	↑

CO, Cardiac output; *LVEDV,* left ventricular end-diastolic volume; *MAP,* mean arterial pressure; *PAWP,* pulmonary arterial wedge pressure; *SvO_2,* venous oxygen saturation; *SVR,* systemic vascular resistance.

sepsis-related myocardial depression, patients with septic shock can develop a hypodynamic profile. Similarly, patients in cardiogenic shock after myocardial infarction and cardiac surgery may demonstrate significant vasodilation because of the activation of mediator cascades while on cardiopulmonary bypass.[11] Alternatively, dynamic left ventricular outflow obstruction related to systolic anterior movement of the mitral valve may complicate ischemic and stress-related cardiogenic shock.[12]

Progression of Shock

Critical reductions in tissue perfusion elicit a complex set of reflexes that are directed at maintaining cardiac output and arterial pressure.[13] Activation of the sympathetic nervous system increases heart rate and contractility. The release of catecholamines, angiotensin, vasopressin, and endothelins increases arteriolar and venous tone, thereby increasing arterial blood pressure and shifting blood volume from the capacitance vessels to the central circulation. In addition, blood flow is redirected from skeletal muscle, subcutaneous tissue, and splanchnic circulation to the heart and brain. Vasopressin and activation of the renin–angiotensin system serve to enhance water and sodium retention, thereby protecting intravascular blood volume.

Progression of the shock state is marked by further declines in blood pressure that compromise coronary perfusion and cardiac performance. Increases in peripheral vascular resistance increase afterload and impede left ventricular ejection. Damage-associated molecular patterns are activated, initiating a systemic inflammatory response. Terminal phases of shock are marked by the development of an endotheliopathy with resulting damage to the endothelial glycocalyx, breakdown in paracellular tight junctions, and increase in microvascular permeability.[14] Microvascular vasomotor dysfunction is marked by loss of arteriolar tone with paradoxically increased venular resistance. Leukostasis, impaired erythrocyte rheology, platelet activation, and activation of the coagulation cascade further impair microvascular blood flow.

This pathophysiology is altered in hyperdynamic forms of circulatory failure such as septic shock, in which inflammatory mediators released by interaction of microbial-associated molecular patterns with pattern-recognition receptors play a prominent role.[15] These patients are characterized by arterial and venous vasodilation coupled with an increased cardiac output. The influence of vasodilatory substances such as nitric oxide and prostacyclin predominates over the effects of endogenous and exogenous vasopressor substances. In some forms of vasodilatory shock, inappropriately low levels of vasopressin, cortisol, and angiotensin II may contribute to refractoriness to catecholamines. Decreases in capillary cross-sectional area, secondary to the interactions of activated leukocytes, platelets, endothelial cells, and activation of the clotting cascade, limit effective nutrient blood flow despite the increase in cardiac output.[16] Concomitant injury to the endothelial glycocalyx and paracellular tight junctions increases microvascular permeability, resulting in loss of intravascular fluid. Progressive hypotension, which is refractory to fluid infusion and vasopressors, results in worsening tissue hypoperfusion, acidosis, and organ failure. A hypodynamic circulation develops as a terminal event.

Oxidative Metabolism in Shock

The primary metabolic defect in circulatory shock is impaired oxidative metabolism with resulting cellular and organ failure. This impairment is most commonly the result of decreases in tissue oxygen supply caused by either global decreases in blood flow or maldistribution of blood flow at a regional or microcirculatory level. Systemic oxygen consumption may initially be increased yet inadequate to meet tissue metabolic requirements; however, the terminal phases of all forms of shock are characterized by decreases in oxygen consumption. In experimental studies, mortality is directly related to the cumulated deficit in oxygen metabolism.[17]

Oxygen delivery is determined by cardiac output, hemoglobin concentration, and arterial oxygen saturation. Under normal circumstances, oxygen consumption is independent of oxygen delivery and cardiac output (Fig. 79.1). Increases in cellular oxygen extraction, from a normal level of 25% to a maximum of level of 80%, maintain oxygen consumption as blood flow is reduced. When oxygen extraction is maximized, a critical level of oxygen delivery (DO_2crit) is reached below which oxygen consumption decreases and anaerobic metabolism ensues. Alterations in vasomotor reflexes caused by sepsis or drugs limit maximal oxygen extraction, resulting in critical tissue hypoxia and anaerobic metabolism at higher levels of oxygen delivery.

Aerobic adenosine triphosphate (ATP) generation is dependent on glycolysis occurring in the cytoplasm and oxidative phosphorylation occurring in the mitochondria (Fig. 79.2). Under anaerobic conditions, ATP generation is limited to the 2 moles of ATP generated in the cytoplasm, compared with the 38 moles of ATP generated aerobically. The decreased entry of pyruvate into the citric acid cycle results in the accumulation of lactic acid and the generation of additional hydrogen ions from the hydrolysis of ATP. Accordingly, the presence of lactic acidosis serves as an indicator of critical cellular deficits in high-energy phosphate metabolism. The normal level of lactate is 0.4–1.2 mEq/L. Levels greater than 1.5 mEq/L are associated with an increased mortality rate in septic shock.[18]

Oxidative metabolism may also be altered by mechanisms independent of tissue hypoperfusion. Indeed, decreased mitochondrial activity in sepsis has been postulated to be potentially adaptive and represent a state of hibernation. Alternatively, inflammatory mediators, including nitric oxide, oxygen radicals, calcium, and tumor necrosis factor, may directly

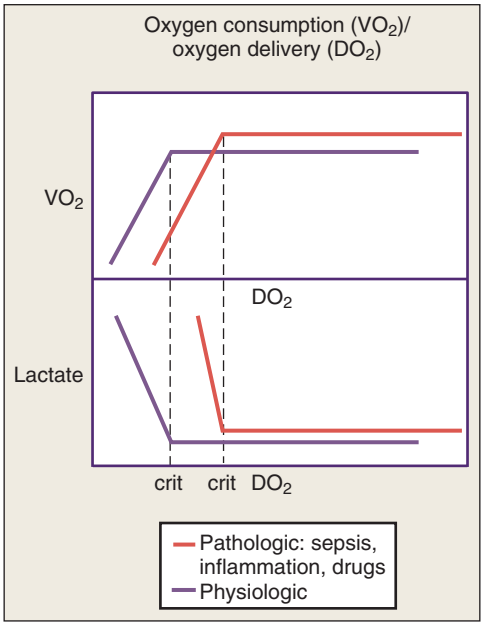

Fig. 79.1 Oxygen consumption–oxygen delivery relationships. Oxygen consumption (VO_2) is independent of oxygen delivery (DO_2) until a critical level of DO_2 is reached at which oxygen extraction is maximized. At that level of oxygen delivery (DO_2crit), VO_2 becomes linearly dependent on DO_2, and anaerobic metabolism manifested by lactic acidosis ensues. This relationship shifts upward and to the right when the ability of the tissues to extract oxygen is impaired because of alterations in the distribution of blood flow.

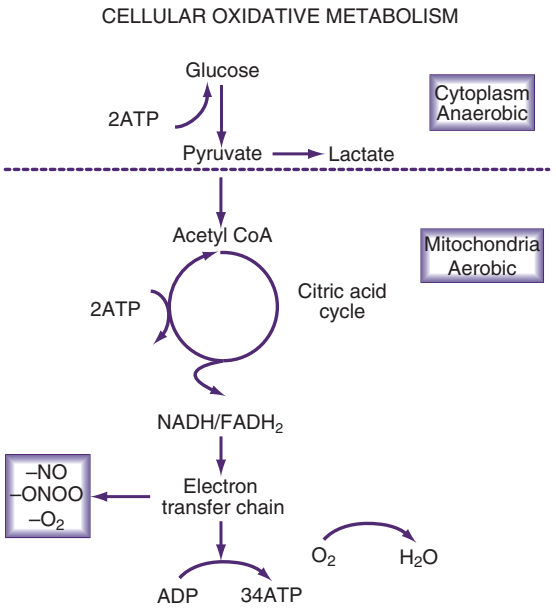

Fig. 79.2 Cellular oxidative metabolism. Glucose is metabolized anaerobically in the cytoplasm and aerobically in the mitochondria under conditions of normal tissue perfusion. Under conditions of shock, high-energy phosphate generation (adenosine triphosphate [*ATP*]) is limited to anaerobic pathways. Nitric oxide (*NO*), peroxynitrite ($ONOO^-$), and superoxide (O_2^-) are potential inhibitors of the electron transfer chain. *ADP,* Adenosine diphosphate; $FADH_2$, reduced flavin adenine dinucleotide; *NADH,* reduced nicotinamide adenine dinucleotide.

impair mitochondrial function. Decreased mitochondrial biogenesis, mitochondrial swelling, increased mitochondrial autophagy, and decreased mitochondrial respiratory complex activity have all been observed in patients with septic shock.[19,20] Similarly, impaired mitochondrial function has been described in animal models of traumatic and hemorrhagic shock. The specific role of mitochondrial abnormalities in organ dysfunction in shock is still being elucidated and could potentially lead to mitochondrial-based therapeutic interventions.[19,20]

The accumulation of tissue carbon dioxide (CO_2) parallels the decrease in oxygen metabolism in circulatory shock.[21] Increases in tissue CO_2 levels are manifested by venous hypercapnia and decreases in venous pH. The resulting widening of the arterial-venous CO_2 gradient is proportional to the degree of circulatory failure.[22] The normal gradient is less than 5 mm Hg, and it increases to 40 mm Hg or more during cardiac arrest. Decreased clearance of CO_2 generated by oxidative processes is responsible for the initial increase in tissue CO_2 levels. With the onset of anaerobic metabolism, a tissue CO_2 excess is generated from the titration of anaerobically derived acids by bicarbonate. The increase in tissue CO_2 levels has been associated with impaired myocardial performance in vitro.

Monitoring Perfusion Failure

Acute circulatory failure can be identified by clinical evaluation focusing on mentation, urine output, and peripheral perfusion. Heart rate, arterial pressure, and cardiac output are important but correlate poorly with survival in critically ill patients.[5,6] The primary difficulty with each of these measures is in the early stages of circulatory failure where compensatory mechanisms may frequently obfuscate the degree of systemic hypoperfusion.[23] Similarly, despite stabilization after initial resuscitative efforts, patients with septic shock and high-risk surgical patients will frequently have evidence of persisting deficits in tissue perfusion that are associated with increased mortality.[5,24] These observations have led to the use of indices of tissue oxygen metabolism as markers of tissue perfusion and the adequacy of resuscitative efforts.

Mixed venous oxygen saturation (SvO_2), measured on blood taken from the pulmonary artery, is used as an index of tissue oxygenation. Venous blood is in equilibrium with the tissues. Mixed venous blood, representing a weighted mean of all the venous effluents, reflects overall tissue oxygenation. Because increased oxygen extraction is the primary compensatory mechanism to maintain oxygen consumption, decreases in SvO_2 are an early marker of compromised tissue perfusion. In cardiogenic shock, SvO_2 tracks cardiac function and systemic perfusion.[2] The same is not true in septic shock and other settings, where the relationship between venous blood and tissue oxygenation is altered by maldistribution of blood flow.[10] In these circumstances, the ability of the tissues to extract oxygen is limited by decreases in effective nutrient flow such that SvO_2 may be normal or increased despite the presence of tissue hypoxia and anaerobic metabolism. Accordingly, although mixed venous desaturation is indicative of tissue hypoxia, normal levels do not preclude tissue hypoperfusion.

Central venous oxygen saturation ($ScvO_2$), measured in samples taken from the superior vena cava and right atrium, serves as an alternative to SvO_2. In critically ill patients, $ScvO_2$ is generally 5% higher than SvO_2; however, the correlation is inconsistent depending, in part, on the location of the tip of the central venous catheter. Although targeting therapy to $ScvO_2$ does not improve outcome in septic shock, persistence of $ScvO_2$ <70% of levels is associated with increased mortality in sepsis and identifies a group of patients that could benefit from efforts to increase oxygen delivery.[25]

Lactate concentration is a useful marker of critical hypoperfusion. Increases in lactate levels indicate the presence of anaerobic metabolism and tissue energy deficits. Although the initial blood level of lactate has prognostic significance, the inability to clear lactate over time is more discriminating and is associated with increased mortality in a broad range of critically ill patients.[26,27] In patients with septic shock, factors other than hypoperfusion may contribute to lactate accumulation. These factors include increased muscle ATPase activity, increased hepatic flux of alanine from skeletal muscle, decreased pyruvate dehydrogenase activity, decreased hepatic clearance of lactate, and dysfunctional mitochondrial respiration. Despite these concerns, increases in lactate concentration are associated with decreases in the intracellular redox potential in patients with septic shock, suggesting that it is a useful marker of cellular energy metabolism.[28]

Oxygen consumption and oxygen delivery are global markers of systemic oxygen metabolism. Oxygen consumption, a measure of overall metabolic requirements, is calculated from cardiac index, hemoglobin, and arterial and venous oxygen saturation. It can also be measured directly from expired gases. Oxygen delivery is calculated from cardiac output, hemoglobin, and arterial saturation; it is a measure of the total amount of oxygen being delivered to the tissues. Although increased values of oxygen consumption and oxygen delivery have been observed in survivors compared with nonsurvivors, considerable overlap exists between the two groups. Efforts to titrate therapy to values associated with survival, "optimal goals," have produced mixed results.[29] These differences, in part, reflect the varying metabolic requirements of individual patients and the heterogeneity in the response of the control and treatment groups to hemodynamic interventions.

The decrease in CO_2 clearance in circulatory shock can be used to monitor ongoing perfusion failure. Widening of the gap between central venous and arterial partial pressure of CO_2 (PCO_2) to >6 mm Hg can be used to identify patients who may not be adequately resuscitated despite $ScvO_2$ >70%.[30] End-tidal CO_2 measurements are useful in monitoring perfusion during cardiopulmonary resuscitation.

Cardiac arrest results in marked decreases in pulmonary blood flow and accompanying decreases in CO_2 excretion. End-tidal CO_2 values move toward zero during arrest and increase with successful resuscitation.[31]

There have been many attempts to use measures of local or regional perfusion as indices of overall systemic perfusion. These are all predicated on the premise that decreased blood flow to specific organs may serve as an early indicator of systemic hypoperfusion. Toe temperature, subcutaneous oxygen tensions, transcutaneous oxygen tension, gastric tonometry, sublingual tonometry, laser Doppler, and near-infrared spectroscopy are some examples of regional measures that did not achieve widespread clinical use. Newer efforts aimed at tissue oxygen monitoring include the use of specialized urinary catheters to track bladder tissue oxygen levels. A recent study revisited the importance of monitoring peripheral tissue perfusion by comparing interventions guided by digital capillary refill time (CRT) with those guided by lactate clearance in patients with septic shock.[32] No significant differences in mortality and organ failure were observed between the two groups. However, lower Sequential Organ Failure Assessment (SOFA) scores and lower mortality in the CRT patients with less severe organ dysfunction suggest that regional measures may be complementary to systemic measures in assessing for underlying tissue hypoperfusion.

An area of current interest is the monitoring of the microcirculation in critically ill patients. Techniques such as orthogonal polarization spectral imaging, sidestream dark-field imaging, and more recently, incident dark-field imaging have been used to directly visualize microcirculatory flow using handheld vital microscopy. Alterations in microcirculatory function have been described in a number of disease states.[33] Decreases in capillary blood flow have correlated with mortality in patients with septic and cardiogenic shock. Using these techniques, evidence of impaired microvascular blood flow has been reported in critically ill patients despite improvement in systemic hemodynamic variables. This incongruence between the response of the macrocirculation and that of the microcirculation may have important clinical implications.[34] Optimal techniques, the most discriminating measurements, and whether titration of therapy to these indices of microcirculatory blood flow will affect the outcome remain to be elucidated.[33]

Organ Failure

The primary causes of organ dysfunction in circulatory shock are ischemic injury, mediator-related organ dysfunction, and reperfusion injury. Ischemic injury occurs when anaerobic metabolism ensues and high-energy phosphate production falls below the level required to maintain cellular pumps and membrane integrity. It is the major factor contributing to organ failure in patients with cardiogenic and hypovolemic shock. The direct effect of inflammatory mediators, coupled with an ischemic injury, plays a major role in organ dysfunction in septic shock. Tumor necrosis factor, nitric oxide, and superoxide radicals are examples of mediators directly affecting cellular and organ function. Reperfusion injury occurs upon restoration of tissue perfusion after an absence of blood flow (Fig. 79.3). The initial injury is related to the release of oxygen radicals, increased membrane permeability, and intracellular calcium accumulation. The later phase involves cytokines, activated neutrophils, endothelial cell dysfunction, and microvascular occlusion.[35] Reperfusion injury may be important in hemorrhagic and traumatic shock; its role in cardiogenic shock and septic shock is less clear.

Cardiac dysfunction is related to ischemia and myocardial necrosis in shock secondary to myocardial infarction. Reperfusion injury may play a role in patients after acute coronary revascularization. Myocardial depressant substances such as nitric oxide and cytokines cause myocardial depression in patients in septic shock and possibly in hemorrhagic shock.[36] Impaired responsiveness to catecholamines and adrenergic receptor downregulation occur in septic and cardiogenic

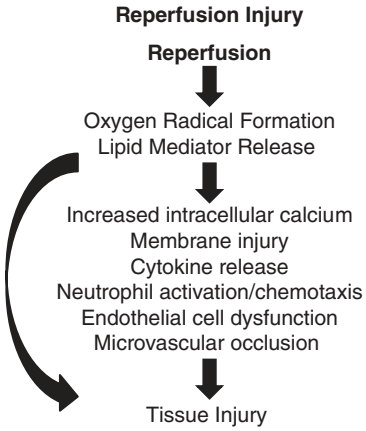

Fig. 79.3 Reperfusion injury. Under ischemic conditions, adenosine triphosphate (ATP) is metabolized to hypoxanthine and xanthine dehydrogenase is converted into xanthine oxidase. During reperfusion, superoxide is produced from hypoxanthine and oxygen by xanthine oxidase. Superoxide and its metabolites produce cellular injury and membrane disruption, resulting in the release of prostanoids and leukotrienes. The lipid mediators and oxygen radicals act as chemoattractants for neutrophils, which injure tissues through the release of elastases, proteases, and additional oxygen radicals.

shock. Increases in pulmonary vascular resistance cause right ventricular failure in patients with pulmonary embolism and may be important in septic shock, particularly when acute respiratory distress syndrome is present.

Respiratory failure frequently complicates circulatory shock. Cardiac failure, fluid overload, and acute lung injury related to the release of inflammatory mediators and activation of neutrophils result in increased lung water and intrapulmonary shunt. Dead space may be increased because of either underlying disease and/or pulmonary vascular endothelial damage in acute lung injury syndromes. Decreased respiratory muscle perfusion, coupled with hypoxia and increased work of breathing, contributes to respiratory muscle failure. In patients with septic shock, inflammatory mediators may also directly impair diaphragmatic activity.[37]

Renal dysfunction in shock is related to multiple mechanisms. Initially, as cardiac output decreases, glomerular filtration is maintained by increases in efferent arteriolar tone. Release of atrial natriuretic peptide related to increased atrial pressures may help protect renal blood flow in patients with cardiogenic shock. As shock progresses, the increases in afferent arteriolar tone result in renal ischemia and acute tubular necrosis. The activation of neutrophils and endothelial cells coupled with tubular epithelial cell injury and intrarenal shunting also plays important roles in renal injury associated with septic shock.[38]

A characteristic pattern that involves centrilobar necrosis and marked transaminase elevation is observed in patients with ischemic hepatic injury associated with hypodynamic circulatory states.[39] Activation of Kupffer cells and release of inflammatory mediators exacerbate ischemic injury in patients in septic and traumatic shock. In septic shock, hepatobiliary transporters and canalicular cell contractility are impaired, resulting in intrahepatic cholestasis. Hepatic metabolic failure and impaired amino acid clearance are also features of septic shock.

Splanchnic mucosal blood flow is compromised early in shock, as blood flow gets redirected to more vital organs Splanchnic hypoperfusion related to shock and the use of vasopressors contribute to the development of stress ulceration, acalculous cholecystitis, intestinal necrosis, and pancreatitis. Loss of the integrity of the intestinal barrier leads to the release of inflammatory mediators into the mesenteric

lymphatics and, less frequently, the translocation of bacteria, which in turn contribute to organ failure.[40]

Thrombocytopenia is observed in a majority of patients with septic shock. The coagulation cascade is activated in septic and traumatic shock by the pathogen and damage-associated molecular patterns.[14] Disseminated intravascular coagulation is marked by impaired fibrinolysis and increased consumption of clotting factors. Clinical manifestations are bleeding and microvascular thrombosis. Large-volume asanguineous fluid resuscitation may unmask these tendencies by additional hemodilution of clotting factors and platelets. The development of hypothermia exacerbates coagulopathies in patients with circulatory shock.

Disorientation and delirium are common in patients in shock. Hypotension, metabolic abnormalities, hypoxia, and medications all contribute to neurologic dysfunction. Alterations in cerebrovascular reactivity and direct toxic effects of inflammatory mediators may also play a role in cerebral injury.[41] Severe hypotension, mean arterial pressure well below 60 mm Hg, can result in ischemic injury of the arterial border zones in the cortex and spinal cord. In some survivors of critical illness, long-term impairment of cognitive function has been reported.

Microvascular blood flow is impaired in all forms of circulatory failure.[14,16,33] The microcirculation is characterized by heterogeneous blood flow and decreased capillary perfusion. Rheologic abnormalities of neutrophils and erythrocytes impede microvascular blood flow. Increased expression of neutrophil integrins, platelet P-selectin, endothelial cell adhesion molecules, and thrombin activation result in cellular aggregation and microvascular obstruction. Decreased endothelial cell nitric oxide synthetase activity impairs normal vasodilatory reflexes and decreases the microvascular response to hypoxia.

Shock is associated with impairment of regulation of immunologic function. Immunosuppressive substances, including interleukin-10, transforming growth factor beta, and adenosine, are released that decrease cellular and humoral immunity. Altered signaling in afferent and efferent neural pathways contributes to impaired immune homeostasis. Dendritic cell- and monocyte-mediated antigen processing is impaired, as is neutrophil function. Apoptosis of lymphocytes, dendritic cells, and monocytes is increased. In addition, expansion of myeloid-derived suppressor cells may contribute to the persistent inflammation, immunosuppression, and catabolism syndrome resulting in recurrent infections and prolonged intensive care unit (ICU) stay.[42]

CLINICAL ASPECTS OF SHOCK

Approach to Circulatory Shock

The approach to patients with circulatory shock involves restoration of cardiopulmonary stability and rapid assessment of the underlying disease process (Fig. 79.4). Patients should be assessed for clinical evidence of organ hypoperfusion. Initial efforts should be directed at achieving a minimal level of blood pressure and ventilation associated with survival. The VIP approach prioritizes these efforts by focusing on *v*entilation, *i*nfusion, and *p*ump activity.[43] Subsequent interventions should be focused on restoration of perfusion and organ function. A systematic approach, which incorporates physiologic endpoints, indices of systemic perfusion, and an algorithm for therapeutic interventions based on the pathophysiology of the underlying shock state, results in the best outcomes.[4] Definitive therapy depends on the cause of the shock state and may require additional diagnostic and therapeutic interventions. These efforts should be pursued in a timely manner and, by necessity, may need to occur concurrently with resuscitative efforts. Finally, deviation from the expected clinical course and response to therapy should prompt a reassessment of the presumed cause of the shock state.

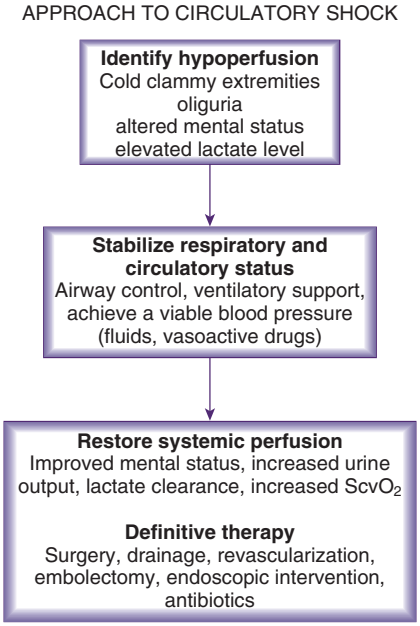

Fig. 79.4 Initial approach to patients with circulatory shock. *$ScvO_2$*, Central venous oxygen saturation.

KEY POINTS

- Circulatory shock is defined as a syndrome in which blood flow is inadequate to meet cellular metabolic requirements. The principal clinical manifestation of shock is that of organ hypoperfusion, which is most evident in the peripheral circulation, kidneys, and brain.
- The development of shock is related to alterations in the major components of the circulatory system that regulate cardiovascular performance. These are intravascular volume, cardiac function, arteriolar resistance, capillary circulation, venules, the venous capacitance circuit, and mainstream patency.
- Circulatory performance can be assessed from the cardiac rate and rhythm, arterial blood pressure, cardiac filling pressures, cardiac output, and systemic vascular resistance. Although shock is frequently defined by hypotension, the level of arterial pressure is not a reliable indicator of circulatory performance and tissue perfusion.
- Circulatory shock can be divided into four subsets: hypovolemic, cardiogenic, distributive, and obstructive. This classification can be simplified into two broad categories with typical hemodynamic profiles. The first category, hypodynamic shock, includes the hypovolemic, cardiogenic, and obstructive shock subsets. The second category, hyperdynamic shock, includes distributive shock. The central features of hypodynamic shock are a low cardiac output and vasoconstriction manifested by a high vascular resistance. Hyperdynamic circulatory shock is characterized by a high cardiac output, and vasodilation is manifested by a low vascular resistance.
- The primary metabolic defect in circulatory shock is impaired oxidative metabolism. This impairment is most commonly caused by decreases in tissue oxygen supply owing to either global decreases in blood flow or maldistribution of blood flow. Cellular oxidative metabolism may also be impaired by mechanisms independent of tissue hypoperfusion. Accumulation of tissue CO_2 parallels the development of tissue hypoxia in circulatory shock.
- Controversy exists over the optimal manner in which to monitor tissue perfusion in patients with circulatory shock. Commonly used variables such as heart rate, arterial pressure, and cardiac output correlate poorly with survival in critically ill patients. These observations have led to the use of indices of systemic oxygen metabolism as markers of tissue perfusion and the adequacy of resuscitative efforts.

- The primary causes of organ dysfunction in circulatory shock are ischemic injury related to tissue hypoperfusion, mediator-related organ dysfunction, and reperfusion injury. The relative importance of these mechanisms varies with the cause of the shock state and the specific organ being examined.
- The approach to patients with circulatory shock involves a rapid assessment of the underlying disease process and restoration of cardiopulmonary stability. The patient should be assessed for the etiology of the shock syndrome and evidence of organ hypoperfusion. Initial efforts to achieve cardiopulmonary stability should focus on ventilation, fluid infusion, and cardiac function. Restoration of systemic perfusion and definitive therapy directed at the etiology of the shock state should follow.

References for this chapter can be found at expertconsult.com.

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Resuscitation From Circulatory Shock

Antonio Messina, Massimiliano Greco, Alessandro Protti, and Maurizio Cecconi

INTRODUCTION

Shock can be defined as a state of circulatory failure to deliver sufficient oxygen to balance the demands of the tissues, which results in tissue hypoxia: a deficiency in the bioavailability of oxygen to the tissues of the body. Circulatory shock assessment is often a challenging and common clinical scenario (i.e., up to one-third of patients admitted to the intensive care unit [ICU] are in circulatory shock[1]). This should be considered a time-related syndrome needing prompt recognition to avoid multiorgan dysfunction and death. For this purpose, the assessment of clinical and nonclinical signs of acute circulatory dysfunction is of pivotal importance to define and target the therapeutic strategy at the bedside. First of all, the source of the hemodynamic instability should primarily be presumed by the physical examination of the patient and from details retrieved from the past and present medical history. For instance, in the large multicentric randomized European Sepsis Occurrence in Acutely Ill Patients II (SOAP II) trial, acute circulatory dysfunction was related to septic shock in the vast majority of the 1679 ICU patients enrolled (62%), whereas cardiogenic shock (16%), hypovolemic shock (16%), and other types of distributive (4%) or obstructive (2%) shock were less frequent.[2] Considering this prevalence, a de novo acute circulatory failure presented in the emergency department should be primarily considered a septic event, and accordingly treated, in the absence of any evident clinical signs of a different pattern (i.e., an evident fluid or blood loss, signs and symptoms of severe right or left acute ventricle dysfunction). The challenge of shock management is to balance fluid administration (preload), heart contractility, and vascular tone (afterload) to avoid the detrimental effects of over-resuscitation or under-resuscitation.[3–5] Basically, circulatory shock may be caused by a deficit related to the pump (heart function or heart flow) or by reduced circulatory flow. Hypovolemia can be "absolute" after severe hydration defects, plasma, or blood loss; it can be "relative" when fluid administration is insufficient to compensate for a loss in vascular tone in the context of sepsis or anaphylaxis (or use of large doses of sedative drugs). In that context, there is a discrepancy between the content (volume) and vascular capacity, and abnormal sympathetic tone is associated with altered capillary recruitment. The clinical examination is a cornerstone in shock, but is notoriously inaccurate in assessing the exact value of cardiac output (CO) and the intravascular volume status.[6,7] For these reasons, the goal of shock management can be achieved only adding bedside quantitative and qualitative evaluation of cardiovascular system function, based on an integrated approach of clinical examination, critical care echocardiography, and hemodynamic monitoring.[1]

FROM MACRO TO MICRO CIRCULATION: PATHOPHYSIOLOGY OF INADEQUATE OXYGEN USE BY THE CELLS

To better understand the systemic effects of the imbalance between oxygen delivery and consumption, some basic concepts of oxygen delivery to the cells and cellular energy metabolism should be appraised (Fig. 80.1).

1. Global oxygen delivery (DO_2) is the total oxygen carried by blood to the cells and is calculated as the product of the oxygen content in arterial blood (CaO_2) and CO.

$$DO_2 = CO * CaO_2 = CO * (1.36 \times Hb * \%saturation) + (0.003 \times PO_2)$$

   Dissolved oxygen contributes little to total oxygen content because of the limited solubility.
2. The DO_2 continuously balances the peripheral oxygen uptake or consumption (VO_2). Failure to maintain the DO_2:VO_2 ratio is initially compensated by increased oxygen extraction and a fall in mixed venous oxygen content. The normal ratio of delivery to consumption (DO_2:VO_2 ratio) is approximately 5:1. In fact, DO_2 and VO_2 are linked by a simple relationship called the *oxygen extraction ratio* (ERo_2 − %). Under physiologic conditions, DO_2 is larger than VO_2 and the ERo_2 is roughly 20% (<2.4 mL O_2/kg/min for a 12 mL O_2/kg/min DO_2). This DO_2:VO_2 ratio is high enough that cellular respiration is not supply dependent, and VO_2 is predominantly a function of tissue oxygen demand: "consumption drives delivery." VO_2 becomes supply dependent when the DO_2:VO_2 ratio falls below 2:1, producing a biphasic DO_2:VO_2 relationship.[8] This critical level of the DO_2:VO_2 relationship (the so-called "critical DO_2") corresponds to the maximal oxygen extraction.
3. Cells require oxygen for the production of adenosine triphosphate (ATP), the principal energy source. ATP is hydrolyzed to adenosine diphosphate (ADP) and inorganic phosphate (Pi) by ATPs in the cytosol:

$$ATP \leftrightarrow ADP + Pi + H^+ \text{ (yielding 7.3 kcal/mol)}$$

   Energy released is used for the maintenance of membrane integrity, ionic pumps, and other specialized functions, such as contractility of muscle cells and impulse transmission in neurons.
4. Because the body's stores of ATP will last no more than a few minutes, it must be continuously synthesized, and under physiologic conditions, the vast majority of ATP molecules are generated by the process of oxidative phosphorylation of glucose. Aerobic generation of ATP occurs in the mitochondria via oxidative phosphorylation

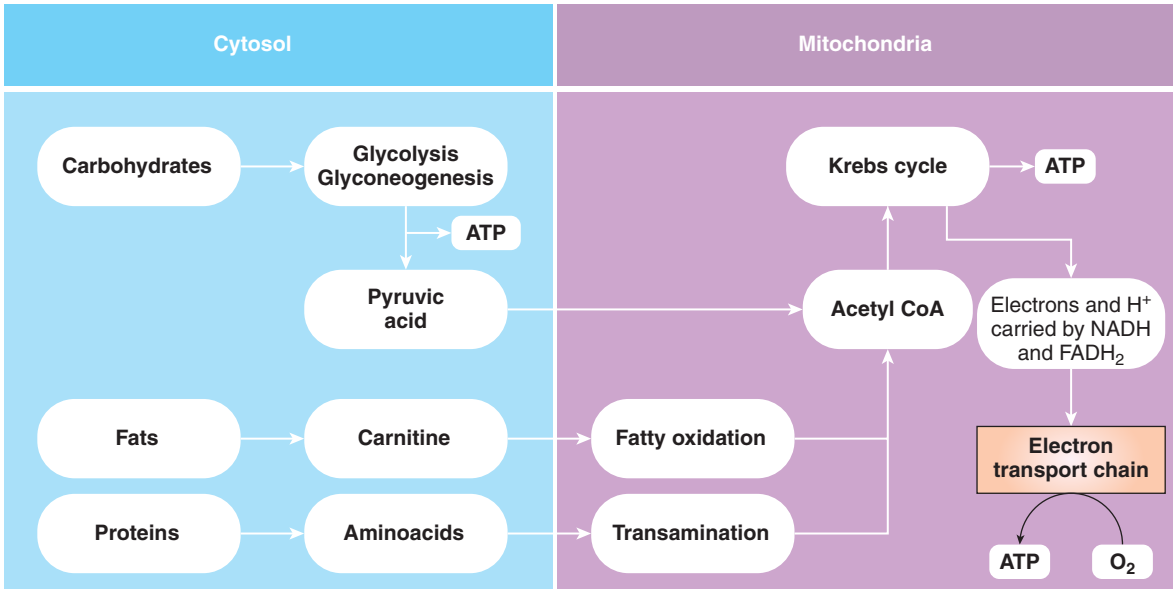

Fig. 80.1 Schematic Illustration of the Energetic Substrate Metabolism in Cells. NADH and $FADH_2$ are redox cofactor created during the Krebs cycle and used during the last part of cellular respiration, the electron transport chain. *ATP,* Adenosine triphosphate; *$FADH_2$,* reduced flavin adenine dinucleotide; *NADH,* reduced nicotinamide adenine dinucleotide.

along the electron transport chain in which reduced nicotine adenine dinucleotide (NADH) and reduced flavin adenine dinucleotide ($FADH_2$) are reduction-oxidized (redox) by molecular oxygen:

$$NADH + ½\ \mathbf{O_2} + H^+ \leftrightarrow H_2O + NAD^+$$

This yields 52.6 kcal/mol, which is used in the electron transport chain to create ATP from ADP + Pi + H^+.

The first stage of oxidative phosphorylation is the conversion of glucose to pyruvic acid; this occurs in the cytoplasm. The second stage, the oxidation of pyruvic acid, can only occur in the mitochondria as part of the Krebs (citric acid) cycle (Fig. 80.1). Oxidative phosphorylation is a more efficient process than substrate-level phosphorylation, yielding up to eight times more ATP than the anaerobic pathway per mole of glucose. In fact, this process produces a net 36 molecules of ATP (or 1270 kJ of available energy) for every glucose molecule oxidized.

5. Anaerobic generation of ATP occurs in the cytosol and in the mitochondria via ATP-generating reactions that catalyze the following substrates with ADP into ATP:

1,3-Diphosphoglycerate + ADP ↔* 3-diphosphoglycerate + ATP*

Phosphoenolpyruvate + ADP ↔** pyruvate + ATP

1,3-Succinyl CoA + ADP ↔*** succinate + ATP

* = Phosphoglycerate kinase (related enzyme)
** = Pyruvate kinase (related enzyme)
*** = Succinyl CoA synthase (related enzyme)

6. Lactate increase in blood level is the consequence of alterations in cellular energy metabolism caused by acquired derangements in cellular respiration. Lactate is produced according to the following cytoplasmic reaction:

$$Pyruvate + NADH + H^+ \leftrightarrow Lactate + NAD^+$$

This biochemical reaction promotes lactate formation, causing a 10-fold lactate/pyruvate ratio. Hence, the lactate increase in the blood is the result of a pyruvate production exceeding its use by the mitochondria. Because the pyruvate is essentially produced via glycolysis, any increase in glycolysis, regardless of its origin, can cause lactatemia. Pyruvate is principally metabolized into the mitochondria by means of the aerobic oxidation pathway, using the Krebs cycle. The synthesis of lactate in the cell is dependent on the ATP/ADP and NADH/NAD ratios, which are both related to the oxygen use in the mitochondria. In fact, hypoxia inhibits mitochondrial oxidative phosphorylation, leading to a decrease in the ATP/ADP ratio and an increase in the NADH/NAD ratio. This metabolic condition inhibits both the pyruvate carboxylase (converting pyruvate into oxaloacetate) and the pyruvate dehydrogenase (converting pyruvate into acetyl CoA).[9] When the physiologic pathway of pyruvate use is affected by alterations in the redox potential of the cell, the excess of pyruvate concentration is shifted to lactate production and to the less efficient anaerobic glycolysis.

According to Connett and colleagues,[10] it is possible to define three theoretical thresholds of cell hypoxia:

1. The first is crossed when cellular oxygen decreases but ATP production is maintained at a level sufficient to match ATP demand by metabolic adaptation (i.e., redox recruitment, alteration of phosphorylation states, increased glycolysis). The critical level of mitochondrial PO_2 for oxidative phosphorylation depends on the ability of a cell to adapt the phosphorylation process metabolically and the level of ATP demand.
2. The second occurs when steady-state ATP turnover can be maintained only by the production of ATP from anaerobic glycolysis by the Embden-Meyerhof pathway. This highly inefficient pathway generates only 2 molecules of ATP per 1 molecule of glucose metabolized. For highly metabolic tissues such as the brain, kidney, and liver, anaerobic glycolysis is too cumbersome to be effective, and these organs develop ATP depletion rapidly under hypoxic conditions. Dysoxia can be defined below this threshold.
3. The third threshold is crossed when glycolysis becomes insufficient to produce enough ATP to maintain cell function and structural integrity. This last step leads to cellular damage and death.

FROM MICRO TO MACRO CIRCULATION: SYSTEMIC TARGETS OF RESUSCITATION FROM CIRCULATORY SHOCK

Circulatory shock is a clinical diagnosis based on signs and symptoms of inadequate tissue perfusion. This implies an often-neglected physiologic cornerstone (Table 80.1): there is no correlation between the pure CO and mean arterial pressure (MAP) measurements, and shock. Moreover, whenever present, this correlation is not linear. Clearly, very low values of CO and MAP are harmful; however, neither their absolute values nor the changes in response to therapy accurately reflect the adequacy of peripheral blood flow. In other words, normal or even high values of CO and MAP could be insufficient if metabolic demand is unbalanced (Fig. 80.2).

As a matter of fact, the ability of ICU physicians to correctly estimate CO values at the bedside is particularly misleading. In a recent review, physicians' estimates of CO based on clinical examinations were correct in 42%–62% (more or less the accuracy of flipping a coin), and two studies reported that 20%–25% of the CO estimations were completely incongruent (meaning that the estimated CO was increased, whereas the objective CO was decreased or vice versa).[6] For this reason, the diagnosis of circulatory shock should be mainly based on the clinical assessment of DO_2-VO_2 mismatch.

Eighty years ago, Ebert et al. described the skin of septic shock patients as being "pale, often sweaty."[11] Mottling skin has been recently proposed using a semiquantitative approach based on mottling extension around the knee: a clinical score ranging from 0 (indicating no mottling) to 5 (an extremely severe mottling area that goes beyond the fold of the groin). Scores ≥4 and persistence of high values during the first 6 hours after ICU admission were both associated with the lowest chance of survival.[12] An increase in mottling was associated with increased lactate levels and decreasing urinary output, but not with CO values, confirming that the progression of shock cannot be assessed only by CO.[12,13]

TABLE 80.1 Physiologic Targets and Goals During Circulatory Shock

Physiological Variables	Advantages	Drawbacks	Clinical Utility
Blood pressure	Easy to perform Costless index Target value (SBP >90 mm Hg, MAP >65 mm Hg)	Low SBP and MAP, when taken alone, are not predictors of fluid responsiveness	Part of the bedside standard clinical examination Hypotension must be promptly recognized and when associated with tachycardia should trigger the clinician to start fluid resuscitation unless clear evidence of severe cardiac failure
SI	Easy to perform Costless index (normal value 0.5–0.7) Linear and inverse correlation with CO	SI >1 could also be increased in cardiogenic and obstructive shock	Useful index facing a shocked patient SI ≥1 is a possible sign of hypovolemia, but a cardiogenic component of the shock must be excluded
CRT	Easy to perform Costless index	Operator dependent Affected by different durations of pressure, ambient, and skin temperatures	Part of the bedside standard clinical examination in the ICU If CRT ≤2 seconds, should be considered normal To standardize the maneuver, use just enough pressure to remove the blood at the tip of the physician's nail, illustrated by the appearance of a thin white distal crescent (blanching) under the nail, for 15 seconds
Skin mottling	Easy to perform Costless index	Operator dependent Not applicable in patients with dark skin Affected by the ambient and skin temperatures	Part of the bedside standard clinical examination in the ICU Should be standardized considering a score ranging from 0 (indicating no mottling) to 5 (an extremely severe mottling area that goes beyond the fold of the groin)
Lactate	Quickly available May trigger further evaluation in subclinical (cryptic) shock Target value (≤2 mmol/L)	Normolactatemia does not exclude ACD It is not a direct measure of tissue perfusion Influenced by lactate clearance	Lactate normalization is indicative of successful resuscitation Persistence of severe hyperlactatemia (>10 mmol/L for >24 h) is associated with negative prognosis Patients with lactate level >2 mmol/L should be carefully monitored Patients with persistent lactate level >4 mmol/L should be considered for ICU admission
$ScVO_2$	Quickly available Target value (when low at presentation)	Need for a CVC in the superior cava vein	The optimization of low $ScVO_2$ (<70%) has been successfully used in a protocolized approach to septic shock Normal or high values are less indicative of the degree of shock
ΔPCO_2	Quickly available Target value (2–6 mm Hg)	Need for a CVC in the superior cava vein	High values (>6 mm Hg) can identify inadequate resuscitated patients (insufficient blood flow to the tissues)

See the text for further explanations.
ACD, Acute circulatory dysfunction; *CO,* cardiac output; *CRT,* capillary refill time; *CVC,* central venous catheter; ΔPCO_2 (also called GAP CO_2), the venous-to-arterial CO_2 tension difference; *ICU,* intensive care unit; *MAP,* mean arterial pressure; *SBP,* systolic blood pressure; $ScVO_2$, central venous oxygen saturation; *SI,* shock index.

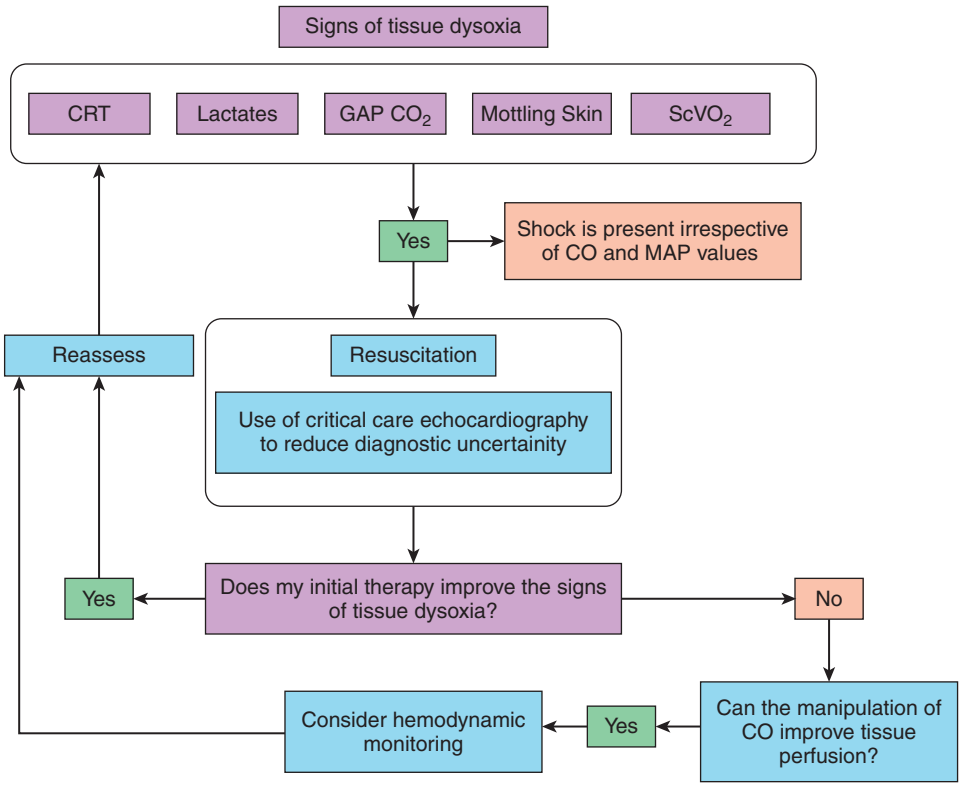

Fig. 80.2 Schematic Illustration of an Integrated Approach to Circulatory Shock. The clinical presentation and examination, with the past medical history of the patient, are key aspects of initial diagnosis. Consider the source of hemodynamic instability starting from the most common: septic shock → cardiogenic shock → hypovolemic shock → distributive → obstructive. Whenever available, the critical care echocardiography (i.e., an oriented and focused echocardiographic examination performed and interpreted at the bedside by the intensivists) could help in the initial diagnosis and further assessment of the response to fluid therapy. *CO,* Cardiac output; *CRT,* capillary refill time; *GAP CO_2,* the venous-to-arterial CO_2 tension difference; *MAP,* mean arterial pressure; *$ScVO_2$,* central venous oxygen saturation.

Another easy-to-learn, inexpensive, repeatable, and reliable bedside clinical parameter is the capillary refill time (CRT). The CRT measures the time required to recolor the tip of a finger after pressure is applied to cause blanching. Because this maneuver depends on the applied pressure, Ait-Oufella and colleagues recommended using just enough pressure to remove the blood at the tip of the physician's nail, illustrated by the appearance of a thin white distal crescent under the nail, for 15 seconds.[11] CRT at 6 hours after inclusion was strongly predictive of 14-day mortality (area under the curve of 0.84 [75 - 94]). Hernández and colleagues reported that CRT <4 seconds detected 6 hours after resuscitation was associated with resuscitation success, with normalization of lactate levels 24 hours after the occurrence of severe sepsis/septic shock.[14] A prospective cohort study of 1320 adult patients hospitalized in the emergency room for hypotension showed a consistent association between CRT and in-hospital mortality.[15]

Serum lactate is a more objective metabolic surrogate to guide fluid resuscitation. The Surviving Sepsis Campaign guideline suggests guiding resuscitation to normalize lactate in patients with elevated levels.[16] Irrespective of the source, increased lactate levels are associated with worse outcomes,[17] and lactate-guided resuscitation significantly reduced mortality as compared with resuscitation without lactate monitoring.[16] Because serum lactate is not a direct measure of tissue perfusion,[18] this single value is less informative than the trend of lactate clearance. However, serum lactate normalization is indicative of shock reversal, whereas severe hyperlactatemia is associated with very poor outcomes. Recently published data showed that lactate >4 mmol/L associated with hypotension led to a mortality rate of 44.5% in ICU patients with severe sepsis or septic shock.[17] For instance, a large retrospective study showed that a subgroup of ICU patients with severe hyperlactatemia (lactate >10 mmol/L) had a 78.2% chance of mortality, which increased up to 95% if hyperlactatemia persisted for more than 24 hours.[19]

The venous-to-arterial CO_2 tension difference (ΔPCO_2) and central venous oxygen saturation ($ScVO_2$) provides adjunctive relevant clinical information. According to a modified Fick equation, ΔPCO_2 is linearly linked to CO_2 generation and inversely linked to CO.[20] ΔPCO_2 ranges between 2 and 6 mm Hg under normal conditions and should be considered as a marker of the adequacy of blood flow to wash out the CO_2 produced by the tissues rather than as a marker of tissue oxygen deficit.[20]

$ScVO_2$ reflects the balance between oxygen delivery and consumption, being a surrogate value of mixed venous oxygen saturation (normally the $ScVO_2$ is 2%–3% lower than SvO_2).[21] Because a low $ScVO_2$ is indicative of inadequate oxygen delivery, this parameter has been previously considered a therapeutic target in the management of early phases of septic shock.[22–24] However, this approach has been challenged by the negative results of three subsequent large multicenter randomized controlled trials[25–27] and is no longer recommended.[16] Given that the ARISE, PROMISE, and PROCESS trials probably included populations of less severe critically ill patients with respect to the study of Rivers and colleagues[22] (i.e., lower baseline lactate levels, $ScVO_2$ at or above the target value at the admission, and lower mortality in the control group[25–27]),

the normalization of low $ScvO_2$ in the early phase of septic shock can still be considered a good predictor of successful resuscitation. On the contrary, the persistence of high blood values of $ScvO_2$ is associated with mortality in septic shock patients, probably indicating an irreversible impairment of the oxygen extraction by the cells.[28]

Arterial blood pressure (ABP) depends on several factors: the amount of blood ejected by the heart, the arterial compliance, and the systemic vascular resistance; the arterial system modulates vessel tone in order to keep perfusion pressure (i.e., MAP) constant.

Although arterial hypotension is not per se a sign of acute circulatory dysfunction, a systolic ABP lower than 90 mm Hg (or less than 40 mm Hg in previously hypertensive patients) or a MAP less than 65 mm Hg should be promptly recognized. Facing a shocked patient in the first minutes, one of the fundamental questions should be if she or he would benefit from fluid therapy. The MAP value alone is not sufficient to trigger fluid resuscitation: a low MAP may not be associated with hypovolemic or septic shock or, in contrast, might be maintained adequately thanks to a compensatory mechanism like an increase in vascular resistance.[1] Moreover, low systolic ABP could be associated with either a normal or a low diastolic ABP-value (i.e., 40 mm Hg). As one of the main determinants of diastolic ABP is the arteriolar tone, a low systolic and diastolic ABP suggest a low vascular tone, especially in the presence of tachycardia, and therefore the need for an early vasopressor may be warranted.[29]

Tachycardia is an important early sign of shock, but it can also be caused by pain, anxiety, fever, anemia, or inflammation. For these reasons, it should not be used alone as a predictor of fluid responsiveness.[1,30] In a patient in shock, both hypotension and tachycardia should trigger the clinician to start fluid resuscitation unless clear evidence of severe cardiac failure is present.

A useful and easy indicator of hypovolemia is the "shock index" (SI): that is, the ratio of heart rate divided by systolic blood pressure (HR/SBP). This index was originally described in trauma patients, but its relevance has also been demonstrated in septic patients.[31] The SI has a linear and inverse correlation with the CO, and in healthy adults the normal range is 0.5–0.7. A value ≥ 1 is related to the extent of hypovolemia, but it is important to underline that it could also be increased in cardiogenic and obstructive shock. Therefore with an SI ≥ 1, fluid therapy should be started, while always checking for a possible cardiac component of the shock.[29]

Another insidious marker of possible hypoperfusion is urinary output.[29] Oliguria is a nonspecific symptom and could already be present with mild dehydration. Moreover, urinary output may not reflect systemic hypoperfusion during early circulatory dysfunction: some neurohormonal compensatory mechanisms could be responsible for preserving and sometimes even increasing renal blood flow, and in this case extra fluids could alter renal perfusion by increasing venous congestion. In synthesis, fluid administration does not necessary lead to a restoration of normal diuresis, and oliguria could be the result of profound intrarenal microcirculatory abnormalities that are not related to hypoperfusion.[32]

Finally, an attractive method to investigate a hypovolemic status is the passive leg raising (PLR) test. It can be considered a brief and completely reversible "self-volume challenge" because of the shift of around 300 mL of blood from the legs to the intrathoracic compartment to avoid the risk of fluid overload. Of course, the effect of PLR is time limited, with the apex of the increasing CO occurring 1 minute after starting the manuver.[33,34] The reliability of the PLR is known to be significant when a direct measurement of the CO is available. However, changes in the pulse pressure after the PLR (i.e., the difference between systolic and diastolic pressure) could be useful in the assessment of fluid responsiveness, despite a lower sensitivity and specificity as compared with changes in CO.[35]

A PHYSIOLOGIC CAUSE-RELATED APPROACH TO CIRCULATORY SHOCK

Circulatory Shock Caused by CO Limitation (Cardiogenic, Obstructive)

Cardiogenic shock is characterized by a global reduction in DO_2 because of a reduction in CO caused by either a myocardial dysfunction (myogenic injury—infectious, viral, or ischemic disease; a major valvular disease; a severe arrhythmia) or a mechanical obstacle to the cardiac flow (pulmonary embolism, tension pneumothorax, or a raised pericardial pressure). Cardiogenic shock complicates 5%–10% of cases of acute myocardial infarction and is the leading cause of death after this event.

Principles of treatment of myocardial dysfunction (see also Chapters 70 and 74): The characteristic of cardiogenic shock after myocardial dysfunction is the peripheral vasoconstriction and vital end-organ damage, which reflect ineffective CO and insufficient circulatory compensation. This compensatory effect may initially improve coronary and peripheral perfusion; however, it contributes to increased cardiac afterload, which exacerbates the damage in the myocardium. Inotropes are routinely used to improve CO in cardiogenic shock, but at the expense of tachyarrhythmias, increased myocardial VO_2, and adverse effects on regional blood flow. Vasopressors could be used in this setting and should be titrated to a MAP with a typical goal of >65 mm Hg. Vasopressin has less pulmonary vasoconstriction than norepinephrine and may be more beneficial as a first-line vasopressor in patients with acute right ventricle failure.[36]

Specific treatments of CO limitation-related mechanic conditions are reported elsewhere in this book (see Chapters 65, 66, 75, and E9).

Circulatory Shock Caused by Volume Depletion: Decreased Cao_2 (Anemia)

The goals of initial resuscitation for hemorrhagic shock are (1) to arrest ongoing bleeding, (2) to restore the effective circulating blood volume, and (3) to restore tissue perfusion. The modern management protocol of hemorrhagic shock has been mainly developed based on the treatment of trauma patients. This involves prompt control of the source of bleeding by means of damage control surgery and has been expanded to the early management of trauma patients as damage control resuscitation, with the purpose of preventing the lethal triad of coagulopathy, hypothermia, and acidosis. A degree of hypotension is permitted in this context, and fluid repletion should avoid hemodilution and should be mainly based on transfusion of red blood cells, plasma, and platelets in a high unit ratio (>1:2) or reconstituted whole blood in a 1:1:1 unit ratio. Specific principles of the treatment of hypovolemic shock resulting from hemoglobin loss are reported in Chapters 125 and 141.

Circulatory Shock Caused by Volume Depletion: Decreased Cao_2 (Hypoxemia, Poisoning)

Hemoglobin's capacity to carry O_2 can also be limited by structural damages inhibiting its physiologic activity. For instance, during carbon monoxide poisoning, a decrease in DO_2 results from a loading competition on hemoglobin between carbon monoxide and O_2 and is "maximized" by abnormal O_2 use (carbon monoxide interacts with oxidative phosphorylation) and a decrease in ERO_2 capabilities. In this particular case, shock is both quantitative and distributive. In the presence of severe hypoxemia because of an acute respiratory disorder, decreased SaO_2 leads to a decreased CaO_2, and Do_2 that largely depends on an associated increase in CO. Specific principles of the treatment of poisoning are reported in Chapter 140. For a comprehensive evaluation of hypoxemic disorders, please refer to Part IV of this book.

Circulatory Shock Caused by Decreased ER_{O_2}: Distributive Shock

This type of shock is related to:

1. Altered flow redistribution among organs secondary to inflammation (mainly caused by sepsis), anaphylaxis, or some drugs (e.g., large doses of sedative agents)
2. Decrease in capillary recruitment secondary to altered vascular reactivity, increased intravascular coagulation, increased blood cell adhesion, and/or endothelial edema
3. Abnormal mitochondrial function (mitochondrial injury or dysfunction) described as "cytopathic hypoxia," or more precisely as cytopathic dysoxia, a situation in which cells cannot synthesize ATP despite having sufficient global DO_2.

Although septic shock is one of the distributive shocks, the pathophysiology of septic shock is different from other distributive shock diseases. The pathophysiology and the clinical course of septic shock are more complex and vary over the course of the disease, with variable degrees of intravascular volume depletion, peripheral vasodilation, and cardiac dysfunction. Specific principles of the treatment of septic shock are reported in Chapter 118.

KEY POINTS

- Shock can be defined as a state of circulatory failure to deliver sufficient oxygen to balance the demands of the tissues, which results in tissue hypoxia—a deficiency in the bioavailability of oxygen to the tissues of the body.
- The challenge of shock management is to balance fluid administration (preload), heart contractility, and vascular tone (afterload) to avoid the detrimental effects of over-resuscitation or under-resuscitation.
- Shock is caused by a septic source in the vast majority of critically ill patients, whereas cardiogenic, hypovolemic, and other types of distributive or obstructive shock are less frequent.
- Circulatory shock is a clinical diagnosis based on signs and symptoms of inadequate tissue perfusion. This implies an often-neglected physiologic cornerstone: there is not (always) a correlation between the pure CO and MAP measurements and shock.
- The clinical examination is a cornerstone in shock but is notoriously inaccurate to assess the exact value of CO and the intravascular volume status.
- The goal of shock management can be achieved only by adding bedside quantitative and qualitative evaluation of cardiovascular system function, based on an integrated approach of clinical examination, critical care echocardiography, and hemodynamic monitoring.

References for this chapter can be found at expertconsult.com.

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The European Society of Intensive Care Medicine invited 12 experts to form a task force to update a previous consensus (Antonelli et al. Intensive Care Med. *2007;33:575–590). The task force was developed to answer the following questions: (1) What are the epidemiologic and pathophysiologic features of shock in the ICU? (2) Should we monitor preload and fluid responsiveness in shock? (3) How and when should we monitor stroke volume or CO in shock? (4) What markers of regional and microcirculation can be monitored, and how can cellular function be assessed in shock? (5) What is the evidence for using hemodynamic monitoring to direct therapy in shock?*

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Inotropic Therapy

Jean-Louis Teboul, Xavier Monnet, and Mathieu Jozwiak

RATIONALE FOR USING INOTROPIC THERAPY IN THE CRITICALLY ILL

Two different objectives for using inotropes in the critically ill have been considered: (1) the attempt to improve cardiac function in patients with low blood flow related to reduced myocardial contractility and (2) the attempt to achieve supranormal values of cardiac output in order to prevent or reduce oxygen debt; in this situation, inotropes might be given after volume resuscitation, even in the absence of formally documented myocardial depression.

Use of Inotropes for Reversing Impaired Myocardial Contractility

The first category of situations where inotropic therapy is generally considered includes cardiogenic shock, acute heart failure, or acute exacerbation of chronic heart failure. However, although the use of such therapy in these clinical conditions seems logical on a classic pathophysiologic basis, no demonstration of a beneficial impact on morbidity and mortality can be found in the literature. Moreover, almost all the commercially available inotropes have been shown to be associated with an increased mortality rate when given on a long-term basis to patients with chronic heart failure. It has been postulated that the long-term use of inotropes leads to the deterioration of left ventricular function through the acceleration of myocardial cell apoptosis.[1] Additionally, the beneficial effects on the mortality rate with agents known to have negative inotropic effects such as beta-blockers is now well established in patients with chronic heart failure with preserved ejection fraction[2] or reduced ejection fraction.[3] Therefore inotropic therapy is generally reserved for patients with cardiogenic shock. Under these conditions, clinicians can expect short-term positive effects of intravenous inotropic therapy, allowing cardiovascular stabilization. Inotropic therapy can also be used in patients with refractory heart failure who are waiting for mechanical circulatory support (left ventricular assist devices, extracorporeal life support) and/or cardiac transplantation. In those with potentially reversible causes of acute heart failure (such as myocardial infarction or acute myocarditis), short-term inotropic therapy must be considered as an appropriate bridge to coronary revascularization or recovery. The development of bedside echocardiography in the intensive care unit (ICU) should allow the appropriate use of inotropic therapy because this method provides a more accurate assessment of systolic cardiac function than traditional invasive methods such as pulmonary artery catheterization.

Use of Inotropes for Achieving Supranormal Levels of Oxygen Delivery or for Being Incorporated in a Goal-Directed Therapeutic Approach

High-Risk Surgical Patients

The concept of attempting to achieve supranormal hemodynamic endpoints emerged from studies in high-risk surgical patients. In a prospective study in high-risk patients undergoing surgery, Shoemaker and colleagues showed that the use of supranormal hemodynamic values as therapeutic endpoints was associated with a reduction in mortality rate from 33% to 4%.[4] In the protocol group, dobutamine and dopamine were given as inotropic drugs, even in the absence of evidence of reduced cardiac contractility, when volume resuscitation (and packed red blood cells, if necessary) failed to achieve supranormal values of oxygen delivery[4] (>600 mL/min/m^2). Thereafter, some debate concerning the perioperative fluid management strategy has emerged, especially during abdominal surgery. On the one hand, restricted perioperative fluid management could decrease the rate of postoperative complications and promote faster recovery.[5–7] On the other hand, randomized trials did not confirm the supposed benefits of fluid restriction on recovery after elective surgery.[8,9] Excessive fluid restriction could lead to higher rates of acute kidney injury and renal replacement therapy[9] and more postoperative complications such as anastomotic leaks and surgical site infection.[10]

In fact, the most important point was not the use of the perioperative fluid strategy itself, but rather the use of a goal-directed strategy based on stroke volume,[11–13] oxygen delivery index,[14,15] or cardiac index.[16] In these randomized studies, the volume of intraoperative fluids was decreased,[14,15] unchanged,[16] or increased.[11–13] Nevertheless, in all these studies, postoperative complications or hospital length of stay was decreased. The potential beneficial effects of intraoperative goal-directed fluid therapy in elective major abdominal surgery in terms of morbidity and hospital and ICU length of stay were confirmed in a meta-analysis.[17] Two reviews confirmed that a deliberate perioperative increase in oxygen delivery above supranormal values using fluid infusion and various inotropic drugs (dobutamine, dopamine, epinephrine, dopexamine) in high-risk patients undergoing surgery was associated with a decreased mortality rate and postoperative complications.[18,19] It is important to emphasize that (1) benefits are most pronounced in patients receiving fluid and inotropic therapy as opposed to fluids alone to achieve supranormal values of cardiac index or oxygen delivery with the use of minimally invasive cardiac output monitors,[20] (2) benefits related to the use of an intraoperative goal-directed therapy could also concern low- and moderate-risk patients,[21] and (3) such an early goal-directed therapy (EGDT) is not considered after complications have already developed.[19] However, more recently, the interest of perioperative goal-directed

therapy has been questioned.[22,23] In a pragmatic, multicenter randomized trial in high-risk patients undergoing major gastrointestinal surgery, Pearse and colleagues assessed the clinical effectiveness of a deliberate perioperative strategy including fluid administration and dopexamine to achieve and maintain a maximal stroke volume.[23] When compared with usual care, goal-directed therapy was not associated with a significant reduction in moderate or major postoperative complications.[23] Nevertheless, after incorporating these results into an updated systematic review and meta-analysis, the deliberate perioperative strategy was associated with a significant reduction in the percentage of patients who developed postoperative complications.[23] It is important to note that in the group of usual care, fluid administration was based on central venous pressures and could be considered, in part, as goal-directed therapy.[23] It remains unclear, however, whether potential benefits could be related to the increased oxygen delivery per se or other antiinflammatory effects of catecholamines.[24] In this regard, it has been demonstrated that the increased oxygen delivery per se improved microvascular flow and tissue oxygenation.[25] Nevertheless, an experimental study of murine septic shock has shown that dopexamine infusion per se reduces the systemic inflammatory response, attenuates leukocyte infiltration, and prevents hepatic and renal injury at doses that have no effects on global or regional hemodynamics.[26] The issue of drug dosage is also essential. A recent meta-analysis has suggested that in the setting of major surgery, dopexamine at low doses, but not at high doses, could improve outcome.[27] From all these findings, it is still reasonable to consider the increase in cardiac output and oxygen delivery toward supranormal values during the perioperative period in high-risk patients undergoing elective major surgery and to guide the perioperative management of these high-risk patients by hemodynamic monitoring.[28]

Critically Ill Patients

It was debated whether a supranormal hemodynamic target approach can be applied to patients admitted to the ICU for acute illnesses. On the one hand, a pathologic oxygen consumption/supply dependency, presumably the result of impaired oxygen extraction capacities, has been reported in various categories of acute illnesses such as sepsis[29] and acute respiratory distress syndrome.[30] Such a phenomenon was reported to correlate with the presence of increased blood lactate, to be a marker of global tissue hypoxia,[29] and to be associated with a poor outcome.[31] This so-called *pathologic oxygen consumption/supply dependency* would incite the clinician to increase oxygen delivery toward supranormal values to overpass its critical level. However, such an aggressive therapeutic approach has been seriously questioned since the publication of randomized clinical trials performed in patients with acute illnesses and who did not demonstrate any benefit from the deliberate manipulation of hemodynamic variables toward values higher than physiologic values.[32,33] In one of these studies, the mortality rate was higher in the group of patients assigned to receive an aggressive treatment aimed at achieving supranormal values of oxygen delivery.[32] It was postulated that the deleterious consequences of the use of high doses of dobutamine in patients in the protocol group were responsible for the increased mortality rate. It should be noted that (1) the patients in the protocol group received high doses of the inotropic agent despite no evidence of any deficit of inotropic function and that (2) in most of these patients the aggressive inotropic support failed to achieve the target value of oxygen consumption (170 mL/min/m^2). The later analysis of the subgroup of septic patients in a study showed that survivors were characterized by their ability to increase both oxygen delivery and oxygen consumption, regardless of their group of randomization.[34] Nonsurviving patients were characterized by their inability to increase oxygen consumption despite the increase in oxygen delivery, suggesting a more marked impairment of peripheral oxygen extraction in nonsurvivors than in survivors.[34] In addition, the ability to increase cardiac output and oxygen delivery was also significantly reduced in nonsurvivors than in survivors, suggesting a decrease in cardiac reserve in patients who will die.[34] This is not a surprising finding because the degree of myocardial dysfunction in septic shock correlates with an increased risk of death. In this regard, it has been suggested that the response to a dobutamine challenge has a prognostic value in septic patients because in two prospective studies survivors were able to increase both oxygen consumption and oxygen delivery in response to dobutamine, whereas nonsurvivors were unable to increase either oxygen delivery or oxygen consumption or both.[35,36]

Data from all the results of randomized controlled studies indicate that a deliberative attempt to achieve supranormal hemodynamic targets in the general population of critically ill patients is no longer recommended.[37,38] Nevertheless, in the early phase of septic shock with low blood flow and oxygen delivery, an aggressive hemodynamic therapy, including inotropes, aimed at rapidly normalizing the central venous oxygen saturation ($ScvO_2$) as a surrogate of oxygen delivery, was demonstrated to result in a better outcome in a monocenter, randomized controlled trial.[39] This result has led to the popularity of the concept of EGDT with ($ScvO_2$) as the main hemodynamic target. Nevertheless, three recent multicenter, randomized studies have shown that EGDT using ($ScvO_2$) did not reduce all-cause mortality,[40–42] duration of organ support, or hospital length of stay.[40,41] In addition, compared with usual care, EGDT resulted in higher hospitalization costs[43] and was associated with increased utilization of ICU resources.[44] However, compared with the study by Rivers and colleagues,[39] patients included in the three multicenter, randomized controlled trials[40–42] were fluid resuscitated before randomization, such that the average baseline ($ScvO_2$) was already higher than 70% (the target of the EGDT arm). Such a fact certainly accounted for the absence of superiority of EGDT over the control arms in these studies.[40–42] This clearly cannot rule out the strategy of increasing oxygen delivery and targeting ($ScvO_2$) higher than 70% when ($ScvO_2$) is lower than 70%, as this was the case in the majority of the patients in the study by Rivers et al.[39] Thus in the early phase of septic shock and maybe in other acute illnesses, it could be essential to rapidly restore normal global blood flow conditions to avoid further deleterious consequences of systemic hypoperfusion. In later stages of the disease, with inflammatory processes and organ dysfunction already developed, no evidence of benefit from a further increase in oxygen delivery has been shown in the literature. Nevertheless, it seems likely that cardiac output should be kept in the normal range by using fluids and/or inotropes to prevent worsening of the insult. It should be stressed that even in the EGDT approach, their use should not only be based on $ScvO_2$ but also on the presence of established cardiac dysfunction, which is at best diagnosed on echocardiography,[35,45] and after checking that hypovolemia and hypotension have been already corrected.[37]

PHARMACOLOGIC PROPERTIES OF INOTROPIC AGENTS

Different inotropic drugs are available. Some of them act on adrenergic receptors located at the surface of the cardiomyocytes, whereas others exert their effects into the myocardial cell. The different treatments targeting inotropy and their pharmacologic properties have been summarized in a recent review.[46]

Adrenergic Signalization

Both natural and synthetic catecholamines increase the Ca^{2+} cytosolic concentration, which is directly related to the force of contraction (Fig. 81.1). Ca^{2+} fixes on the troponin C Ca^{2+}-specific binding site,

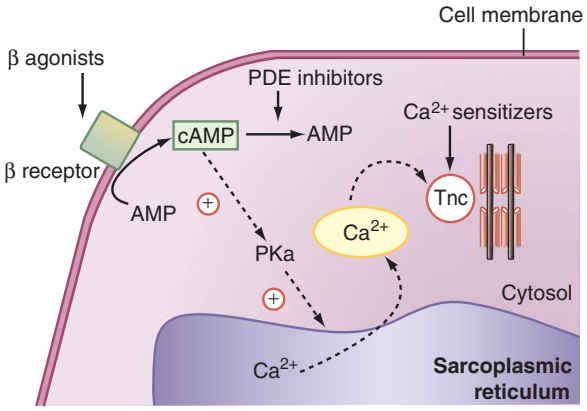

Fig. 81.1 Mechanisms of Action of Inotropic Agents at the Cellular Level. Schematic Representation. Beta-1 agonist agents fix the beta-1 receptor and stimulate the formation of cyclic adenosine monophosphate (*cAMP*) from AMP through adenylate cyclase. cAMP activates protein kinase A (*PKa*), which provokes extrusion of Ca^{2+} from the sarcoplasmic reticulum into the cytosol through phosphorylated ryanodine receptors. Ca^{2+} fixes troponin C (*Tnc*) and finally activates the fixation of actin on myosin filaments. Phosphodiesterase (*PDE*) inhibitors also increase the cAMP concentration by inhibiting its degradation. Ca^{2+} sensitizers increase inotropism through enhancement of troponin C sensitivity for Ca^{2+}. Cardiac myosin activators increase the activity of the ATPase of the myofibrils, increasing the contractile force of the cardiomyocytes without increasing the amount of ATP molecules required for contraction. Istaroxime inhibits the Na^+/K^+-ATPase, increasing the activity of the sarcoplasmic reticulum calcium ATPase pump and increasing the reuptake of Ca^{2+} by the sarcoplasmic reticulum.

inducing a conformational change that leads to the fixation of the myosin head to the actin filament. Hydrolysis of the adenosine triphosphate (ATP) molecule located on the myosin head to adenosine diphosphate (ADP) simultaneously induces the flexion of the myosin neck and the shortening of the contractile apparatus.

A rapid overview of the physiologic response to adrenergic receptor stimulation is essential to understand the pharmacologic properties of these drugs. Receptors of the adrenergic system are classed as alpha-1, alpha-2, beta-1, beta-2, and dopaminergic receptors. Activation of the beta-1 receptors and, to a lesser degree, the alpha-1 receptors, is responsible for the inotropic effect of adrenergic agents.

Beta-1 Adrenergic Receptors

Beta-adrenergic receptors are transmembrane proteins located in the sarcolemma. The beta-1 receptor subtype is mainly represented in the human heart. Its stimulation induces inotropic, lusitropic, chronotropic, and dromotropic effects that result from the enhancement in Ca^{2+} cytosolic concentration. Binding of a beta-1 agonist agent to its receptor stimulates the Gs protein. Guanosine diphosphate, normally fixed to the stimulatory αs subunit of the Gs protein, is replaced by guanosine triphosphate, and the αs–guanosine triphosphate complex binds to adenyl cyclase, which then becomes activated. Cyclic adenosine monophosphate (cAMP) is formed from ATP and activates protein kinase A. Protein kinase A phosphorylates and activates several cellular structures as follows:

- The ryanodine receptors of the sarcoplasmic reticulum, leading to the enhanced extrusion of Ca^{2+} out of the sarcoplasmic reticulum. Indeed, the main part of the Ca^{2+} cytosolic content needed for contraction is provided by the sarcoplasmic Ca^{2+} store. The entry of Ca^{2+} through the membrane L-type channels modifies the molecular conformation of the ryanodine receptor of the sarcoplasmic reticulum. Parts of these ryanodine receptors are Ca^{2+} channels that enable the massive release of Ca^{2+} out of the sarcoplasmic reticulum (see Fig. 81.1).
- The sarcolemmal L-type Ca^{2+} channels, increasing their opening time. This leads to an increased amount of cytosolic Ca^{2+} available for sarcoplasmic reticulum Ca^{2+} release and for contraction. The increase in intracytosolic Ca^{2+} concentration also leads to the activation of calmodulin. This ubiquitous protein enables the phosphorylation of other proteins once it has fixed Ca^{2+}.
- The myosin light chain through the myosin light chain ATPase. This phosphorylation enhances the responsiveness of the cardiac contractile protein to Ca^{2+} and helps increase the affinity of myosin for actin, thus participating in the inotropic effect.
- The phospholamban and the sarcolemmal Na^+/Ca^{2+} exchanger, leading to a faster decrease in Ca^{2+} cytosolic concentration after contraction and accounting for the lusitropic effect. Indeed, relaxation is dependent on Ca^{2+} reuptake by the sarcoplasmic reticulum through the sarcoendoplasmic reticulum Ca^{2+} ATPase pump. The activity of sarcoendoplasmic reticulum Ca^{2+} ATPase is normally inhibited by phospholamban located in the sarcoplasmic reticulum membrane near the Ca^{2+} pump. The phosphorylation of phospholamban relieves this inhibition, and Ca^{2+} uptake by the sarcoplasmic reticulum is thus stimulated.

Beta-2 Adrenergic Receptors

The beta-2 receptor subtype is mainly represented in noncardiac structures. Beta-2 adrenergic stimulation induces arterial and venous relaxation. The effects of beta-2 stimulation in vascular smooth muscle result from a different activation pathway: once the Ca^{2+} intracytosolic concentration increases, it fixes the calmodulin regulatory protein, and the Ca^{2+}–calmodulin complex activates the myosin light chain kinase, leading to the inhibition of phosphorylation of the myosin light chain and finally smooth muscle relaxation.

Alpha-Adrenergic Receptors

When an agonist fixes the alpha-1 receptor, Gh, which is one of the G-protein family, it stimulates phospholipase C, which splits phosphatidyl inositol into inositol triphosphate and 1,2-diacylglycerol. Inositol triphosphate stimulates the release of Ca^{2+} from the sarcoplasmic reticulum. Alpha-2 adrenoreceptor stimulation inhibits adenylate cyclase and reduces cAMP intracellular concentration. Alpha adrenoreceptors are not prominent in the cardiac tissue but are in the vascular wall. Cardiac alpha-1 stimulation induces a positive inotropic effect; alpha-1 and alpha-2 stimulations induce potent arterial and venous constriction.

Pharmacologic Properties of Inotropic Agents Used in Clinical Practice

Epinephrine

Epinephrine is the main physiologic adrenergic hormone of the adrenal medullar gland. It is a potent stimulator of alpha, beta-1, and beta-2 receptors. The alpha-adrenergic effect is responsible for a marked arterial and venous vasoconstriction. Epinephrine increases systolic arterial pressure, but its effect on vasculature is partly counteracted by beta-2–mediated vasodilation. Diastolic blood pressure is thus only slightly affected by epinephrine, and the increase in mean arterial pressure (MAP) is less than that with norepinephrine.

Through cardiac beta-1 stimulation, epinephrine increases heart rate and inotropism. The effects of the combination of the latter, along with the alpha-mediated venous constriction promoting venous return and cardiac preload, results in an increase in cardiac output. Epinephrine

also facilitates ventricular relaxation and enhanced coronary blood flow through the increase in myocardial oxygen consumption.

Norepinephrine

Norepinephrine is the physiologic mediator released by the postganglionic adrenergic nerves. It is a potent alpha and beta-1 adrenergic agonist, but it has little activity on beta-2 receptors. Through its alpha-adrenergic effect, norepinephrine induces potent arterial and venous constriction. It increases systolic and diastolic blood pressure, left ventricular afterload, and cardiac filling pressures. Its alpha-adrenergic effect also induces the reduction of peripheral venous capacitance and thus results in decreased unstressed venous blood volume and increased stressed venous blood volume. This is responsible for increased mean systemic filling pressure, venous return pressure gradient, and venous return.[47,48] Beta-1 stimulation results in a positive inotropic effect and an increase in stroke volume. However, the chronotropic effect is counteracted by baroreflex stimulation after vasoconstriction. Consequently, the heart rate is unchanged or reduced, and the cardiac output can be unchanged. The coronary blood flow is enhanced by norepinephrine because of coronary vasodilation secondary to enhanced cardiac metabolism and the normalization of diastolic blood pressure when low.

Dopamine

Dopamine is the immediate physiologic precursor of norepinephrine and epinephrine. The cardiovascular effects of dopamine are mediated by several types of receptors that are activated at different dopamine concentrations and by norepinephrine produced by the transformation of dopamine.

At low rates of administration (<5 μg/kg/min), dopamine activates D1 receptors located in renal, mesenteric, cerebral, and coronary vessels and induces vasodilation without affecting arterial blood pressure. At higher and intermediate rates of administration (5–10 μg/kg/min), dopamine predominantly stimulates the beta-1 adrenergic receptor and thus enhances inotropism and increases heart rate. At such rates of infusion, dopamine increases systolic blood pressure without altering diastolic blood pressure because stroke volume is enhanced and arterial vascular tone is only slightly altered. Norepinephrine resulting from dopamine transformation contributes to these cardiovascular effects. At higher rates of administration (10–20 μg/kg/min), dopamine predominantly activates vascular alpha-1 adrenergic receptors and induces arterial and venous vasoconstriction, counteracting D1-receptor–mediated vasodilation. This vasoconstriction increases arterial blood pressure, venous return, and cardiac filling pressures. At higher rates of administration, the hemodynamic effects of dopamine are similar to those of norepinephrine.

Dobutamine

Dobutamine is a synthetic adrenergic agonist derived from dopamine. Its effects on adrenergic receptors are complex, but do not result from endogenous transformation to norepinephrine. Dobutamine simultaneously activates different adrenergic receptors with some opposite effects. In fact, the clinically used drug is a racemic mixture of a (−) enantiomer, activating alpha-1 adrenergic receptors, and of a (+) enantiomer, activating beta-1 and beta-2 receptors. The alpha-1 and beta-1 adrenergic stimulation results in inotropic and chronotropic effects. Dobutamine does not exert any intrinsic vascular effect because the vasoconstriction induced by alpha-1 stimulation is counteracted by the beta-2–mediated vasodilating effect. Nevertheless, hypotension caused by a beta-2–induced decreased vascular tone is a potential side effect of dobutamine when this agent is not able to increase stroke volume, as is frequently the case in septic shock, where beta-1 adrenergic receptors can be moderately sensitive to beta-1 adrenergic stimulation.[49]

Dopexamine

Dopexamine is a synthetic catecholamine inducing beta-2 and dopaminergic-receptor activation, with no effect on alpha-adrenergic receptors and a weak direct effect on beta-1 adrenergic receptors. It also exerts indirect effects through the inhibition of the neuronal reuptake of norepinephrine. Its administration induces vasodilation and the inotropic effect with substantially increased stroke volume.

Isoproterenol

Isoproterenol (or isoprenaline) is a potent synthetic beta-adrenergic agonist with a very low affinity for alpha-adrenergic receptors. Through its potent beta-2–mediated vasodilating effect, it induces a fall in diastolic and mean blood pressure, whereas the systolic blood pressure is increased because of the increase in stroke volume related to its beta-1 adrenergic activation. The combination of the latter effect and the marked increase in heart rate leads to an enhanced cardiac output. The resulting increase in myocardial oxygen consumption is not compensated for by coronary blood flow enhancement so that isoproterenol infusion may lead to myocardial ischemia, especially in the case of preexisting coronary artery disease. Because of its proischemic and hypotensive effects, isoproterenol is no longer used as an inotropic agent in clinical practice in the absence of bradycardia.

Phosphodiesterase Inhibitors

Despite the major role of catecholamines in the management of critically ill patients with inadequate cardiac output, problems such as tachycardia, arrhythmias, increased myocardial oxygen consumption, excessive vasoconstriction, or loss of effectiveness with prolonged exposure to beta-agonists may occur. Thus other inotropic drugs such as phosphodiesterase inhibitors (milrinone and enoximone) have been proposed for the management of myocardial dysfunction. These synthetic drugs inhibit the peak III isoform of phosphodiesterase, which catalyzes cAMP (see Fig. 81.1). By increasing intracellular cAMP concentration, they induce a potent vasodilation of the arterial and venous system through the relaxation of vascular smooth muscle. The left ventricular preload is reduced to a greater extent than with dobutamine. At the cardiac level, phosphodiesterase inhibitors induce an inotropic effect similar to that induced by dobutamine. The heart rate is increased only at high rates of administration. The resulting effect is an increase in cardiac output. Because the enhancement of cAMP intracellular concentration also promotes the reuptake of Ca^{2+} by the sarcoplasmic reticulum, phosphodiesterase inhibitors facilitate ventricular relaxation. Finally, because beta-agonists exert their action by increasing the production of cAMP, phosphodiesterase inhibition could enhance their adrenergic effects. This is the pharmacologic basis for the synergic association of beta-agonists and phosphodiesterase inhibitors.

Ca^{2+} Sensitizers

Ca^{2+} sensitizers increase the sensitivity of troponin C for Ca^{2+} and, hence, the force and the duration of cardiomyocyte contraction (see Fig. 81.1). Levosimendan is the leading drug of this therapeutic class. The advantage of levosimendan over classical inotropes is that it increases the force of contraction without enhancing the influx of Ca^{2+} into the cytosol and thus without increasing the risk of arrhythmias related to this ionic alteration. Some degree of phosphodiesterase III inhibitory activity probably also contributes to the inotropic effect of these drugs. It also induces vasodilation by opening ATP-dependent K^+ channels.[50]

Cardiac Myosin Activators

Omecamtiv mecarbil is the leading drug of cardiac myosin activators. These drugs increase the activity of ATPase of the myofibrils, increasing the contractile force of the cardiomyocytes without increasing the concentration of ATP molecules required for contraction (i.e., without increasing the myocardial oxygen consumption).[51] Additionally, these substances increase the cardiac contractile force without the potentially deleterious increase in intracytoplasmic Ca^{2+} concentration. Cardiac myosine activators have been tested in animal studies in which their inotropic properties have been well demonstrated.[51] In humans, two recent studies have demonstrated that cardiac myosin activators are a valuable new class of therapeutic agents in systolic heart failure.[52,53] Cardiac myosin activators are well tolerated,[52,53] including during exercise in patients with ischemic cardiomyopathy.[54] These agents improve cardiac systolic function in a dose- and concentration-related manner,[52,53] without significant changes in diastolic function.[53] In patients hospitalized for acute heart failure with a left ventricular ejection fraction ≤40% (the ATOMIC-AHF study), administration of omecamtiv mecarbil did not improve dyspnea but was well tolerated.[55] In patients with chronic heart failure with a left ventricular ejection fraction ≤40% (the COSMIC-HF study), the oral administration of omecamtiv mecarbil for several weeks improved cardiac function without any adverse effects.[56] An ongoing trial (the GALACTIC-HF study) is evaluating the long-term outcome of patients with chronic heart failure receiving omecamtiv mecarbil (available at www.clinicaltrials.gov, identifier: NCT02929329).

Istaroxime

Istaroxime is a new drug that inhibits Na^+/K^+-ATPase, increasing the activity of the sarcoendoplasmic reticulum Ca^{2+} ATPase pump by relieving phospholamban inhibition.[57] It induces some inotropic and lusitropic effects.[58] In animals, istaroxime was demonstrated to decrease the end-diastolic volume of the left ventricle and increase the left ventricular ejection fraction. In patients with decompensated heart failure without hypotension, istaroxime decreased the pulmonary artery occlusion pressure and improved the diastolic function of the left ventricle.[59] In patients with acute heart failure, istaroxime decreased pulmonary artery occlusion pressure, decreased heart rate in a dose-dependent manner, and increased systolic blood pressure without any effects on neurohormones or troponin levels.[60] A recent randomized controlled trial has shown that istaroxime improved both systolic and diastolic function of patients with heart failure with reduced ejection fraction without significant cardiac adverse effects (arrhythmias and hypotension).[61]

Nitric Oxide Donors

Nitric oxide donors improve cardiac function by direct positive cAMP-independent lusitropic and inotropic effects.[62] These drugs enhance sarcoendoplasmic reticulum Ca^{2+} uptake via modifications of phospholamban, sarcoendoplasmic reticulum Ca^{2+} ATPase pump, and ryanodine receptor. Moreover, nitric oxide donors improve myofilament Ca^{2+} sensitivity.[63] A human study has shown that nitric oxide donors increase cardiac output and decrease both right and left filling pressures in patients with systolic heart failure without any adverse effects.[63]

Ongoing phase I and II trials are testing a new second generation of nitric oxide donors in healthy volunteers (available at www.clinicaltrials.gov, identifier: NCT02819271) and in patients with heart failure (available at www.clinicaltrials.gov, identifier: NCTNCT02157506).

Decrease in Beta-Adrenergic Response

It is well recognized that the response to beta-adrenergic stimulation is decreased in chronic cardiac failure. This may be a response to the increased activity of the sympathetic nervous system, which may itself be a response to the reduced cardiac output. Therefore this negative retrocontrol of the beta-adrenergic response could act as a protection against excessive adrenergic stimulation. The cellular mechanisms involved are a downregulation of beta-1 adrenergic receptors and a stimulation of the Gi protein of the adenyl cyclase system. The decrease in beta-1 adrenergic receptors could result from a decrease in beta-adrenergic receptor mRNA and to an increased internalization and degradation of these receptors. These latter mechanisms are mainly related to the phosphorylation of beta-1 adrenergic receptors by the beta-adrenoreceptor kinase, which is activated. The high level of nitric oxide production during heart failure contributes to the attenuation of the beta-adrenergic response. The effects of exogenous catecholamines during exacerbations of chronic heart failure can thus be reduced.

Similarly, there is evidence for a decreased responsiveness of the myocardium to beta-adrenergic stimulation during septic shock.[49] This phenomenon may be more likely to occur in the later phase (>24 hours) than in the early phase of the septic process.[64] This may be explained by the inhibition of adenyl cyclase activation because of an overexpression of the Gi protein[65] at the gene level.[66]

HEMODYNAMIC EFFECTS OF INOTROPIC AGENTS IN CRITICALLY ILL PATIENTS

Effects on Cardiac Output

Dobutamine

Dobutamine is the beta-adrenergic agent most widely used in critically ill patients when an increase in cardiac output through an increase in myocardial contractility is desired.

In patients with acute heart failure, dobutamine increases cardiac output and heart rate and decreases pulmonary artery occlusion pressure through a dose-response manner (from 0 to 15 μg/kg/min).[67] In patients with cardiogenic shock, dobutamine is also able to increase cardiac output while decreasing pulmonary artery occlusion pressure.[68]

In patients with septic shock and depressed myocardial function, dobutamine is expected to increase stroke volume and heart rate because of its beta-1 adrenergic properties and exert a vasodilatory effect because of its beta-2 adrenergic properties. Accordingly, an increase in cardiac output and a decrease in systemic vascular resistance (SVR) with dobutamine were reported in septic patients.[69,70] This emphasizes the need to give a potent vasopressive agent to patients with septic shock when dobutamine is administered to support cardiac function in the presence of depressed myocardial contractility. One potential advantage of dobutamine is a decrease in cardiac filling pressures that could allow an additional volume infusion to improve further cardiac output when necessary. A change from dopamine to dobutamine was shown to result in lower right and left ventricular filling pressures and an increase in right ventricular ejection fraction for the same pulmonary artery pressure and right ventricular end-diastolic volume, suggesting that dobutamine exerts a more favorable effect on cardiac contractility than dopamine.[71] This has justified the recommendation to administer dobutamine rather than dopamine when the use of inotropic drugs is judged necessary in patients with severe sepsis or septic shock.[37,38] However, because of the alteration of the beta-1 adrenergic pathway in the septic heart, the effect on stroke volume and cardiac output of a beta-1 agonist agent such as dobutamine may be attenuated in patients with sepsis compared with those without sepsis. In this regard, infusion of dobutamine at 5 μg/kg/min, a dose able to increase cardiac output substantially in patients with acute heart failure,[57] has been reported to exert variable effects in the context of

sepsis. For example, dobutamine at 5 μg/kg/min was reported to induce a substantial increase in cardiac output in some studies in patients with severe sepsis[69,72] but to have no significant effect on cardiac output in some studies investigating patients with septic shock.[73–77] It is likely that these differences in response to dobutamine were related to various individual factors, including differences in the vasopressor coadministered and in the degree of myocardial depression and/or beta-receptor downregulation. In this regard, Silverman and colleagues showed that incremental doses of dobutamine (0, 5, 10 μg/kg/min) produced a dose-related increase in cardiac output in patients with sepsis without shock but no increase in cardiac output in patients with septic shock, even for the highest dose.[49] Interestingly, they also found that the post–beta-adrenergic receptor signal transmission was impaired only in patients of the septic shock group and that impairment of beta-adrenergic receptor responsiveness found in both groups was significantly more marked in the septic shock group.[49] These findings, which allow divergent results of numerous studies to be reconciled,[69,72–80] emphasize the unpredictability of the effects of beta-agonist agents in patients with sepsis. It must be stressed that the absence of positive cardiac response to dobutamine seems to be a marker of poor outcome in septic shock patients.[35,36,77] Because dobutamine also has potentially harmful effects (e.g., myocardial ischemia, cardiac arrhythmias), monitoring its effects on cardiac output to check its efficacy is mandatory, especially in patients who are not responding to initial therapy.[37]

Dopamine

In patients with acute heart failure, dopamine increased stroke volume and cardiac output at 4 μg/kg/min, but not at higher doses, presumably because of an increase in left ventricular afterload. It was also reported that pulmonary artery occlusion pressure increased with dopamine, whereas it decreased with dobutamine.[81] Similar results were observed in patients with cardiogenic shock receiving a dose of 15 μg/kg/min of either agent.[68]

In patients with septic shock, it was reported that the restoration of an adequate MAP with dopamine was mainly produced by the increase in cardiac output, whereas minimal effects on SVR were observed despite relatively high doses of this agent.[82] Dopamine was even demonstrated to increase cardiac output markedly, whereas SVR fell in septic patients without shock.[83] Conversely, in another study in patients with severe septic shock, cardiac output did not increase significantly with dopamine at doses of up to 25 μg/kg/min, whereas SVR either did not change or significantly increased.[84] This emphasizes the great heterogeneity of the response to dopamine among patients with sepsis. This also emphasizes the difficulty in predicting clinical hemodynamic effects from pharmacologic properties because of interindividual differences in terms of the severity of the insult, underlying diseases, comorbidities, integrity of the neuro-vegetative status, drugs concomitantly prescribed, and other factors.

Epinephrine and Norepinephrine

Although these agents have beta-1 adrenergic properties and are thus able to increase myocardial contractility, they are used as vasoconstrictive agents in cases of severe hypotension because they also have potent alpha-adrenergic properties. Nevertheless, significant increases in cardiac output with these drugs have been reported in patients with sepsis.[82,85,86] In this regard, norepinephrine was shown to increase cardiac output to the same extent as dopamine for the same increase in MAP.[82] However, the effects of norepinephrine on cardiac output depend on its effect on cardiac preload[87,88] through an increase in mean systemic filling pressure.[89] By contrast, epinephrine appeared as a potent inotropic agent in most studies in patients with sepsis.[75,90]

Dopexamine

The pharmacologic properties of dopexamine should result in a combination of inotropic, afterload-reducing, and renal vasodilating effects, which could be useful for the management of the acute exacerbation of congestive heart failure. In this regard, dopexamine was reported to substantially increase cardiac output in patients with heart failure without altering blood pressure: at doses of up to 4 μg/kg/min, the majority of the effects resulted from an increase in stroke volume. At higher doses, the increase in heart rate made a greater contribution.[91] In cases of human sepsis, dopexamine produced a dose-dependent increase in stroke volume and heart rate but a dose-dependent decrease in SVR.[92] This underlines the marked vasodilating effect of this drug, which should not be administered in severe sepsis in the absence of a potent vasopressor. Under these conditions, dopexamine at doses ranging from 1 to 4 μg/kg/min could still enhance cardiac output without altering blood pressure.[93]

Phosphodiesterase Inhibitors

In patients with heart failure, phosphodiesterase inhibitors significantly increased cardiac output and stroke volume, whereas blood pressure slightly decreased because of a decrease in SVR, confirming the combined inotropic and vasodilating effects of these agents.[94] Because of the ability of beta-agonist agents to increase cAMP levels, thereby providing an increased substrate for phosphodiesterase inhibitors, the combination of these two types of drugs would be attractive. Synergic effects on the cardiac output of dobutamine and enoximone have been observed in patients with heart failure.[95]

Ca^{2+} Sensitizers

It has been well demonstrated that levosimendan induces some beneficial hemodynamic effects in patients with acute heart failure, with an enhanced cardiac output and a decreased pulmonary artery occlusion pressure.[96] In the LIDO study, levosimendan was shown to improve hemodynamic performance more effectively than dobutamine in patients with low-output heart failure.[96] Unlike dobutamine, levosimendan can keep its effects on cardiac performance in patients receiving beta-blockers.[96,97]

Istaroxime

Only a few clinical trials have studied the effect of istaroxime, a new inotropic-lusitropic agent. Two studies demonstrated that in patients with systolic heart failure, istaroxime increased cardiac index[59,98] and decreased pulmonary artery occlusion pressure and heart rate.[59]

Effects on Arterial Oxygen Content

The aim of inotropic therapy in critically ill patients with reduced cardiac contractility is not only to increase cardiac output but also to ultimately improve oxygen delivery to the tissues. Thus attention should be paid to the effects of these drugs on arterial oxygen content. Inotropes may affect arterial oxygen tension through several mechanisms. First, the reduction in lung filtration pressure resulting from an improvement in cardiac function may decrease intrapulmonary shunt fraction and thus improve arterial oxygenation. Second, the increase in cardiac output may result in an increased venous admixture.[99] On the other hand, the increased mixed venous blood oxygen tension resulting from increased cardiac output may improve arterial oxygenation in the presence of ventilation/perfusion mismatching and may thus compensate for the increased venous admixture. Accordingly, when looking at published data, it appears that even if the venous admixture increased with the administration of an inotropic agent, no significant change in arterial oxygen tension was observed.[100,101] Therefore when an inotropic agent increases cardiac output in critically ill patients, it generally increases oxygen delivery to the same extent.[69,82,102,103]

Effects on Tissue Oxygen Utilization

Even though an inotropic agent results in a large increase in oxygen delivery, its effectiveness in reducing oxygen deficit depends on its capacity to provide oxygen in the most hypoxic tissues. This concern is particularly crucial because, first, the redistribution of blood flow is a characteristic pattern of shock states and, second, inotropic drugs may also have vasoactive properties that interact with blood flow distribution.

Cardiogenic Shock

In this setting, the redistribution of blood flow is recognized as a potent compensatory mechanism, which, in response to reduced global oxygen delivery, attempts to redirect blood flow from nonvital organs with a low oxygen extraction ratio toward vital organs with a high oxygen extraction ratio such as the heart or the brain. It must be kept in mind that the administration of drugs with vasoactive properties may interfere with the vasoregulation of regional blood flow. The extent to which this interference is beneficial in increasing oxygen supply and oxygen consumption in hypoxic areas remains speculative. This emphasizes the need to monitor, as far as possible, the perfusion and/or function of critical organs.

Septic Shock

The maldistribution of flow at the macrocirculatory level and the microcirculatory level mainly contributes to defective tissue utilization and eventually to tissue oxygen debt in sepsis, even when systemic oxygen delivery is greater than normal. Besides sepsis-induced microthrombosis, sepsis-induced alteration in vascular reactivity is a major cause of the altered distribution of blood flow between and within organs. In addition, severe sepsis can modify the impact of endogenous catecholamines and adrenergic drugs on regional blood flows, given that a depressed vascular responsiveness to vasoactive agents is likely to occur in this setting. This hypothesis may account for the absence of the reduction of renal blood flow observed during norepinephrine administration in bacteremic animals in comparison with controls.[104]

In cases of human sepsis, numerous studies have examined the effects of adrenergic agents on splanchnic perfusion. Their findings have sometimes varied either because of differences in the methods used for assessing this regional circulation (e.g., gastric tonometry, laser-Doppler flowmetry, indocyanine green dilution) or because of the heterogeneity of the studied populations (e.g., differences in the severity of the septic insult, underlying diseases, or therapy coadministered). However, from the findings of the majority of these studies, some reasonable conclusions can be drawn. First, dobutamine is likely to exert a beneficial effect on gut mucosal perfusion,[70,73,75,79,105] probably via a beta-2 adrenergic effect.[106] Dobutamine may also improve hepatic microcirculation via a beta-1 adrenergic effect.[107] Second, dopamine may have deleterious effects on gut mucosal perfusion,[82] despite its potential vasodilating action through mesenteric dopaminergic receptors. Third, epinephrine is probably the adrenergic agent with the least desirable effects on the splanchnic vasculature, as most studies showed a lower splanchnic blood flow with epinephrine than norepinephrine alone[108] or in combination with dobutamine,[73,75,109] even for similar global hemodynamic effects. Fourth, dopexamine can exert a favorable effect on splanchnic perfusion[110] comparable to that of dobutamine[74] and that is likely to be related to a beta-2 adrenergic effect.

Regarding the effects of inotropic agents on renal circulation in patients with sepsis, two major points must be kept in mind. First, an alpha-adrenergic agent such as norepinephrine is able to increase renal blood flow and urine output,[84,111–113] despite its potential vasoconstricting effect on the afferent glomerular arteries. This is probably because of the beneficial effect of increasing MAP when the renal blood flow is dependent on its perfusion pressure as it occurs in the presence of profound systemic hypotension. Otherwise, the sepsis-induced depressed responsiveness of afferent glomerular arteries to the action of norepinephrine cannot be excluded. Accordingly, there is more evidence that norepinephrine increases, rather than decreases, renal blood flow and urine output when given to patients with sepsis to increase the MAP toward normal values.[84,111,112,114] Moreover, it has been demonstrated in patients with septic shock that elevating the MAP to up to 85 mm Hg with incremental doses of norepinephrine was not associated with a decrease in urine output.[113,115,116] Second, although dopamine at low doses (<5 μg/kg/min) is pharmacologically able to vasodilate renal arteries through its action on dopaminergic receptors, the systematic administration of low doses of dopamine in critically ill patients, including patients with sepsis, does not result in improved outcome[117] and is no longer recommended. Finally, no study focused on the renal effects of levosimendan in patients with septic shock. Nevertheless, a study showed that in postoperative cardiac patients, levosimendan infusion increased both renal blood flow and glomerular filtration, likely via its vasodilatory effects.[118]

Catecholamines can also exert proper effects on the microcirculation. First, the administration of 5 μg/kg/min of dobutamine was shown to improve sublingual microvessel perfusion measured with orthogonal polarizing spectral imaging in patients with septic shock.[119] Interestingly, these changes were independent of changes in systemic hemodynamic variables.[119] The improvement of sublingual microcirculation seems to occur only in patients with severe alterations at baseline.[120] Nevertheless, the effect of dobutamine on microcirculation is still debated. The administration of 5 μg/kg/min in patients with sepsis having hyperlactatemia and a cardiac index of greater than or equal to 2.5 L/min/m^2 failed to improve sublingual perfused vessel density or microvascular flow index in spite of a significant increase in systemic hemodynamics.[102] Compared with the administration of 5 μg/kg/min of dobutamine, an infusion of low doses of levosimendan improved sublingual microcirculatory blood flow patients with septic shock, probably via its vasodilatory effects.[121] Two studies showed no significant effect of increasing MAP with norepinephrine on sublingual microvessels in patients with septic shock who had already been resuscitated.[85,86] However, another study conducted in patients with septic shock requiring norepinephrine for arterial hypotension resistant to fluid administration demonstrated that increasing the MAP from 65 to 85 mm Hg by titrating norepinephrine doses allowed the improvement of sublingual microvessel circulation.[122] Thus at least nonworsening, or even improvement, of microcirculation can result from norepinephrine infusion in patients with septic shock even when a MAP of up to 85 mm Hg is targeted. It is noteworthy that in patients with septic shock who also have a history of chronic hypertension, improved sublingual microcirculation was reported when the usual patient's level (averaged value 93 mm Hg) was targeted compared with 65 mm Hg.[120] This result is in agreement with the results of a multicenter, randomized clinical trial showing that this specific population of patients may benefit from a higher MAP target, at least in terms of renal function, than the population of patients with no chronic hypertension.[123] Nevertheless, a recent study showed that targeting a MAP up to 85–90 mm Hg, as compared with 65 mm Hg, improved sublingual microcirculation in septic shock patients with or without a history of chronic hypertension.[124] Finally, inotropic drugs may also exert nonhemodynamic effects that could affect cellular metabolism and/or organ function.[24,125] For example, the administration of epinephrine in patients with septic shock was demonstrated to increase blood lactate level independently of tissue hypoxia by the stimulation of skeletal muscle cell Na^+/K^+-ATPase, which accelerates aerobic glycolysis and thus the production of pyruvate, and hence of lactate, into the cell.[126]

This metabolic effect is assumed to be related to the activation of the beta-2 adrenergic receptors located at the surface of the skeletal muscle cells.[127] In addition, catecholamines may modulate cytokine response to sepsis, trauma, or major surgery through beta-adrenergic receptor activation.[24] It remains to be evaluated whether this effect (inhibition of proinflammatory cytokines and enhancement of proinflammatory cytokine production) plays a beneficial role in the reversal of tissue hypoxia and organ dysfunction.

MAIN INDICATIONS OF INOTROPIC THERAPY IN PATIENTS WITH CIRCULATORY FAILURE

Acute Heart Failure and Cardiogenic Shock

For the American College of Cardiology Federation/American Heart Association, inotropic agents should be considered in patients with heart failure, in those who are refractory to other therapies, and in those who are suffering consequences from end-organ hypoperfusion.[128,129] In practice, inotropes should be restricted to patients with systolic dysfunction who have a low cardiac index and evidence of systemic hypoperfusion and/or congestion.[128,129] In the European Society of Cardiology guidelines, inotropes should be considered in patients with acute heart failure and in patients having hypotension (systolic blood pressure <90 mm Hg) and/or symptoms of hypoperfusion despite adequate filling status to increase cardiac output, increase blood pressure, and maintain end-organ function.[3] Overall, these indications clearly limit the use of inotropic agents to patients with acute heart failure and low systolic blood pressure, most likely to have increased mortality rates with a strong inverse correlation between systolic blood pressure and survival.[130] For the European Society of Cardiology, dobutamine is currently the first-line inotropic agent in the presence of acute heart failure with low systolic arterial blood pressure.[3] Levosimendan is currently considered the first-choice drug over dobutamine in patients with acute heart failure treated by beta-blocker therapy if beta-blockade is thought to be contributing to hypoperfusion.[3] For the American Heart Association, dobutamine and dopamine are both cited as inotropic agents,[128,129] whereas levosimendan is instead considered as a rescue therapy.[129] Twenty years ago, the SHOCK trial registry (1190 patients) reported that dopamine and dobutamine were used in 89% and 70%, respectively, of patients with cardiogenic shock resulting from massive acute myocardial infarction.[131] However, the use of dopamine is still a matter of debate. In a study comparing dopamine with norepinephrine as the first-line vasopressor agent in the treatment of shock, the use of dopamine was associated with a greater number of cardiac arrhythmias.[132] In addition, in a predefined subgroup analysis, the authors reported that the use of dopamine was associated with an increased risk of death in the subgroup of 280 patients with cardiogenic shock.[132] Finally, a multicenter, placebo-controlled clinical trial demonstrated that the use of low-dose dopamine in patients with acute heart failure and renal dysfunction had no significant effect on the 72-hours' cumulative urine volume and did not improve renal function, assessed by the change in cystatin C levels.[133]

Epinephrine was compared with the combination of norepinephrine and dobutamine in patients with dopamine-resistant cardiogenic shock—for example, with a cardiac index of less than 2.2 L/min/m^2 and a MAP of less than 60 mm Hg.[134] Epinephrine or norepinephrine-dobutamine were titrated to obtain a MAP of greater than 65 mm Hg.[134] Epinephrine infusion was as effective as the combination of norepinephrine and dobutamine to improve cardiac index and oxygen-derived parameters. Nevertheless, epinephrine infusion induced arrhythmia, increased blood lactate level, and impaired splanchnic circulation.[134] More recently, epinephrine was compared with norepinephrine in patients with cardiogenic shock after acute myocardial infarction.[135] Epinephrine or norepinephrine were titrated to obtain a MAP >65 mm Hg. Changes in cardiac index were similar for the first 72 hours with epinephrine and norepinephrine infusion. Nevertheless, epinephrine infusion was associated with tachycardia, increased cardiac double product (an indirect marker of myocardial oxygen consumption), and increased blood lactate level. More importantly, epinephrine infusion was associated with a higher incidence of refractory cardiogenic shock, leading to early termination of the study.[135]

It must be stressed that the intravenous administration of catecholamines such as dobutamine was shown to be associated with an increased risk of death in patients with acute heart failure.[136,137] This emphasizes their restrictive use to patients in whom pump failure results in severe hypotension and peripheral hypoperfusion.[3,128,129]

Phosphodiesterase inhibitors have been proposed as an alternative to beta-adrenergic agents. However, results of trials of long-term oral phosphodiesterase inhibitor therapy in chronic heart failure and of the OPTIME-CHF study in the acute decompensation of congestive heart failure[138] have been disappointing. Thus the use of these agents is limited to a few categories of patients: (1) patients with advanced heart failure awaiting transplantation in whom intravenous milrinone could be better tolerated than dobutamine and its use may allow the continuation of beta-blocker therapy controlling arrhythmias or myocardial ischemia[139]; (2) patients with acute decompensation of chronic heart failure, who are unable to achieve stabilization with the standard treatment; and (3) patients with long-term beta-blocker use, in whom short-term intravenous milrinone may even be preferred to dobutamine.[140] Enoximone, another phosphodiesterase inhibitor, was tested in patients with advanced heart failure. As with milrinone, the results were disappointing. Low doses of enoximone could not improve all-cause mortality or the 6-minute walk test distance.[141] There is now clear evidence that phosphodiesterase inhibitors such as beta-agonists can exert both short-term beneficial hemodynamic effects and serious adverse effects that make them deleterious in terms of long-term outcome. It is likely that their adverse effects (e.g., arrhythmias, increased risk of myocardial ischemia) are related to the increased cAMP concentration in the cytosol of the cardiomyocyte.[142]

The initial enthusiasm in the use of Ca^{2+} sensitizers in patients with heart failure has attenuated in recent years. In the LIDO study, compared with dobutamine, levosimendan significantly decreased mortality rate and improved the hemodynamic condition.[96] Nevertheless, these positive results have been contradicted in two large-scale studies. In the REVIVE study,[143] even though levosimendan improved the composite judgment criteria of clinical signs of heart failure at 5 days compared with placebo, the mortality rate was not significantly changed. In the SURVIVE study,[144] levosimendan was not better than dobutamine in increasing the survival rate in patients with acute heart failure requiring inotropic support. A meta-analysis concluded that in patients with acute severe heart failure, levosimendan improved hemodynamic parameters when compared with placebo, without showing evidence of survival benefit.[145] However, recent meta-analyses demonstrated that levosimendan reduced mortality rate when compared with dobutamine and decreased hospital length of stay in the overall population of cardiologic patients, including but not restricted to patients with heart failure.[146,147] Another indication of levosimendan may be patients with heart failure receiving concomitant use of beta-blocker therapy, a situation where higher doses of dobutamine are usually required to have some efficacy. In such patients, dobutamine was shown to be as effective as levosimendan in the first 24 hours of treatment to increase cardiac index and decrease pulmonary artery occlusion pressure.[148] However, at 48 hours, levosimendan still efficiently improved hemodynamics, whereas dobutamine did not.[148] It must be noted that in a post hoc

analysis of the SURVIVE trial, patients previously receiving beta-blocker therapy had improved short-term survival with levosimendan compared with dobutamine.[148] Moreover, when compared with placebo, levosimendan improved contractility in patients with acute heart failure after myocardial infarction[149] and levosimendan provided rapid and durable symptomatic relief.[150] Nevertheless, levosimendan induced hypotension[149,150] or cardiac arrhythmias.[150] A systematic review found no significant beneficial effects of levosimendan for low cardiac output syndromes in the general population of critically ill patients.[151] A new randomized trial (levoheartShock study) will start soon to compare the effects of an early use of levosimendan with placebo on top of a conventional strategy of inotrope use on a combined morbidity-mortality endpoint in patients with cardiogenic shock (available at www.clinicaltrials.gov, identifier: NCT04020263). In two recent large randomized controlled trials (CHEETAH and LEVO-CTS), levosimendan, as compared with placebo, did not improve the outcome of patients with systolic heart failure undergoing cardiac surgery,[152,153] although levosimendan reduced the use of inotropes after surgery.[153] Finally, a recent meta-analysis of several small trials showed that repeated administration of levosimendan in outpatient settings with advanced heart failure may improve hemodynamics, symptoms, and biomarkers and decrease the rate of rehospitalization of these patients.[154] The recent LION-HEART study[155] confirmed that intermittent intravenous administration of levosimendan in outpatients with advanced heart failure reduced biomarkers, decreased the rate of hospitalization at 12 months, and improved the quality of life of these patients, without any significant adverse effects. Nevertheless, such a strategy of levosimendan use still deserves further studies, such as the ongoing randomized controlled trial (LeoDOR study, available at www.clinicaltrials.gov, identifier: NCT3437226).[156] Currently, all these disappointing results have slowed down the commercialization of levosimendan in many countries. Nevertheless, levosimendan may be an interesting therapeutic option to treat takotsubo syndrome or to facilitate weaning from venoarterial extracorporeal membrane oxygenation.[157]

Nitric oxide synthase inhibitors have been proposed to be used in patients with cardiogenic shock, in whom nitric oxide production is increased, and may exert deleterious effects on cardiac function and vascular tone.[158] Tilarginine is a nonselective nitric oxide synthase inhibitor developed for treating acute heart failure. However, in the TRIUMPH study, tilarginine was unable to improve the survival rate in patients with cardiogenic shock at 3 months in comparison with placebo.[159] These negative results have interrupted the clinical development of this new drug.

Septic Shock

Treating or not treating septic-induced myocardial depression has been a matter of debate. First, it has been thought that left ventricular dilatation and low ventricular ejection fraction denote adaptive mechanisms and then, if so, treating it is questionable. In this regard, left ventricular ejection fraction was reported to be lower and left ventricular end-diastolic volume to be higher in survivors,[160,161] although a meta-analysis showed no difference between survivors for the two parameters. Second, because of the potential, but not constant, hyporesponsiveness of the beta-receptors, the efficacy of beta-agonists is not guaranteed. Third, side effects may occur with these drugs (tachycardia, arrhythmias, and hypotension). It must be stressed that there is an association of inotrope use during septic shock with mortality.[162] For all these reasons, inotropes, and among them dobutamine, should be not systematically administered even when a septic myocardial depression is suspected. It should be reserved for situations where cardiac dysfunction is accompanied by a low or inadequate cardiac output and signs of tissue hypoperfusion in spite of preload optimization.[37] The potential interest of administering dobutamine in patients with septic shock experiencing septic cardiomyopathy in order to reduce tissue hypoperfusion and associated organ dysfunctions will be investigated in a study that will start soon (ADAPT study, available at www.clinicaltrials.gov, identifier: NCT04166331). Bidimensional echocardiography[45,163] is the best tool to diagnose a severe decrease in cardiac contractility. However, bedside echocardiography is not available in all general ICUs; hence, the Surviving Sepsis Campaign recommends the use of dobutamine in patients with septic shock who show evidence of persistent hypoperfusion despite adequate fluid loading and the use of vasopressors.[38] Because dobutamine can exert vasodilatory effects, its use requires the concomitant use of a vasopressor such as norepinephrine. In septic shock, it is clearly recommended to use norepinephrine as the first-choice agent rather than dopamine because the latter is associated with increased mortality.[164] Epinephrine is a potent inotrope with vasopressive properties that could be used as an alternative to the combination of dobutamine and norepinephrine. A randomized study in patients with septic shock and a presumed cardiac dysfunction found no significant difference in patient outcome between epinephrine alone and a combination of norepinephrine and dobutamine.[165] However, this study has been criticized for a lack of statistical power. In the condition of depressed vascular tone and reduced myocardial function, despite similar effects on systemic blood flow and pressure, epinephrine was shown to be inferior to the combination of dobutamine and norepinephrine in terms of splanchnic perfusion[73,75,109] or to norepinephrine alone in terms of myocardial oxygen consumption.[166] A meta-analysis showed that the use of norepinephrine in patients with sepsis reduced the mortality rate, whereas the use of epinephrine did not.[167] For all these reasons, epinephrine is not recommended as the first-choice drug when the treatment of impaired cardiac contractility is considered.[49] The use of levosimendan has been proposed as an alternative to dobutamine in cases of severe septic myocardial depression that no longer responds to dobutamine administration.[168] The rationale for using levosimendan is that the sensitivity of Ca^{2+} to myofilament is reduced during sepsis, probably because of an abnormal phosphorylation of the troponin complex at the site where the Ca^{2+} ion binds to troponin C.[169] Because levosimendan can improve not only left ventricular function but also right ventricular performance through pulmonary vasodilation,[170,171] it might be useful in cases of septic myocardial depression with associated lung injury. Recently, a randomized controlled study (LeoPARDS)[172] showed that systematic levosimendan infusion, when added to standard care, failed to reduce mortality or organ dysfunction at day 28 in patients with septic shock. Importantly, patients receiving levosimendan required a higher dosage of norepinephrine, had more atrial fibrillation, and were less likely to be weaned from mechanical ventilation.[172] A major criticism of this study was that levosimendan was administered in patients without documented cardiac dysfunction in the majority of cases and thus in patients who could have suffered from side effects without getting any benefit in terms of cardiac function. In this regard, dobutamine was administered in less than 10% of the standard care group, suggesting that the incidence of cardiac depression was low in this study.[173] It must be noted that a subgroup analysis of the LeoPARDS study reported no benefit of levosimendan in patients with septic shock and biochemical evidence of myocardial injury or dysfunction, as attested by increased cTnI and Nt-proBNP blood levels.[174] It is important to note that the concept of using beta-blockers in septic conditions to prevent systemic adrenergic activation has recently emerged. In an experimental model, esmolol infusion had no significant effect on cardiac index or systemic arterial pressure and may prevent septic cardiac dysfunction by a preload effect induced by the decrease in heart rate.[175] In patients with septic shock, esmolol infusion was associated with a preserved stroke volume and microcirculation and a decrease in norepinephrine requirement.[176] In this regard, a randomized clinical trial was conducted in patients with septic shock and heart rate of greater than 90 beats/min.[177] Esmolol infusion decreased

heart rate, increased stroke volume and left ventricular stroke work index, and decreased arterial blood lactate level and fluid requirements. Although mortality rate was not the primary endpoint, it should be noted that esmolol infusion was associated with a significant decrease in 28-day mortality.[177] Esmolol infusion also can decrease the arterial elastance of tachycardic patients with septic shock and thus might improve the cardiovascular efficiency in such patients.[178] Nevertheless, patients with severe cardiac dysfunction (i.e., cardiac index ≤2.2 L/min/m^2 in the presence of a pulmonary artery occlusion pressure >18 mm Hg) were excluded.[177,178] As a consequence, the presence of cardiac dysfunction during sepsis cannot be considered as an indication for beta-blockers and should be still considered as a contraindication for their use. The effect of landiolol, a new highly selective beta-blocker with a short-acting effect, is currently tested against placebo in patients with septic shock with cases of tachycardia or tachyarrhythmia.[179]

In summary, given all the available data, it is still recommended to choose the combination of norepinephrine and dobutamine when inotropic therapy is given to reverse cardiac dysfunction in severe sepsis.

KEY POINTS

- Inotropic therapy is considered in patients with cardiogenic shock. In these situations, clinicians expect short-term positive effects of intravenous inotropic drugs, allowing cardiovascular stabilization.
- Inotropic therapy might also be considered in high-risk surgical patients, even in the absence of formally documented myocardial depression, to achieve supranormal levels of oxygen delivery during the perioperative period to prevent tissue hypoxia and organ dysfunction. Such a therapeutic attitude, which is still debated in the perioperative context, is not recommended routinely for critically ill patients with established circulatory shock.
- Most inotropic agents enhance myocardial contractility by increasing the Ca^{2+} concentration in the cytosol of cardiomyocytes after producing an increase in cytosolic cAMP concentration. Synthetic and natural catecholamines enhance cAMP formation after fixing beta-1 adrenergic receptors at the cellular surface, whereas phosphodiesterase inhibitors decrease cAMP degradation.
- Beta-1 adrenergic agents, such as dobutamine, dopamine, and epinephrine, are the most potent inotropic agents.
- Because of the downregulation of beta-1 adrenergic receptors, the myocardial effects of exogenous catecholamines can be attenuated after a few days of administration.
- Sepsis-induced decreased responsiveness of the myocardium to beta-adrenergic stimulation may also result in the attenuation of cardiac effects of exogenous catecholamine administration in patients suffering from septic shock.
- The drugs given to increase cardiac contractility may also exert vasoactive effects that may interfere with the regulation of regional blood flow. The extent to which this interference is beneficial in increasing oxygen supply in hypoxic areas remains speculative. This emphasizes the need to monitor, as far as possible, the perfusion and/or function of critical organs when such agents are given to patients in circulatory shock.

References for this chapter can be found at expertconsult.com.

ANNOTATED REFERENCES

De Backer D, Aldecoa C, Njimi H, et al. Dopamine versus norepinephrine in the treatment of septic shock: a meta-analysis. *Crit Care Med.* 2012; 40(3):725–730.
The objective of this meta-analysis was to compare the effects of norepinephrine and dopamine on outcome and adverse events in patients with septic shock. Six randomized studies (1408 patients) were included. Dopamine administration was associated with greater mortality and a higher incidence of cardiac arrhythmic events compared with norepinephrine administration. This paper is important because it greatly contributed to changing the guidelines of the Surviving Sepsis Campaign, which now recommends the use of norepinephrine as a first-choice vasopressor and to restrict the use of dopamine to highly selected patients (e.g., patients with low risk of tachyarrhythmia and absolute or relative bradycardia).

Hayes MA, Timmins AC, Yau EH, et al. Elevation of systemic oxygen delivery in the treatment of critically ill patients. *N Engl J Med.* 1994;330(24): 1717–1722.
This randomized study showed that attempting to achieve supranormal values of oxygen delivery in patients with an established critical illness may worsen rather than improve outcome.

Levy B, Clere-Jehl R, Legras A, et al. Epinephrine versus norepinephrine for cardiogenic shock after acute myocardial infarction. *J Am Coll Cardiol.* 2018;72(2):173–182.
In this randomized controlled trial, epinephrine and norepinephrine were compared as first-choice vasopressors in cardiogenic shock secondary to acute myocardial infarction. The use of epinephrine was associated with similar effects on arterial pressure and cardiac index but with a higher incidence of refractory shock. This paper confirms the priority place of norepinephrine for reversing hypotension in the majority of shock states.

Mebazaa A, Nieminen MS, Packer M, et al. Levosimendan vs. dobutamine for patients with acute decompensated heart failure: the SURVIVE Randomized Trial. *JAMA.* 2007;297(17):1883–1891.
In 1327 patients with acute decompensated heart failure requiring inotropic support, levosimendan was compared with dobutamine in a randomized double-blind design. Despite an initial reduction in plasma B-type natriuretic peptide level in patients receiving levosimendan, levosimendan did not significantly reduce all-cause mortality at 180 days or affect any secondary clinical outcomes. These disappointing results slowed down commercialization of levosimendan in many countries throughout the world.

Morelli A, De Castro S, Teboul JL, et al. (2005). Effects of levosimendan on systemic and regional hemodynamics in septic myocardial depression. *Intensive Care Med.* 31(5):638–644.
In septic patients with persisting cardiac dysfunction after 48 hours of dobutamine administration, compared with dobutamine continuation, levosimendan improved systemic hemodynamics, improved gastric mucosal perfusion and renal function, and decreased lactate. This study suggested that levosimendan might be an alternative to dobutamine for treating sepsis-induced cardiac dysfunction, especially when dobutamine is no longer effective.

Peake SL, Delaney A, Bailey M, et al. Goal-directed resuscitation for patients with early septic shock. *N Engl J Med.* 2014;371(16):1496–1506.
In this multicenter, randomized controlled trial, 1600 patients presenting to the emergency department with early septic shock were randomly assigned to receive either EGDT or usual care. EGDT did not reduce all-cause mortality at 90 days. This paper contributed to seriously questioning the interest of using EGDT, including $ScvO_2$, in the early phase of septic shock.

Silverman HJ, Penaranda R, Orens JB, et al. Impaired beta-adrenergic receptor stimulation of cyclic adenosine monophosphate in human septic shock: association with myocardial hyporesponsiveness to catecholamines. *Crit Care Med.* 1993;21(1):31–39.
This clinical study demonstrated that patients with septic shock exhibit a decreased hemodynamic response to dobutamine when compared with septic patients without shock. Moreover, the stimulation of circulating lymphocytes of the studied population showed that in patients with septic shock, the degree of impairment of beta-adrenergic receptor responsiveness in addition to that of post–beta-adrenergic receptor signal transmission was greater than in septic patients without shock. This study provides strong evidence of a septic shock–related myocardial hyporesponsiveness to catecholamines that may contribute to the reduced myocardial performance observed in this critical illness.

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Mechanical Support in Cardiogenic Shock

Laura M. Seese, Arman Kilic, and Thomas G. Gleason

Heart disease remains the leading cause of death in both men and women among African Americans, Hispanics, and Caucasians in the United States, accounting for nearly 650,000 deaths annually.[1] Significant progress has been made over the past few decades in defining and recognizing cardiogenic shock (CS), and although there are many potential causes of this condition, acute myocardial infarction (AMI) with a large loss of functioning myocardium is the most frequent.[2,3] Despite advances in early reperfusion and mechanical support treatment approaches, CS remains the most common cause of in-hospital mortality after AMI, with rates exceeding 50%.[2]

In 1912 James Herrick was the first to link observations of patients with AMI with autopsy findings of patients who had died from CS.[3] His contention at the time, which was initially rejected by the medical community, was that AMI was not always immediately fatal and that efforts were needed to diagnose and treat the condition while the patient was still alive.[3] It was not until the mid-to-late 20th century when selective coronary angiography became available in humans that DeWood and others reported evidence of coronary occlusion in patients suffering AMIs.[4] These findings laid the foundational basis for developing interventional and medical treatments for AMI to intervene and support patients who were diagnosed with CS. A standard definition of CS was proposed by Binder and colleagues in 1955, which included factors such as a systolic blood pressure less than 80 mm Hg and tachycardia to greater than 100 bpm with signs of peripheral vascular collapse.[5] At the time this definition was developed, the mortality associated with CS after AMI was still close to 100%.[5]

Over the past several decades, the general definition of CS has evolved into a severe impairment of myocardial performance that results in diminished cardiac output (CO), end-organ perfusion, and hypoxia.[6] Despite an updated definition, a level of uncertainty in the outcomes of CS persists, with some contemporary clinical trials lacking uniformity in their definitions for identifying CS. For instance, although the SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) and Intra-Aortic Balloon Pump (IABP)-SHOCK II trials used systolic blood pressure ≤90 mm Hg for ≥30 minutes, their exact parameters for confirming end-organ hypoperfusion were diverse (Table 82.1).[7,8] Clinically CS is recognized to be on a continuum, but the presence of hypotension refractory to volume resuscitation and features of end-organ hypoperfusion requiring pharmacologic or mechanical support are the crux of this diagnosis.[9] AMI remains the instigator of 81% of CS events.[10] Furthermore, the incidence of CS in myocardial infarction has remained relatively constant in recent decades (,7%) and remains the leading cause of death in patients with AMI.[7]

HISTORY OF MECHANICAL CIRCULATORY SUPPORT

The evolution of mechanical circulatory support (MCS) dates to the early 1950s when Gibbon developed the prototype cardiopulmonary bypass (CPB) apparatus.[11] In the years that followed, Lillehei, Kirklin, and others applied the heart-lung machine to facilitate open heart surgery; their pioneering work and early observations led directly to the development of modern MCS systems.[12–14] Their initial publications introduced the concept that left ventricular (LV) decompression and myocardial rest could afford enhanced cardiac recovery after the insult of open heart surgery. Clinical use of extracorporeal CPB for heart surgery became widespread in the early 1960s. Simultaneously, several groups of investigators were testing means of MCS for use outside the operating room to support patients in CS. The current modes of MCS are derivations of those originally developed.

The decision on the type of MCS used is based on the acuity of the patient's presentation, level of flow or adjunctive CO, and the overall goals of therapy. This decision often changes as the patient's clinical picture evolves. MCS devices include the intraaortic balloon pump (IABP), continuous flow pumps with or without an oxygenator, percutaneous devices, and durable continuous flow pumps. Temporary MCS devices are used in CS as a bridge to recovery (BTR), bridge-to-bridge with a long-term implantable MCS device, bridge to transplant (BTT), or bridge to decision. Some temporary MCS devices can be inserted percutaneously, whereas others require surgical implantation. Long-term MCS devices are used as a BTR, a BTT, or the definitive means of treatment for the patient's remaining lifespan—that is, destination therapy (DT). These devices have been employed for a variety of causes of CS, including AMI, inability to wean from CPB (postcardiotomy CS), acute decompensation of chronic heart failure (HF), acute myocarditis, peripartum cardiomyopathy, HF secondary to acute or chronic valvular heart disease, and congenital heart defects.

History of Aortic Counterpulsation

The concept of arterial counterpulsation was introduced in 1961 by Clauss and coworkers. It involved use of an external "ventricular" chamber that filled with blood from a catheter in the iliac artery and was subsequently compressed by a piston. Compression of the "ventricle" was synchronized to either the QRS complex of an electrocardiogram (ECG) or the impulse of a pacemaker so that a counterpulse of blood was delivered into the arterial system during diastole.[15] It was demonstrated in dogs that cardiac stroke work and LV end-systolic pressures were substantially reduced with the use of a counterpulsation into the aorta. The following year, Moulopoulus and associates adapted the model to create an IABP that could provide a similar

TABLE 82.1 Available Definitions of Cardiogenic Shock

Clinical Definition	SHOCK Trial	IABP-SHOCK II	ESC HF Guidelines
Cardiac disorder that results in both clinical and biochemical evidence of tissue hypoperfusion	Clinical criteria: SBP <90 mm Hg for >30 minutes OR support to maintain SBP >90 mm Hg AND end-organ hypoperfusion (urine output <30 mL/hr or cool extremities) Hemodynamic criteria: CI of <2.2L·m^{-2} AND PCWP >15 mm Hg.	Clinical criteria: SBP <90 mmHg for >30 minutes OR catecholamines to maintain SBP >90 mm Hg AND clinical pulmonary congestion AND impaired organ perfusion (altered mental status, cold/clammy skin and extremities, urine output <30 mL/hr or lactate >2.0 mmol/L)	Clinical criteria: SBP <90 mm Hg with adequate volume and clinical or laboratory signs of hypoperfusion. Clinical hypoperfusion: cold extremities, oliguria, mental confusion, dizziness, narrow pulse pressure. Laboratory hypoperfusion: metabolic acidosis, elevated serum lactate, elevated serum creatinine

From van Diepen S, Katz JN, Albert NM, et al. Contemporary management of cardiogenic shock: A scientific statement from the American Heart Association. *Circulation*. 2017;136(16):e232–e268.
CI, confidence interval; *PCWP,* pulmonary capillary wedge pressure; *SBP,* systolic blood pressure.

counterpulsation without the need for blood reservoirs.[16] The investigators used a balloon that was rapidly inflated and deflated with carbon dioxide during native diastole. The IABP was subsequently adapted and described for clinical use by Kantrowitz and colleagues in 1968.[17] There is little difference in the modern IABP and that originally described, other than the availability of different-sized balloons (30- to 50-mL balloons), the use of helium instead of carbon dioxide, and subtle differences in the materials used to make the catheters.

History of Mechanical Assist Devices

The need for effective MCS devices with more options for greater cardiac flow support became apparent in the 1950s during the development of CPB for open heart surgery. The first attempt at isolated extracorporeal LV support was with a simple roller pump in 1962.[18] Initial attempts with prolonged postoperative CPB demonstrated that the bypass circuit was damaging to both end-organ function and blood constituents after several hours of use.[19] Subsequently, femoral venous–to–femoral arterial CPB was successfully used by Spencer and colleagues in four patients with postcardiotomy cardiac failure.[20] Simultaneous to Spencer and colleagues' work with extracorporeal systems, DeBakey designed the first intracorporeal LV assist device (LVAD), the DeBakey blood pump.[21] A remodeled extracorporeal version was subsequently used for postcardiotomy failure in a 37-year-old woman after aortic and mitral valve replacements. The device was needed for 10 days, and the patient survived.[22]

By 1972 investigators at the Texas Heart Institute had developed a pneumatically driven LVAD designed to be implanted in the abdomen.[23] This device had a blood chamber compressed by pulses of air delivered into the pump by a percutaneous driveline. Modern devices have chamber compression that is electrically powered via percutaneous drivelines. Paracorporeal, pneumatically driven devices were a parallel development. Paramount to the evolution of these devices was the sponsorship of the Artificial Heart Program of the National Heart, Lung, and Blood Institute, which was chartered in 1964.

By the 1960s continuous flow pumps, as compared with pulsatile pumps, were under development.[24,25] Over the subsequent 15 years, continuous flow centrifugal pumps were perfected and introduced into clinical use. These pumps work on the principle of a forced, constrained vortex devised from three magnetic cones.[26,27] They have been shown to be useful in a variety of clinical settings where short-term MCS is needed and an IABP is inadequate. Several types of small, axial-flow, or rotary pumps have also been developed, including some that allow for percutaneous deployment.[28–41] These pumps generally contain a magnetically suspended impeller that rotates at fast rates between 25,000 and 35,000 rpm. The latest generation of rotary pump technology comprises continuous flow devices that use fully magnetically levitated rotors that eliminate the need for seals or bearings. This technology reduces the risk of damage to blood elements and has been shown to lead to lower rates of thromboembolism.[42]

INITIAL MANAGEMENT OF CARDIOGENIC SHOCK

The initial focus in the treatment of CS is to prevent end-organ failure through stabilization of CO and the establishment of hemodynamic stability while simultaneously diagnosing and treating the reversible causes of CS. Fig. 82.1 illustrates an algorithm for the management strategies in CS. Identification of the primary cause of CS can allow for the appropriate pharmacologic or mechanical therapies to be applied. The American Heart Association recommends that patients undergo noninvasive testing with chest x-ray, resting 12-lead ECG, and echocardiography.[6] Suggested laboratory tests include complete blood count, electrolytes, hepatic function tests, serum creatinine, mixed venous oxygen saturation, natriuretic peptides, serial troponin levels, arterial blood gas, and lactate.[6] The mainstay of evidence supports timely reperfusion in patients presenting with CS caused by AMI. The potential revascularization strategies can be noninvasive, with tissue fibrinogen activator or streptokinase, or invasive, with percutaneous coronary interventions (PCI) or coronary artery bypass grafting (CAGB).[7,43,44] Vasoactive medications are often required for support in patients with CS, and the decision for which medication to initiate in CS remains challenging. The SOAP II trial (Sepsis Occurrence in Acutely Ill Patients) evaluated vasopressor selection in a subgroup of patients with CS and found that dopamine was associated with a higher rate of arrhythmias in addition to increased mortality, which may be the result of a tachycardia-induced ischemic propogation.[45] This has led to assertion of using norepinephrine as a first-line agent. Unfortunately, the methodology and clinical definitions of CS used within the SOAP II trial caused major concerns regarding the generalizability and applicability of the findings. Additional studies have suggested that epinephrine should also not be used in the initial management of CS because of its effect in increasing lactate levels, increasing oxygen consumption, lowered arrhythmogenicity thresholds, and association with higher mortality.[46,47] Additionally, in a recent randomized clinical trial (RCT), norepinephrine was found to be superior to epinephrine in achieving hemodynamic stability without increasing lactate levels in patients in CS after AMI.[48] Escalating doses of vasopressors and inotropes in patients with CS are associated with increased mortality.[47] In the setting of refractory CS and impending or worsening end-organ failure, MCS

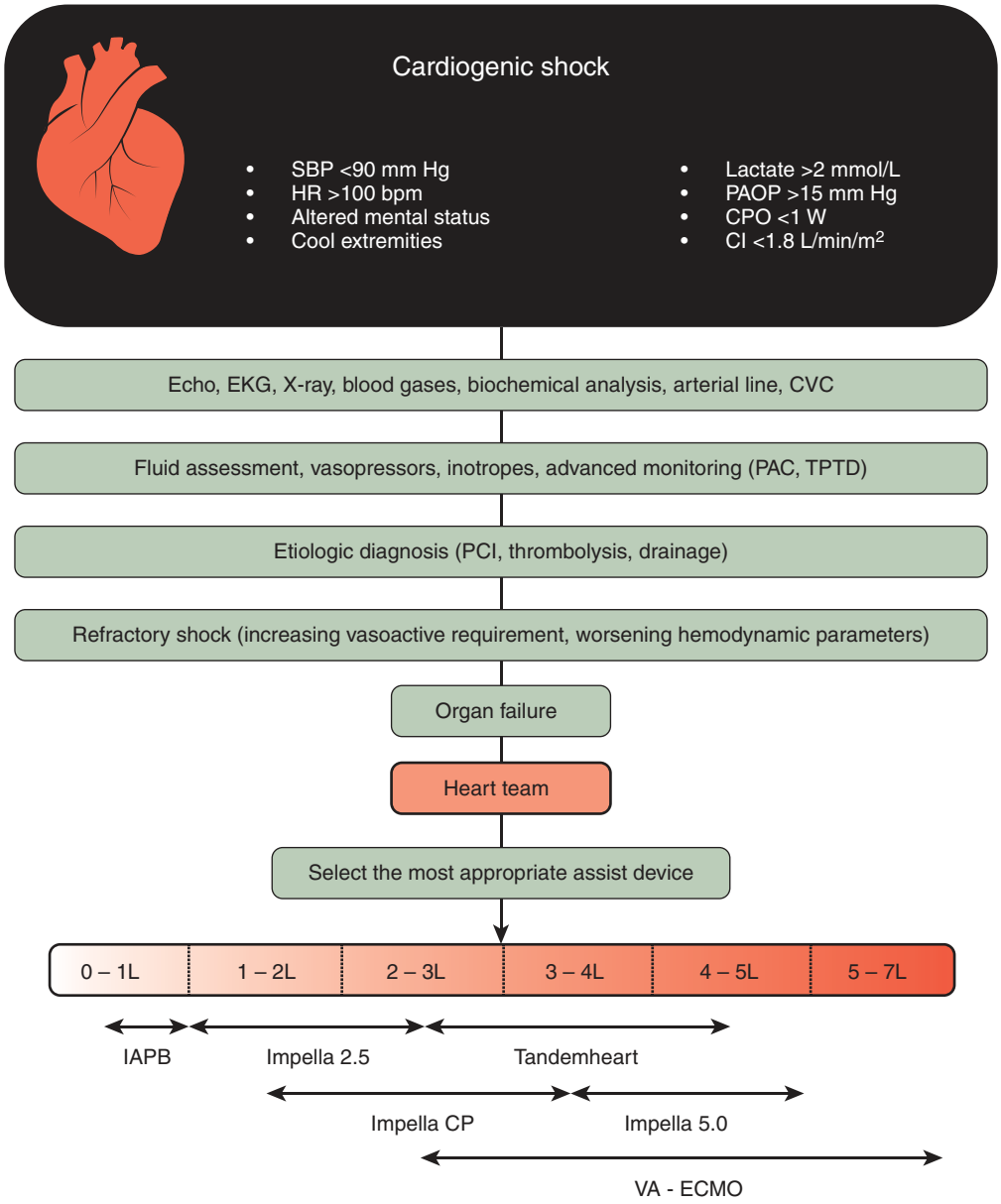


Fig. 82.1 Management schema for cardiogenic shock. (From Hajjar LA, Teboul JL. Mechanical circulatory support devices for cardiogenic shock: State of the art. *Crit Care*. 2019;23[1]:76.)

should be discussed with the multidisciplinary heart team and initiated in appropriate candidates.

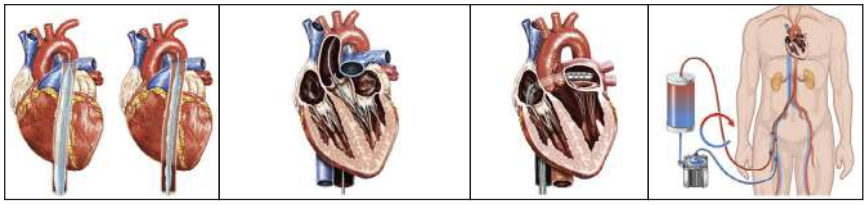
The lethality of CS and limited availability of donor hearts for patients with chronic HF has been the impetus for the ongoing search for an ideal form of MCS over the past 60 years. The complexity and heterogeneity of this patient population have led to the development of a vast array of devices, none of which has proven optimal for support in all patients across the spectrum. The decision for which type of MCS device to use is based on the amount of supplemental flow required or CO that the patient requires, the duration of support required, and the patient's candidacy for cardiac transplantation (Figs. 82.2 and 82.3).[49] The biologic barriers to MCS present a constant challenge to clinicians, and the types of MCS devices available are continually evolving. Nonetheless, MCS remains an important adjunct in the treatment of CS and HF, with many devices demonstrating significant improvement in survival and quality of life. Accordingly, the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines recommend nondurable MCS as a reasonable "bridge to recovery" or "bridge to decision" for patients with acute profound heart failure and a durable MCS for carefully selected patients with stage D heart failure and reduced ejection fraction (class IIa; level B).[50] The current indications, benefits, and limitations of MCS devices are outlined in this chapter.

CURRENT USE OF MECHANICAL CIRCULATORY SUPPORT DEVICES

Temporary Mechanical Circulatory Support

Percutaneous Insertion

Intraaortic balloon pump. The physiologic rationale for the efficacy of the IABP is that balloon deflation provides a rapid, synchronized



	IABP	Impella	TandemHeart	VA-ECMO
Cardiac flow	0.3–0.5 L/min	1–5 L/min (Impella 2.5, Impella CP, Impella 5)	2.5–5 L/min	3–7 L/min
Mechanism	Aorta	LV → AO	LA → AO	RA → AO
Maximum implant days	Weeks	7 days	14 days	Weeks
Shealth size	7–8 Fr	13–14 Fr Impella 5.0 - 21 Fr	15–17 Fr arterial 21 Fr venous	14–16 Fr arterial 18–21 Fr venous
Femoral artery size	>4 mm	Impella 2.5 & CP - 5–5.5 mm Impella 5 - 8 mm	8 mm	8 mm
Cardiac synchrony or stable rhythm	Yes	No	No	No
Afterload	↓	↓	↑	↑↑↑
MAP	↑	↑↑	↑↑	↑↑
Cardiac flow	↑	↑↑	↑↑	↑↑
Cardiac power	↑	↑↑	↑↑	↑↑
LVEDP	↓	↓↓	↓↓	↔
PCWP	↓	↓↓	↓↓	↔
LV preload	---	↓↓	↓↓	↓
Coronary perfusion	↑	↑	---	---
Myocardial oxygen demand	↓	↓↓	↔↓	↔

Fig. 82.2 Adjunctive mechanical circulatory support options and their mechanisms, implant requirements, and hemodynamic effects. *AO,* Aorta; *IABP,* intraaortic balloon pump; *LA,* left atrium; *LV,* left ventricle; *LVEDP,* left ventricular end-diastolic pressure; *MAP,* mean arterial pressure; *PCWP,* pulmonary capillary wedge pressure; *RA,* right atrium; *VA-ECMO,* venoarterial extracorporeal membrane oxygenation. (From Atkinson TM, Ohman EM, O'Neill WW, et al. A practical approach to mechanical circulatory support in patients undergoing percutaneous coronary intervention: An interventional perspective. *JACC Cardiovasc Interv.* 2016;9[9]:871–883.)

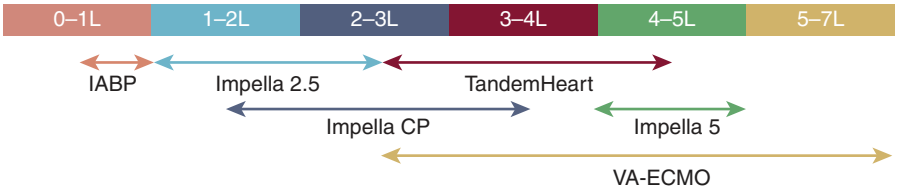


Fig. 82.3 Comparison of mechanical circulatory support devices and their impacts on cardiac flow. (See Fig. 82.2 for abbreviations.) (From Atkinson TM, Ohman EM, O'Neill WW, et al. A practical approach to mechanical circulatory support in patients undergoing percutaneous coronary intervention: An interventional perspective. *JACC Cardiovasc Interv.* 2016;9[9]:871–883.)

reduction in impedance (afterload) during isovolemic LV contraction. This is followed by a rapid, synchronized increase in aortic pressure during isovolemic LV relaxation (diastolic augmentation) caused by balloon inflation. In combination, these events achieve two important goals. First, LV systolic unloading directly reduces stroke work, which in turn reduces myocardial oxygen consumption during the cardiac cycle. Second, diastolic augmentation raises arterial blood pressure and provides better coronary arterial perfusion during diastole, yielding increased oxygen delivery to the myocardium. The IABP does not directly move or redistribute blood flow; however, peak diastolic coronary flow velocity can be increased as much as 87% with IABP augmentation and peak diastolic flow velocity by as much as 117%.[51] Since its introduction into clinical use in 1968, the IABP has remained an important adjunct to supporting patients in CS. Myocardial recovery is promoted

by the reduction of cardiac work and the simultaneous increase in myocardial oxygen supply. However, therapeutic success is dependent on the patient having a minimum degree of LV function that, in combination with IABP support, facilitates an adequate CO to sustain end-organ function. When this minimal CO is not met, alternative MCS must be considered.

The absolute indications for IABP placement include CS, uncontrolled angina pectoris, acute postinfarction ventricular septal defect (VSD), postinfarction mitral regurgitation (MR) secondary to papillary muscle rupture, and postcardiotomy left-sided HF with low CO.[52] In these settings, IABP should be considered as a primary therapy that should not be delayed. It is important to recognize that blood pressure alone is not an adequate indication of hemodynamic or cardiac stability. Limb perfusion, renal function, mental status, and even gastrointestinal function need to be considered in the assessment of adequate resuscitation and homeostasis. Additional measurable indices include arterial (SaO_2) and mixed venous oxygen saturation, acid-base status, urine output, and body temperature. A multivariate analysis of data accrued from 391 postcardiotomy patients requiring an IABP demonstrated that epinephrine requirements greater than 0.5 μg/kg/min, a left atrial pressure greater than 15 mm Hg, urine output less than 100 mL/hr, and mixed venous oxygen saturation less than 60% correlated with mortality.[53] These criteria were used to help predict mortality and the need for subsequent MCS.

Other relative indications for IABP use include (1) high-risk, catheter-based interventional procedures such as left main coronary artery angioplasty, (2) after unsuccessful attempts at catheter-based intervention in patients with poorly controlled ventricular arrhythmias and concomitant poor LV function, and (3) in settings of persistent stunned, ischemic myocardium. These are circumstances in which reduction of LV systolic wall tension and oxygen consumption by the IABP might enhance myocardial recovery after intervention. The Benchmark Counterpulsation Outcomes Registry of IABP use in 22,663 patients from 250 hospitals worldwide demonstrated that CS and high-risk angioplasty were the most common indications for use of the device.[54]

The optimal site of insertion of an IABP is a common femoral artery that can be accessed either percutaneously with the Seldinger technique or by surgical cutdown. Modern intraaortic balloon catheters are available for adults and children, according to the appropriate size and length for a given height and weight of the patient. Adult intraaortic balloons have a range in volume filled between 30 and 50 mL, with a standard balloon size holding 40 mL of helium. IABP catheters placed through the femoral artery are positioned so that the tip is just distal to the takeoff of the left subclavian artery in the proximal descending thoracic aorta. Optimally, the tip of the catheter should be positioned with transesophageal echocardiographic or fluoroscopic guidance.[55] To reduce the diameter of femoral cannulation, the sheathless IABP technique can be used and is our preferred method.[56]

Inflation of the balloon should be timed with closure of the aortic valve (at the dicrotic notch of the aortic pressure tracing) and should be inflated to nearly occlude the descending thoracic aorta. Timing can be synchronized in one of three ways: (1) using an arterial (preferably aortic) pressure tracing in synchrony with the dicrotic notch, (2) using the descent of the R wave on a rhythm tracing, or (3) timed after a ventricular pacing spike when a pacemaker is in use.[56–63] The optimal physiologic benefit of the IABP is significantly improved by proper timing of inflation and deflation, which can be difficult when there is an accelerated heart rate, cardiac rhythm disturbances, atrioventricular dyssynchrony, or low mean arterial pressure. Timing should be adjusted to maximize diastolic augmentation; hence, deflation should be as late as possible but just before opening of the aortic valve. If this cannot be gauged by pressure tracing, it can be timed to the onset of the R wave on ECG tracing or with the use of M-mode echocardiography.[63]

When femoral arterial cannulation is not desirable because of aortoiliac occlusive disease or extensive peripheral vascular disease (PVD), the subclavian artery or the ascending aorta can be used.[64–68] With either technique, the IABP catheter is advanced antegrade down the descending thoracic aorta so that the balloon tip sits above the level of the diaphragmatic hiatus, and the most proximal end of the balloon is distal to the takeoff of the left subclavian artery. These antegrade balloons should always be placed with either fluoroscopic or echocardiographic guidance. They should be removed with open arterial repair in all cases.

IABP catheters should not be left in place after weaning because of the risk of thrombus formation and embolization. An IABP should be weaned stepwise from a rate that is equivalent to heart rate (1:1) down to a ratio of 1:4 just before removal. Balloon catheters placed via the open surgical technique should also be removed surgically. Percutaneous removal of catheters placed in the iliac artery above the inguinal ligament (most common in obese individuals) can result in significant retroperitoneal bleeding. Consideration of operative removal is warranted.

Relative contraindications to IABP use include severe atheromatous disease of the descending thoracic aorta, descending aortic dissection or aneurysm, recent descending thoracic aortic surgery, and mild to moderate aortic insufficiency. Severe aortic insufficiency is an absolute contraindication to use because diastolic augmentation cannot be accomplished, and LV end-diastolic volume and pressure are actually increased rather than decreased.

The overall complication rate of IABP use is between 5% and 10%. Major complications occur at a rate of about 3% and include severe bleeding, major limb ischemia or amputation, infection, visceral or spinal cord ischemia, and attributable IABP mortality.[54,69] In the Benchmark registry, rates of complications were quite low; the most common complications were access site bleeding (4.3%) and limb ischemia (2.3%). The rates of amputation, stroke, visceral or spinal cord ischemia, and IABP-related mortality were all 0.1% or less.[70] Intraaortic balloon entrapment is a rare complication.[70–72] The incidence of major vascular complications according to the STS National Database (1996–1997) and the Benchmark Registry (1997–1999) was 5.4% and 1.4%, respectively.[55,69] Ipsilateral limb ischemia should be immediately addressed after its recognition. This usually requires removal of the IABP with replacement at another location if it is still indicated. The ischemic limb may require thrombectomy with or without revascularization and fasciotomy.[73–79]

The SHOCK trial showed that early revascularization in CS after AMI, often facilitated by IABP use (86%), yielded a lower 6-month mortality rate (50%) than that with medical therapy alone (63%).[7] Additional studies have shown that in patients undergoing urgent or emergent revascularization after an AMI, those supported preoperatively with an IABP had a lower operative mortality than those in whom an IABP was not used (5.3%–8.8% vs. 11.8%–28.2%).[69] These data seem to justify a strategy of aggressive IABP use to facilitate early revascularization in a postinfarction patient. The Second Angioplasty in Myocardial Infarction (PAMI-II) Trial data examined high-risk patients with AMI revascularized by PCI only and demonstrated a modest survival advantage at 6 months with the use of periprocedural IABP support.[54] When evaluating hospital mortality rates among patients undergoing CABG and/or valve surgery who received preoperative IABP or required intraoperative/postoperative IABP support, the mortality rate was significantly lower among patients supported preoperatively, as depicted in Table 82.2.[55,58] Hence, there appears to be a survival advantage to earlier IABP support for

TABLE 82.2 Hospital Mortality (Outcome Parameter) for Patients Undergoing Cardiac Surgery Who Either Received Preoperative IABP or Intra/Postoperative IABP Support

Type of Therapy	Benchmark Registry 1997–1999 Mortality/Total Operations With IABP, N (%)	STS National Database 1996–1997 Mortality/Total Operations With IABP, N (%)	STS National Database 1996–1997 Mortality/Total Operations Without IABP, N (%)
Preoperative IABP	8.8 (329/3721)	9.5 (2487/26,077)	2.9 (10,919/378,810)
Intraoperative/ postoperative IABP	28.2 (954/3380)	23.6 (3528/14,933)	2.5 (9878/389,954)

From Christenson JT, Cohen M, Ferguson JJ 3rd, et al. Trends in intraaortic balloon counterpulsation: Complications and outcomes in cardiac surgery. *Ann Thorac Surg.* 2002;74:1086–1090.
Based on data from the Benchmark Counterpulsation Registry 1997–1999 and the STS National Database 1996–1997 compared with hospital mortality for patients who had neither preoperative nor intraoperative/postoperative IABP support.

patients with CS after AMI who undergo revascularization. In the setting of an acute VSD or acute MR after an AMI, IABP support can offer a dramatic improvement in the hemodynamic response of the patient.[80–85] It is clear that the mortality rate of patients in CS after AMI remain high. However, these studies suggest that IABP support, combined with revascularization, portends a better prognosis than adjunctive IABP use with medical therapy alone.[54] This benefit is likely greatest in those who are revascularized and present with class 3 or 4 HF.[86] A meta-analysis of 16 studies demonstrated a significant survival benefit for the use of IABP in CS after AMI (relative risk [RR]: 0.78; confidence interval [CI]: 0.60–0.86; $P < 0.0004$).[87] However, no benefit was seen in patients with high-risk AMI that was not complicated by CS.

Conversely, a Cochrane Database meta-analysis of six RCTs reviewed the use of IABP in CS after AMI in 190 patients and found no significant improvement in in-hospital, 30-day, or 6-month all-cause mortality.[88,89] A meta-analysis of cohort studies of IABP use in patients in CS after AMI by Sjauw and colleagues found an 18% decrease in 30-day mortality in patients treated with thrombolysis and IABP. However, in patients treated with PCI, they noted a 6% increase in mortality associated with the additional use of an IABP.[90] In the prospective IABP-SHOCK II trial, 600 patients in CS after AMI were randomized with and without placement of IABP after undergoing revascularization, primarily with PCI (>95%).[91] No difference in the primary endpoint of 30-day, all-cause mortality was seen (39.7% IABP, 41.3% control). However, a 10% crossover to the IABP arm was noted. Additionally, a meta-analysis of 12 RCTs found no improvement in 30-day mortality with the use of IABP in patients with AMI, regardless of whether or not the patients suffered from CS.[92] From this compilation of results, it may be concluded that the use of IABP in CS after AMI has little benefit in any treatment strategy that does not employ the use of early revascularization. Furthermore, improvement in the patient's hemodynamics often seen with the use of IABP does not suffice as a surrogate marker for survival in patients in CS after AMI. An IABP should be placed in the case of acute postinfarction VSD or acute MR without delay.

TandemHeart. The TandemHeart System (Cardiac Assist, Inc., Pittsburgh, PA) is an external centrifugal pump system that allows for percutaneous LV support by pumping blood from the left atrium into the femoral artery (Fig. 82.4).[93] Placement of the 21F venous inflow cannula is performed by accessing the femoral vein percutaneously and positioning the cannula tip in the left atrium via an atrial transseptal puncture. Outflow is established into the contralateral or ipsilateral femoral artery via a 15F or 17F cannula. The centrifugal pump is strapped to the thigh adjacent to the arterial cannula. The device contains a built-in heparin delivery system to decrease thrombin formation. An experienced team

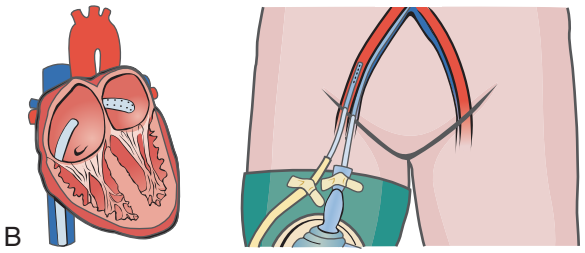


Fig. 82.4 A, Components of the TandemHeart device: 21F left atrial drainage cannula and 15–17F femoral arterial cannula *(left)*; continuous flow centrifugal pump *(right)*. **B,** Schematic demonstrating transseptal left atrial drainage and femoral access points. (From Windecker S. Percutaneous left ventricular assist devices for treatment of patients with cardiogenic shock. *Curr Opin Crit Care.* 2007;13:521–527.)

can establish MCS with TandemHeart in as little as 1 hour.[94] However, this is still longer than required for institution of extracorporeal membrane oxygenation (ECMO) support. Therefore its use may be limited in truly emergent cases and in conditions requiring cardiopulmonary resuscitation (CPR). The TandemHeart does provide more robust left-sided decompression as compared with ECMO.

Contraindications to placement of TandemHeart include severe PVD and isolated right ventricular (RV) failure. It also cannot be used in the presence of a VSD because of the potential for right-to-left shunting.[95] Right-to-left shunting is a known complication that can also occur if the transseptal cannula becomes dislodged into the right atrium (RA). Other complications include limb ischemia and thromboembolism.

TandemHeart has mostly been used as an MCS in CS.[96–98] Support has been employed for various indications, including postcardiotomy failure,[99–101] until corrective valvular surgery is performed,[102–104] until recovery of fulminant myocarditis,[105,106] or as a bridge to LVAD or BTT.[98,107,108] It has also been used successfully for MCS during high-risk PCI.[109–112] TandemHeart has been shown to be a more effective means of improving hemodynamic parameters in CS than IABP; however, no improvement in 30-day mortality has been demonstrated.[113,114]

Impella. The Impella Recover axial flow pump (Abiomed, Inc., Danvers, MA) is an addition to the treatment armamentarium for

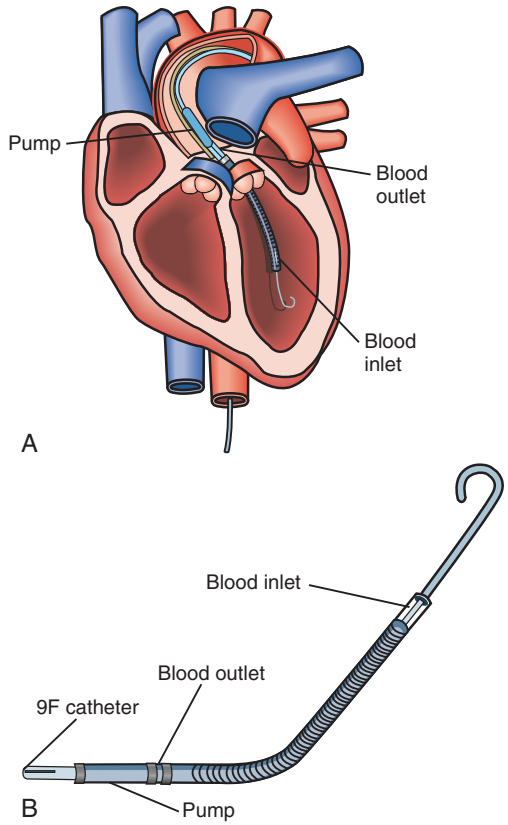


Fig. 82.5 A, Schematic demonstrating retrograde placement of the Impella Recover LP 2.5 device across the aortic valve. **B,** Components of the device. Blood from the ventricle enters the inlet portion of the device and is propelled by a 12F microaxial pump to the outlet portion positioned in the ascending aorta, establishing left ventricular decompression. (From Windecker S. Percutaneous left ventricular assist devices for treatment of patients with cardiogenic shock. *Curr Opin Crit Care.* 2007;13:521–527.)

acute short-term MCS (Fig. 82.5). The device is placed retrograde across the aortic valve with the tip situated in the LV. It can be placed percutaneously or surgically via the femoral artery under fluoroscopic guidance. It may also be placed surgically via an 8-mm T-graft sewn to the subclavian artery[115,116] or directly into the ascending aorta during cardiac surgery. There are several versions of the Impella device, including the 2.5, 5.0, and CP (flow rates of 2.5, 5.0, and 5.0 L/min, respectively). Whereas the 2.5 and the CP can be placed percutaneously or surgically, the larger Impella 5.0 requires surgical placement. Contraindications for the use of Impella include patients with severe aortic stenosis and those who have had a previous mechanical aortic valve replacement. Severe PVD may make percutaneous deployment impossible or mandate a surgical cutdown for placement.

Similar to other devices, Impella has been used for MCS for several indications, including high-risk PCI[117,118]; postcardiotomy failure[119–121]; CS after AMI[97,122–125]; severe allograft rejection after heart transplant[126,127]; myocarditis[128,129]; and as a bridge to placement of a long-term device, BTR, or BTT.[97] RCTs comparing support with Impella 2.5 with IABP in CS AMI have demonstrated improved hemodynamic and laboratory parameters (CI, mean arterial pressure, serum lactate levels) with the use of Impella.[113,114] However, this did not translate into improved 30-day survival. In contrast, the recent PROTECT-II RCT comparing these two devices in high-risk PCI demonstrated lower rates of the two composite endpoints of major adverse events (MAEs) and major adverse cardiac and cerebral events (MACCEs = death, stroke, myocardial infarction, and repeat revascularization).[117] At the 3-month follow-up, the rates of both composite endpoints were lower in the Impella group than in the IABP group (MAE, 37% vs. 49%, $P = 0.014$; MACCE, 22% vs. 31%, $P = 0.034$) at 3 months.

In addition to the Impella devices for LV support, the Impella RP is available for RV support. The Impella RP is a 22F percutaneous, microaxial pump mounted on an 11F catheter. The catheter pump is advanced antegrade through the femoral vein under fluoroscopic guidance and positioned across the tricuspid and pulmonic valves.[130] The pump inflow aspirates blood from the inferior vena cava and ejects it into the pulmonary artery at a rate of up to 4.0 liters per minute. The intended use for the Impella RP is 14 days; however, if there is echocardiographic and hemodynamic evidence of improved RV function, the device can be weaned earlier. During pump operation, an activated clotting time of 160–180 seconds is required. The RECOVER RIGHT study was a prospective, multicenter trial that demonstrated improved hemodynamics and a 73% 30-day survival in patients with RV failure after AMI.[131]

Protek duo. The tandem heart Protek Duo is a device used for isolated RV support accessed via the right internal jugular vein. The device contains two lumens within the 29F or 31F cannula.[130] One serves as the inflow cannula, which is positioned across the superior vena cava and RA, where it removes blood and delivers it to a centrifugal pump. The second lumen is the outflow cannula, which has a multifenestrated tip to deliver blood into the main PA. This system effectively bypasses the RV. The Protek Duo can flow between 2 and 4 liters per minute.[132] The Protek Duo has been reported for use after AMI with RV infarcts, myocarditis, posttransplant RV failure, postcardiotomy RV failure and post-LVAD RV failure.[133]

Extracorporeal membrane oxygenation. Since the 1970s, ECMO has been used in the adult population for short-term MCS when CS is complicated by concomitant pulmonary insufficiency. It provides full cardiopulmonary support to allow reversal of the systemic malperfusion that occurs in CS until definitive surgical correction is performed. It can also serve as a BTR, a BTT, or a bridge-to-bridge to longer-term MCS (i.e., VAD).[134–136] It may be employed for a period of 1–3 days in cases when the neurologic status of a patient is unclear, but longer-term support is generally not appropriate until this status is clarified.

The ECMO circuit consists of inflow and outflow cannulas, a continuous flow centrifugal pump, a hollow-fiber oxygenator, and a heat exchanger. Historically, roller pumps and centrifugal pumps have both been used. Roller pumps remain in widespread use for CPB during cardiac surgery; applications outside the operating room have been virtually abandoned because of higher rates of circuit disruption, particle emboli, and hemolysis.[137] Bio-Medicus Biopump (Medtronic Corp., Minneapolis, MN) and CentriMag (Levitronix LLC, Waltham, MA) are two centrifugal pumps commonly used in ECMO circuits. The Bio-Medicus Biopump generates a constrained vortex within an acrylic shell that houses concentric magnetic cones. The cones rotate as a magnetic rotary motor spins adjacent to the base of the cones and can generate very high flows with less trauma to blood cells than roller pumps.[137–141] The cannulation strategy most often used in acute CS is peripherally via the femoral vessels with either the percutaneous Seldinger or surgical technique. Alternatively, central cannulation via the RA and aorta is used to provide temporary MCS in the case of postcardiotomy failure or in patients who require further ventricular decompression with LV vents in lieu of left thoracotomy drainage approaches or additional percutaneous device therapy. When faced with acute refractory CS, ECMO can facilitate patient stabilization for subsequent transport to a tertiary medical center for VAD evaluation. One particular ECMO system is the CardioHelp (Maquet Cardiopulmonary AG, Hechingen, Germany). It is a miniaturized system that combines the

pump and oxygenator in a single unit. Considering the economical size, it is ideal for patients who require urgent interhospital transport.[142]

Disadvantages in using the peripheral cardiopulmonary support or ECMO include the greater potential for ipsilateral limb complications, higher rates of hemolysis, the requirement for anticoagulation to prevent thrombosis of the oxygenator and circuit, and failure to adequately decompress the left ventricle.[143–149] Inadequate LV decompression with peripheral cardiopulmonary support/ECMO systems may be the mechanism responsible for some treatment failures. Regardless of the etiology of CS, a rested ventricle (i.e., decompressed) has a better chance of recovery than a distended ventricle. Lower extremity ischemia may be resolved or prevented by placing an additional perfusion cannula (8–14F) down the ipsilateral superficial femoral artery.[150] Alternatively, limb ischemia may be prevented with the use of an 8-mm T-graft sutured to the side of the femoral artery.[151] However, this increases the complexity of instituting ECMO and can be impractical in cases of CS with ongoing CPR where efficiency is key.

The use of ECMO in the adult population for reasons other than primary cardiac failure with secondary pulmonary insufficiency has limited advantages over conventional therapies.[151,152] However, a substantial subset of patients who present with CS and are initially resuscitated with cardiopulmonary support/ECMO survive to revascularization, transplantation, or recovery, with survival rates as high as 75%.[153–164] ECMO used as a bridge to VAD placement for profound CS can yield survival rates higher than 40%.[165] This strategy is pragmatic and offers immediate end-organ support while a subsequent definitive treatment plan can be designed. In an outcome study by Combes and colleagues, early predictors of death on ECMO support include hepatic failure, renal failure, or placement of ECMO while undergoing CPR. Of the greater than 40% who did survive to discharge, many reported continued physical and social problems, including the ability to return to work.[166] This underscores the importance of long-term follow-up and the need for continued psychosocial support of these patients.

Improvements in pump and oxygenator technology have made EMCO a relatively simple means to establish MCS, allowing reversal of end-organ malperfusion that inevitably accompanies CS not promptly corrected with medical therapy alone. However, complications of bleeding, infection, stroke, and limb ischemia increase with time on ECMO support.[167] As with any form of MCS, the plan for separation from support or transition to a more permanent means begins upon institution of ECMO. Once end-organ malperfusion has been corrected, the feasibility of ECMO weaning is determined on a daily basis. Weaning trials are guided based on the patient's hemodynamic parameters, oxygenation, and ventilation. Pulmonary and circulatory support can be weaned independently or simultaneously. Pulmonary weaning consists of increasing support from mechanical ventilation while the amount of oxygenation and ventilation provided by ECMO is reduced. Circulatory weaning is done by gradually decreasing the amount of pump flow in a stepwise fashion while assessing hemodynamic and echocardiographic parameters to evaluate the cardiac response to ventricular loading that occurs with decreasing pump flow. Once it is determined that the patient can maintain adequate perfusion and pulmonary function, a plan is made to separate the patient from ECMO and remove the cannulas. The cannulas are most often removed in the operating room with direct vascular repair of the femoral artery. If the patient cannot be successfully weaned from EMCO, the plan for conversion to VAD or transplant is undertaken. This period of support, weaning, and determining the long-term strategy is done with the collaboration of a multidisciplinary heart team, including surgeons, cardiologists, and critical care providers.

Temporary Surgically Inserted Devices

Short-term MCS using continuous flow pumps for CS is a relatively simple means of establishing immediate and complete MCS, requiring no additional equipment other than that needed for standard CPB support during cardiac surgery. As previously discussed, some MCS pumps can be used with percutaneous cannulation for ECMO support. These same pumps may be placed by surgical insertion. The most common indication for temporary MCS where surgical insertion is used is for postcardiotomy CS. This can be achieved by conversion from the CPB circuit used during the primary cardiac operation to a temporary VAD system, using the existing cannulas in the RA and aorta. Temporary VAD support may be required for several days to allow myocardial recovery. If the decision is made to leave the chest open, the cannulas can be brought out through the lower portion of the sternotomy incision and covered with a sealed temporary dressing. Alternatively, they can be brought out through separate incisions inferior to the sternotomy, allowing the sternum to be closed temporarily. The patient can then be brought back to the operating room within several days to explant the cannulas once cardiac recovery has occurred or converted to a long-term LVAD. Under the most recent United Network for Organ Sharing (UNOS) cardiac allocation policy change on October 18, 2018, the priority of patients on nondischargeable, surgically implanted MCS has increased. As such, these devices are frequently considered in patients who are potential candidates for BTT.[168] Temporary, surgically implanted MCS can be withdrawn in cases where severe multiorgan failure ensues despite therapy or conversion to long-term MCS or BTT is not appropriate (advanced age, lack of appropriate psychosocial support). However, it is best to determine candidacy for definitive treatment with the multidisciplinary heart team initially and discuss the goals of treatment before performing any high-risk surgical case.

CentriMag ventricular assist. The CentriMag system uses fully magnetically levitated technology to provide MCS in a fashion similar to the Bio-Medicus Biopump. The CentriMag system has many advantages that make it attractive for temporary MCS in the acute setting.[169] These advantages include ease of implantation, direct outflow cannulation of the ventricle for improved decompression, and less damage to blood elements compared with traditional devices such as the Bio-Medicus pump. It has been used effectively for univentricular or biventricular support in the setting of postcardiotomy failure as a bridge to decision, BTR, BTT, or bridge to a long-term MCS device. For patients with concomitant pulmonary insufficiency, an oxygenator may be spliced into the circuit, effectively converting it to an ECMO system.

Durable Ventricular Assist Devices

Continuous Flow Left Ventricular Assist Devices

In the continued search for smaller, implantable LVADs with increased durability, many advances in technology have led to an array of continuous flow pumps, each with unique features. These axial or centrifugal flow pumps are smaller and more durable than pulsatile devices, making them well suited for long-term support as a BTT, BTR, or DT.[170–172] They are placed within the pericardium or in a preperitoneal pocket, with only an external driveline exposed to provide power and device control. These devices are relatively costly, provide isolated LV support, and require specialized training to implant, although they provide significantly improved survival and quality-of-life outcomes over patients with refractory heart failure treated with optimal medical therapy. In the setting of limited donor organs, these devices continue to be a significant treatment approach for patients with HF.

HeartMate II (HMII). HeartMate II (Abbott Inc., Chicago, IL) is an implantable axial flow LVAD that has been used as a BTT and DT.[171–174] The device is implanted in a preperitoneal pocket with the inflow cannula situated in the LV apex. Outflow is via a graft anastomosed to the ascending aorta. The device was approved for DT by the Food and Drug Administration (FDA) in 2010. A prospective postapproval study confirmed the efficacy of the device and demonstrated a reduction in

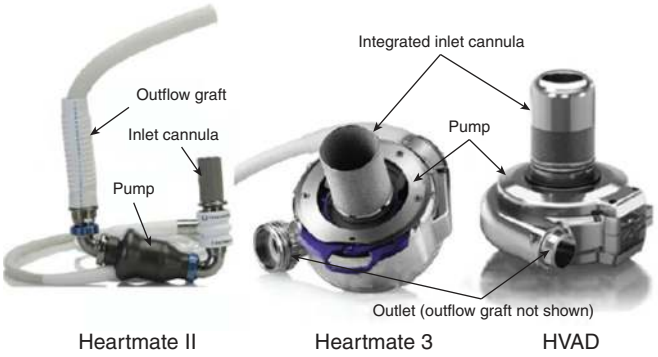


Fig. 82.6 Implantable continuous flow ventricular assist devices currently in commonly in clinical use. (From Stulak JM, Abou El Ela A, Pagani FD. Implantation of a durable left ventricular assist device: How I teach it. *Ann Thorac Surg.* 2017;103[6]:1687–1692.)

the median length of stay by 6 days as compared with the pivotal DT trial.[175] Results of the ROADMAP trial demonstrated that limited HF patients treated with the HeartMate II LVAD had significant improvement in the primary outcome composite of survival and improvement in a 6-minute walk test at 1 year compared with similar patients treated with optimal medical therapy.[176]

Jarvik 2000. Jarvik 2000 (Jarvik Heart, Inc., New York, NY) is an implantable axial flow pump used as a BTT and for DT.[177,178] It is unique in that the pump itself resides within the LV cavity, providing outflow via the LV apex to a graft anastomosed to the ascending or descending thoracic aorta. It is a direct current (DC) battery–powered device, using alternating current (AC) power only to recharge the batteries.

HeartWare ventricular assist device (HVAD). The HVAD (HeartWare, Inc., Framingham, MA) is a centrifugal pump that is implanted within the pericardial space. The pump is attached directly to the LV apex where inflow is provided. Outflow is via a graft sewn to the ascending aorta. Based on results from the ADVANCE clinical trial, the HVAD received FDA approval as a BTT device.[179] Additionally, the ENDURANCE trial found centrifugal flow pumps (HVAD) to be noninferior to axial flow pumps (Heartmate II), with higher rates of strokes (29.7% vs. 12.1%, $P < 0.001$) reported in the HVAD group.[180] The ENDURANCE supplemental study subsequently confirmed the associations between poorly controlled hypertension and strokes in LVAD patients and thus the importance of blood pressure management in the LVAD population.[181]

Heartmate III. The Heartmate III (Abbott, Inc., Chicago, IL) device is a centrifugal flow pump with a bearingless, fully magnetic levitated motor with wide blood-flow passages and no mechanical bearings (Fig. 82.6).[182] Additionally, the Heartmate III is programmed to facilitate rapid changes in rotor speed to create an intrinsic artificial pulse that can potentially reduce stasis and thrombus within the pump.[183] The MOMENTUM 3 trial compared the Heartmate II axial flow pump with the Heartmate III centrifugal flow pump. At 2-year follow-up, the investigators found that the Heartmate III was superior with fewer disabling strokes, reoperations for pump thrombosis, and major bleeding events when compared with the Heartmate II.[184]

TREATMENT OF CARDIOGENIC SHOCK: AN ALGORITHM FOR MECHANICAL CIRCULATORY SUPPORT

The hallmarks of CS are low CO, hypotension, peripheral vasoconstriction, cold extremities, poor urine output, and altered mental status. As the pathophysiologic state progresses, pulmonary insufficiency and pulmonary edema ensue. Extrinsic causes of CS most commonly manifest as circulatory collapse secondary to pericardial tamponade. Acute tamponade is easily diagnosed by echocardiography and requires surgical or percutaneous evacuation and subsequent treatment of that which caused the tamponade (e.g., traumatic injury, aortic dissection, ruptured aneurysm). Extrinsic causes of CS usually require immediate surgical intervention but rarely necessitate mechanical assistance. However, intrinsic causes of CS can be refractory to both medical and surgical therapies and may require MCS. Intrinsic causes can be divided into four pathophysiologic classifications: (1) acute valvular insufficiency, (2) AMI, (3) acute myocarditis, and (4) postcardiotomy cardiac failure. Irrespective of the etiology of CS, the approach toward the initial management of patients should be fairly uniform. Irrespective of the etiology of CS, the approach toward the initial management of patients should be fairly uniform. A suggested management algorithm is outlined in Fig. 82.7.

First, insertion of a pulmonary arterial catheter and echocardiography should be done to help formulate a differential diagnosis. Severe valvular insufficiency or a VSD can usually be effectively excluded at this juncture. If severe aortic insufficiency is present, chronotropic control (heart rate 80–100 beats/min) and afterload reduction with inotropic support should be the initial maneuvers. An IABP is contraindicated because aortic regurgitation will worsen; these patients should be prepared for immediate aortic valve replacement. For patients with acute MR or a VSD, an IABP should be placed immediately in conjunction with inotropic support and afterload reduction. Surgical intervention should proceed emergently. Cardiac catheterization is pursued preoperatively to identify coronary lesions that would require CABG or if PCI is more appropriate.

Acute fulminant myocarditis usually presents in a previously healthy individual with no history of cardiac disease. Patients with presumed myocarditis who do not stabilize after the insertion of an IABP and concomitant inotropic infusion should be diverted to further temporary VAD support expeditiously. A remarkable percentage of these patients will recover if adequately supported during the acute phase of this disease. Short-term to intermediate-term VADs are optimal in these patients because of the ease of their insertion and removal and the anticipation for relatively short-term recovery. Giant cell myocarditis is one exception to this rule, because most patients with this diagnosis will require transplantation or durable MCS.[185–187]

AMI requires pharmacologic support along with emergent cardiac catheterization and PCI as indicated. MCS can be rapidly instituted with IABP placement and should be considered in conjunction with PCI. If a mechanical complication (i.e., severe MR or VSD) has occurred, an IABP should be placed without delay. Urgent surgical intervention is usually required for these mechanical complications. The culprit vessel resulting in the AMI is treated immediately with PCI. The number of diseased arteries remaining and the clinical status usually determine subsequent allocation to further PCI or CABG. This can be accomplished several days later, once the myocardium is recovered and the shock state has resolved. Patients who remain in CS after AMI despite PCI, IABP, and inotropic support should be considered for VAD support.

Postcardiotomy CS should be managed intraoperatively with an initial trial of IABP and inotropic support. If there is persistent shock or an inability to be weaned from CPB, VAD implantation is the next therapeutic step, provided a meaningful recovery is predictable or a plan for transplantation or permanent therapy can be clarified. The general recommendation for implantation of a VAD for postcardiotomy failure is within 1 hour of the first failed attempt to wean from CPB.

The mode of MCS used for CS is determined by a number of factors. First is the degree of pulmonary insufficiency. If there is pulmonary

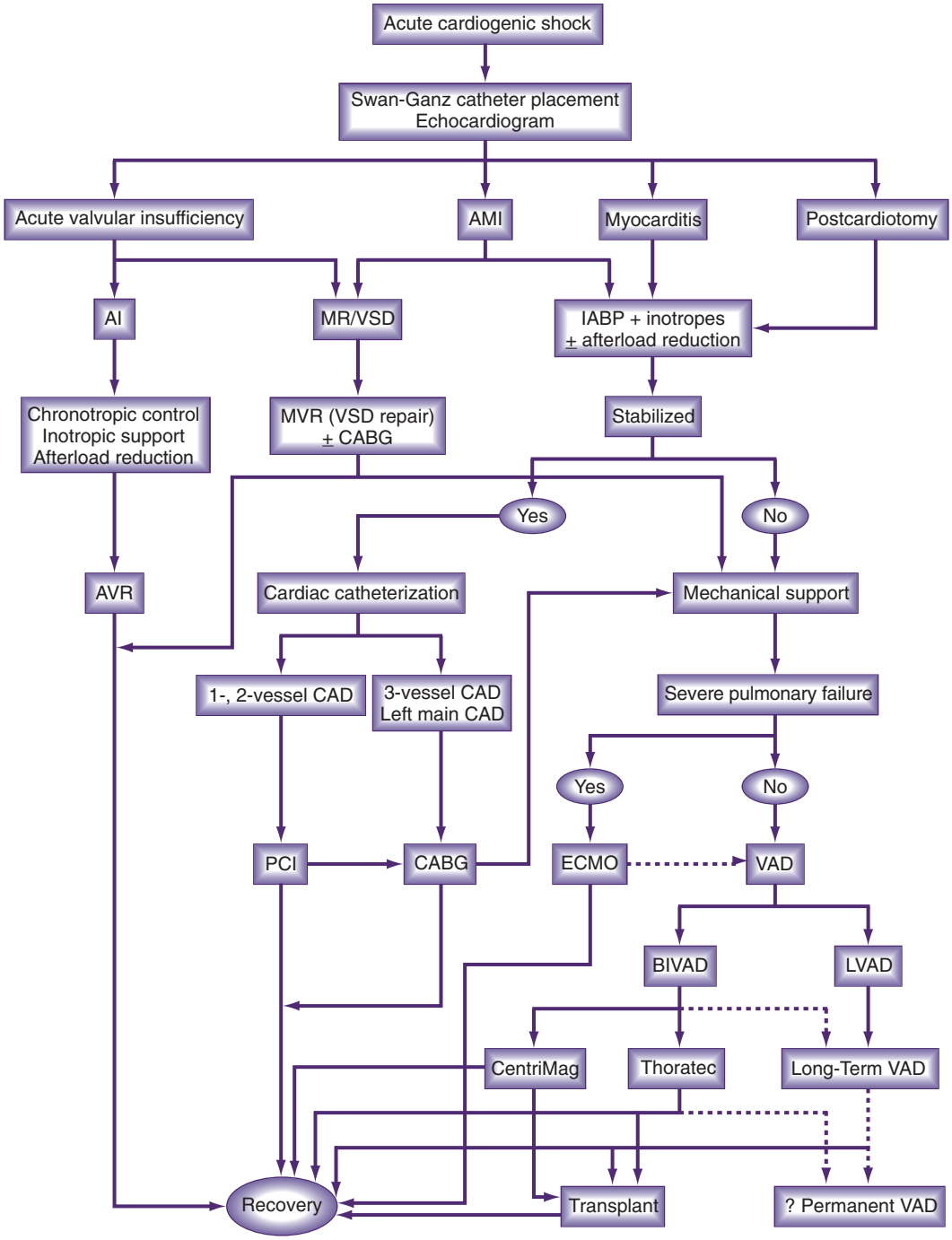


Fig. 82.7 Algorithm for the management of acute cardiogenic shock.

failure with a very large alveolar-to-arterial oxygen gradient on maximal ventilatory support, ECMO support is indicated. A small percentage of ECMO patients in this setting will recover, some will require VAD placement as a BTT, and fewer still will bridge to VAD and then to recovery. If the degree of pulmonary insufficiency is limited to pulmonary edema that is likely to recover with adequate CO, patients should undergo VAD placement directly. The choice of VAD in this situation is also dependent on several factors, including the predicted need for short- or longer-term support, the need for univentricular versus biventricular support, the chance of ventricular recovery, the institutional experience with different devices, device availability, and the relative risks of anticoagulation.[187]

The Levitronix CentriMag system is an attractive option for postcardiotomy cardiac failure in those patients predicted to recover within days to a week of surgery for cases when neurologic function is not known or is markedly compromised but may need a BTR or bridge to a durable device or BTT once stabilized. Both are easy to insert. Therefore in cases of profound CS when operative brevity is paramount, these devices may be beneficial. Additionally, the CentriMag devices allow for arterial cannulation via an inflow graft sewn onto the aorta, which may make conversion to other long-term VAD systems technically easier.

Initial placement of continuous flow VADs (e.g., HeartMate II, Heartmate III or HeartWare HVAD) for MCS in patients with CS is

generally not indicated. These devices may be used as a second bridge ("bridge-to-bridge") toward recovery, BTT, or DT. Typically the only patients with CS who are candidates for direct, durable LVAD placement are those who are more stable without profound end-organ failure, can sustain longer operative times, and are unlikely to achieve myocardial recovery.[188]

OUTCOMES OF CARDIOGENIC SHOCK WITH MCS SUPPORT

As recently as 2017, there were a reported 25,145 adult patients who had undergone MCS implant, with the majority (76.3%) receiving durable, continuous flow LVADs and a minority (2.7%) receiving biventricular support.[189] Although the burden of adverse events remains high for these patients, overall survival at 1 year is >80% and approximately 70% at 2 years.[190] The most commonly encountered adverse events in patients on durable LVAD support, listed in decreasing incidence of hazard, are neurologic dysfunction, multisystem organ failure, infection, device malfunction, and right heart failure.

In adult patients with refractory CS requiring ECMO support, survival to hospital discharge currently ranges from 42% to 66.7%,[191] although patients with chronic renal failure, pre-ECMO end-organ failure, pre-ECMO cardiac arrest, congenital heart disease, lower pulse pressures, and lower serum bicarbonate were at higher risk for mortality.[192] Patients with postcardiotomy CS requiring ECMO have traditionally been poor, with in-hospital mortality rates between 59% and 84%; however, in the modern era, successful weaning from postcardiotomy ECMO has been reported in up to 63.3% of patients, with survival to discharge near 25%.[193]

The evidence surrounding the use of Impella devices is continuing to evolve. A propensity-matched study compared CS patients after an AMI who were supported with an Impella 2.5, Impella CP, IABP or only medical therapy found Impella to be superior to IABP and medical therapy.[194] Furthermore, the IMPRESS (Impella versus IABP Reduces Mortality in STEMI Patients Treated with Primary PCI in Severe Cardiogenic Shock) in Severe Shock trial demonstrated that patients randomized to an Impella CP had similar survival outcomes at 2 years when compared with IABP-supported patients.[195]

HEART TEAM APPROACH TO CS REQUIRING MCS

In the setting of CS, the multidisciplinary heart team, which includes HF cardiologists, interventional cardiologists, HF surgeons, and intensivists, helps evaluate each individual patient and develop a care plan that best suits the individual patient's needs. The hallmarks of a successful heart team approach for CS requiring MCS include early activation, rapid initiation of revascularization and MCS when appropriate, hemodynamic-guided management, and strict protocol adherence.[196] The implementation of a dedicated heart team approach in patients with CS requiring MCS has been shown to improve 30-day survival from 47% to 77%.[197] An example of the heart team approach for CS patients is illustrated in Fig. 82.8.[198] Key aspects include an immediate heart team activation call once CS is suspected. If the patient is within the hospital, they are immediately transferred to the cardiac catheterization laboratory or the cardiac intensive care unit. If the patient is outside of the hospital system, they are emergently transferred by air if available. If the patient is not actively in an arrest situation, hemodynamic, angiographic, and laboratory data are collected and then the decision to pursue MCS is evaluated by the heart team. If an arrest situation is evolving, the heart team will discuss the patient's appropriateness for either ECMO or an alternative percutaneous MCS approach.

CONCLUSION

CS remains a lethal problem with a mortality rate as high as 75%.[3,187,188] Patients who cannot be stabilized with inotropic support and an IABP should be considered for MCS with a VAD. The use of MCS for acute CS has facilitated impressive improvements in survival for certain disease cohorts, such as those with acute myocarditis, with survival rates over 70%.[154] VADs have had less remarkable an impact on patients with postcardiotomy shock or CS after AMI, but results in these patient populations are continuing to improve.[161] Inherent to achieving better results is our understanding that patients who present with CS typically have significant underlying comorbidities with multiple-system organ dysfunction and marked derangements in both coagulation and inflammatory mediators that complicate management. They need to be approached by an integrated multidisciplinary team, including cardiologists, cardiac surgeons, anesthesiologists, critical care specialists, and experienced nursing staff, to implement efficient and decisive treatment plans. These integrated systems offer the greatest chance for salvage.[197,198] The future holds exciting promise with the continued expansion of available devices, both temporary and durable, which will no doubt continue to improve outcomes in this challenging population.

KEY POINTS

- The leading cause of death among hospitalized patients with AMI continues to be CS. Mortality remains high at approximately 40%.
- The hallmarks of CS and low CO are hypotension, peripheral vasoconstriction, cold extremities, poor urine output, and altered mental status.
- Intrinsic causes of CS can be divided into four pathophysiologic classifications: (1) acute valvular insufficiency, (2) AMI, (3) acute myocarditis, and (4) postcardiotomy cardiac failure.
- Echocardiography should be done to help formulate a differential diagnosis, and insertion of a pulmonary artery balloon catheter should be considered.
- CS with AMI requires immediate cardiac catheterization. Concomitant IABP placement or other temporary VAD support may be considered in addition to pharmacologic support for patients with refractory CS.
- Pioneering surgeons recognized by the 1960s that LV decompression and myocardial rest could afford enhanced cardiac recovery.
- The physiologic rationale for the efficacy of the IABP includes (1) LV systolic unloading directly reduces stroke work, which in turn reduces myocardial oxygen consumption during the cardiac cycle, and (2) diastolic augmentation, which raises arterial blood pressure and provides better coronary arterial perfusion during diastole, yielding increased oxygen delivery to the myocardium.
- Relative contraindications to IABP use include severe atheromatous and atherosclerotic descending thoracic aorta, descending aortic aneurysm, recent descending thoracic aortic surgery, and mild to moderate aortic insufficiency.
- Short-term cardiopulmonary support for CS is an important adjunctive therapy. It is a relatively simple means of establishing immediate and complete circulatory support, requiring no additional equipment other than that needed for standard CPB support during cardiac surgery.
- Initial placement of durable VADs for MCS in patients with acute CS is generally not indicated. These devices are best suited as a bridge-to-bridge once the shock state has resolved, often with a temporary MCS device.

References for this chapter can be found at expertconsult.com.

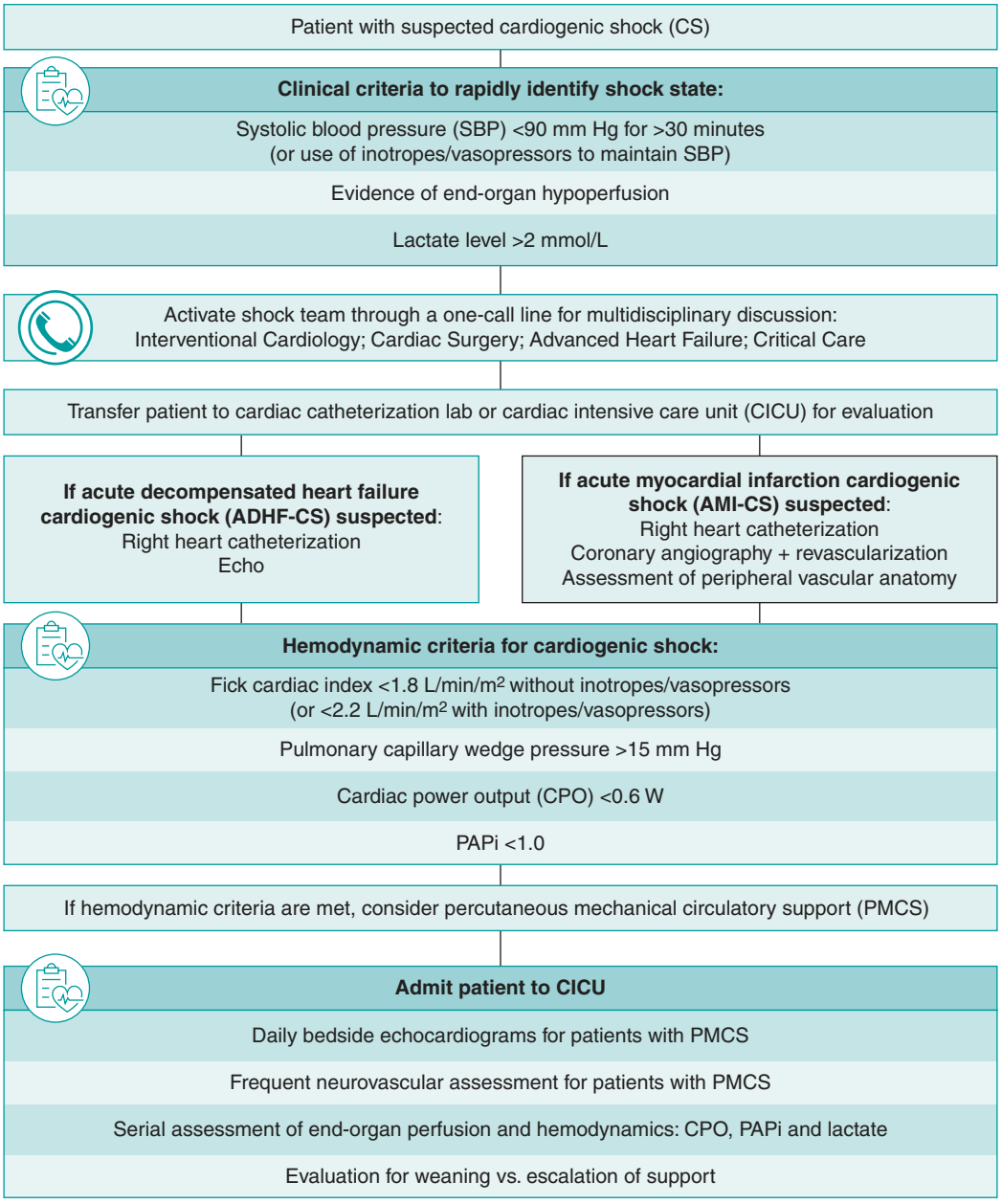


Fig. 82.8 Algorithm for the management from the integration of a multidisciplinary heart team in the management of cardiogenic shock. (From Tehrani BN, Truesdell AG, Sherwood MW, et al. Standardized team-based care for cardiogenic shock. *J Am Coll Cardiol.* 2019;73[13]:1659–1669.)

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Results from this multicenter registry study demonstrated that patients supported with Impella 2.5 devices had improved hemodynamics and reductions in lactate levels, suggesting improved end-organ perfusion. However, the mortality rates of Impella 2.5–supported CS patients remained high at 64.2%. The major complications that were most frequently seen were bleeding, hemolysis, and pericardial tamponade. Age above 65 years and lactate >3.8 mmol/L at admission were identified as predictors of 30-day mortality.

Mehra MR, Uriel N, Naka Y, et al. A fully magnetically levitated left ventricular assist device – Final report. *New Engl J Med.* 2019;380(17):1618–1627.
Results of the MOMENTUM 3 randomized clinical trial demonstrated that patients supported with a HeartMate III centrifugal-flow device, compared with a HeartMate II axial flow device, were less likely to experience disabling strokes or pump thrombosis. Additionally, rates of major bleeding and gastrointestinal bleeding were lower in the HeartMate III group.

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This retrospective analysis evaluated patients with refractory CS who were supported with venoarterial ECMO and found acceptable survival, with 42% alive at hospital discharge. Chronic renal failure, longer durations of pre-ECMO mechanical ventilation, pre-ECMO end-organ failure, cardiac arrest, and congenital heart disease were all risk factors found to be associated with mortality.

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Portal Hypertension: Critical Care Considerations

Paolo Angeli, Marta Tonon, Carmine Gambino, and Alessandra Brocca

THE CHANGE OF A PARADIGM

Portal Hypertension Is Not the Only Driver of Complications of Cirrhosis

Cirrhosis is typically classified as compensated or decompensated, based on the absence or presence (or previous history) of variceal bleeding, ascites, jaundice, or encephalopathy.[1–3] The significantly longer survival—usually symptomless—and better quality of life experienced by patients with compensated cirrhosis compared with those with decompensated cirrhosis have brought about the concept that compensated and decompensated cirrhosis are distinct clinical stages of the disease.[4,5] Further disease stages have been identified according to the presence of esophageal varices and to the presence of only one or more disease complications.[4–10] Four stages were proposed at the Baveno IV Consensus Conference: stage 1, compensated cirrhosis without esophageal varices; stage 2, compensated cirrhosis with varices; stage 3, ascites with or without varices; and stage 4, bleeding with or without ascites. The four stages are characterized by a significant increase in the risk of death.[11] We went on for decades thinking that the only driver in the stage progression of cirrhosis was the progressive increase in portal pressure. In accordance with the theory of splanchnic arterial vasodilation, the progressive impairment of the cardiocirculatory function characterized by arterial vasodilatation and inadequate cardiac output, in addition to the progressive increase in the degree of activation of the endogenous vasoconstrictive and sodium-retaining systems were in fact attributed only to the progressive increase in portal pressure[12,13] (Fig. 83.1). However, today, we can affirm that this is only partially true on the basis of the following, more recent findings.

First, it has not been confirmed in larger cohorts of patients that there is a progressive increase of the grade of activation of the endogenous vasoconstrictive and sodium-retaining systems, at least in the more advanced phases of liver disease.[14] Second, it is possible to reduce significantly the grade of activation of those systems without achieving any clinical result in terms of reduction of the rate of cirrhosis-related complications and/or mortality.[15] Third, during the last 8 years we have learned that another syndrome may develop in any patient with cirrhosis, but particularly in those with decompensated cirrhosis. This syndrome has been called *acute on chronic liver failure* (ACLF)[16]. ACLF is characterized by an acute decompensation (AD) of the liver disease, the development of organ failure, and a 28-day mortality rate >15%. ACLF can develop even in the presence of a normal grade of activation of the endogenous vasoconstrictive and sodium-retaining systems, but never without an increased plasma level of proinflammatory cytokines in absence of systemic inflammation (SI).[17] Taking into account that SI precedes the development of a clinically overt ascites[18] and organ failure[19] and that there is a strong relationship between its grade and both the stage progression of cirrhosis[20] and the severity of ACLF,[16] SI should be considered as another driver of decompensation in patients with cirrhosis.[19] There is some evidence that an SI-related oxidative stress (OS) can be another potential driver of decompensation in these patients.[17] How can we put together these three drivers of decompensation? By proposing a new pathophysiologic theory.[14] We have recently proposed a new theory according to which the main consequence of portal hypertension is thought to be bacterial translocation (BT). BT is the main cause of SI and OS, which, in turn, are the main drivers of the derangement of the cardiovascular function and of the consequent reduction of the effective circulating volume. All these factors together are responsible for the onset of ascites and for other major complications of cirrhosis. In addition, SI and OS can generate a vicious circle whose consequence is a sequential chain of related events, including a further increase in portal pressure and/or in the severity of liver failure and thus in the extent of BT. Thus the final ring of this chain is a further increase in the degree of SI and OS. This may be the most credible, plausible, and acceptable explanation for the possibility of the onset of organ failure in patients with cirrhosis when a precipitating event cannot be detected (Fig. 83.2).[14] In an attempt to quantify, if possible, the relative weight of individual heart failure drivers in the various stages of cirrhosis, it has recently been observed that progression of portal pressure occurs mostly in patients with compensated cirrhosis, whereas SI increases substantially only across the different stages of decompensated cirrhosis.[21] The mechanisms of the effect of SI and OS on organ integrity and function are beyond the aim of this chapter; however they are several and not mutually exclusive. The first mechanism is quite obvious and is an increase in the nitric oxide–mediated vasodilatory effect on arterial splanchnic circulation, resulting in overactivation of the endogenous vasoconstrictor systems, which elicit intense vasoconstriction and hypoperfusion of some organs, in particular, the kidney. The second mechanism is immunopathology, which is an immune-mediated tissue damage that is extremely variable in terms of pathways and impact on the different organs. The third mechanism is related to the relative storage of essential nutrients in several organs because of the fact that SI is energetically quite an expensive process, requiring reallocation of nutrients to fuel immuneactivation.[22]

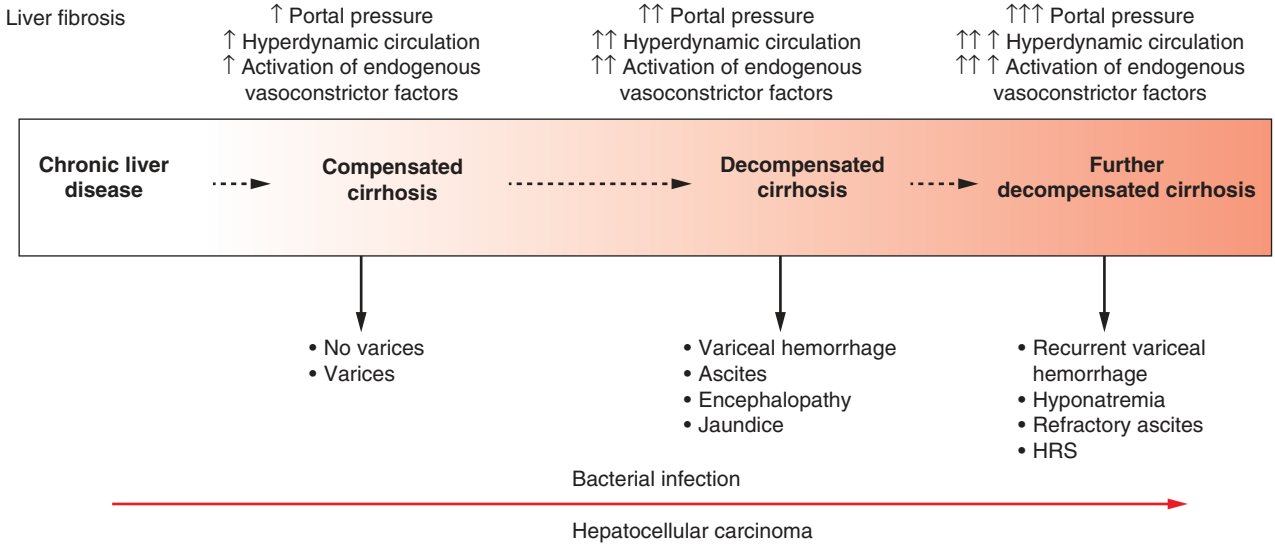

Fig. 83.1 Traditional view of the pathophysiology of the development of decompensation and organ failure in patients with cirrhosis. (Adapted from Albillos A, Garcia-Tsao G. Classification of cirrhosis: The clinical use of HVPG measurements. *Dis Markers*. 2011;31:121–128.)

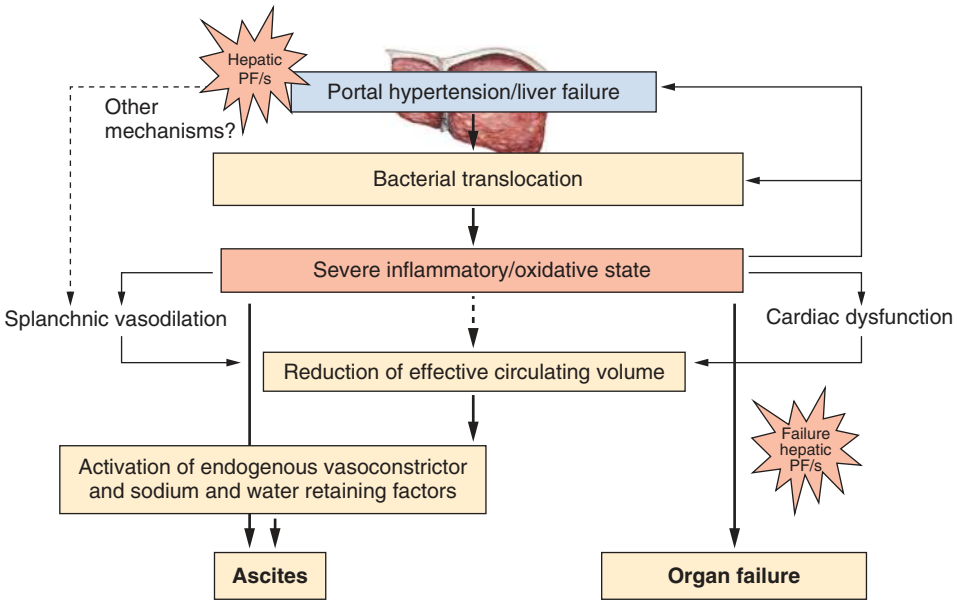

Fig. 83.2 The new systemic inflammation hypothesis on the development of decompensation and organ failure in patients with cirrhosis. Abnormal gut translocation of bacteria and bacterial products induced by portal hypertension and/or liver failure is responsible for systemic inflammation (SI) and oxidative stress (OS). Proinflammatory cytokines and oxidative/nitrosative stress impair effective hypovolemia by enhancing arterial vasodilation, mainly mediated by nitric oxide (NO), and preventing cardiac output to fulfill the needs of the peripheral circulation. SI and OS generate a vicious circle, which is responsible for a progressive increase in the degree of portal pressure and/or the severity of liver failure and of the same intensity of SI and OS. Thus at any time along the course of the liver disease, organ failure can develop, with or without the occurrence of hepatic or extrahepatic precipitating factors (PFs). (Adapted from Bernardi M, Moreau R, Angeli P, et al. Mechanisms of decompensation and organ failure in cirrhosis: From peripheral arterial vasodilation to systemic inflammation hypothesis. *J Hepatol*. 2015;63:1272–1284.)

A New Vision on the Dynamics and Classification of Decompensation in Patients With Cirrhosis

AD has been defined as "the acute development of large ascites, hepatic encephalopathy, gastrointestinal hemorrhage, bacterial infection, or any combination of these requiring an emergent hospitalization."[16] However, the majority of patients with cirrhosis may develop progressive ascites or mild to moderate hepatic encephalopathy (HE) without requiring hospitalization at the first stage of decompensation. This pathway of decompensation can be defined as nonacute decompensation (NAD), and it often precedes AD. Thus focusing on ascites, we

should outline that, in keeping with the new pathophysiologic theory, SI is already present in patients with grade 1 ascites, which is defined as an ascites that can be detected only by abdominal ultrasonography[19] and that ascites of any grade, together with a high Model for End-Stage Liver Disease (MELD) score, a low mean arterial pressure (MAP), and the presence of anemia, is a predictive factor in the development of organ failure and ACLF.[23] Thus we can state that NAD and AD represent the two main ways of transitioning from compensated to decompensated cirrhosis in clinical practice. Patients with NAD may then develop one or more episodes of AD, and when this happens, the subsequent evolution of the liver disease can follow three main trajectories.[24] They may develop ACLF, unstable decompensated cirrhosis (UDC), or stable decompensated cirrhosis (SDC). Patients who develop ACLF have 3-month and 1-year mortality rates of 53.7% and 67.4%, respectively. Those who develop UDC, defined by the absence of organ failure but with a need of at least one hospital readmission during the following 3 months, have a 3-month and 1-year mortality of 21.0% and 35.6%, respectively. Patients with SDC, defined by the absence of both the development of ACLF and the need for hospital readmission during the 3 months after AD, have a 1-year mortality of 9.5%.[24] Therefore this new vision of the dynamics and classification of decompensation can be summarized as shown in Fig. 83.3. Several aspects of decompensation should be further investigated, and thus the new vision is certainly new but also equally certainly partial. In fact, the temporal relationship of the sequence from NAD to AD and the long-term outcome of patients with ACLF, UDC, and SDC are not known. In addition, we do not know the outcome of patients recovering from decompensation. We need a consensus definition on how to define recompensation. It would probably require a symptom-free interval from the previous decompensation and the ability to maintain this stage without treatment. However, this can sometimes occur as a result of effective antiviral treatment in cirrhosis patients with hepatitis B virus (HBV)[25] or hepatitis C virus (HCV)[26] and of abstinence in those with alcohol-related cirrhosis.[27] If recompensation is not taken for granted for etiologic treatments, it is not even expected as a result of disease-modifying agents such as long-term use of human albumin, beta-blockers, and/or statins when exposure to the etiologic agent is still ongoing. However, these treatments may prevent further episodes of decompensation.[28,29]

SOME NEW ACHIEVEMENTS IN THE MANAGEMENT OF COMPLICATIONS OF CIRRHOSIS

Management of Grade 1 Ascites

As previously mentioned, grade 1 ascites has been defined as an ascites that can be detected only by abdominal ultrasonography. For more than 30 years, it has been stated that grade 1 ascites should not be treated by medical therapy (i.e., dietary sodium restriction and/or diuretics). However, this statement was entirely anecdotal and not based on evidence because nothing was known about the clinical course of patients with grade 1 ascites. We have recently proved its correctness because it has been observed that these patients do not have a higher probability of developing an overt ascites than those without any evidence of ascites on ultrasonography. Nonetheless, patients with grade 1 ascites have a higher risk of developing ACLF and dying than those without ascites, and consequently, they should be followed more closely.[19]

The Long-Term Use of Human Albumin Solution in the Treatment of Ascites

An albumin molecule has several biologic properties, oncotic and nononcotic. Albumin represents approximately 75% of plasma oncotic pressure. A large body of evidence exists for its use as a plasma expander in patients with cirrhosis. But with regard to the nononcotic properties, it has been proven that in an experimental model of decompensated cirrhosis, albumin was capable of reducing OS, SI, and inflammation in the cardiac tissue, restoring cardiac contractility. More recently, it has been shown that albumin also attenuates SI even in patients with decompensated cirrhosis. Notably, recent in vitro studies attribute the antiinflammatory properties of albumin to its uptake by immune cells by blocking the endosomal toll-like receptor (TLR) signaling. Thus the long-term use of human albumin solution (HAS) can represent a therapeutic approach in patients with cirrhosis potentially capable of interrupting the pathophysiologic cascade responsible for decompensation. For example, in the ANSWER trial, a nonprofit, multicenter, randomized, open-label study, it was proven that in patients with responsive ascites on diuretic treatment, the long-term administration of HAS on top of the standard medical treatment (SMT) was associated with a significantly better 18-month overall survival as compared with those receiving only the SMT. Furthermore, the cumulative incidence of complications of cirrhosis, including spontaneous bacterial peritonitis (SBP), non-SBP infections, episodes of impairment of renal function, grade III and IV HE, and potential diuretic-induced side effects, was significantly reduced in the group receiving HAS.[28]

The core results of the ANSWER trial were confirmed by a prospective, nonrandomized study that enrolled 70 patients with cirrhosis and refractory ascites. Patients who received SMT + albumin (20 g twice a week) had a significantly lower 24-month mortality than those receiving SMT. Treatment with albumin was the sole independent protective factor against death and was associated with a lower cumulative incidence of rehospitalizations because of any complication of cirrhosis with the exception of gastrointestinal (GI) bleeding.[30]

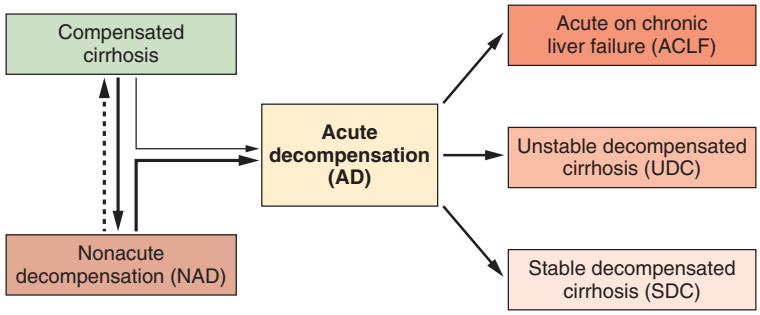

Fig. 83.3 A new vision of the dynamics, classification, and trajectories of decompensation in patients with cirrhosis. AD develops in almost one-third of the cases in patients with compensated cirrhosis and in two-thirds of the cases in patients who have already developed NAD. The dotted line indicates the possibility of recompensation. *AD,* Acute decompensation; *NAD,* nonacute decompensation.

The results of these studies were not confirmed by the MACHT study, which was performed in patients with ascites listed for liver transplantation (LT). Instead, it challenges these results. In this clinical trial, patients were randomized to receive SMT plus 40 g of albumin every 15 days and the alpha-1-receptor agonist midodrine or SMT + placebos. Despite a mild improvement in effective hypovolemia, no difference was observed in either the probability of developing complications or death.[15] The most relevant difference between the ANSWER and MACTH trials is the fact that the amount of albumin administered in the MACHT trial was about half of that administered in the ANSWER trial, so no effect on serum albumin concentration was seen in the MACHT study, whereas a significant and sustained increase by 0.6–0.8 g/L to a median value close to 4 g/dL occurred in the ANSWER study. Interestingly, preliminary results from a post hoc analysis of the ANSWER database showed that the level of serum albumin concentration reached after 1 month of treatment predicts the probability of 18-month overall survival, which was greater than 90% in those patients presenting a level of 4 g/dL. The importance of increasing the serum albumin levels beyond a certain point to obtain the maximal effect of albumin treatment was confirmed by two recent studies.[31,32] In particular, the Spanish study demonstrated that a steady suppression of plasma renin activity and a significant reduction of systemic inflammation were achieved in patients with decompensated cirrhosis receiving high doses (1.5 g/kg per body weight every week) but not low doses (1 g/kg per body weight every 10 days) of albumin.[31] Interestingly, only high doses of albumin were able to normalize serum albumin concentrations.

The Preemptive Use of TIPS in the Treatment of Ascites

Most of the data that compare the effect of a transjugular portosystemic shunt (TIPS) with repeated large-volume paracentesis (LVP) plus albumin have been obtained in the "era" of bare stents in a mixed population of patients with refractory or recurrent ascites.[33–38] Seven different meta-analyses of these studies have been performed,[39–45] but the only definitive and shared conclusion was that TIPS assures better control of ascites but increases the risk of encephalopathy. An advantage in terms of transplant-free survival was evident in only one meta-analysis and seemed more evident in patients with recurrent ascites. In a more recent randomized controlled trial (RCT), the use of a small-diameter covered TIPS in patients with recurrent ascites was associated with better control of ascites and an increased rate of transplant-free survival without any increased risk of developing HE.[46] These results have opened the discussion on the opportunity to anticipate the preemptive use of TIPS before ascites becomes refractory, following the same path used in the treatment of variceal bleeding.[47,48] Accordingly, several experts have mentioned the need to introduce a new diagnostic category (i.e., "difficult-to-treat ascites" or "recurrent ascites"), without almost anyone noticing that a definition of "recurrent ascites" was proposed by International Club of Ascites (ICA) in 1986,[49] in addition to the fact that it has been recently reproposed by the European Association for the Study of the Liver (EASL) clinical practice guidelines (CPGs) on the management of decompensated cirrhosis.[50] According to that definition, recurrent ascites is defined by three episodes of grade 3 ascites during 12 months. By applying this definition, it has recently been observed that recurrent ascites has the same mortality rate as responsive ascites, which is quite lower than that of refractory ascites. This should be taken into account in patients with recurrent ascites when planning the use of TIPS.[19] In the same way, contraindications to the placement of TIPS must be defined. In fact, accurate and reliable indicators predictive of the therapeutic advantage or failure of TIPS are still missing. Patients with severe liver failure have not been included in RCTs. However, the severity of liver failure has arbitrarily been qualified using different parameters and related cutoffs (Child-Pugh score >11, serum bilirubin >5 mg/dL, international normalization ratio [INR] >2). Likewise, a cutoff of serum creatinine >3 mg/dL was used in the RCTs to exclude patients with kidney failure, but without taking into account the nature and the clinical course of this complication. Finally, the impact of other complications such as sarcopenia or syndromes such as ACLF has not been evaluated.

Other Options for the Treatment of Refractory Ascites

Although contraindications to the placement of TIPS should be defined, several patients with cirrhosis and refractory ascites simply are not a candidate for TIPS. What can we offer these patients for a better management of ascites beyond LVP? The automated low-flow pump system (Alfapump) has recently emerged as a potential treatment for refractory ascites in cirrhotic patients. In a small RCT comparing Alfapump with LVP plus albumin infusion in the setting of refractory ascites, Alfapump significantly reduced the need for paracentesis[51] and improved the quality of life[52] in just 6 months. However, patients with the implant had a high risk of renal dysfunction and often needed a reintervention because of technical issues or infections.[51,53,54] Thus after improving both the techniques and the procedure, another RCT was begun. In the near future it will be possible to evaluate the potential role of Alfapump in the management of ascites in patients with cirrhosis.

SOME STILL UNMET OR NEW AIMS IN THE MANAGEMENT OF COMPLICATIONS

Noninvasive Monitoring of the Effect of Nonselective Beta-Blockers

The discovery of the lowering effect on portal pressure of nonselective beta-blockers (NSBBs) represents one of the most important achievements of hepatology research in the last 50 years.[55] The use of NSBBs in the primary and secondary prevention of variceal bleeding has dramatically reduced the rate of this complication and of related mortality in patients with cirrhosis. However, despite all the research done, a noninvasive parameter has not been identified yet to evaluate its effect and therefore to identify patient responders, and even today, the measurement of the hepatic venous pressure gradient (HVPG) represents the only reliable tool in this context.[56] However, it was claimed in the Baveno VI Consensus workshop that the decision to treat with NSBBs should be taken into account when indicated, independent of the possibility to measure HVPG.[56] In the era of precision medicine and/or personalized medicine, this represents a huge vulnerability for their use in clinical practice, in the sense that, in the real world, NSBBs are in fact prescribed without monitoring their effect on portal pressure. Thus in order to follow the current CPGs, what should we do in clinical practice in a patient with cirrhosis who needs NSBBs? Should we prescribe NSBBs and then wait and see if an episode of variceal bleeding occurs or not? Should we wait for an episode of variceal bleeding in order to identify a patient as a nonresponder to NSBBs and thus to change the prophylactic strategy? This would be certainly respectful of the CPGs, but it is unacceptable in clinical practice to such an extent that we want to relate an anecdote. During a recent meeting of the panelists of the GPGs of the Italian Association for the Study of the Liver on the management of portal hypertension, the following request was raised: "Please raise your hand who would monitor a patient with esophageal varices on prophylaxis with NSBBs with an annual upper endoscopy?" All raised their hands. Of course we understand that the strategy of repeating an upper endoscopy every year is not well accepted by patients—it has some potential biases related to interobserver and intraobserver variability and should also be proven to be

cost-effective. Nevertheless, we have some preliminary and still unpublished data showing that this strategy in patients on prophylaxis with NSBBs can reduce the rate of bleeding and the rate of mortality.[57] All this, however, means that in clinical practice, we are deviating from the CPGs, and this is not good for knowledge and science. Therefore the search for a noninvasive, instrumental, or metabolomic tool to monitor the effect on portal pressure of NSBBs represents, in our opinion, an urgent scientific need.

Preventing Bacterial Infections in Patients With Cirrhosis

For many years debate and research on the prevention of infections in patients with cirrhosis have been developed only in reference to a specific type of infection: SBP.[58] This seems today only a partial view of the problem of infections of those patients in light of at least two main considerations: (1) other types of infection besides SBP are extremely dangerous in patients with cirrhosis, particularly when severe, nosocomial, or sustained by multidrug-resistant (MDR) or extensively drug-resistant (XDR) agents, and (2) all types of infections can be complicated by the appearance of organ failure and therefore can precipitate or complicate ACLF. To support the first statement, it is sufficient to consider new epidemiologic data[59] in addition to the fact that the rate of mortality from cirrhosis has decreased over the years for all its major complications with only one exception, sepsis.[60] Regarding the second option, it should be remembered that ACLF is precipitated in about 44% of cases by a bacterial infection[61] or, conversely, that 40%–60% of bacterial infections in cirrhotic patients were complicated by an ACLF with relevant geographic discrepancies.[59] Finally, almost 45%–50% of patients who developed an ACLF not related to a bacterial infection developed bacterial infections during follow-up.[62] Thus the potential candidates for the prevention of infections among patients with cirrhosis should include not only those who experience an episode of SBP or those who are at risk for developing a first episode of SBP but all patients at risk for developing a bacterial infection, all those with AD, and all those with ACLF when not precipitated by a bacterial infection.

Quinolones,[63] and more frequently norfloxacin, have traditionally been used in the primary and secondary prophylaxis of SBP in patients with cirrhosis.[58] In spite of a recent Cochrane meta-analysis,[64] its efficacy has been demonstrated in some RCTs and meta-analyses.[58,65–68] However, some concerns still exist on their use in these patients. First, there is an increasing rate of strains of gram-negative bacteria that are resistant to fluoroquinolones. In fact, their broad spectrum of activity, combined with the high frequency of mutations in the target bacterial enzymes, led to a change in the microbiota of cirrhotic patients with a high prevalence of gram-positive bacteria and extended-spectrum beta-lactamase–producing Enterobacteriaceae.[69] Second, another important point is related to the growing concerns about the fluoroquinolone safety profile. On November 16 2018, the European Medicines Agency released a review on quinolone and fluoroquinolone antibiotics, recommending a restriction in the use of these drugs owing to the possible long-lasting, disabling, and potentially permanent side effects involving tendons, muscles, joints, and the nervous system.[70] In 2016 the Food and Drug Administration coined the term *fluoroquinolone-associated disability* to describe the syndrome related to fluoroquinolone exposure.[7] Moreover, recently published works have shown an increased incidence of aortic aneurysm or dissection in association with the use of oral fluoroquinolone.[71] Taken together, all these data suggest that we have to rethink the use of quinolones and fluoroquinolones for the prevention of infections, including SBP, in patients with cirrhosis. With regard to considering alternative/new antibiotic regimens, a small RCT failed to demonstrate a difference between norfloxacin and trimethoprim-sulfamethoxazole in their effects on preventing infections in patients with liver cirrhosis.[72] Experimental and clinical data showed that rifaximin has a broad-spectrum antibacterial action covering gram-positive and gram-negative aerobic and anaerobic bacteria. Rifaximin has also the advantage of changing the gut microbiome in a limited way, thus inducing a low microbial resistance and also the advantage of having few systemic adverse effects. In addition, rifaximin, with its peculiar pharmacokinetic properties that limit the systemic values of the drug, and thus the side effects, is a promising alternative.[73] Many patients receive rifaximin to prevent recurrent episodes of HE, and rifaximin may also be effective in the prevention of SBP.[73–75] However, large and well-conducted RCTs are needed to establish the efficacy and safety of rifaximin compared with systemic antibiotics for infection prophylaxis in patients with cirrhosis and particularly in those with AD or ACLF.

It is very clear that the main and urgent aim of research in this field is to provide the possibility of a nonantibiotic strategy to prevent bacterial infections in these patients. Thus we are looking forward with great interest to the development of new molecules such as Carbalive, a macroporous carbon of tailored porosity that has a special physical structure that adsorbs both large and small molecules in the gut. Up to now, Carbalive was found to be safe, based on detailed clinical and biochemical assessments compared with placebo. In addition, it was well tolerated with a compliance rate of more than 90%. Preliminary data are quite promising because they showed trends in the improvement of a wide range of biomarkers of systemic inflammation, which is especially notable because Carbalive is not systemically absorbed.[75]

Treating Patients With Acute on Chronic Liver Failure

The short-term prognosis of cirrhotic patients with persistent ACLF 2–3 days after its onset and two or three organs failing is extremely poor. Mortality correlates with the number of organs failing, defined by the chronic liver failure (CLIF) sequential organ failure assessment score and based on the CLIF organ failure scoring system, reaching more than 80% at 30 days in patients with three organs failing. Highly intensive medical treatment and early LT are the only therapeutical options in these patients. However, some aspects of this approach are still controversial and deserve to be discussed. The first is the application of unrestricted intensive care unit (ICU) support, and the second is the feasibility, adequacy, and applicability of an early LT in patients with grade 3 ACLF. Cirrhotic patients with organ failure admitted to the ICU have a mortality rate, ranging from 36% to 89%, depending on the type and number of organ failures.[76–78] These high mortality rates commonly affect the decision not to admit these patients to the ICU, especially when they are not regarded as eligible candidates for LT because of a perception of futility. Notwithstanding that the decision to admit a patient to the ICU is always the result of a multidisciplinary discussion and has to be done on a case-by-case basis, it is beyond question that in some cases there has been—and was particularly during the COVID pandemic—a certain reluctance to give this possibility to patients with ACLF. This is not justified, as a general attitude, by the data available today. A recent study showed that the ICU course and outcome are not different when patients with ACLF are compared with other ICU patients when matched for severity of illness, suggesting that ACLF deserves the same ICU care given to other ICU populations.[79]

In terms of specific therapeutical options in patients with ACLF, it is relevant to underscore, beyond the need for an adequate prevention or treatment of bacterial infections, one aspect related to the treatment of hepatic renal syndrome/acute kidney injury (HRS/AKI). It is well known that according to the algorithm for the management of AKI proposed by the International Club of Ascites in 2015 (Fig. 83.4), once the diagnosis of HRS/AKI stage >1A has been made, patients should

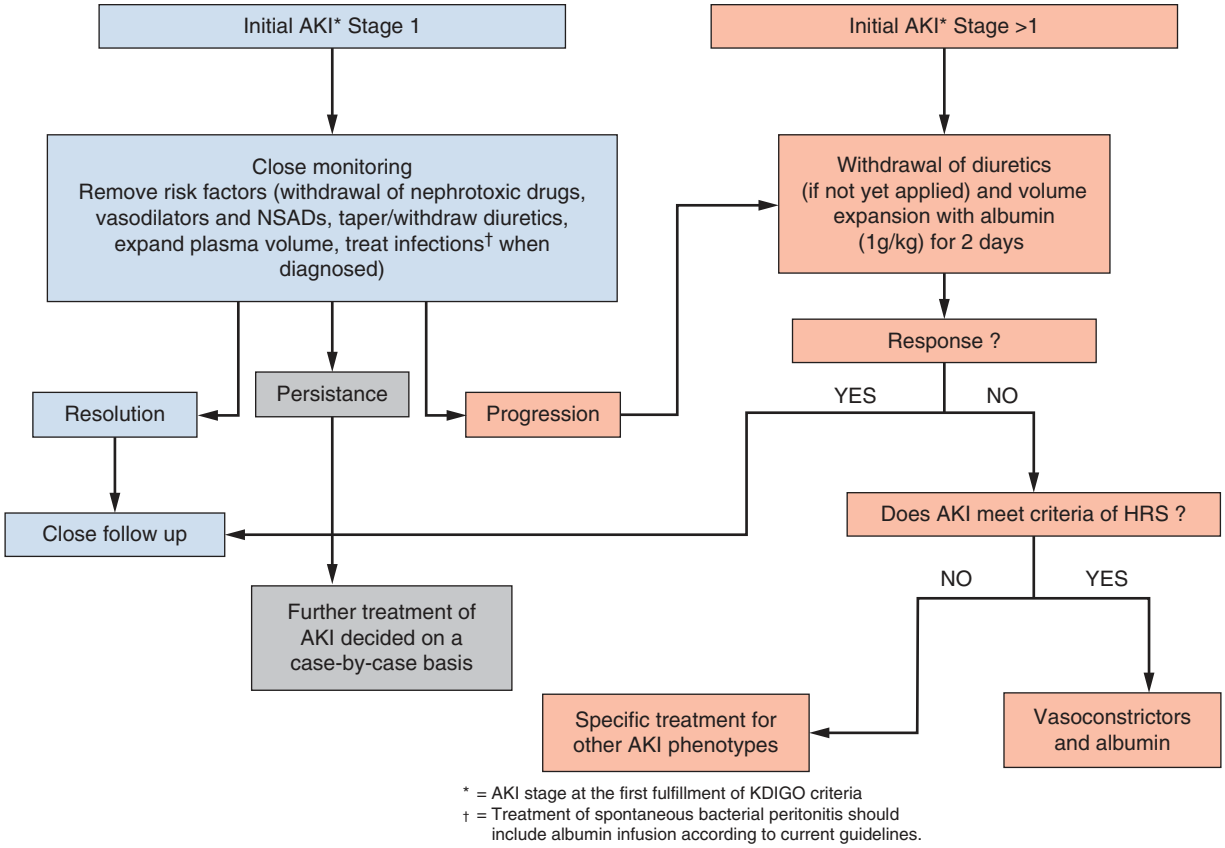

Fig. 83.4 Algorithm for the management of acute kidney injury (AKI) in patients with cirrhosis. (From Angeli P, Gines P, Wong F, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: Revised consensus recommendations of the International Club of Ascites. *J Hepatol.* 2015;62:968–974.)

promptly receive vasoconstrictive drugs in association with albumin.[80] The rationale for using vasoconstrictors is to counteract the splanchnic arterial vasodilation, thus improving renal perfusion. Terlipressin plus albumin is the first therapeutic option.[81,82] Terlipressin was initially proposed to be given by intravenous boluses at the initial dose of 1 mg every 4–6 hours. However, it was also observed that when terlipressin is given by continuous intravenous infusion at the initial dose of 2 mg/day, it is possible to reduce the total daily dose of the drug and thus the rate of its adverse effects.[83] In case of nonresponse, defined by a decrease in sCr <25% from its peak value within 2 days, the dose of terlipressin should be progressively increased up to a maximum of 12 mg/day. It should be highlighted that the rate of response in patients with ACLF progressively declines moving from those with ACLF grade 1 to those with ACLF grade 3.[84] Noradrenaline is an alternative to terlipressin.[85,86] However, noradrenaline is less effective than terlipressin in patients with HRS/AKI and in patients with ACLF.[87] Both of these observations can be explained by the fact that terlipressin, rather than noradrenalin, is capable of exerting a certain but weak inhibitory effect on inducible nitric oxide synthases and thus reducing the damage related to SI.[88]

With regard to early LT in patients with ACLF grade 3, recent studies suggest that LT is feasible and associated with a clear survival benefit. In particular, we have shown that the 180-day probability of survival of patients with persistent ACLF grade 2 or 3 after 3–7 days from its onset who undergo LT within the 28-day follow-up, was 80.9%, whereas it was only 10% in those who were not transplanted.[89] These results were substantially supported by a French retrospective study, showing that 1-year survival of transplanted patients with ACLF grade 3 was higher than that of nontransplanted controls: 83.9 vs. 7.9%, and not different from that of matched control patients with no ACLF (90%), ACLF grade 1 (82.3%), or ACLF grade 2 (86.2%).[90] All the same, the authors introduced the concept of a "transplantation window" in the debate, showing that a higher rate of complications was observed in patients with ACLF grade 3 at the time of LT (100% vs. 51.2% vs. 76.5% vs. 74.3%, respectively), with a longer hospital stay. The debate has been further fueled by another retrospective study showing that the 90-day and 1-year survival probability in patients with ACLF grade 1 or 2 were 84.5% and 77.2%, respectively, whereas they were 60% and 43.3%, respectively, in patients with ACLF grade 3 and that the presence of ACLF was among the six independent predictors of 90-day mortality after LT together with age, gender, primary diagnosis at listing (end-stage liver disease or hepatocellular carcinoma), and infection during the month prior to LT.[91] The authors also introduced the concept of "potentially inappropriate LT," referring to potential candidates who have a high risk of not surviving LT during the early postoperative period (i.e., 3 months).[92] The debate that follows tries to address this main question: What compromises the outcome of transplantation in patients with ACLF: the number of organs failing and/or the type of organs failing? One of the largest retrospective studies, published by Thuluvath and colleagues, showed that the number of organ failures and the type of organ failures had only a minimal impact on survival after LT and that only mechanical ventilation was identified as an independent negative predictor of survival post-LT.[93] These results were confirmed by Sundaram and colleagues, who showed that mechanical ventilation at LT, donor risk index above 1.7, and LT within 30 days of listing were independently associated

with 1-year survival after LT in patients with ACLF grade 3.[94] Considering the rationing of organs because of shortages, well-designed prospective studies are needed to assess the impact of recipient and donor characteristics on outcome and to define the protocol for quick pre-LT assessment, along with objective criteria for listing and delisting rules in patients with ACLF-3 and multiorgan failure. Nonetheless, there is even a more urgent need, which is to develop a new score in order to prioritize candidates with ACLF on the waiting list because it has been clearly demonstrated that MELD or MELD Na are completely inadequate and should not be used. It has also been proven that their application is associated with a higher rate of death or removal from the waiting list in patients with ACLF than in those without ACLF, a result that cannot be accepted from an ethical point of view.[94,95] Thus further prospective studies are urgently needed to evaluate the optimum timing and selection and prioritization criteria for LT in cirrhotic patients with ACLF.

KEY POINTS

- SI and OS act synergistically with portal hypertension in the pathophysiology of decompensation and organ failure in patients with cirrhosis.
- The clinical course of cirrhosis can be characterized by NAD and/or AD.
- After an episode of AD, patients with cirrhosis can follow three different trajectories: they can develop ACLF, UDC, or SDC.
- The long-term infusion of HAS can reduce the rate of complications and mortality in patients with responsive ascites and in those with refractory ascites.
- The placement of a small-diameter covered TIPS can improve the control of ascites and survival in patients with recurrent ascites.

References for this chapter can be found at expertconsult.com.

ANNOTATED REFERENCES

Arroyo V, Angeli P, Moreau R, et al. The systemic inflammation hypothesis: Towards a new paradigm of acute decompensation and multiorgan failure in cirrhosis. J Hepatol. 2021 Mar;74(3):670–685. doi: 10.1016/j.jhep.2020.11.04.
The authors discuss the systemic inflammation hypothesis in detail, suggesting that systemic inflammation acts synergistically with the traditional mechanisms involved in the development of AD. In particular, the authors highlight that systemic inflammation may impair organ system function through different mechanisms, which are not mutually exclusive. The first mechanism is a nitric oxide–mediated accentuation of the preexisting splanchnic vasodilation resulting in the overactivation of the endogenous vasoconstrictor systems, which induces hypoperfusion in vascular beds of different organs, particularly the kidney. Second, systemic inflammation may cause immune-mediated tissue damage, a process that is called immunopathology. Third, systemic inflammation may induce important metabolic changes.

Bernardi M, Moreau R, Angeli P, et al. Mechanisms of decompensation and organ failure in cirrhosis: From peripheral arterial vasodilation to systemic inflammation hypothesis. *J Hepatol* 2015;63:1272–1284.
The authors introduce the systemic inflammation hypothesis of decompensation in patients with cirrhosis. Accordingly, they propose that bacterial translocation progressively affects the natural course of cirrhosis, from the preascitic compensated stage to advanced decompensation and hepatorenal syndrome. An abrupt increase in systemic inflammation represents the pathophysiologic background for ACLF. As with any hypothesis, many, but not all, concepts are demonstrated, and future research on these matters is warranted.

Bureau C, Thabut D, Oberti F, et al. Transjugular intrahepatic portosystemic shunts with covered stents increase transplant-free survival of patients with cirrhosis and recurrent ascites. *Gastroenterology.* 2017;152:157–163.
In this randomized trial, the authors show that covered stents for TIPS can increase the proportion of patients with cirrhosis and recurrent ascites who survive transplantation-free for 1 year, compared with patients given repeated large-volume paracentesis plus albumin. These findings support TIPS as the first-line intervention in such patients.

Caraceni P, Riggio O, Angeli P, et al. Long-term albumin administration in decompensated cirrhosis (ANSWER): An open-label randomised trial. *Lancet.* 2018;391:2417–2429.
In this randomized multicenter trial, long-term HA administration prolongs overall survival and might act as a disease-modifying treatment in patients with decompensated cirrhosis.

Moreau R, Jalan R, Gines P, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology.* 2013;144:1426–1437.
The authors introduce the definition of AD, organ failure, and ACLF. They analyze data from patients with cirrhosis and AD to establish diagnostic criteria for ACLF and showed that it is distinct from AD, based not only on the presence of organ failure and a high mortality rate but also on age, precipitating events, and systemic inflammation. ACLF mortality is associated with loss of organ function and high leukocyte counts. ACLF is especially severe in patients with no prior history of AD.
In this study the authors show that grade 1 ascites is associated with systemic inflammation and that systemic inflammation progressively increases in those with grade 2 or 3 ascites, particularly when they fit the criteria for recurrent of refractory ascites. In addition, the authors show that patients with grade 1 ascites do not develop grade 2 or 3 ascites more frequently than patients without any evidence of ascites but develop more frequently other complications, including ACLF, and have a higher mortality rate. The authors also show that the mortality rate does not differ significantly between patients with recurrent ascites vs. ascites responsive to medical treatment.

Piano S, Tonon M, Vettore E, et al. Incidence, predictors and outcomes of acute-on-chronic liver failure in outpatients with cirrhosis. *J Hepatol* 2017;67:1177–1184.
In this study, the authors identify four simple predictors of ACLF: MELD score, ascites, mean arterial pressure, and hemoglobin. These variables may help to identify patients with cirrhosis at a high risk of developing ACLF that are candidates for new strategies of surveillance and prevention.

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84

Hepatorenal Syndrome

Brent Ershoff, Colby Tanner, and Anahat Dhillon

An association between advanced liver disease, ascites, and renal failure described in 1861 was named *hepatorenal syndrome* (HRS) by Helvig and Schutz in 1932.[1] Until recently, HRS has been thought of as a purely functional form of renal failure without renal histologic changes.[2] HRS is characterized by intense renal vasoconstriction, impaired renal perfusion, and low glomerular filtration rate (GFR) in the setting of splanchnic and systemic vasodilation.[3] Among individuals with advanced cirrhosis, the incidence of HRS is 18% within 1 year and up to 40% at 5 years.[4,5] The variability in the incidence is related to the degree of liver dysfunction, with higher Model for End-stage Liver Disease (MELD) scores portending an increased risk. HRS heralds a poor prognosis, with nearly half of the patients with HRS type 1 (HRS-1) who do not undergo transplantation dying within 2 weeks.[4,6,7]

RENAL DYSFUNCTION IN CIRRHOSIS

Renal dysfunction in the setting of cirrhosis is common and is associated with adverse outcomes.[8,9] The MELD system was implemented in 2002 to prioritize patients for liver transplantation with renal dysfunction weighted heavily. This has led to an increase in the number of patients with renal dysfunction undergoing liver transplantation.[10] Although HRS is the focus of this chapter; there may be other causes of acute kidney injury (AKI) in patients with cirrhosis. Common causes of prerenal AKI include the use of diuretics, lactulose, and hypovolemia. Intrinsic etiologies of AKI include glomerulonephritis, acute interstitial nephritis, bile cast nephropathy,[11,12] and acute tubular necrosis (ATN).[13] The etiology of renal disease is independently associated with prognosis, with HRS having the lowest 3-month probability of survival.[14]

Several consensus definitions of AKI have been formulated. In 2004, the Acute Dialysis Quality Initiative (ADQI) group proposed the risk, injury, failure, loss of kidney function, and end-stage kidney disease (RIFLE) criteria, which categorized renal dysfunction into grades of increasing severity based on urine output and changes in serum creatinine.[15] Given that even small increases in serum creatinine can reflect kidney injury and adverse outcomes, the Acute Kidney Injury Network (AKIN) criteria were proposed in 2007. In line with new classifications of AKI, in 2015, the International Club of Ascites (ICA) proposed an adjustment to the criteria for a diagnosis of AKI in patients with cirrhosis. The new ICA-AKI criteria propose a move away from a fixed serum creatinine (sCr) cutoff for the diagnosis of AKI in favor of an sCr increase of 0.3 mg/dL or ≥50% from baseline. Further staging of the severity of AKI from grades 1 to 3, corresponding to the magnitude of the elevation of sCr, was also proposed.[16] Follow-up studies on outcomes for patients with cirrhosis complicated by AKI have continued to demonstrate that HRS is the most severe form of AKI with the highest mortality, although no mortality differences among AKI stages 1, 2, and 3 have been noted.[17]

PATHOGENESIS OF HRS

Low blood pressure; a very low GFR (<40 mL/min); and an increase in plasma levels of renin, norepinephrine, and antidiuretic characterize HRS.[2] The increase in sheer stress in the splanchnic vasculature is a result of portal hypertension, leading to the overproduction of nitric oxide and other vasodilators.[18] Other factors contributing to splanchnic vasodilation include increased bacterial translocation, mesenteric angiogenesis, and hyporesponsiveness of the splanchnic vasculature to vasoconstrictors.[19]

Sodium retention, impaired free-water excretion, and decreased renal perfusion and GFR are the main abnormalities in HRS and are progressive. The first abnormality is the reduced ability to excrete sodium secondary to mineralocorticoid effects. As the disease progresses, patients are unable to excrete the sodium ingested in their diet, and ascites develops. When renal sodium avidity is extremely high, the plasma renin activity and the plasma concentrations of aldosterone and norepinephrine are elevated.[20,21] Circulatory dysfunction is greater at this stage, with increased activity of the sympathetic nervous and the renin – angiotensin systems.

Renal perfusion and GFR are dependent on increased renal production of prostaglandins. These lipid mediators are vasodilators that antagonize the vasoconstricting actions of angiotensin II and norepinephrine. A syndrome indistinguishable from HRS can be produced in patients with cirrhosis, ascites, and increased plasma renin activity if prostaglandin synthesis is inhibited by nonsteroidal antiinflammatory drugs.[21,22]

Peripheral arterial vasodilation has been implicated in HRS but primarily affects the splanchnic arterial vascular bed. Doppler ultrasonography studies demonstrate vasoconstriction in renal, brachial, femoral, and cerebral beds.[23,24] Several endogenous vasodilators have been implicated in splanchnic vasodilation, including nitric oxide, carbon monoxide, glucagon, prostacyclin, and endogenous opiates.[25–27]

End-stage liver disease is associated with reduced systolic and diastolic response to stress, enlarged cardiac chambers, and repolarization changes, termed *cirrhotic cardiomyopathy*.[28] The development of HRS has been associated with a lower arterial pressure, a marked decrease in cardiac output, and increases in plasma renin activity and plasma norepinephrine[29] (Fig. 84.1).

Recently, the role of the systemic inflammatory response seen in advanced cirrhosis has been implicated in the pathogenesis of hepatorenal syndrome.[30] The presence of a distinct additional pathophysiologic basis for HRS may explain the lack of response to vasoconstrictors observed in some patients.[31] Further elucidation of the pathophysiology of HRS may lead to novel therapeutic targets in the future. Although HRS has traditionally been viewed as a purely functional form of renal disease, new data suggest that there exists some

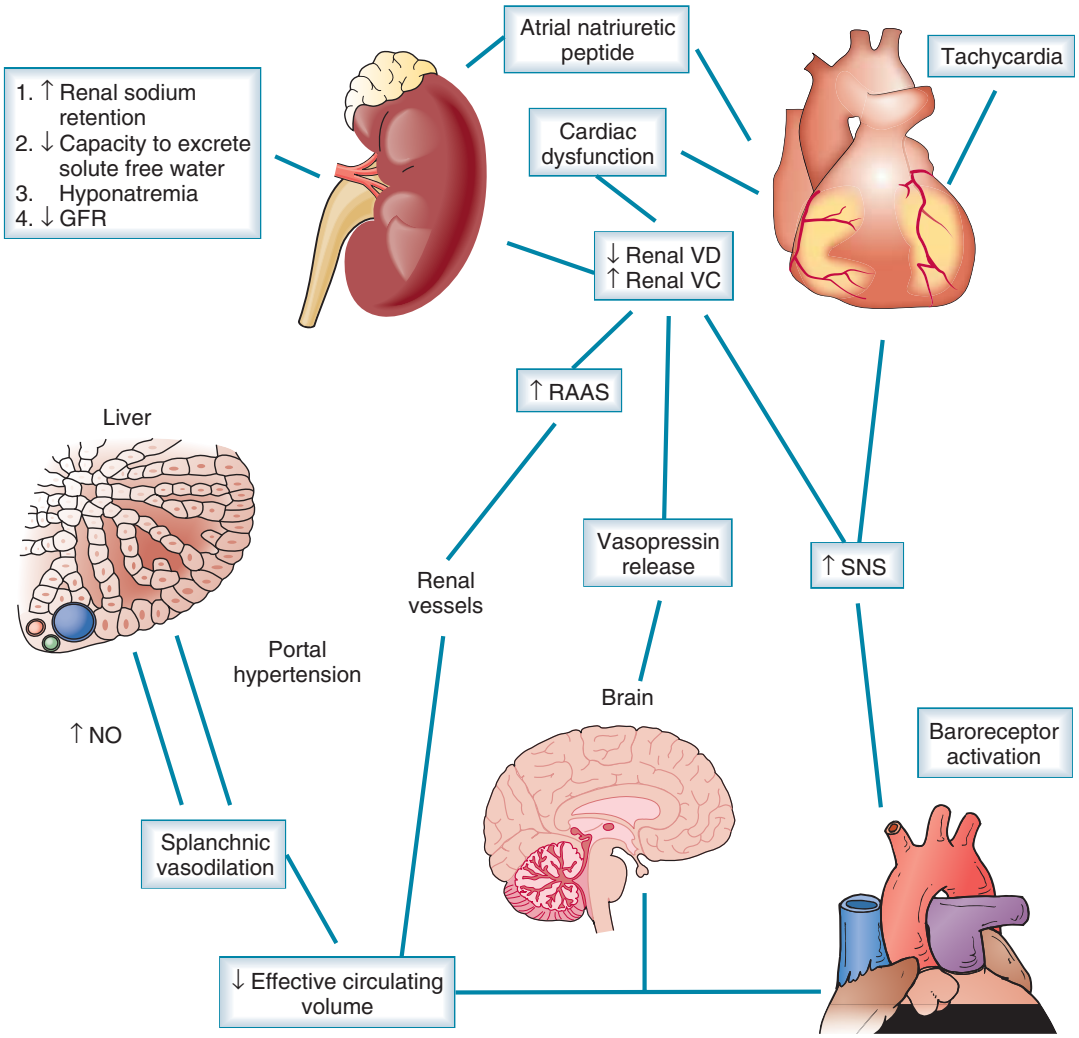

Fig. 84.1 Pathophysiologic Mechanisms of HRS. *GFR,* Glomerular filtration rate; *HRS,* hepatorenal syndrome; *NO,* nitric oxide; *RAAS,* renin–angiotensin–aldosterone system; *renal VC,* renal vasoconstrictors; *renal VD,* renal vasodilators; *SNS,* sympathetic nervous system. (From Wadei HM, Mai ML, Ahsan N, Gonwa TA. Hepatorenal syndrome: pathophysiology and management. *Clin J Am Soc Nephrol.* 2006;1:1066–1079.)

component of parenchymal damage. Neutrophil gelatinase-associated lipocalin (NGAL) is one biomarker reflective of renal structural damage. NGAL is significantly elevated in ATN; however, elevations can be seen in HRS. This suggests a component of structural damage and that ATN and HRS may exist as a spectrum of the same disease rather than as distinct entities.[32,33]

DIAGNOSIS

In 2015, the ICA updated the diagnostic criteria for HRS to include the new definition of AKI, which requires an elevation in serum creatinine of 0.3 mg/dL or ≥50% above baseline in the absence of other potential causes of renal failure (Table 84.1).[16] These criteria are slightly different from previously defined criteria and will be discussed in more detail later. The first step in the diagnosis of HRS is a demonstration of elevated creatinine, which greatly underestimates the decrease in GFR in advanced cirrhosis.[2,34] Similarly, urea is synthesized by the liver, and urea synthesis may be reduced as a consequence of hepatic insufficiency.[35,36] Many patients may not meet the diagnostic criteria for HRS yet have significant renal injury similar to HRS.[37]

TABLE 84.1 Diagnostic Criteria of Hepatorenal Syndrome (HRS) Type of Acute Kidney Injury (AKI) in Patients with Cirrhosis (International Club of Ascites [ICA])

Cirrhosis with ascites
Diagnosis of AKI according to ICA-AKI criteria
No improvement in serum creatinine after at least 2 days with diuretic withdrawal and volume expansion with albumin. The recommended dose of albumin is 1 g/kg of body weight per day up to a maximum of 100 g/day
Absence of shock
No current or recent treatment with nephrotoxic medications
Absence of parenchymal kidney disease as evidenced by proteinuria, microhematuria, and/or abnormal renal ultrasound

From Angeli P, Ginès P, Wong F, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites [published correction appears in *J Hepatol.* 2015;63(1):290]. *J Hepatol.* 2015;62(4):968–974. Box 1.

CLINICAL TYPES

HRS has been classified into two types according to the severity and form of presentation of renal failure.[31] Type I HRS (HRS-1) is characterized by a rapid reduction in renal function and is defined by a doubling of the serum creatinine concentration to 2.5 mg/dL in less than 2 weeks. HRS-1 is often precipitated by an infection, hemorrhage, paracentesis, surgery, or acute hepatitis. The association between HRS and spontaneous bacterial peritonitis (SBP) has been carefully investigated.[38–40] HRS-1 develops in approximately 30% of patients with SBP despite rapid and successful treatment. Patients with an intense systemic inflammatory response and high cytokine levels in plasma and ascitic fluid are especially prone to developing HRS-1 after infection. HRS-1 has a 2-week median survival in patients who do not undergo liver transplantation. HRS-2 is characterized by a more moderate and steady decrease in renal function, with a serum creatinine >1.5 mg/dL that fails to satisfy the diagnostic criteria of HRS-1. The dominant clinical feature is severe ascites with poor or no response to diuretics. Patients with HRS-2 are especially predisposed to developing HRS-1 after precipitating events.[38–40] The median survival of patients with HRS-2 is 6 months, which is worse than patients with nonazotemic cirrhosis with ascites.

The ICA has recently recommended reclassifying hepatorenal syndrome into two new categories: HRS-AKI (in place of HRS-1) and HRS-NAKI (in place of HRS-2). Although the changes have caused some confusion and are in some sense semantic in nature, the reclassification is based on the evolving changes in the definition of AKI, recognizing that even small increases in creatinine are suggestive of kidney injury. The original definition of HRS-1 required that an advanced stage of AKI (at least stage 2) be present, which may have limited the efficacy of vasoconstrictor therapy.[41] With this new definition of HRS-AKI, the ICA is encouraging clinicians to initiate treatment of patients quickly, even when increases in sCr are more modest.

The ICA proposes that the diagnosis of HRS-NAKI be made in the context of chronic kidney disease (CKD) or acute kidney disease (AKD) that does not meet the criteria for AKI and lasts for <90 days. HRS-NAKI is characterized by an estimated GFR <60 mL/min but a percent increase in sCr <50% from baseline. It is further broken down into HRS-AKD in patients who have had a decreased estimated GFR (eGFR) for <3 months and HRS-CKD in patients with decreased eGFR for ≥3 months.[31]

TREATMENT

Goals of therapy include improvement of liver function, as in the recovery of alcoholic hepatitis; treatment of decompensated hepatitis B[42]; or medical therapy, including pharmacotherapeutics and renal replacement therapy (RRT), as a bridge to either liver transplantation or simultaneous liver-kidney transplantation (SLK). To date, no single therapeutic agent has been found to permanently reverse HRS. Dopamine, fenoldopam, endothelin antagonists, natriuretic peptides, and angiotensin-converting enzyme inhibitors have been shown to either have no benefit or worsen the outcome of HRS.[43]

Liver Transplantation

Liver transplantation is the treatment of choice for HRS.[44–48] Immediately after transplantation, further impairment in GFR may be observed with the need for RRT.[44] Delay in the administration of nephrotoxic medications for 48–72 hours after transplantation may be considered.[49] GFR improves by 1–2 months postoperatively, but a moderate level of renal dysfunction persists and is more marked than in patients without HRS.[50] The hemodynamic and neurohormonal abnormalities associated with HRS usually resolve within the first month. However, not all patients exhibit renal recovery. Predictors of an HRS-1 reversal after liver transplantation are younger age, lack of CKD, shorter durations of HRS and pretransplant dialysis, and lower preoperative creatinine.[51] There is heterogeneity in the results of studies examining renal recovery posttransplant, with results ranging from 58% to 100%.[52,53]

Patients with HRS who undergo transplantation have more complications, longer intensive care unit stay, and higher in-hospital mortality rates.[44–48] The 3-year probability of survival is 60%,[44–48] which is only slightly less than that for liver transplant recipients without HRS.

SLK

SLK transplant is an option for patients at risk for nonrecovery. SLK should be used only for those who have irreversible kidney injury.[54,55] At this time, however, renal recovery remains difficult to predict. The Organ Procurement and Transplantation Network (OPTN) Liver and Intestine Committee and Kidney Committee proposed listing criteria for SLK candidate selection and allocation. Limitations include the definition and duration of AKI, GFR determination, and timing of initiation and duration of dialysis.[37,56] Whereas some studies suggest that patients on RRT for more than 8–12 weeks have improved survival with SLK compared with liver transplant alone, there is significant variability.[55,57,58] The consensus panel suggested liver transplantation alone in patients with HRS for less than 4 weeks.

Volume Expansion and Vasoconstrictors

Vasoconstrictors and volume expansion to increase splanchnic vasoconstriction and improve circulating volume may be the most promising medical approach for HRS. Over the past decade, many small studies have evaluated vasoconstrictors with and without a volume expander.

Volume administration, particularly with albumin, is an important tenet of therapy, with several studies showing that vasopressors alone are not as effective. It is important to avoid fluid overload. Assessment of intravascular volume is challenging, with physical examination findings or static measurements of filling pressures having poor accuracy in predicting a response to a fluid bolus.[59] The choice of fluid remains controversial,[60] although a consensus panel recommended albumin. The recommended albumin dose is 1 g of albumin/kg for 2 days, up to a maximum of 100 g/day, followed by 20–40 g/day.[16,37] "Chloride liberal" fluid administration may be associated with AKI in critically ill patients and liver transplant recipients.[61,62] Studies in HRS need to be conducted.

Vasopressin is an endogenous hormone with three major identified receptors. The V1 receptor, found on vascular smooth muscle, promotes vasoconstriction. The V2 receptor is involved in the osmoregulation of the kidney, and the V3 receptor affects corticotropin secretion. The V1 receptor has been the target of interest for vasopressin analogs designed to increase splanchnic vasoconstriction.[43,63] The original studies were conducted with ornipressin, but the recent focus has been on terlipressin, which has a greater effect on the V1 receptor and fewer side effects.[64] Complications with vasopressor therapy have been reported in an average of 12% of patients treated and it is contraindicated in patients with ischemic heart disease, peripheral vascular disease, and cerebrovascular disease.[65]

Monotherapy with either albumin or a vasoconstrictor is not as effective as combined therapy. Two randomized trials comparing terlipressin with albumin to either agent alone showed an improved response with combination therapy.[66] Two meta-analyses have shown improved outcomes with the use of terlipressin versus a placebo.[64,67] Fabrizi and colleagues[64] analyzed 10 clinical trials and found a reversal of HRS in 52% of cases. Dobre and colleagues[67] identified eight eligible trials, four of which compared terlipressin with placebo. The

terlipressin group had improved outcomes, including reversal of HRS (odds ratio [OR] of 7.47), improvement in mean arterial pressure (MAP), improvement in urine output, and reduction in serum creatinine. Sanyal and colleagues[68] conducted a randomized controlled trial (RCT), and a subgroup of patients who received terlipressin for more than 3 days had a greater response to therapy compared with the placebo group (52.8% vs. 18%, $P = .002$). These data support the contention that length of therapy may contribute to some of the variability in treatment efficacy. Sanyal and colleagues[69] also showed that earlier therapy increased the probability of reversal. Treatment with terlipressin and albumin may be associated with a survival benefit when including studies other than just placebo control studies.[65]

The terlipressin dose ranges used vary from 1 to 2 mg every 4–6 hours. Incremental increases in dosing while monitoring creatinine have been recommended.[68] Additionally, a maximal dose of 12 mg/day with minimum duration of 3–5 days has been proposed.[63] There are variable data on the rates of recurrence after discontinuation of therapy, ranging from 5.3% to 50%.[43,63,70]

Alpha-adrenergic agonists also have been used to augment renal perfusion. Two RCTs compared norepinephrine with terlipressin.[71,72] In the first study, reversal of HRS occurred in 70% of the patients in the norepinephrine group versus 83% in the terlipressin group. In the second study, norepinephrine was effective in increasing MAP and urine output and decreasing creatinine. A recent meta-analysis found that norepinephrine is as effective as terlipressin when used in conjunction with albumin and that it appears to be associated with fewer adverse events.[73] Although evidence regarding treatment of HRS-2 has historically been scant, an RCT by Ghosh and colleagues found that both terlipressin and norepinephrine are safe and effective, with response rates of 74%.[74]

As treatment with norepinephrine is limited to inpatient and critical care settings, alternative vasopressor regimens, including oral midodrine and octreotide, have emerged. Several studies have shown that oral midodrine used in conjunction with intravenous (IV) albumin and subcutaneous octreotide results in improved renal perfusion, GFR, serum blood urea nitrogen, creatinine, and sodium.[75] Furthermore, the treatment regimen has also been associated with increased survival in both HRS-1 and HRS-2 when compared with untreated controls.[76,77] Studies of monotherapy of octreotide, however, have not shown a benefit over placebo. The combination of midodrine plus octreotide is a promising regimen for HRS-2 as outpatients.

A recent meta-analysis evaluated 10 RCTs that compared terlipressin with other vasopressor regimens, including norepinephrine, dopamine, octreotide, and midodrine, all in conjunction with albumin administration. There was little evidence to support the superiority of terlipressin over alternative vasopressor therapies, including two studies that found it to be inferior in regard to mortality.[78] Additional research has focused on identifying predictors of treatment efficacy with vasoconstrictors. A change in MAP during treatment was the sole independent predictor of patient survival.[79] An increase in MAP of more than 10 mm Hg was associated with better overall survival, with no further improvement despite higher targets. A treat-to-the-target concept by the use of a specific MAP goal may guide management.

In summary, these studies show the following:

1. HRS-1 can be reversible with IV albumin and vasoconstrictors.
2. Both components of the treatment are important.
3. Infusion of vasoconstrictors is associated with ischemic complications.
4. There is a delay between improvement in circulatory function and an increase in GFR.
5. Reversal of HRS improves survival, with a significant number surviving to transplantation.

Transjugular Intrahepatic Portosystemic Shunt

Decreasing portal pressure by portosystemic anastomosis to improve the circulatory compromise of cirrhosis has been targeted as a treatment for HRS. Case reports show that HRS can be reversed after a surgical portosystemic shunt.[80,81]

Transjugular intrahepatic portosystemic shunt (TIPS) in the management of HRS-1 has been evaluated in small-scale studies and may be of benefit in conjunction with vasopressors.[82–84] In one study of patients with HRS-1 who were not candidates for transplantation, it was found that the survival rates at 3, 6, and 12 months after TIPS were 64%, 50%, and 20%, respectively.[82] TIPS may be beneficial in patients with HRS-2 with refractory ascites, with improvements in renal function without improved survival.[85] A more recent meta-analysis by Salerno and colleagues, however, found TIPS significantly improved transplant-free survival of patients with cirrhosis and refractory ascites. Further research is needed to define the role of TIPS in the treatment of HRS.[86]

Other Therapeutic Methods

Hemodialysis and arteriovenous or venovenous hemofiltration are a frequent bridge to liver transplantation or for treating an acute but reversible decompensation.[87] Continuous RRT is often selected in hemodynamically unstable patients, but there are no published studies that allow for evidence-based guidelines on one modality over the other.[88] Given that the prognosis of HRS-1 is poor without transplantation, strong consideration should be had for withholding RRT in patients who are not liver transplant candidates. These decisions should be made within the context of the patient's goals of care and involve shared decision making.

Noncell-based extracorporeal support systems are available that perform detoxifying functions of the liver. One such noncell-based support system uses an albumin-containing dialysate that is recirculated and perfused through charcoal and anion-exchanger columns. This modality has been shown to improve hemodynamics and reduce plasma renin in patients with HRS-1.[89,90] In a small series of patients, improved survival was reported.[91] Modalities such as the Prometheus system and single-pass albumin dialysis have been used in a few patients with some success.[92,93] However, further studies are needed in this area.

PREVENTION

Preventing precipitating factors, such as infections and acute alcoholic hepatitis, may decrease the incidence of HRS-1. Three randomized controlled studies enrolling a large series of patients have shown that HRS can be prevented in specific clinical settings. In the first study,[94] albumin together with cefotaxime was compared with cefotaxime alone in patients with SBP. Treatment with albumin markedly reduced the incidence of impaired circulatory function and the occurrence of HRS-1. The second study showed that oral prophylaxis using norfloxacin decreased the 1-year probability of developing SBP and HRS-1 and improved survival.[95] In a third study,[5] administration of the tumor necrosis factor synthesis inhibitor pentoxifylline to patients with severe acute alcoholic hepatitis reduced the occurrence of HRS (8% vs. 35%) and hospital mortality (24% vs. 46%).

CONCLUSION

The pathophysiology of HRS is characterized by intense vasoconstriction with splanchnic arterial vasodilation. HRS-1, now classified as HRS-AKI, is characterized by rapid and progressive deterioration of circulatory and renal function. It often develops after a precipitating

event and carries a very poor prognosis (median survival rate <2 weeks without liver transplantation). HRS-2, or HRS-NAKI, is characterized by steady deterioration of circulatory and renal function with refractory ascites. Patients with HRS-2 have a median survival of 6 months. The administration of albumin plus a vasoconstrictor is an effective treatment for HRS. These approaches may improve survival and may serve as a bridge to liver transplantation, which is the treatment of choice for these patients.

KEY POINTS

- Portal hypertension leads to the production of vasodilators causing splanchnic vasodilation. This leads to activation of the renin – angiotensin – aldosterone system and the sympathetic nervous system, which causes renal vasoconstriction. Decreased renal perfusion caused by an imbalance between extremely high vasoconstrictor tone and the decreased production of renal vasodilators leads to HRS.
- Criteria of the ICA define HRS-AKI (see Table 84.1) as an increase in sCr >0.3 mg/dL or an increase by ≥50% above baseline.
- HRS is classified into two types:
  - HRS-1 or HRS-AKI: severe and rapidly progressive renal failure, usually after a precipitating event, with a median survival of 2 weeks.
  - HRS-2 or HRS-NAKI: moderate and steady development of renal failure, clinically characterized by refractory ascites, with a median survival of 6 months.
- Liver transplantation is the treatment of choice for HRS. The recovery of renal function neurohumoral physiology may take 1 month.
- The 3-year probability of survival in transplanted patients with HRS is 60%.
- HRS-1 may be reversible after treatment with IV albumin and vasoconstrictors.
- Successful prevention of HRS has been achieved in the setting of SBP and acute alcoholic hepatitis.

References for this chapter can be found at expertconsult.com.

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Hepatopulmonary Syndrome

Cody D. Turner, Nasim Motayar, and David C. Kaufman

DEFINITION

Hepatopulmonary syndrome (HPS) is defined by an abnormally low arterial oxygen level associated with intrapulmonary vascular dilatations (IPVDs) in patients with liver disease.[1] The presence of coexisting cardiopulmonary disease, which may contribute to impaired gas exchange, should be considered but does not exclude this diagnosis.[2–5] HPS is most commonly associated with cirrhosis[1] and portal hypertension, but neither of these is required for its diagnosis.[6] The correlation between the degree of liver dysfunction and the presence[7,8] and severity[3,4,7,9,10] of this syndrome is debated.

CLINICAL FEATURES

HPS usually presents as dyspnea[6,11] in patients with liver disease. A sensitive but not specific clinical finding is the presence of platypnea, which refers to worsening of dyspnea when going from the supine to upright position (Fig. 85.1). The subsequent drop in arterial oxygenation during this position change is referred to as orthodeoxea.[11,12]

HPS-induced hypoxemia can be corrected with the application of supplemental oxygen;[1,3,4,10,13] unresponsiveness to oxygen therapy should prompt clinicians to search for other causes. Although there are no consistently noted physical examination findings,[6,14] some clinical findings observed include the presence of digital clubbing, cyanosis, and diffuse telangiectasias.[1]

PATHOPHYSIOLOGY

Dilated precapillary vessels and pleural-based arteriovenous (AV) connections are noted at autopsy in cases of HPS.[15] Current thinking suggests that these abnormal vessels develop as a result of an excess of pulmonary vasodilators,[1] which cause hypoxia through ventilation/perfusion (V/Q) mismatching, AV shunting, and the limitation of oxygen diffusion to red blood cells (RBCs) in the center of the vessel.[15–17] The hyperdynamic circulation, which is characteristic of cirrhosis, exacerbates this problem by decreasing RBC transit time through the pulmonary capillaries, further limiting oxygen diffusion.[15,17] Orthodeoxia is caused by a worsening of V/Q mismatch and AV shunting in the standing position.[18]

Nitric oxide (NO) has been implicated as a key vasodilator in HPS. Exhaled NO levels are elevated in patients with cirrhosis compared with healthy controls and in HPS patients compared with cirrhotic patients without HPS. NO levels correlate with the severity of cirrhosis and gas exchange abnormalities.[19] In rat models of HPS induced by common bile duct ligation (CBDL), increased levels of endothelial[20] and inducible NO synthase (eNOS and iNOS) have been observed, and the administration of an NO synthase inhibitor prevents the development of pulmonary vasodilation and HPS.[21]

Excess eNOS, located in the pulmonary arteries and capillaries, is associated with impaired vasoconstriction. Levels of this enzyme correlate with the degree of gas exchange abnormalities.[20] CBDL rats demonstrate increased hepatic production of endothelin-1 (ET-1)[22] and increased vascular expression of the endothelin-B receptor (ET-B)[23] in proportion to the severity of gas exchange abnormalities.[22,24] Interaction between the ET-1 and the ET-B receptor is believed to be the trigger for increased eNOS expression. This theory is supported by data that show a reduction in eNOS expression and an improvement in HPS when CBDL animals are treated with ET-B receptor antagonists.[24]

iNOS is expressed in macrophages found in the lungs of CBDL rats,[21] whereas treatment with norfloxacin is associated with a reduction in the rate of gram-negative bacterial translocation, accumulation of pulmonary macrophages, production of iNOS, and severity of HPS.[25] Pulmonary macrophages in CBDL rats also express elevated levels of heme-oxygenase-1 (HO-1), an enzyme that catalyzes the formation of the vasodilating gas and carbon monoxide (CO).[26] Increased levels of carboxyhemoglobin (COHb) have been observed in rat[26] and human[27] subjects with HPS, and treatment with an HO-1 inhibitor normalizes COHb levels and partially alleviates HPS in CBDL rats.[26] These data suggest that CO also contributes to pulmonary vasodilation in HPS.

Tumor necrosis factor-alpha (TNF-α) rises in CBDL rats in association with ET-1 and endotoxin levels, and it has been proposed to influence the accumulation of the iNOS and HO-1–producing pulmonary macrophages.[28] Administration of pentoxifylline, a phosphodiesterase inhibitor that suppresses the production of TNF-α, is associated with a reduction in pulmonary macrophage accumulation, ET-B receptor and eNOS expression, and the severity of HPS.[29]

More recently, ET-1 and ET-B receptor activation have been shown to increase pulmonary intravascular monocyte adherence through the monocyte chemokine fractalkine.[30,31] Fractalkine promotes angiogenesis directly and through monocyte secretion of vascular endothelial growth factor-A.[31] Angiogenesis is an important feature in experimental models of HPS and may provide new therapeutic targets, in addition to explaining the delay in the resolution of hypoxia in patients posttransplantation.

DIAGNOSIS

HPS should be considered in any patient with liver disease and dyspnea or hypoxemia. Evaluation should begin with the measurement of arterial blood gas (ABG), with the patient in a resting seated position while breathing ambient air.[6,17] A partial pressure of oxygen (PaO_2) <80 mm Hg or an alveolar-arterial oxygen gradient (A-a gradient) ≥ 15 mm Hg (≥ 20 mm Hg for patients over the age of 64)[17] is suggestive of HPS and

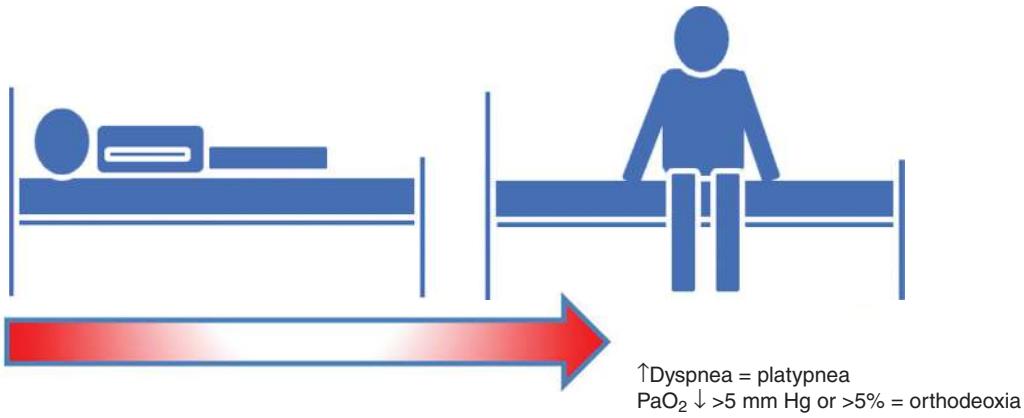

Fig. 85.1 Platypnea Refers to Worsening of Dyspnea when Going from a Supine to Upright Position. The subsequent drop in arterial oxygenation during this position change is referred to as orthodeoxia. Platypnea is a sensitive, but not specific, clinical finding of hepatopulmonary syndrome. *PaO_2*, Partial pressure of oxygen.

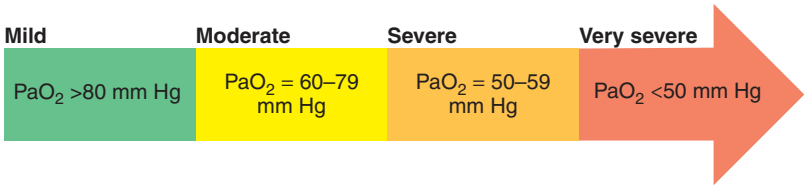

Fig. 85.2 Grading Severity of Hepatopulmonary Syndrome Based on the Measurement of Arterial Blood Gas. *PaO_2*, Partial pressure of oxygen.

should prompt further evaluation. Pulse oximetry has been suggested as a potentially cost-effective and noninvasive screening tool for HPS[1,32]; however, current literature does not support its adequacy.[33] ABG is also preferred because it allows for grading the severity of HPS (Fig. 85.2).

Chest imaging and pulmonary function testing have been used adjunctively to rule out other etiologies for coexisting cardiopulmonary disease that may contribute to abnormal gas exchange, such as chronic obstructive pulmonary disease, congestive heart failure, restrictive lung disease caused by ascites or hepatic hydrothorax, α_1-antitrypsin deficiency, and portopulmonary hypertension.[12] Common but nonspecific findings include increased markings at the lung base on chest x-ray (CXR)[1,6,8] and reduced diffusion capacity for carbon monoxide (DLCO).[3,4,7,14,18] HPS can be distinguished from portopulmonary hypertension by the presence of increased pulmonary artery pressure and vascular resistance.[34]

Contrast-enhanced echocardiography (CEE) is the gold standard for evaluation of HPS once abnormal oxygenation is identified. The benefit of CEE is that it permits concurrent evaluation of cardiac function in addition to evaluating for IPVD, which is required for the diagnosis of HPS.[12] Agitated saline is used as a contrast media, which creates a stream of microbubbles after injection. In healthy subjects, these microbubbles opacify the right heart only as they are filtered through the pulmonary capillary bed because of their size (greater than 15 μm in diameter).[9,35] Intracardiac shunts can be distinguished from intrapulmonary shunts based on the number of cardiac cycles required for agitated saline to pass from the right to the left atrium in the apical four-chamber view (Fig. 85.3). In general, contrast appears in the left atrium within three cycles in intracardiac shunts, whereas it takes four to six cycles in intrapulmonary shunts.[9,35] CEE is highly sensitive for the evaluation of IPVDs[36] and may document them in up to 82% of patients tested.[35] Patients with a positive CEE have a greater incidence of dyspnea[37] and abnormal CXRs,[9,37] in addition to more advanced cirrhosis[9,35,37] and gas exchange abnormalities.[9,37] However, many patients with liver disease and IPVDs demonstrated by CEE do not develop HPS, which additionally requires the presence of impaired gas exchange,[5,8,14,35,37] and so this test is not specific for HPS.[36]

Technetium-99m–labeled macroaggregated albumin (MAA) perfusion lung scanning is an alternative test for IPVDs. It is expensive, requires radiation exposure,[14] and cannot document the site of shunting. However, it can provide a quantitative shunt fraction[14,17,36] that correlates directly with the A-a gradient[3,10,13] and inversely with the room air PaO_2 and oxygen saturation.[3,10,13,38] Perfusion scanning is less sensitive than CEE for IPVD detection but more specific.[5,10,38] These test characteristics have enabled CEE to be advocated as the first line for evaluating patients with liver disease and abnormal gas exchange.[5,10,17] If CEE is positive but the relative contributions of other cardiopulmonary disease and HPS are not clear, perfusion lung scanning can differentiate the degree of hypoxemia from IPVD in comparison to nonvascular pulmonary abnormalities.[5,10,12,17] Recent studies have also demonstrated HPS patients have increased levels of alveolar exhaled NO; however, this has not been validated for HPS screening or diagnosis.[39] Another marker that may be of future interest is von Willebrand factor antigen, which is a surrogate for endothelial dysfunction and was shown to be elevated in patients with HPS in a 2014 prospective study.[40]

PREVALENCE

The prevalence of HPS varies by etiology and has been reported in patients with chronic viral hepatitis (10%), Budd-Chiari syndrome (28%), and cirrhosis (15%–23%)[41–43] and in 5%–30% of patients with cirrhosis being evaluated for liver transplantation.[1]

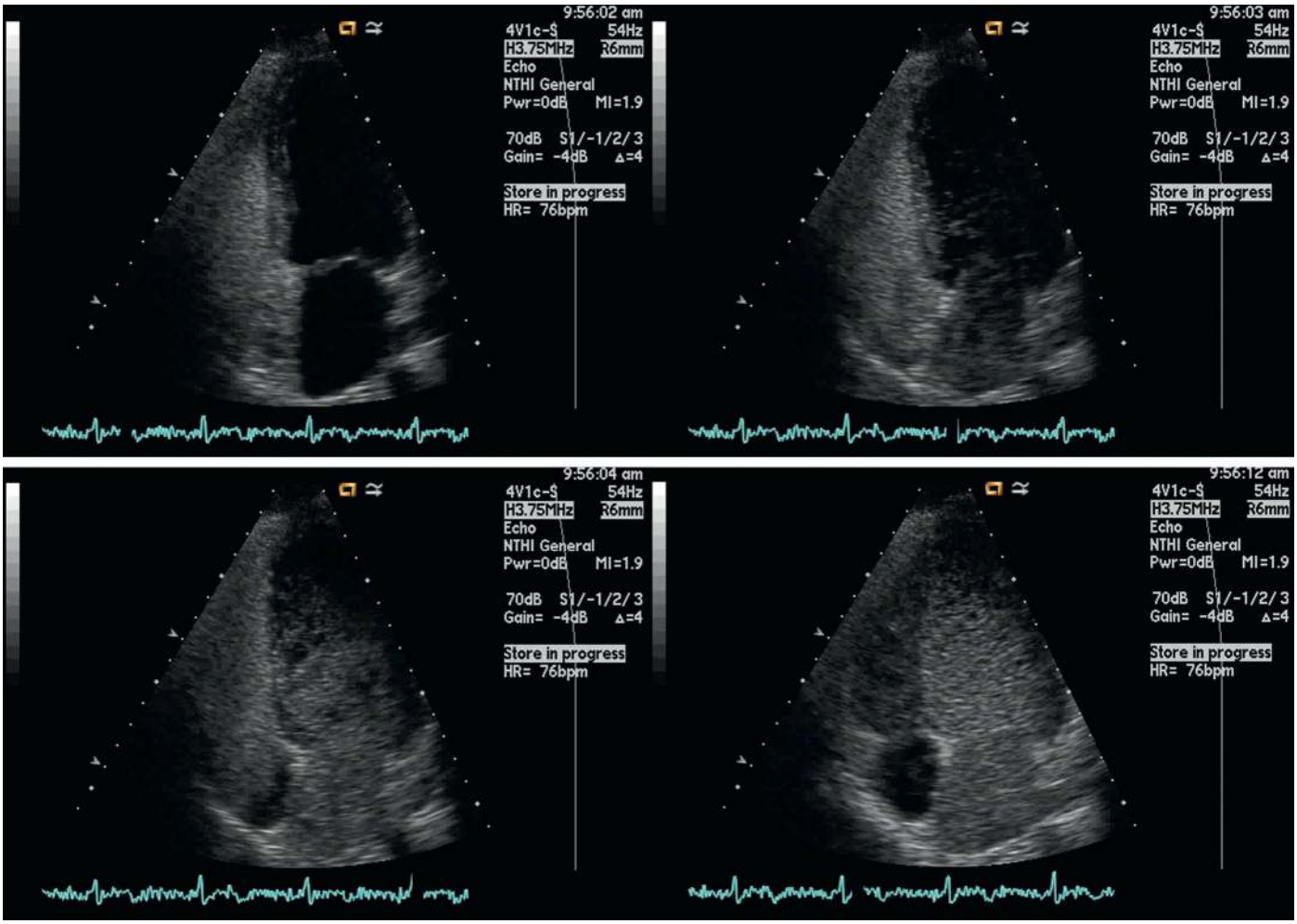

Fig. 85.3 Photos of Contrast-Enhanced Echocardiography. *Top left:* Agitated saline enters the right ventricle. *Top right:* Saline enters the left atrium posteriorly. *Bottom left:* Saline density is equal in the right and left ventricles. *Bottom right:* Saline density in the left ventricle exceeds the right ventricle after multiple cardiac cycles. (Photos courtesy of Karl Q. Schwarz, MD. University of Rochester Medical Center, Rochester, NY.)

PROGNOSIS

In the absence of liver transplantation, patients with HPS have a poorer functional status, reduced self-reported quality of life,[8] and twofold increase in mortality[7,8,44] in comparison with non-HPS controls matched for severity of liver disease. HPS patients who die during follow-up have been noted to have greater room air PaO_2 reductions, A-a gradient elevations, and shunt fractions than those who survive,[3,7,44] but this is not a universal finding.[8] Without transplant, HPS patients demonstrate progressive hypoxemia,[44] with a reduction of approximately 5 mm Hg per year.[8,41] Despite this, death is usually caused by complications of liver disease[7,17,44] rather than primary respiratory failure.[44]

THERAPY

Liver transplantation is the only definitive therapy for HPS and should be considered when patients are symptomatic or have a $PaO_2 \leq 60$ mm Hg.[6,17] Multiple therapies have been tried for HPS without clear efficacy, including inhibitors of NO,[45–47] antibiotics,[48] pentoxifylline,[29,49,50] mycophenolate mofetil,[51] transjugular intrahepatic portosystemic shunt,[12,52] the tyrosine kinase inhibitor sorafenib,[53] and pulmonary angiography with embolization of dilated capillaries[54] or AV communications.[55] Oxygen therapy also has been recommended, although clinical benefit has not been confirmed.[1,6,11,12,17,56]

Because of the increased mortality associated with HPS and the lack of other effective therapies, the United Network for Organ Sharing (UNOS) has adjusted organ allocation algorithms to prioritize patients with HPS, using exception points, which increase a potential recipients score to give them a higher priority for transplant.[57] An analysis of the UNOS database demonstrated increased mortality in patients with a $PaO_2 \leq 44$ mm Hg.[57] Among those patients who survive the perioperative period, improvement in or resolution of HPS is noted in the majority of cases, although the amelioration of symptoms may require a year or more to occur.[4,13,44]

KEY POINTS

- HPS consists of a triad of liver disease, abnormally low arterial oxygen level, and IPVD. It most commonly presents as dyspnea or hypoxemia in patients with liver disease.
- HPS is believed to result from excessive pulmonary vasodilation. Pulmonary vasodilatation leads to hypoxemia through ventilation/perfusion mismatching, AV shunting, and limitations to oxygen diffusion.
- The diagnosis of HPS requires a seated, room air ABG to document abnormal gas exchange, in addition to confirmation of an intrapulmonary shunt using echo or lung perfusion scanning. The prevalence of HPS is 5%–30% in patients undergoing evaluation for liver transplantation.
- Patients with liver disease and HPS have an increased risk of death relative to patients with liver disease alone. Liver transplantation is the only effective therapy. Transplant evaluation should be pursued in patients with HPS.

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Hepatic Encephalopathy

Alvaro Martinez-Camacho, Brett E. Fortune, and Lisa Forman

Hepatic encephalopathy encompasses a spectrum of neuropsychiatric abnormalities that occur in patients with liver disease in the absence of other brain disease.[1,2] The spectrum includes personality changes, impaired mental function, motor abnormalities (i.e., asterixis, tremors, hyperventilation, hyperactive reflexes), and altered consciousness. A consensus panel of experts proposed the classification of hepatic encephalopathy into *type A,* associated with acute liver failure (ALF); *type B,* associated with portosystemic bypass without intrinsic liver disease; and *type C,* associated with chronic liver disease.[3]

The encephalopathy accompanying ALF (type A) is commonly associated with cerebral edema and increased intracranial pressure (ICP). Patients exhibit an abrupt onset with a short prodrome and rapid sequential progression from drowsiness, delirium, agitation or convulsions, decerebrate rigidity, unresponsiveness, and then deep coma within hours to days of symptom onset.[4,5] Irreversible neurologic damage may occur as a result of brain ischemia or herniation. Patients who develop coma in the setting of ALF have a grave prognosis; less than 20% survive without liver transplantation.[6]

In patients with chronic liver disease, encephalopathy (type C) develops insidiously and is heralded by a change in mental or behavioral status. Encephalopathy may be episodic, persistent, or minimal and subclinical.[3] Episodes are sporadic, characterized by exacerbations and remissions, and are generally precipitated by inciting events.[1,2] Although the initial manifestation of portosystemic encephalopathy (PSE) is usually a subtle change in mentation, neurologic dysfunction may progress and be classified according to confusion, lethargy, and even coma (Table 86.1). Neurologic signs vary and fluctuate but usually include asterixis, hyperreflexia, clonus, and an extensor plantar response. Causes of PSE may not always be apparent but should always be investigated (Box 86.1). Minimal encephalopathy is not clinically obvious and requires psychometric testing for diagnosis. By these tests, about two-thirds of cirrhotic patients with portal hypertension have unsuspected minimal hepatic encephalopathy.[7–9] Patients who undergo portosystemic shunt or bypass procedures, either surgical or transjugular intrahepatic portosystemic shunt (TIPS), are at risk for hepatic encephalopathy (type B), which is similar to type C encephalopathy.

CURRENT CONCEPTS ON THE PATHOPHYSIOLOGY ASSOCIATED WITH HEPATIC ENCEPHALOPATHY

No single abnormality of hepatic or neurologic metabolism adequately explains all of the clinical, biochemical, physiologic, or experimental findings of encephalopathy occurring in patient or animal models.[1,2,5] Abnormalities of multiple neurotransmitters, including glutamate, gamma-aminobutyric acid (GABA), dopamine, serotonin, and opioids, have been described, in addition to increased plasma levels of a wide array of potential neurotoxins (ammonia [NH_3], short-chain fatty acids, and methanethiols).[10,11] Regardless of the mechanism(s) of hepatic encephalopathy, marked changes in central nervous system (CNS) glial cells are noted on neuropathologic examination in patients with hepatic encephalopathy. Encephalopathy associated with ALF is typically characterized by astrocytic swelling, whereas encephalopathy from chronic liver disease is characterized by Alzheimer type II astrocytosis.[11]

Ammonia Hypothesis

The *ammonia hypothesis* states that the major mechanism of hepatic encephalopathy is excessive accumulation of NH_3, which induces neuronal metabolic derangements and promotes astrocytic swelling.[12] In addition, NH_3 perturbs cerebral nitric oxide metabolism, which can mediate some of these effects.[13] Blood NH_3 originates mainly from four sources: intrahepatic deamination of amino acids, extrahepatic metabolism of nucleotides, gut metabolism of glutamine, and bacterial degradation of intestinal protein and urea.[14] More than 50% of blood NH_3 is derived from the latter source.

NH_3 is normally metabolized by the liver to either urea or glutamine by the actions of carbamoyl-phosphate synthetase I and glutamine synthetase, respectively. Patients with hepatic failure have impaired NH_3 metabolism related to liver dysfunction and an increase in portosystemic shunting. Certain clinical and experimental observations link the increase in blood NH_3 concentration to hepatic encephalopathy.[10,11,15,16] Hyperammonemia and elevated concentrations of NH_3 within the cerebrospinal fluid (CSF) are features of acute and chronic hepatic encephalopathy, Reye syndrome, deficiencies of urea cycle enzymes, and sodium valproate toxicity. In patients with cirrhosis or portosystemic shunts, ingestion of NH_3-generating substances (proteins, amino acids, urea, ammonium salts) may precipitate encephalopathy. In animal models, chronic administration of ammonium salts results in Alzheimer type II astrocytosis, a change indistinguishable from that observed in patients with chronic hepatic encephalopathy.[11]

Other clinical and experimental observations refute the link between NH_3 and hepatic encephalopathy. For example, blood levels of NH_3 are frequently elevated in patients with cirrhosis, regardless of the presence or absence of clinical encephalopathy. The grade of hepatic encephalopathy does not correlate with the absolute blood concentration of NH_3. Finally, seizures and hyperexcitability are commonly observed in animal models of NH_3 intoxication and in human congenital hyperammonemia but are rarely observed in patients with chronic hepatic encephalopathy.

Cerebral Blood Flow

In ALF, the brain is potentially subject to hypoxic injury caused by complications such as systemic arterial hypotension, respiratory

failure, and a reduction in cerebral blood flow that accompanies cerebral edema and intracranial hypertension (ICH).[4,5] Clinical data suggest that cerebral blood flow is relatively low initially but subsequently increases with increasing blood concentrations of NH_3.[17–20] Paradoxically, increases in cerebral blood flow may aggravate cerebral edema and worsen neurologic damage. Changes in cerebral blood flow do not appear to play a major role in hepatic encephalopathy related to chronic liver disease.

Cerebral Glucose and Oxygen Metabolism

Brain energy metabolism is unique in that glucose is the only substrate under physiologic conditions, and its uptake by the brain is independent of insulin.[21–25] Ammonia accumulation during hepatic failure is associated with altered cerebral glucose metabolism. In early ALF, before the onset of ICH, cerebral glucose metabolism and oxygen consumption are proportionately diminished.[21] There is no evidence of cerebral hypoxia, implying that reduced glucose and oxygen utilization reflects a diminished metabolic demand by the brain at this early stage. After the development of ICH, oxygen metabolism remains reduced, but measurements of cerebral glucose utilization vary from reduced to increased rates, and glycolysis may be accelerated.[22,23,25] These findings suggest that the progression of ALF and development of ICH are associated with relative cerebral hypoxia and a switch to anaerobic metabolism.

Other Potential Hypotheses for Hepatic Encephalopathy

The glutamine-glutamatergic neurotransmitter system has been implicated in the pathogenesis of hepatic encephalopathy because the glutamatergic excitatory neurotransmitter system in the CNS is markedly altered in patients with both acute and chronic liver disease and in animal models.[6,21,22] Astrocytes are a major regulatory cell in the glutamatergic system and are responsible for the termination of glutamate-induced excitation.[11] When glutamate is taken up by the astrocyte, it is metabolized to glutamine via the action of glutamine synthetase, which uses blood-derived NH_3 (Fig. 86.1). The accumulation of osmotically active glutamine in the astrocyte is associated with cell swelling and can lead to accumulation of glutamate in the extracellular fluid.

The GABA-benzodiazepine receptor hypothesis is another important mechanism that likely plays a role in hepatic encephalopathy.[26] The *GABA hypothesis* states that an excess of GABA or increased sensitivity of GABA receptors to neurosteroids is responsible for hepatic encephalopathy.[26,27] GABA originates from the intestine, and plasma levels increase in hepatic failure caused by inadequate hepatic extraction. During ALF, the blood-brain barrier (BBB) becomes more permeable, and increased amounts of GABA enter the CNS. Once in the brain, GABA binds to its receptor to produce

TABLE 86.1 Stages of Encephalopathy in Chronic Liver Disease (West Haven Criteria)

Stage	Clinical Signs
Stage I	Mental slowness, euphoria or anxiety, shortened attention span, impaired calculating ability
Stage II	Lethargy or apathy, inappropriate behavior, personality change, more obvious problems with calculations
Stage III	Lethargic, somnolent, marked confusion and disorientation but responds to verbal stimuli
Stage IV	Coma, patient may or may not respond to noxious stimuli

Patients with chronic liver disease rarely, if ever, demonstrate cerebral edema, regardless of the stage of encephalopathy.

Box 86.1 Clinical Events Precipitating Hepatic Encephalopathy in Patients With Cirrhosis

Gastrointestinal hemorrhage
Infection (including spontaneous bacterial peritonitis)
Sepsis
Dehydration
Imbalance of electrolytes or acid-base
Renal failure
Drugs, toxins, medications (especially sedative-hypnotics or narcotics)
Illicit substances
Alcohol
Dietary indiscretion (excessive protein intake)

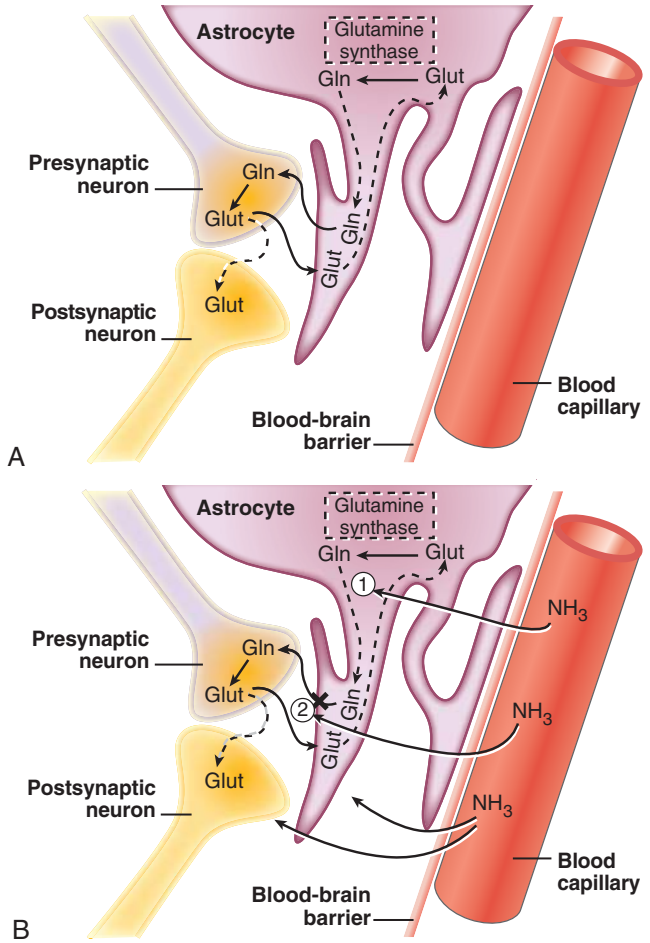

Fig. 86.1 A, Glutamine (*Gln*) forms predominantly in the astrocyte, is pumped out, and is taken up by presynaptic neurons, where it is converted to glutamate (*Glut*). Nerve stimulation releases glutamate from the presynaptic neuron to serve as an excitatory neurotransmitter. Astrocytes avidly take up glutamate from the synaptic cleft to abolish neuronal stimulation. **B,** Ammonia (NH_3) freely diffuses across the blood-brain barrier and stimulates formation of glutamine by the astrocyte via the action of glutamine synthase *(1)*. Ammonia also blocks the export of glutamine from the astrocyte at the synaptic cleft *(2)*. The net effect of these two actions is increased concentration of glutamine within astrocytes, which promotes astrocyte swelling.

neuroinhibition. A key component to understanding the relationship of GABA and benzodiazepines was the recognition that the GABA receptor was tightly linked to and modulated by the benzodiazepine receptor.[27–31] The GABA hypothesis predicts that benzodiazepines would increase the severity of hepatic encephalopathy and that benzodiazepine antagonists such as flumazenil might ameliorate hepatic encephalopathy. Recent studies demonstrated that patients with hepatic encephalopathy had increased plasma levels of benzodiazepines or "natural" benzodiazepine-like compounds that may act as "false neurotransmitters."[32,33] Clinical experience suggests that cirrhotic patients, especially those with encephalopathy, are particularly sensitive to the amnesic and sedative effects of benzodiazepines.

Previously Studied Agents Associated With Hepatic Encephalopathy

Numerous clinical studies reported alterations in levels of other agents or pathways in patients with hepatic encephalopathy. These agents or pathways include the dopaminergic and serotonergic systems, taurine, methanethiols, short-chain fatty acids, manganese, and zinc. However, conclusive evidence to support or refute their association with hepatic encephalopathy is lacking, and clinical and bench research of these agents as causative or therapeutic targets has been abandoned.

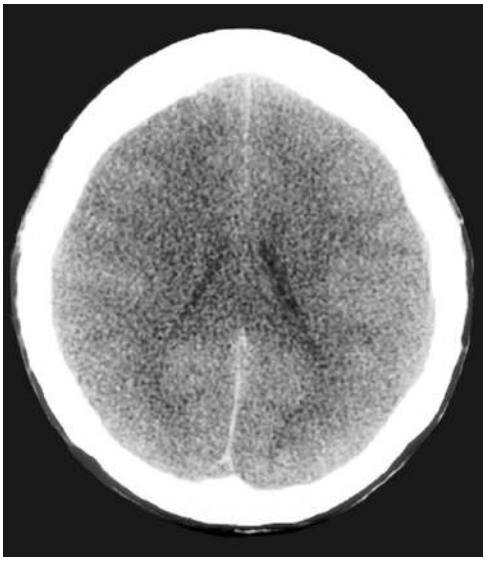

Fig. 86.2 Magnetic resonance image (MRI) of a T1-weighted sagittal view of the brain demonstrating hyperintensity of the globus pallidus (whitish area) that may be related to manganese deposition.

ENCEPHALOPATHY IN THE SETTING OF ACUTE LIVER FAILURE

Definition

ALF, also referred to as *fulminant hepatic failure,* is defined by the development of coagulopathy (prothrombin time [PT] >20 seconds prolonged with an international normalized ratio [INR] >1.5) and hepatic encephalopathy in a patient who lacks underlying chronic liver disease (except in Wilson disease).[34–37] Patients with ALF usually have extreme elevations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) with the initial injury (e.g., 1000–5000 IU/L), are often jaundiced, and exhibit constitutional symptoms. They are at risk of encephalopathy, although most recover uneventfully. Progressive hepatic encephalopathy is a poor prognostic sign and signals the need for emergent liver transplantation.

Prognosis

A major determinant of prognosis is the level of encephalopathy (see Table 86.1). Patients with ALF who have progressed to higher stages of encephalopathy (i.e., stage III or IV) have the worst prognosis. The King's College Criteria and Glasgow Coma Scale are useful in assessing the need for transplantation.[36,38] Cerebral edema on computed tomography (CT) scan of the brain is a late feature of progressive encephalopathy (Fig. 86.2). Additional clinical features that indicate a poor prognosis include metabolic acidosis, renal failure, severe jaundice, or markedly prolonged PT.[37]

General Clinical Management

Once recognized, patients with acute liver injury and encephalopathy should be quickly transferred to a liver transplant center. Further recommendations on intensive care management of the patient with ALF are addressed elsewhere (see Chapter 96).

Use of Intracranial Pressure Monitoring

Use of ICP monitoring is controversial, and it remains unclear which patients would most benefit from such monitoring. Even though the incidence of ICH has recently decreased, it affects up to one-third of patients with significant hepatic encephalopathy (grades III and IV).[37] Preference in ICP monitoring device will depend on institutional expertise.

Advantages

Patients with ALF often do not have classic findings of cerebral edema (decerebration, dilated pupils, Cushing triad), and CT findings can be discordant. An ICP monitor is the gold standard for measuring and following ICP and therefore may be quite helpful in this patient population. It allows direct continuous measurements of ICP in real time. Several studies advocate ICP monitoring for its ability to provide important prognostic information about neurologic recovery after liver transplantation and in managing ICH while awaiting transplantation.[38–40] Changes in ICP can quickly be acted upon and may affect the decision to proceed with liver transplant. For example, ICP >20 mm Hg would indicate treatment with mannitol, whereas sustained ICP >40 mm Hg for >2 hours may preclude liver transplantation. Additionally, ICP monitoring may reveal unsuspected sustained ICH, which would require intervention.[40] Therefore ICP monitoring could be considered for patients with high risk for the development of ICH (young age, kidney failure, shorter jaundice-to-hepatic encephalopathy interval, etc.) who are under consideration for liver transplantation. Also, centers could consider ICP monitoring in nontransplant candidates if there is a reasonable likelihood of spontaneous recovery, such as in acetaminophen-induced ALF. In addition to helping with the management of ICH, ICP devices assist with close monitoring during the perioperative period of liver transplantation, because a transient increase in ICP that can last up to 12 hours postoperatively has been reported.[38]

Disadvantages

The use of ICP monitoring may lead to severe complications such as ICH in these critically ill patients with coagulopathy, in addition to infection. A recent multicenter retrospective study of 629 patients (140 with ICP monitors) did not demonstrate any 21-day mortality

difference (33% vs. 38%, P =.24), and subgroup analysis of the nonacetaminophen ALF group actually demonstrated an increased mortality (odds ratio [OR] 3.04, P = .014).[39] Moreover, improved management, as mentioned previously, is not necessarily synonymous with improved survival. It is important to note that studies were limited by the heterogeneity of ICP monitor use, variability in transducers (subdural vs. intraparenchymal), and level of center experience. One prospective study of 92 patients with ALF, high-grade encephalopathy, and ICP monitoring found a 10.3% rate of ICH that likely contributed to the death of two patients.[41] However, nearly half of the cases of intracranial bleeding were incidental radiographic findings without clinical consequence. Regardless of ICP monitor usage, 30-day survival posttransplant was approximately 85% in this study. Other reports confirm that bleeding complications from the placement of ICP monitoring devices in patients with ALF are mostly mild and without clinical significance.[41,42] And one study demonstrated the effectiveness of recombinant factor VIIa in preventing intracranial bleeding in 11 patients with ALF who required ICP monitoring.[43] Overall, use of ICP monitoring remains controversial, but experts agree that these devices should not be used in patients with mild hepatic encephalopathy (i.e., stage I or II) or in patients with evidence of cerebral herniation, hypotension, or imminent death. Ideally it should be performed only in centers vastly experienced with ALF and ICP monitoring and in patients with high risk of ICH.[44,45]

MANAGEMENT OF ENCEPHALOPATHY AND INTRACRANIAL HYPERTENSION

Encephalopathy is a hallmark of ALF. The encephalopathy of ALF is related to both metabolic factors, such as progressive elevation in blood NH_3 concentration, and cerebral edema. Progressively worsening encephalopathy is an ominous clinical feature in ALF; development of grade III or IV encephalopathy may herald the death of the patient as a result of cerebral edema, increased ICP, and central herniation of the brain. Efforts to control the encephalopathy of ALF are directed at preventing or resolving cerebral edema (Box 86.2).[46–49] Arterial hyperammonemia at the time of admission was associated with higher rates of hepatic encephalopathy, ICH, and mortality in patients with ALF cared for at liver transplant centers.[50,51] Therefore most liver transplant centers recommend that lactulose (20–40 g/day in divided doses) be administered enterally to purge the bowel. Exact threshold values of at-risk hyperammonemia are not clear, but usually values greater than 124 μmol/L warrant attention. However, one must exercise caution when using lactulose in the setting of ALF; dosing should be monitored carefully and adjusted to avoid excessive diarrhea, alterations in electrolytes, and volume depletion. If oral (PO) lactulose is given simultaneously with intravenous (IV) mannitol, marked deficits of free water can develop, inducing severe hypernatremia. Alternatively, continuous renal replacement therapy (CRRT) initiated early during admission for ALF demonstrated appreciable reductions in ammonia values over 5 days of therapy.[52] Reduction of hyperammonemia was independent of the type of CRRT (continuous venovenous hemodiafiltration vs. continuous venovenous hemofiltration) or intensity (i.e., ultrafiltration volume) but was associated with a longer duration of CRRT. Although one recent study suggested that infusion of hypertonic (3%) saline to maintain serum sodium concentration between 145 and 155 mEq/L is beneficial to reduce ICH,[53] rapid shifts in sodium concentration have been associated with central pontine myelinolysis (CPM). Further discussion of hypertonic saline is provided later in this chapter. Administration of terlipressin or vasopressin may worsen ICH and should be avoided.[54]

Reversal of coagulopathy before placement of ICP transducers is recommended, but exact targets (INR <1.5–1.9) vary from center to center. Caution should be used, as reversal of coagulopathy may be difficult and require large volumes of fresh frozen plasma (FFP), potentially contributing to volume overload and worsening of cerebral

Box 86.2 Measures Used to Monitor and Control Cerebral Edema Caused by Acute Liver Failure

1. Correction of metabolic abnormalities.
   - Electrolytes (Na, K, Cl, HCO_3).
   - Acid-base (if patient is on mechanical ventilation, induce mild respiratory alkalosis).
   - Glucose (maintenance intravenous glucose infusion).
2. Avoid overtransfusion or overhydration.
   - Carefully match intake and output once patient is euvolemic.
   - Daily weight.
   - Avoid use of blood products unless indicated for ongoing bleeding and correction of coagulopathy or to maintain hemostasis when intracranial monitor has been placed. In the latter circumstance, the patient may require diuresis to avoid an excess in intravascular volume, especially from plasma.
3. Institute dialysis in patients in renal failure.
   - Continuous arteriovenous or venovenous hemodialysis is preferred over standard hemodialysis.
   - Avoid severe volume shifts, stabilize blood pressure, maintain euvolemia, correct electrolyte and acid-base abnormalities.
4. Mechanical ventilation (worsening encephalopathy, >grade II).
   - Main indication in liver failure is airway protection to prevent aspiration pneumonia.
   - Induce mild respiratory alkalosis (pH 7.45–7.50, Pco_2 20–30 mm Hg).
   - Elevate head of bed 15–30 degrees.
   - Use sedation to avoid having the patient "fight the endotracheal (ET) tube."
5. Consider placement of intracranial pressure (ICP) monitor in the epidural space.
   - Should be considered when patients evolve from stage II (agitated confusion) to stage III (stuporous) encephalopathy.
   - Maintain adequate platelet count (>60,000) with platelet transfusions and INR <1.5 with fresh frozen plasma if necessary.
   - Mannitol is used to control ICP in patients with intact renal function or in those on dialysis. Mannitol is given in 0.5–1 g/kg doses. Serum electrolytes, glucose, and osmolarity should be checked every 4–6 hours. If ICP is elevated, osmolarity <310, and Na <145, then give mannitol. Mannitol should be withheld if the patient has excessive serum osmolarity or significant hypernatremia.

edema. Recombinant human factor VIIa infusion (40 to 90 μg/kg bolus, repeated as needed every 4 hours to correct INR) may be preferred over FFP in this setting for limiting volume infusion and rapidly correcting the PT/INR.

Hepatic glycogen, the main storage supply of glucose, is depleted early in the course of ALF, predisposing to severe, potentially life-threatening hypoglycemia and worsening of cerebral energy metabolism. All patients with ALF should be treated with glucose infusions, and blood glucose concentration must be monitored frequently.

Second-Line Therapies for Treatment of Mannitol-Refractory Intracranial Hypertension

Hypothermia in Acute Liver Failure

Therapeutic hypothermia, or intentional reduction of core body temperatures, has been increasingly used to treat hypoxic brain injury after cardiac arrest. Animal models of ALF suggest that hypothermia may be effective in the prevention of cerebral edema.[55,56] Several case series suggest that therapeutic hypothermia may show efficacy in patients awaiting liver transplantation.[57–59] However, a multicenter retrospective cohort study from the US Acute Liver Failure Study Group revealed that hypothermia (body temperature target 32°C–35°C) improved 21-day overall and transplant-free survival in only a subset of young (<25 years) patients with acetaminophen-associated ALF and high-grade encephalopathy, but not for the entire cohort of 97 patients.[60] Based on this analysis, physicians must wait for a prospective trial to further elucidate the use of hypothermia in this clinical setting.

Hypertonic Saline in Acute Liver Failure

Another possible method for treating refractory ICH during ALF is the use of hypertonic saline. Hypertonic saline infusion requires extreme caution because of the potential consequence of osmotic shifts across the BBB. However, a presumed advantage of hypertonic saline for the treatment of ICH is a higher osmotic reflection coefficient across the BBB.[61–63] Thus hypertonic saline could potentially lead to a reduction in cerebral edema, lower ICPs, and improved perfusion by developing a higher osmotic gradient in the cerebral vascular compartment. In a randomized placebo-controlled study, Murphy and colleagues studied the effect of hypertonic saline infusion on the induction of hypernatremia in patients with ICP and clinical outcomes among intensive care unit (ICU) patients with ALF.[64] Fifteen patients were treated with 30% hypertonic saline (5–20 mL/h) to maintain serum sodium levels between 145 and 155 mmol/L. After 24–72 hours, ICP reduction was significantly greater in the treatment group compared with the standard care group. However, high osmolar loads and continuous hemofiltration were required. Nevertheless, mortality was similar between both treatment and standard care groups. The use of hypertonic saline in the management of ICH in ALF warrants further investigation, but its use is accepted as prophylactic therapy by societal guidelines for patients with the highest risk of developing cerebral edema.[65]

Other Options for Refractory ICH

Other potential therapies that can be considered in ALF patients with refractory ICH include barbiturates such as pentobarbital or thiopental and indomethacin. By inducing a comatose state and reducing cerebral edema, pentobarbital (3–5 mg/kg IV load, then 1–3 mg/kg/h infusion) or thiopental (5–10 mg/kg load, then 3–5 mg/kg/h infusion) showed some benefit in refractory ICH.[66] However, severe side effects such as arterial hypotension, hypokalemia, and prolonged coma limit their use and often necessitate the coadministration of vasopressors in order to maintain cerebral perfusion pressure (CPP) above 50 mm Hg. Indomethacin (dosed at 25 mg IV over 1 minute) also has the potential to cause an acute decrease in ICP and an acute increase in CPP by causing cerebral vasoconstriction but has not been validated in a trial.[67,68] Therefore these medications may play a role as second- or third-line options for patients with persistent refractory ICH.

Experimental Therapies

Several other methods were tested in ALF: exchange blood transfusion, plasmapheresis, cross-circulation with human and baboon donors, hemoperfusion through isolated human or animal livers, hemodialysis (conventional and polyacrylonitrate), and column hemoperfusion (microencapsulated charcoal, albumin-covered Amberlite XAD-7 resin). Because none of these techniques were demonstrated to improve survival, their use in the management of ALF is not currently recommended.

Promising strategies that were investigated in the management of patients with high-grade encephalopathy in the setting of ALF include an extracorporeal liver assist device based on albumin dialysis (molecular adsorbent recirculation system [MARS]). However, its use did not yield clear survival benefit.[69] Bioartificial liver (BAL) machines have also emerged as a potential therapeutic intervention. To date, there was only one large randomized multicenter trial of the use of BAL in ALF, and it did not conclude a survival benefit.[70] Finally, the use of human hepatocyte transplantation in the setting of ALF as a bridge to transplantation is in persistent development.[71,72]

Liver Transplantation

Liver transplantation is the only treatment that was proven to improve survival in patients with ALF and high-grade encephalopathy.[6,73] Survival without transplantation is 10%–20% in this patient subset. Survival increases to 60%–80% with liver transplantation. In the largest series of living donor liver transplants for ALF, Lee and colleagues reported patient survival as 82.3% at 5 years after transplantation.[74] These results are similar to those of deceased donor liver transplantation for ALF and demonstrated the durability of living donor allografts.

At some stage cerebral edema becomes irreversible and patients, despite transplantation, will experience brain death or irreversible brain injury.[75] The risk of irreversible neurologic injury is greatest in those with CPP less than 40 mm Hg for more than 4 hours. Lesser increases in ICP may be associated with neurologic injury, but usually cerebral edema resolves in the posttransplant period, and complete or partial neurologic recovery may be expected. In most cases of ALF, all the manifestations of neurologic illness (cerebral edema, encephalopathy, and coma) reverse without sequelae after successful liver transplantation. One complication, CPM, may occur in the absence of cerebral edema and may be related to fluctuations in plasma sodium during resuscitative measures in the ICU, such as IV fluids, transfusions, antibiotics, sedatives, narcotics, invasive procedures, and ventilatory support. Despite the serious nature of CPM, significant neurologic recovery can occur.

ENCEPHALOPATHY IN THE SETTING OF CHRONIC LIVER DISEASE

Patients with cirrhosis of any cause and chronic PSE may present with a host of neuropsychiatric symptoms, ranging from subtle changes in mental status to coma. Fetor hepaticus (a peculiar odor to

the breath in people with severe liver disease) is common but not invariable. Asterixis, the "flapping tremor," is caused by involuntary intermittent relaxation of sustained motor activity but is less specific than fetor hepaticus for hepatic encephalopathy and is usually only present during the late stages of encephalopathy. Although reported, cerebral edema rarely occurs in patients with encephalopathy in the setting of chronic liver disease. As the patient recovers from hepatic encephalopathy, asterixis and other manifestations of encephalopathy resolve.

Risk Factors and Precipitating Events: Implications for Diagnostic Testing and Treatment

Flares of chronic encephalopathy may occur spontaneously without an identifiable precipitant in patients with very severe hepatic impairment and/or extensive portosystemic shunting. However, in the majority of cases, acute worsening of chronic encephalopathy is precipitated by one or more of a number of common events.

Gastrointestinal Hemorrhage

Hemodynamically significant gastrointestinal (GI) hemorrhage is a major precipitant of hepatic encephalopathy. Delivery of a large protein load to the GI tract via hemorrhage stimulates bacterial metabolism of luminal blood and release of NH_3, GABA, and other chemicals or compounds that may inhibit neurotransmission. Poor hepatic function or shunting of portal blood via portosystemic collaterals impairs hepatic clearance and enhances delivery of these molecules to the brain.

Infection

Infection—in particular, sepsis—may precipitate hepatic encephalopathy in patients with chronic liver disease. Spontaneous bacterial peritonitis (SBP) always should be considered in the differential diagnosis of patients with ascites and new-onset encephalopathy. Fever may be absent, and clinical signs (abdominal pain, ileus) are lacking. SBP is presumptively diagnosed if the absolute neutrophil count in ascitic fluid exceeds 250 cells/mL. Patients with cirrhosis and malnutrition are susceptible to infections as a result of reduced leukocyte migration, decreased serum bactericidal activity, depressed white cell mobilization, and impaired phagocytosis. Infection increases protein catabolism, releasing aromatic amino acids that may contribute to the encephalopathy.

Medications (Sedatives)

There are no safe sedatives for administration in cirrhotic patients who have hepatic encephalopathy. Because liver metabolism is usually severely impaired in these patients, the clearance of benzodiazepines, barbiturates, chlorpromazine, morphine, and opioid derivatives such as methadone, meperidine, and codeine are reduced. With repeated dosing, all these compounds tend to accumulate in cirrhotic patients, increasing the degree and prolonging the duration of sedation.

Renal Failure

A common precipitant of hepatic encephalopathy is excessive diuresis, resulting in relative depletion of intravascular volume and prerenal azotemia. Factors contributing to the encephalopathy include electrolyte imbalances; disordered acid-base metabolism; reduced fluid volume; and impaired renal clearance of metabolites, drugs, and toxins.

Fluid, Electrolyte, and Acid-Base Imbalance

Hepatic encephalopathy may be precipitated by dehydration, hypokalemia, and alkalosis. Metabolic alkalosis promotes an increase in levels of nonionic NH_3, which diffuses very rapidly into the CNS. Diffusion of NH_3 into the brain and enhanced glutamine production may precipitate encephalopathy as a result of either astrocyte swelling and dysfunction or impairment of glutamatergic neurotransmission. With hepatic impairment, the kidneys produce glucose from branched-chain amino acids (gluconeogenesis) in an attempt to maintain peripheral energy supply. This process results in decreased circulating levels of branched-chain amino acids and an increase in circulating levels of the relatively more toxic aromatic amino acids, which may diffuse into the brain.

Surgical Shunt Procedure or Tips

Hepatic encephalopathy is a common complication of portal diversion after surgical portosystemic shunts or TIPS.[76] Predictors of postshunt encephalopathy include preshunt encephalopathy, severe liver disease (Child-Pugh score >10 or Model-for-End-Stage-Liver-Disease [MELD] score >16), renal failure, and elderly age. The mechanisms of hepatic encephalopathy after placement of a portosystemic shunt include lack of compensatory dilatation of the hepatic artery, lack of perfusion of the liver via the portal vein, and reduction in hepatocyte function. Clinically apparent encephalopathy after placement of a shunt usually responds to medical treatment. In rare circumstances, narrowing of the shunt with a flow-reducing stent or occlusion of the shunt may be necessary to control encephalopathy.[77]

Portosystemic Shunting from Collaterals

In cases of refractory encephalopathy, patients should undergo contrast-enhanced abdominal imaging to visualize the presence of prominent portosystemic collateral vessels. If large collaterals are seen, selected patients may benefit from embolization of these collaterals.[78,79]

Noncompliance with Therapy

One of the most common factors precipitating encephalopathy is noncompliance with prescribed outpatient medical treatments (e.g., lactulose). A careful history, focusing on adherence to medical therapy, is necessary in the evaluation of encephalopathic patients.

Microbiota Dysbiosis

Research regarding gut microbiota dysbiosis has gained recent interest. Dysbiosis in chronic liver disease was associated with increased intestinal permeability, systemic inflammation and endotoxemia, and increased impairment of cognition and rates of hepatic encephalopathy.[80] Clinical improvement in patients with recurrent hepatic encephalopathy treated with fecal microbiota transplant supports the role of gut dysbiosis as a potential mechanism of disease.[81]

Diagnosis

The diagnosis of PSE is based upon clinical suspicion in patients with chronic liver disease, and the impression is confirmed by resolution after medical therapy.[82] Occasionally, it may be necessary to employ additional testing to confirm a diagnosis of PSE. Additional testing is particularly useful when encephalopathy is the primary clinical manifestation of otherwise unsuspected liver disease or if the manifestations of encephalopathy are predominantly a change in behavior or an unusual neurologic syndrome (seizures, focal neurologic deficits). Rarely, cerebral edema complicates chronic liver disease.[83]

Plasma Ammonia

An elevated blood NH_3 level is common in cirrhotic patients, especially those with encephalopathy. Some studies have demonstrated a correlation between blood NH_3 levels and the presence and grade of encephalopathy, whereas others have not. In general, blood NH_3 levels might be useful as a marker of liver disease but are of little diagnostic or clinical value in managing the cirrhotic patient with hepatic encephalopathy.

Electroencephalography

Electroencephalographic (EEG) abnormalities are relatively nonspecific in hepatic encephalopathy. Two findings have some specificity with regard to hepatic encephalopathy: reduced brainstem auditory-evoked potentials and diminished visual-evoked potentials. In various studies, the percentage of encephalopathic cirrhotics with EEG abnormalities is highly variable, ranging from 14% to 78% of patients.

Radiologic Imaging

Standard CT scans or nuclear brain scans exhibit little or no specific distinguishing features, although loss of cortical volume may be common in patients with Laënnec cirrhosis and chronic encephalopathy. CT may be used to document cerebral edema or to exclude CNS complications such as tumor, infection, or hemorrhage. Magnetic resonance imaging (MRI) studies have revealed a few features relatively unique to hepatic encephalopathy. One feature, hyperintensity on T1-weighted images of the globus pallidus (Fig. 86.3), correlates with (extrapyramidal) motor disorders and excess accumulation of manganese.

Neuropsychiatric Testing

In general, neuropsychiatric testing is used primarily to monitor efficacy of treatment or diagnose subclinical or minimal encephalopathy. A battery of tests is employed to distinguish hepatic encephalopathy and organic brain syndrome from other causes of encephalopathy and underlying psychiatric disease. These tests are itemized in Table 86.2. Poor performance on number connection tests correlates reasonably well with severity of encephalopathy and Child-Pugh and/or MELD classifications.

Therapeutic Options

Past thoughts on the treatment of hepatic encephalopathy included a protein-restricted diet of 40 grams or less per day.[84,85] However, cirrhotic patients often develop severe muscle wasting; thus in patients with advanced disease, unnecessary protein restriction might further worsen the poor nutritional state. Therefore hepatologists currently avoid the use of protein restriction in the management of chronic hepatic encephalopathy.

Lactulose

The mainstay of therapy in the treatment of hepatic encephalopathy is lactulose, a nonabsorbable disaccharide that is fermented by bacteria in the intestine to yield acetic, butyric, propionic, and lactic acids.[85–88] The fermentation of lactulose produces an acidic milieu that alters the composition of gut bacterial flora, lowers colonic pH, and produces an osmotic diarrhea. Each of these effects may be responsible for the ameliorative effects of lactulose on hepatic encephalopathy. Changing the composition of the bacterial flora may alter the metabolism of fecal contents and reduce the production of toxins, NH_3, and methanethiols that are responsible for encephalopathy. The acidic luminal milieu creates an environment capable of trapping NH_3:

$$NH_3 + H^+ \Rightarrow NH_4^+$$

Ammonia is neutral and freely diffuses across the mucosal barrier of the colon, where it can enter the portal circulation for delivery to the rest of the body. In contrast, the ammonium ion (NH_4^+) produced from the reaction of NH_3 with hydrogen ions is ionized, highly polar, and unable to diffuse readily across the lipid bilayer of mucosal cells.

Fig. 86.3 Computed tomography (CT) scan of the brain of a patient with acute liver failure, stage IV hepatic coma, and cerebral edema. Note the diminished sulci and lack of distinction between white and gray matter. This patient's cerebral edema resolved with medical management, and she subsequently underwent transplantation. She achieved complete neurologic recovery posttransplant.

TABLE 86.2 Neuropsychiatric Tests Used to Evaluate Hepatic Encephalopathy

Cerebral Function	Test
Learning and delayed recall	Story Memory Test
	Figure Memory Test
Concentration	Digit Vigilance Test
Fine motor coordination	Grooved Pegboard
Sequential procedures	Trail Making Test
Problem solving	Wisconsin Card Sorting Test
Attention	WAIS-R* Digit Symbol Subtest
Vocabulary	WAIS-R Vocabulary Subtest
Verbal fluency skills	Controlled Oral Word Association
	Animal Naming
Auditory comprehension	Complex Material
Visual-spatial analysis	WAIS-R Block Design Subtest
Psychological function	MMPI-2†

*WAIS-R, Wechsler Adult Intelligence Scale–Revised.
†MMPI-2, Minnesota Multiphasic Personality Inventory.

This ammonium ion is "trapped" in the fecal effluent and eliminated with passage of the bowel movement. In addition to these properties, the breakdown of each molecule of lactulose produces at least four osmotically active particles. Water diffuses into the lumen and down the osmotic gradient, increasing fecal water content, and if enough lactulose is given, a dose-dependent osmotic diarrhea results. The purgative effect of lactulose may also be responsible for altering the composition of colonic bacteria and helping to eliminate toxins and waste that might otherwise accumulate. The usual recommendation is that enough lactulose be given to produce two to three loose, semiformed stools each day. Excessive dosing with lactulose will produce severe diarrhea with large volume losses and electrolyte imbalances and should be avoided.

Rifaximin

Rifaximin is a nonabsorbable antibiotic derivative of rifamycin with broad antimicrobial activity and has become an important adjunct agent along with lactulose for the treatment of hepatic encephalopathy. A randomized controlled trial of 299 patients demonstrated a reduction of recurrent hepatic encephalopathy episodes and number of hospitalizations resulting from hepatic encephalopathy.[89] In comparison studies of rifaximin with lactulose versus lactulose monotherapy, patients treated with rifaximin showed greater improvement in the degree of hepatic encephalopathy, had lower NH_3 levels, and had lower PSE index scores.[90]

Branched-Chain Amino Acids

Early studies demonstrated that cirrhotic patients had an increase in aromatic amino acids and a decrease in branched-chain amino acids in blood samples. Subsequent clinical work suggested that patients with the greatest imbalance in plasma amino acids were more likely to be encephalopathic and to experience early and higher mortality. For this reason, there were at least 14 controlled trials of the use of branched-chain amino acids in the treatment of cirrhotic patients with chronic encephalopathy. However, results of these trials have been inconsistent, and separate meta-analyses yielded opposite conclusions.[91] A trial of branched-chain amino acids might be considered in patients who develop encephalopathy on standard protein diets and manifest protein-calorie malnutrition.

Benzodiazepine Antagonists

There were several randomized controlled trials of short-term administration of flumazenil in the treatment of hepatic encephalopathy.[92–94] In some studies, flumazenil was superior to placebo in improving the grade of encephalopathy; 30%–60% of encephalopathic patients improved after administration of flumazenil, and EEG changes paralleled this improvement. In other studies, however, flumazenil was no better than placebo in ameliorating the symptoms of encephalopathy, and EEGs did not improve. Overall, flumazenil has a limited role in the treatment of hepatic encephalopathy.

L-Ornithine-L-Aspartate and Ammonia Scavengers

l-ornithine-l-aspartate (LOLA) is a compound salt that was shown to reduce NH_3 levels by increasing NH_3 disposal through enhanced peripheral metabolism. LOLA increases the activity of hepatic urea cycle enzymes and increases the rate of glutamine production within skeletal muscle. Although a large randomized controlled study using LOLA in ALF did not find significant changes in survival,[95] other studies investigated its potential use in hepatic encephalopathy from chronic liver disease. A meta-analysis consisting of three randomized trials and a pool of 212 patients found an overall significant improvement in chronic hepatic encephalopathy symptoms, although lower-grade encephalopathic patients had the greatest benefit.[96]

Additional agents (i.e., glycerol phenylbutyrate and ornithine phenylacetate) that were initially developed for ammonia reduction in patients with inborn urea cycle defects are also being tested in clinical trials for the management of chronic hepatic encephalopathy.[97,98]

Neomycin and Metronidazole

The systemic antibiotics neomycin and metronidazole are used as second-line therapy of chronic hepatic encephalopathy with the goal of therapy being alteration of the colonic bacterial composition. Neomycin's advantage over metronidazole is its limited entrance to the circulation.[99] The main disadvantage is that nephrotoxicity may occur despite its poor absorption.

Some studies demonstrated that oral metronidazole was as effective as neomycin or lactulose in controlling encephalopathy.[100] Other studies did not observe similar efficacy and measured little effect of metronidazole on NH_3 levels. The main disadvantages of metronidazole are that many patients complain of epigastric discomfort (leading to poor compliance with long-term treatment) and development of ototoxicity and neurotoxicity that can be irreversible. Maintenance therapy with metronidazole can be expected to cause peripheral neuropathy (already a problem in patients with advanced liver disease) and was reported to cause the "disulfiram reaction" when alcohol was consumed. The physician prescribing metronidazole to cirrhotic patients should be aware that this drug undergoes extensive hepatic metabolism. Given the establishment of rifaximin, neomycin and metronidazole are now rarely used. If these antibiotics are used in selected cases, it is recommended to give only short courses lasting 2–8 weeks.

Liver Transplantation

The development of encephalopathy in a patient with chronic liver disease indicates the presence of portosystemic shunting and hepatic dysfunction. The prognosis for patients who develop this complication is grim; one recent study indicated that the 1-year survival rate is 42% and the 3-year survival rate is 23%.[101] In addition, there are numerous comorbidities in encephalopathic patients, including the inability to continue gainful employment, poor function at home, nursing strains on spouse or family, inability to drive a vehicle, and inability to handle personal finances. Although medical therapies can ameliorate the major symptoms of encephalopathy, they are rarely effective enough to return the patient to full function. Often the patient with encephalopathy is at risk of other life-threatening complications of liver disease such as variceal hemorrhage and SBP. For all of these reasons, any patient with hepatic encephalopathy should be considered for liver transplantation.

CONCLUSION

This chapter discussed several key issues regarding hepatic encephalopathy, including definitions, clinical syndromes, diagnostic tests, precipitants, prognosis, and outcomes with therapy, including liver transplantation. The section on pathogenesis defines current knowledge regarding mechanisms of encephalopathy in both ALF and chronic liver disease. The clinician faced with neuropsychiatric syndromes in patients with liver disease must differentiate the nature of the underlying liver disorder (ALF versus chronic liver disease), evaluate diagnostic tests, and institute appropriate therapy. Overall outcomes of patients with encephalopathy depend on the general condition of the patient, severity of underlying liver disease, comorbid conditions, and, when in ALF, the presence of cerebral edema and ICH. Liver transplantation, including the option of living donor liver transplantation, may yield favorable outcomes without neurologic sequelae if instituted before excessive and prolonged ICH in the case of ALF, or before multiorgan failure in the case of chronic liver disease.

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KEY POINTS

- Clinical presentation and prognosis of hepatic encephalopathy vary by presence of ALF or chronic liver disease.
- Patients with hepatic encephalopathy and ALF should urgently be referred to a liver transplant center.
- The routine use of ICP monitors in patients with ALF is controversial.
- Mannitol and hypertonic saline are common therapies for ICH in the setting of ALF.
- Precipitants of hepatic encephalopathy should be assessed with each episode in the setting of chronic liver disease.
- Lactulose is the mainstay of therapy in patients with hepatic encephalopathy and chronic liver disease.
- Rifaximin has become an important therapy to prevent recurrent episodes of hepatic encephalopathy in the setting of chronic liver disease.

References for this chapter can be found at expertconsult.com.

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Acute Liver Failure

Stephen Warrillow and Caleb Fisher

INTRODUCTION

Acute liver failure (ALF), also known as *fulminant hepatic failure,* is a compelling example of complex critical illness. The initiating event is extreme liver injury from a variety of possible causes. Thereafter, a severe multisystem critical illness rapidly develops, involving disruption of function in virtually all organ systems (Fig. 87.1). Although ALF is a relatively rare cause of admission to the intensive care unit (ICU),[1] it is important because it predominately affects those who are young and have few comorbidities, yet it has a high mortality. Management challenges include hepatic encephalopathy, cerebral edema, disordered hemostatic parameters, hemodynamic instability, metabolic abnormalities, renal failure, and vulnerability to infection. Although some causes of ALF have etiology-specific treatments, most ICU management involves supportive care and prevention of complications, with the hope that life can be sustained until either hepatic regeneration takes place or emergency liver transplantation can occur. As with any complex or rare condition, a systematic and coordinated approach is required so as to ensure that all problems are anticipated and addressed.

Definition

Despite a lack of a consensus definition,[2] it is generally accepted that the diagnosis of ALF requires the triad of encephalopathy (regardless of severity), abnormal measures of hemostasis (generally elevation of the international normalized ratio [INR] or prolongation of the prothrombin time [PT]), and the development of overt liver failure over a short interval in the absence of previously known liver disease. A number of classification systems have sought to define the cardinal features of ALF and patterns of presentation. In particular, the duration of illness before the onset of encephalopathy is strongly associated with specific underlying etiologies and associated outcomes.[3] Hyperacute patients develop an altered mental state within a week of first becoming unwell and are often critically ill at initial presentation. Acute presentations are those with an illness duration of 7–21 days before encephalopathy, whereas subacute presentations involve the onset of encephalopathy up to 26 weeks after initial symptoms occur. Paradoxically, hyperacute patients have the highest spontaneous survival rate.

Etiology

Although the causes of ALF are myriad (Box 87.1), there is marked variation in etiology across regions, with a relatively small number of underlying causes being responsible in any given locality.[4] This has important implications for management and outcomes.

Drug-Induced Liver Injury

Drugs, traditional remedies, and toxins are important causes of ALF in most countries. There are two broad types of drug-induced liver injury: direct hepatotoxicity and idiosyncratic hepatotoxicity.

Direct Hepatotoxicity

Severe liver injury from exposure to a known hepatotoxin that produces dose-related liver damage is the most common single cause of ALF in many countries. The typical onset of ALF after ingestion of a supratherapeutic or toxic dose is abrupt for most drugs, and the usual pattern is of major hepatic necrosis.

Acetaminophen (Paracetamol)

Acetaminophen is the most common cause of ALF in most anglophone countries, where it may account for more than half of all ALF cases.[1] A single major overdose (often with delayed presentation) is typical; however, some result from staggered supratherapeutic ingestion that may be deliberate, inadvertent, or iatrogenic. Poor nutrition, low body mass, and cytochrome P-450 enzyme–inducing medications may predispose to toxicity. The link between chronic alcohol excess and vulnerability to acetaminophen poisoning has not been fully elucidated.[5] A thorough history (including from family members) may identify the timing and amount ingested; however, information may be unreliable, limiting the utility of nomograms to determine risk and guide treatment decisions. Acetaminophen usually undergoes glucuronidation and is then excreted into the bile. The toxicity of acetaminophen overdose occurs through the generation of a toxic metabolite (*N*-acetyl-*p*-benzoquinone imine [NAPQI]) by cytochrome P-450 enzymes. If the ability to metabolize acetaminophen via glucuronidation is overwhelmed and the capacity to detoxify NAPQI through conjugation with glutathione is exceeded, massive hepatic necrosis will follow. The early initiation of n-acetylcysteine (NAC) may prevent the development of serious liver injury and attenuate it if hepatic necrosis has already commenced.

Nonacetaminophen Direct Hepatotoxins

A range of other medications can also cause liver injury via direct mechanisms (see Box 87.1). Patterns of acute hepatic injury vary from hepatic necrosis, to sinusoidal obstruction syndrome, to microvesicular steatosis.

Idiosyncratic Drug-Induced Liver Injury

Idiosyncratic liver injury usually takes the form of acute hepatocellular hepatitis, with a period of latency that typically extends to several weeks. Other less common forms include cholestatic hepatitis and mixed hepatitis. Antiinfectives, psychotropics, and nonsteroidal antiinflammatory drugs are commonly implicated. Idiosyncratic drug-induced hepatitis may variably be accompanied by hypersensitivity features, such as rash, fever, and eosinophilia.

Herbal Remedies, Nutritional Supplements, Traditional Medicines, and Illicit Drugs

Nonprescription alternative therapies and illicit drugs are widely used in many populations and represent an important cause of ALF.

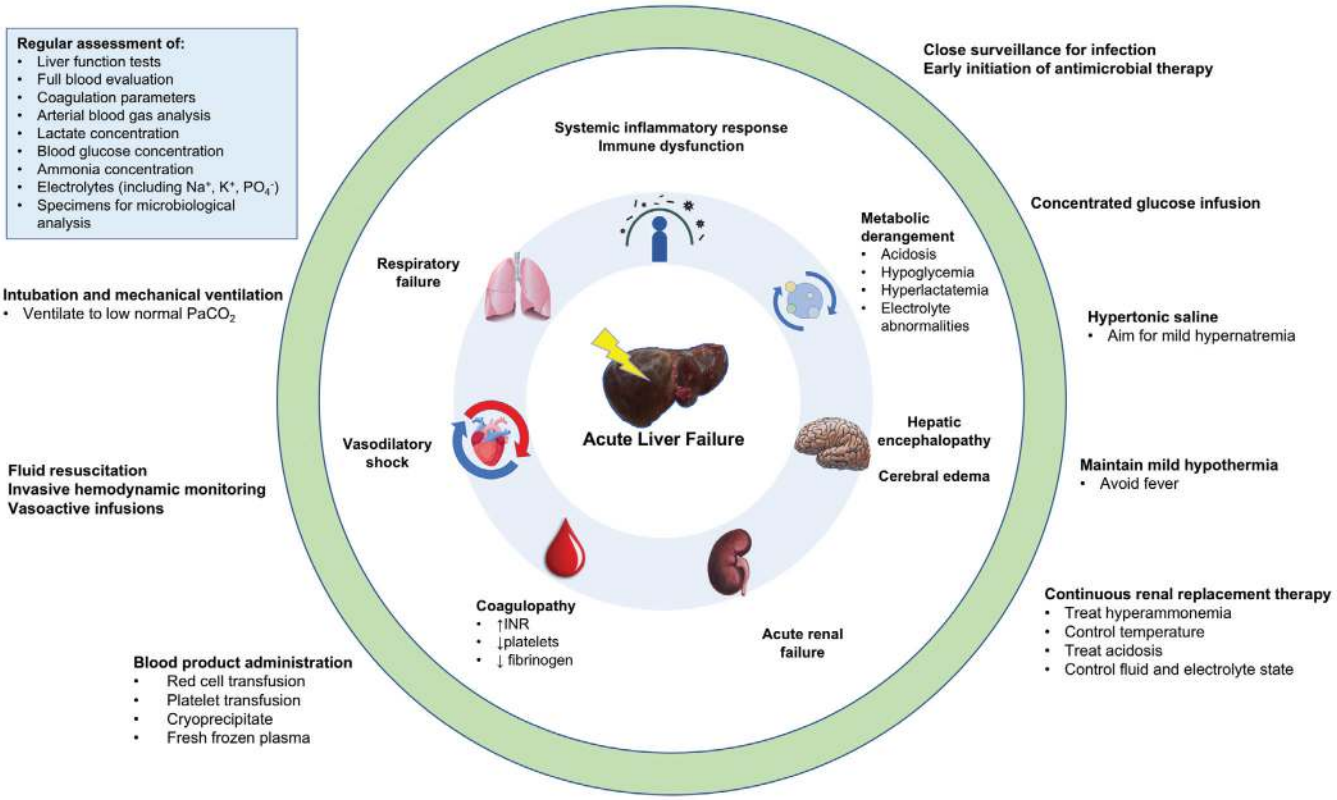

Fig. 87.1 Key management challenges in acute liver failure.

BOX 87.1 Causes of Acute Liver Failure

Drugs

Dose related (predictable):
- Acetaminophen
- Aspirin
- Niacin

Idiosyncratic (unpredictable and individually rare):
- Isoniazid
- β-lactams
- NSAIDs
- Herbal remedies
- 3,4-Methylenedioxymethamphetamine (ecstasy)

Toxins
- *Amanita* mushroom
- Carbon tetrachloride
- Yellow phosphorous

Viral

Hepatotropic:
- HAV
- HBV
- HDV
- HEV

Nonhepatotropic:
- HSV
- CMV
- EBV
- Parvovirus B19

Vascular Thrombosis
- Budd-Chiari syndrome

Inherited Metabolic Disorders
- Wilson disease

Pregnancy-Related
- Acute fatty liver of pregnancy

Other
- Autoimmune hepatitis
- Reye syndrome
- Cryptogenic

CMV, Cytomegalovirus; *EBV,* Epstein-Barr virus; *HAV,* hepatitis A virus; *HBV,* hepatitis B virus; *HDV,* hepatitis D virus; *HEV,* hepatitis E virus; *HSV,* herpes simplex virus; *NSAID,* nonsteroidal antiinflammatory drug.

Patients may not disclose the use of such agents, and direct enquiry is necessary.

Viral Hepatitis

Hepatotropic Viruses

Four out of the five generally recognized hepatotropic viruses are established causes of ALF. Hepatitis C virus (HCV) is a prominent cause of chronic liver disease, but almost never results in ALF.[6]

Hepatitis A

Most cases of hepatitis A virus (HAV) follow a relatively benign course, but occasional cases lead to life-threatening ALF, especially for adults with preexisting liver disease. The virus is spread via the fecal-oral route (usually ingestion of contaminated food or drinking water), and vaccination is protective when traveling to endemic regions. Serologic diagnosis is generally made on detection of anti-HAV immunoglobulin M (IgM) antibodies.

Hepatitis B

Hepatitis B virus (HBV) can cause ALF at the time of initial acquisition, through reactivation of a latent infection, or with coinfection by hepatitis D virus (HDV). The virus may be vertically transmitted during pregnancy or acquired through either blood exposure or unprotected sexual activity. Detection of IgM antibodies against hepatitis B core antigen (HbcAg) is the key serologic marker indicator of active disease. Immunosuppression may reactivate HBV in chronic carriers, resulting in a subacute presentation that is associated with a poor prognosis.[7]

Hepatitis D

HDV is a defective virus that can only replicate in circumstances of coinfection with HBV, and its acquisition in chronic HBV carriers has been reported to occasionally result in ALF.[6] Diagnosis of acute infection by HDV may be determined through the detection of HDV RNA or the presence of HDV antigen and anti-HDV IgM antibody.

Hepatitis E

Whereas hepatitis E virus (HEV) is rare in developed regions, it is a common cause of ALF in some resource-limited countries, with pregnant women being disproportionally affected. ALF from HEV is associated with high maternal and fetal mortality. Instances of HEV being transmitted by travelers returning from endemic regions have been reported. Similar to HAV, the virus is spread via the fecal-oral route and is diagnosed through the detection of anti-HEV IgM antibodies.

Other Viral Causes of ALF

Several nonhepatotropic viruses, especially Herpesviridae, are recognized to cause sporadic ALF and should especially be considered in situations where there are typical features of a specific infective agent (e.g., mucocutaneous lesions from varicella) in the absence of another clear cause.

Cryptogenic Acute Liver Failure

No clear cause can be found for ALF in up to a fifth of cases.[1] These may represent infection with as yet unidentified viral pathogens, unusual manifestations of autoimmune hepatitis (AIH), or unrecognized idiosyncratic drug reactions.

Other Causes of ALF

Ischemic Hepatitis

Cases of severe shock, especially if associated with hepatic congestion (e.g., cardiac tamponade), can result in ALF. The underlying cause of circulatory failure is the main determinant of outcome, rather than the extent of liver injury per se. If effective resuscitation and reversal of the primary problem occur, hepatic recovery usually follows, and specific liver-directed therapies are rarely required.

Autoimmune Hepatitis

Although AIH usually manifests as a chronic disorder, an important minority of cases may present with a subacute progression to ALF. Women are most commonly affected, and autoimmune markers in addition to liver biopsy are usually required for diagnosis. Corticosteroids for immunosuppression may achieve effective disease control in some patients, occasionally preventing deterioration and need for emergency liver transplantation (ELT).

Amanita Mushroom Poisoning

Amanita phalloides has a wide geographic spread and an appearance similar to several common edible mushrooms. Amatoxins are heat stable, and a single large mushroom may contain sufficient amounts to cause ALF. Many patients will experience early gastrointestinal upset that resolves before subsequent overt liver failure occurring several days later.

Wilson Disease

Wilson disease is a rare inherited disorder of copper accumulation that is typically diagnosed before the onset of overt liver failure, but may occasionally present with ALF, hemolysis, and thrombocytopenia as the first presentation. The prognosis without ELT is extremely poor, and treatment is focused on supportive measures until transplantation can occur.

Budd-Chiari Syndrome

Thrombosis of the hepatic vein is a rare cause of ALF and is usually associated with an underlying prothrombotic state, such as malignancy (especially myeloproliferative disorders). The overall prognosis is poor, especially if occurring in the context of malignancy.[8]

Acute Fatty Liver of Pregnancy

This catastrophic illness occurs exclusively in the third trimester of pregnancy and is characterized by microvesicular fatty infiltration of hepatocytes causing ALF. Fetal defects in fatty acid oxidation appear to be the underlying trigger. Urgent recognition and delivery are essential to prevent fetal and maternal death.[9]

Reye Syndrome

Reye syndrome is a rare pediatric condition strongly linked to aspirin use in the setting of a viral illness. Clinical features, rather than specific investigations, are key to making the diagnosis. Supportive care achieves full recovery in the majority of those affected.[10]

Predictive Scoring Systems

ELT is the only intervention proven to improve survival in ALF, yet many patients may achieve ELT-free survival with supportive care alone. The decision to proceed with ELT can therefore be extremely challenging. Several systems to guide clinical decision making have been developed in order to differentiate patients at high risk of death without ELT from those who may be reasonably expected to survive with supportive care alone. It is clear that in addition to the severity of liver damage and associated complications, important determining factors for outcome include the underlying etiology and patient age.[11] Several of the main predictive criteria are summarized in Box 87.2. The

BOX 87.2 Predictive Criteria for Death Without Emergency Liver Transplantation

King's College Criteria[14]

Acetaminophen Overdose

- Arterial pH <7.3 (irrespective of grade of encephalopathy)

or

- PT >100 seconds (INR >6.5) and
- Serum creatinine >3.4 mg/dL (>300 μmol/L) and
- Patients with West Haven grade III and IV hepatic encephalopathy

Nonacetaminophen-Induced Liver Injury

Acute form (delayed jaundice-encephalopathy <7 days):

- PT >100 seconds (INR >6.5) (irrespective of grade of encephalopathy)

or any three of the following variables:

- Aged <10 or >40 years
- Non-A, non-B hepatitis, halothane hepatitis, idiosyncratic drug reactions

Subacute form: delayed encephalopathy >7 days

- Serum bilirubin 17.4 mg/dL (300 μmol/L)
- PT >50 seconds

Clichy Criteria[15]

- Grade III or IV encephalopathy

and

- Factor V <20% in patients <30 years

or

- Factor V <30% in patients >30 years

Liver Biopsy[13]

- ≤60% necrosis on transjugular biopsy associated with ELT-free survival

Computed Tomography[12]

- Liver volume <1000 cm^3 predicts failure to achieve ELT-free survival for nonacetaminophen ALF

ELT, Emergency liver transplantation; *INR,* international normalized ratio; *PT,* prothrombin time.

utility of such scoring systems has been questioned, as some elements may be subjective (e.g., grade of encephalopathy) and many others are inevitably altered by various critical care interventions (e.g., use of continuous renal replacement therapy [CRRT]). Although they remain in widespread use, improvements in outcome (especially for the hyperacute pattern of ALF such as acetaminophen related) justify concerns that none demonstrate sufficient precision to be the sole determinant for selecting ELT candidates.[11] Imaging with computed tomography (CT) to ascertain residual liver volume may assist prognostically.[12] Liver biopsy may be safer via a transjugular route than the percutaneous approach and can be diagnostically useful in some circumstances.[13]

Although acetaminophen often presents as hyperacute liver failure with extreme physiologic and biochemical derangement, ELT-free survival is considerably more common than for other causes of ALF.[1] Similar findings apply to HAV and acute fatty liver of pregnancy (AFLP), where patients generally achieve ELT-free survival with optimal supportive care. This is often not the case for patients with ALF caused by idiosyncratic drug reactions, HBV, AIH, Wilson disease, or Budd-Chiari syndrome (BCS). Paradoxically, patients with hyperacute ALF presentations often have higher initial illness severity, yet are more likely to survive through spontaneous hepatic regeneration and supportive care, whereas patients with a subacute ALF pattern may be less dramatically unwell at presentation, but relentlessly deteriorate and die without ELT. Regardless of etiology, given the high risk of death and the potential for rapid deterioration, transfer to a center capable of providing ELT should be considered in all ALF patients where this is feasible.

CLINICAL FEATURES OF ACUTE LIVER FAILURE

Regardless of etiology, ALF has a characteristic pattern of critical illness. Patients may complain of constitutional symptoms such as fatigue, nausea, and anorexia. Consistent with diagnostic definitions, derangement in hemostatic parameters (especially of INR) are always evident, as are jaundice and hepatic encephalopathy (HE). It is this latter finding that differentiates ALF from the less severe acute liver injury (ALI), in which there is no neurologic impairment.[16] Laboratory tests are confirmatory, with elevations in amino acid transaminase levels (up to 25 times the normal upper limit) and bilirubin, in addition to a tendency to hypoglycemia and hyperlactatemia. Hyperammonemia is a cardinal feature, especially in the setting of significant HE. In addition to an elevated INR, thrombocytopenia and hypofibrinogenemia frequently occur and suggest a likely bleeding tendency. Arterial blood gas analysis typically reveals a combination of respiratory alkalosis and metabolic acidosis.[17] Spontaneous improvement of the INR indicates recovery, whereas progressive worsening, even in the setting of reductions in transaminase levels, portend deterioration. The absolute values of elevated amino acid transaminase levels do not reflect prognosis.

Management Challenges in ALF

Hepatic Encephalopathy, Cerebral Edema, and Intracranial Hypertension

HE is the result of a complex pathophysiologic process that reflects serious underlying liver failure. A combination of metabolic toxins, false neurotransmitters, benzodiazepine-like compounds, and inflammatory mediators accumulate in liver failure, resulting in a metabolic delirium that can proceed to drowsiness and overt coma.

Whereas HE occurs in both decompensated chronic liver disease and ALF, cerebral edema occurs almost exclusively in the latter. Hyperammonemia develops in hepatic failure because of the major role the liver plays in its detoxification via the urea cycle. Ammonia is a neurotoxic by-product of protein metabolism that is converted to less toxic urea, which becomes the vehicle for excreting nitrogenous waste in the urine. Although some conversion of ammonia to urea occurs in other organs, severe liver failure will invariably result in ammonia accumulation and low blood urea concentrations. Cytotoxic cerebral edema occurs when ammonia crosses the blood-brain barrier (BBB), leading to increasing concentrations in brain tissue that cause glutamine-mediated astrocyte swelling, neuroexcitation, and disruption of many neuronal metabolic and signaling processes. In cases of severe HE and progressive cerebral edema, normal autoregulation of cerebral blood flow and the integrity of the BBB are lost, leading to cerebral hyperemia and vasogenic edema. Up to 80% of patients with high-grade HE may develop cerebral edema, and ammonia concentrations of more than 150 μmol/L are associated with intracranial hypertension that may be complicated by neurologic injury and death from brainstem herniation.[18] Progressive neurologic deterioration can be difficult to detect on clinical assessment of critically ill patients, and early intracranial hypertension may not be obvious on neuroimaging.[19] Monitoring strategies such as near-infrared spectroscopy, jugular venous bulb saturation monitoring, electroencephalogram (EEG), Doppler ultrasound, and intracranial pressure (ICP) monitoring all have significant limitations and none has been shown to improve patient outcomes. Invasive ICP monitoring in particular has associated risks of bleeding and infection.[20] Although it is used routinely in many specialist centers,[21] the technique has been abandoned by many in favor of other strategies. For most patients who recover either through ELT or spontaneous liver regeneration, resolution of HE and full neurologic recovery is the usual outcome.[22]

Deranged Hemostatic Parameters

Abnormalities of hemostatic parameters are part of the definition of ALF. Reduced hepatic synthesis of factors II, V, VII, IX, and X results in prolongation of the PT (and INR) and, later on, the activated partial thromboplastin time (aPTT). Although this results in a pattern of hemostatic derangement suggestive of high bleeding risk, the situation is complicated, with simultaneous reductions in the hepatic synthesis of anticoagulant factors such as proteins S and C, the accumulation of microparticles, and generalized inflammation that combine to promote a prothrombotic state.[23] For many patients, neither overt bleeding nor thrombosis occur,[24] suggesting that although routine measures of clotting appear markedly deranged, hemostasis remains functionally balanced and intact. The INR is a poor predictor of bleeding risk in ALF, whereas thrombocytopenia and hypofibrinogenemia may be more strongly associated with haemorrhage.[24]

Vasodilatory Shock

A vasodilated, hyperdynamic systemic circulation occurs in most patients with ALF, with the pattern of hemodynamic instability strongly resembling septic shock. Severe inflammation, endothelial injury, and abnormal neurohormonal control are all important factors leading to circulatory dysfunction. Relative or absolute hypovolemia may be present as a result of poor fluid intake before presentation, gastrointestinal losses, and capillary leakage. After appropriate fluid resuscitation, vasopressor therapy with agents such as norepinephrine administered by continuous infusion according to similar treatment principles for managing septic shock is recommended. Occasionally, patients may develop a low cardiac output state caused by preexisting cardiovascular disease or overwhelming critical illness such that inotropic support becomes necessary. In circumstances of advanced circulatory failure, general malperfusion ensues, contributing to multiple organ failure.

Metabolic Abnormalities

Severe metabolic derangement is a hallmark of ALF. Hyperlactatemia can develop secondary to generalized malperfusion combined with

high circulating catecholamine levels. Reduced hepatic clearance and direct impairment of mitochondrial function by toxic levels of acetaminophen may also contribute.[25]

Hypoglycemia is a serious development and suggests extreme liver injury. Failure of gluconeogenesis and loss of glycogen stores may lead to refractory hypoglycemia unless concentrated intravenous dextrose is administered.

Hyponatremia is occasionally present early on and is associated with worse outcomes in acute liver dysfunction.[26] Hypokalemia and hypophosphatemia may also occur, especially if high-dose CRRT is undertaken.

Relative or absolute adrenal insufficiency has been described in acute liver failure,[27] and steroid replacement therapy should be considered in the setting of refractory shock.[28]

Renal Failure

Acute renal failure occurs commonly in ALF, either secondary to the primary insult that caused liver injury (e.g., acetaminophen overdose) or from the systemic inflammatory response and associated shocked state. Uremia is notably rare because of reduced hepatic synthesis of urea; however, fluid accumulation, acidosis, and electrolyte derangement may all develop and cause complications. The initiation of CRRT should not be delayed until overt renal failure is evident, as it plays a key neuroprotective role by removing ammonia and other water-soluble toxins that contribute to HE and cerebral edema.

Respiratory Failure

Respiratory failure is rarely a prominent feature of ALF at initial presentation. ALF patients have a tendency to hyperventilation and develop a respiratory alkalosis; hypoxia is relatively uncommon. Over time, however, complications such as pulmonary edema, aspiration pneumonitis, atelectasis, and pneumonia are common, and severe hypoxic respiratory failure may develop. Hepatopulmonary syndrome is rare in ALF, but has been reported.[29]

Susceptibility to Infection and Sepsis

Severe susceptibility to bacterial and fungal infection is a hallmark of ALF and a major contributor to poor outcomes.[30] Contributing factors include compromised reticuloendothelial function, reduced complement levels, impaired phagocytosis, and the presence of vascular access catheters. Common sites for infection are the lower respiratory tract, urinary tract, and vascular access devices with associated bacteremia, and common pathogens include gram-positive cocci, gram-negative bacilli, and fungal species such as *Candida*. Infection may arise from the patient's own microbiome or from the hospital environment.

Fluid and Electrolyte Abnormalities

Critically ill patients with shock and multiple organ failure often receive considerable amounts of intravenous fluids, and this is also true for ALF. A strongly positive fluid balance is undesirable in patients at high risk of cerebral edema, and a strategy that aims to avoid excessive fluid accumulation is appropriate. Abnormalities of potassium and phosphate also occur frequently and need to be tested for and supplemented as necessary.[31]

Initial Assessment and Management

After initial resuscitation, a comprehensive history (either first person or from family members) is the most important part of initial assessment. Essential details include previous overall health, past history of liver disease, family history of liver disease, and risk factors for hepatotropic viruses (especially intravenous drug use, blood exposure, sexual history, and travel). All recent medications, alternative therapies, nutritional supplements, alcohol intake, use of illicit drugs, and possible mushroom ingestion must be evaluated. Female patients should be asked about the possibility of pregnancy.

A thorough clinical examination should also be completed. In addition to a general appraisal of vital systems, a directed search for signs of chronic liver disease (e.g., generalized sarcopenia, clubbing, leukonychia, spider nevi, gynecomastia, prominent abdominal wall veins, and significant ascites) in order to differentiate ALF from decompensated cirrhosis is essential. The presence of HE is a defining element of ALF but may be subtle early on. The West Haven criteria are often used to grade HE severity; however, critical care clinicians may be more familiar with using the Glasgow Coma Scale (GCS) to make an initial assessment and follow progress. Cutaneous lesions such as herpetic vesicles, tattoos, and needle marks may suggest the possibility of a viral etiology, and ophthalmic review may assist in checking for Kayser-Fleischer rings that are diagnostic of Wilson disease. Abdominal examination should evaluate liver and spleen size and for the presence of ascites.

INVESTIGATIONS

All ALF patients require a panel of investigations, as outlined in Table 87.1. Hemostatic parameters (INR, fibrinogen, platelet count) and blood concentrations of bilirubin, transaminases, albumin, glucose, and lactate can reveal the extent of liver injury and assist in detecting deterioration. Point-of-care arterial blood gas analysis is extremely helpful to assess oxygenation, ventilation, metabolic profile, and acid-base status. Blood ammonia concentrations should be checked in all patients with high-grade encephalopathy and any patient who is intubated. The persistence of extreme elevations is associated with neurologic complications. Pancreatitis is easily missed in a critically ill ALF patient, and serum lipase should be checked. All of these investigations should be repeated regularly to guide ongoing management. All female patients should be tested for pregnancy. Acetaminophen levels must be performed in every patient presenting with acute liver injury, even in the absence of a clear evidence for overdose. Interpreting the results may be difficult in the absence of a reliable history regarding the timing of and nature of ingestion (e.g., single overdose versus staggered supratherapeutic doses over time); empiric treatment with NAC is wise when there is any doubt regarding the significance of test results. A screen for illicit drugs may be appropriate if circumstances are suggestive. Tests for relevant hepatotropic viruses (HAV, HBV, HEV) in addition to Epstein-Barr virus (EBV), cytomegalovirus (CMV), and herpes simplex virus (HSV) are essential, as are copper studies and an autoimmune screen. Abdominal ultrasound with Doppler evaluation of vascular integrity (especially of the hepatic vein) should occur early during assessment and may also be helpful in detecting ascites. For patients with focal neurologic deficits, a history of trauma, or other concerns for intracranial pathology, neuroimaging with CT should be arranged. A focused hemodynamic assessment with echocardiography may guide treatment for patients with progressive hemodynamic compromise and shock who do not respond to vasoactive infusions and fluid resuscitation.

MANAGEMENT

Patients with ALF almost always develop a severe critical illness. They often follow an unpredictable, rapidly progressive clinical course with high risk of complications and require admission to the ICU in all circumstances where this is possible. Ward-based care will rarely suffice.

TABLE 87.1 Investigations in Acute Liver Failure

Investigation	Purpose	Suggested Frequency
Hematology		
Full blood examination	Anemia and thrombocytopenia for bleeding risk	Daily
Hemostatic parameters:		Daily
INR	Measure of hepatic insufficiency	Daily
Fibrinogen	Measure of hepatic insufficiency and bleeding risk	Daily
Blood film	Assess for hemolysis in Wilson disease and AIH	At presentation
Biochemistry		
Serum electrolytes	Management of Na^+, K^+	6-hourly
Liver function tests		Daily
AST, ALT	Assess hepatocyte injury and necrosis	Daily
Bilirubin, ALP, GGT	Assess hepatic insufficiency and cholestasis	Daily
Phosphate	Often low with liver failure, especially with CRRT	Daily
Creatinine	Measure of renal function	
Urea	Usually low in liver failure	Daily
Ammonia	Hyperammonemia associated with neurologic injury	Daily (at least)
Lactate	Measure of hepatic and circulatory failure	6-hourly
Blood glucose	Measure of hepatic insufficiency	6-hourly
Arterial blood gas analysis	Assess ventilation, oxygenation, and acid-base status	6-hourly
Acetaminophen concentration	Check for acetaminophen overdose in all ALF patients	At presentation
Copper studies	Ceruloplasmin low in Wilson disease	At presentation
β-hCG	Screen for pregnancy in female patients	At presentation
Lipase	Assess for pancreatitis	As indicated
Toxicologic screen	Assess for illicit drug use according to local practice	As indicated
Microbiology		
Serology		
Hepatotropic viruses	HAV, HBV, HDV, HEV as causes of ALF	At presentation
Nonhepatotropic viruses	EBV, CMV, HSV, VZV, parvovirus B19	At presentation
Microscopy and culture	Low threshold to assess for sepsis: blood, sputum, etc.	As indicated
Autoimmune markers		**At presentation**
ANA, ANCA, AMA, anti-LKM, anti-SM	Varying patterns in AIH	At presentation
Imaging		
Liver ultrasound with Doppler	Assess liver size, parenchyma, vascular integrity for Budd-Chiari	At presentation
Chest x-ray	Assess for pulmonary complications	Daily
CT brain	If evidence of trauma or focal neurologic deficits	As indicated
CT abdomen	Volumetric assessment of liver for prognosis	As indicated
Other		
ECG	Assess for toxidromes, arrhythmia, ischemia	Daily
EEG	Assess for possible seizure activity	As indicated
Liver biopsy	Assess for AIH or possible underlying cirrhosis	As indicated

ABG, Arterial blood gas; *ALP,* alkaline phosphatase; *ALT,* alanine transaminase; *ANA,* antinuclear antibody; *ANCA,* antineutrophil cytoplasmic antibody; *anti-LKM,* anti–liver kidney microsomal antibody; *anti-SM,* anti–Smith antibody; *APTT,* activated partial thromboplastin time; *ARDS,* acute respiratory distress syndrome; *AST,* aspartate transaminase; β-hCG, beta human chorionic gonadotrophin; *CMV,* cytomegalovirus; *EBV,* Epstein-Barr virus; *ECG,* electrocardiograph; *EEG,* electroencephalograph; *GGT,* gamma glutamyl transpeptidase; *HAV,* hepatitis A virus; *HBV,* hepatitis B virus; *HDV,* hepatitis D virus; *HEV,* hepatitis E virus; *HSV,* herpes simplex virus.

Treatment Directed at Specific Causes of ALF

Although supportive care is the most important aspect of management for most ALF patients, some etiologies have specific treatments that may limit further injury or reverse the underlying process.

NAC by intravenous infusion should be started immediately for all known or suspected cases of acetaminophen overdose. Delays must be avoided, and it should be continued until critical illness has resolved. There may also be a role for its use in other causes of ALF,[32,33] even though a survival benefit has not been clearly demonstrated.[34] Given its favorable safety profile, NAC is recommended by several guidelines in such circumstances.[35,36]

Specific antiviral therapies may occasionally have a role, such as nucleoside analogues for HBV or acyclovir for HSV. Emergency delivery is the definitive treatment for AFLP, and an expedited approach achieves the best outcomes. For BCS, an attempt at catheter-directed thrombolysis or shunt placement (e.g., transjugular portosystemic shunt [TIPS]), may be worthwhile. AIH-induced ALF may variably respond to high-dose steroids; however, it should be anticipated that ELT may prove necessary in many affected patients, especially those with high-grade encephalopathy.[37] Evidence for antidotes is limited, but high-dose penicillin (as a continuous infusion) or silibinin may be considered for *Amanita* mushroom poisoning.

Neurologic Care

Patients with high-grade HE from ALF can develop severe cerebral edema and intracranial hypertension. Although the incidence of cerebral edema in this setting may be falling,[38,39] affected patients are at high risk of neurologic complications and death.[40] Intubation is recommended for all patients with progressive HE to ensure airway protection and facilitate other elements of care. The head should remain elevated to 30 degrees at all times and maintained in a neutral position. Except for ELT, no individual intervention has been demonstrated to improve outcomes, so a coordinated approach is required to ensure that the various underlying processes may be simultaneously addressed. A combination of early CRRT, osmotherapy with hypertonic saline, optimized ventilation, and careful temperature management is recommended (Table 87.2).[41]

Hemofiltration

Intubated ALF patients should commence renal replacement therapy to treat hyperammonemia as soon as possible, rather than waiting for overt acute renal failure to manifest.[42,43] Continuous modalities are preferred, as they offer benefits that include continuously titratable fluid management, effective thermoregulation, control of pH, management of electrolyte abnormalities, minimal hemodynamic impact, and a lower risk of exacerbating intracranial hypertension.[44] A dual-lumen vascular access catheter can be safely inserted with ultrasound guidance, and only extreme derangement of hemostatic parameters necessitates prophylaxis with clotting factors. Bicarbonate buffered replacement fluid is preferred to avoid exogenous lactate loading. Although there is little evidence on which to recommend a specific mode of CRRT, a strategy that incorporates a diffusive component may improve ammonia clearance. Most CRRT machines incorporate an integrated heater that may be turned off in order to allow the patient's temperature to be lowered. High blood flows (e.g., >250 mL/min) with effective vascular access help lower the risk of clotting within the circuit, and anticoagulation may not be required. If anticoagulation proves necessary, low-dose heparin or epoprostenol may be tried, whereas citrate regional anticoagulation should generally be avoided in the setting of severe hepatic insufficiency. Ammonia exhibits similar kinetics to urea and is effectively cleared in a similar manner, especially at an hourly exchange dose of 40 mL/kg/hr or more. Early initiation and continuity of therapy are essential to ensure ammonia concentrations are rapidly lowered and then maintained at a safe level.[43] Serial monitoring of ammonia levels is recommended, and failure to achieve reductions down to near the normal range or frequent interruptions to therapy should prompt efforts to optimize the application of CRRT. This approach may result in electrolyte abnormalities such as hypokalemia and hypophosphatemia, so diligent testing and preemptive supplementation are required. A strategy to avoid a strongly cumulative fluid balance is advisable in order to avoid potentiating cerebral edema.

TABLE 87.2 Management of Intubated ALF Patients With High-Grade Hepatic Encephalopathy at Risk of Cerebral Edema and Intracranial Hypertension

Neuroprotective Intervention[41]	Therapeutic Target	Method of Therapy	Mechanism
Hemodiafiltration	Blood ammonia <60 μmol/L and even daily fluid balance	High-volume CRRT using dialysis and filtration	Treats hyperammonemia and allows precise metabolic, electrolyte, and fluid management and provides a cooling effect
Hypernatremia	Serum sodium 145–155 mmol/L	Continuous infusion of concentrated saline via central venous catheter	Increases serum tonicity and reduces cerebral edema
mild Hyperventilation	Lower of $PaCO_2$ = 35 mm Hg or that achieved by the patient before intubation	Set ventilator to provide minute ventilation sufficient to achieve target	Attenuates cerebral hyperemia and lowers intracranial pressure
mild Hypothermia	Core temperature 35°C Always prevent fever	CRRT Active cooling device	Reduces ammonia production and CNS uptake, attenuates cerebral hyperemia, reduces cerebral metabolic rate, reduces neuroexcitation and, has anti-inflammatory effects

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CNS, Central nervous system; *CRRT,* continuous renal replacement therapy.

General measures include sedation, elevation of head to 30 degrees, avoidance of hypotension and hypertension, and avoidance of hypoxemia. "Rescue" measures for refractory intracranial hypertension include deep sedation, hyperventilation, moderate hypothermia, bolus hypertonic saline or mannitol, indomethacin, and advanced blood purification (e.g., plasmapheresis).

Hypertonic Saline

Osmotherapy is an established treatment for cerebral edema. The two major therapeutic options are mannitol and hypertonic saline. Although mannitol is often used in many regions, there is a theoretical risk of rebound cerebral edema after repeated use, as it may leech into the brain parenchyma and induce a "reverse" osmotic gradient. Hypertonic saline (HTS) is at least as effective as mannitol[45] and has been suggested both as a prophylactic strategy for cerebral edema in ALF and as treatment for associated intracranial hypertension.[46–49] Either bolus dosing or continuous infusion of HTS via a central venous catheter may be used, with the latter having the advantage of being titratable as guided by point-of-care testing. Other proposed advantages of HTS for the brain include antiinflammatory effects, reduced hyperemia, improved microcirculation, and maintenance of intravascular volume without excessive fluid loading.[50] A target serum sodium concentration of 145–155 mmol/L is recommended,[48] and achieving this goal is more important than the method of administration (bolus or continuous infusion) or the absolute dose given.[46] The serum sodium should not be permitted to exceed 160 mmol/L,[51] and it is important to avoid rapid increases in patients who are hyponatremic at presentation and therefore at risk of central nervous system (CNS) demyelination syndromes.

Mechanical Ventilation

Spontaneous hyperventilation is typical of ALF, even in patients who are obtunded.[52,53] Patients with high-grade HE should be intubated. The arterial carbon dioxide tension exerts considerable influence over cerebral vascular resistance, which in turn is a major determinant of cerebral perfusion. Cerebral blood flow is reduced by approximately 3% per 1 mm Hg reduction in partial pressure of carbon dioxide ($PaCO_2$).[54] Although perfusion and cerebral metabolic requirements are usually well matched (including in patients with early HE), autoregulation may be lost in patients with severe HE who are at the highest risk of cerebral edema and intracranial hypertension.[53] Whether relative or absolute, cerebral hyperemia exacerbates cerebral edema and intracranial hypertension. Careful control of $PaCO_2$ can restore cerebral blood flow autoregulation in ALF, and a target $PaCO_2$ similar to that achieved by the patient before intubation or at the lower end of the normal physiologic range is recommended.[35,55] Adjustments to minute volume can be guided by end-tidal CO_2 monitoring and regular arterial blood gas analysis. Hypercapnia must be avoided, especially during vulnerable periods such as during intubation and patient transport. More aggressive deliberate hyperventilation provides no clear benefit when applied routinely, and the associated reductions in ICP are transient. It should be reserved for situations where, despite other measures, severe cerebral edema is complicated by intracranial hypertension and it is necessary to achieve an urgent reduction so that a definitive intervention such as ELT can proceed.[56] Consistent with current recommendations, an approach that targets safe tidal volumes and plateau pressures, uses positive expiratory-end pressure (PEEP) effectively, and achieves satisfactory oxygenation is a fundamental element of respiratory care.

Targeted Temperature Management

It is widely accepted that fever is especially detrimental to patients with cerebral edema, who are prone to intracranial hypertension.[57] Evidence suggests a range of potential benefits from mild therapeutic hypothermia, especially for younger patients with acetaminophen overdose, and it can be safely undertaken with low risk of complications.[58] More aggressive lowering of temperature provides no additional benefit, and it is therefore appropriate to reserve cooling lower than 34°C for situations of severe cerebral edema where ELT is planned.[59] Many of the benefits from therapeutic hypothermia are obtained by targeting a temperature of 35°C (i.e., slightly subphysiologic) and ensuring that fever never occurs.[60] This approach also minimizes theoretical risks of exacerbating coagulopathy, immunosuppression, or arrythmias.

Other Potential Neuroprotective Therapies

Other therapies may be tried in the setting of refractory intracranial hypertension in instances where it is necessary to support a patient for sufficient time to undertake a definitive intervention, such as ELT. Most of these have little evidence and often entail a risk of complications. Deep sedation with barbiturates may lower ICP but risks cardiovascular compromise. Indomethacin has been shown to be helpful in models of ALF-associated cerebral edema, but evidence in humans is limited.[61] Anticonvulsants should only be used in the setting of clinically evident or EEG-proven seizure activity. Lactulose is often used in the setting of HE complicating chronic liver disease; however, it has little evidence for use in ALF, and it causes diarrhea and bowel distension, which may be problematic. Similarly, enteral antibiotics such as rifaximin are often administered to cirrhotic patients with HE but have not been well-studied in ALF patients. l-ornithine-l-aspartate and l-ornithine phenylacetate may provide a novel means of enhancing ammonia detoxification but have not shown benefit in human studies. Complex blood purification techniques such as coupled plasma filtration adsorption (CPFA), molecular adsorbent recirculation system (MARS), and bioartificial devices have not been shown to improve survival and have a limited role outside of clinical trials.[62]

Other Care

Circulatory Support

An approach similar to the resuscitation and ongoing circulatory support for septic shock is appropriate for the hemodynamic abnormalities resulting from ALF. The early placement of an indwelling arterial catheter and multilumen central venous catheter permits continuous hemodynamic monitoring, regular blood sampling, and the administration of essential infusions. Routine administration of clotting factors is not necessary; however, extreme derangement of hemostatic parameters should be corrected before the insertion of invasive monitoring lines. Pulse contour analysis and bedside echocardiography may guide the selection of hemodynamic supports with minimal additional risk to the patient. After hypovolemia has been addressed with fluid resuscitation, most patients will require vasopressor support. Norepinephrine via continuous infusion is a common approach, and if high doses are required (e.g., >0.5 μg/kg/min), additional agents such as vasopressin by continuous infusion and corticosteroids may improve vasomotor tone. Similar to other critically ill patients, ALF patients often accrue a positive fluid balance and are at risk of generalized edema. This may increase their risk of complications such as cerebral and pulmonary edema. After the initial resuscitation phase, it is prudent to avoid excessive fluid loading and consider strategies such as concentrated albumin (e.g., 20% human albumin or similar) to maintain intravascular volume while minimizing the volume of fluid administration.

Management of Deranged Hemostatic Parameters

Although measures of hemostasis in ALF suggest a high risk of bleeding, this does not eventuate in most patients. INR is not a reliable guide to bleeding tendency, and isolated elevations should not prompt administration of clotting factors such as fresh frozen plasma. Similarly, it is not necessary to routinely administer clotting factors on the basis of INR before most invasive procedures.[35] Thrombocytopenia and hypofibrinogenemia are clearly associated with bleeding risk, however, and extreme derangements should be corrected.[24] Daily assessment of

TABLE 87.3 General ICU Care of Acute Liver Failure Patients

Intervention	Suggested Target/Approach	Method/Examples
Treatment for specific underlying etiology	Reversal of pathologic process and minimization of ongoing injury	• N-acetyl cysteine infusion for acetaminophen overdose • Withdrawal of hepatotoxic drugs • Nucleoside analogues for HBV • Penicillin or silibinin for *Amanita* mushroom poisoning • Urgent delivery of fetus for AFLP
Hemodynamic support	Hemodynamic parameters according to patient's clinical progress: • CVP 6–10 mm Hg • MAP 65–70 mm Hg • Even daily fluid balance	• Fluid administration • Vasoactive infusions (e.g., norepinephrine) • Low-dose corticosteroid administration if persisting shock
Sepsis care	• Low threshold for empiric broad-spectrum antibiotics if clinical suspicion of infection • Consider antifungal therapy if deterioration after several days of critical illness • Regular cultures of blood, urine, and sputum • Daily CXR	• Extended-spectrum β-lactams • Liposomal amphotericin or echinocandin antifungal therapy if deterioration after several days of critical illness
Respiratory support	See hyperventilation section of Table 87.2	• Intubate patients with high-grade encephalopathy • Avoid hypoventilation, especially during vulnerable periods such as during intubation, neuroimaging, and transfers
Renal support	See hemodiafiltration section of Table 87.2	• Ensure blood flow >200 mL/min • Use high exchange rates of lactate-free replacement fluid (40–50 mL/kg/hr) • Turn off heater • Aim for blood ammonia within normal range • Monitor electrolytes (especially phosphate, potassium, magnesium) • Administer hypertonic saline by continuous infusion to avoid reduced serum osmolarity while on CRRT
Hematologic support	• Hb >7.0 g/dL • INR <6 • Platelet count >75 × 10^9/L • Fibrinogen >1.5 g/L	• Avoid treating isolated derangements in hemostatic parameters • Prophylactic FFP is not recommended before most procedures • Avoid extreme hypofibrinogenemia and thrombocytopenia • Administer vitamin K 10 mg IV daily • Use FFP, platelets, and cryoprecipitate if factor support is required
Metabolic/gastrointestinal/nutritional care	• Blood glucose 6–10 mmol/L • Stress ulcer prophylaxis • Enteral feeding	• Concentrated dextrose infusion via central line • H_2 blocker or PPI therapy • Enteral feeding via nasogastric tube

AFLP, Acute fatty liver of pregnancy; *CVP,* central venous pressure; *CXR,* chest x-ray; *FFP,* fresh frozen plasma; *Hb,* hemoglobin; *HBV,* hepatitis B virus; *INR,* international normalized ratio; *MAP,* mean arterial pressure; *PPI,* proton pump inhibitor.

all hemostatic parameters is recommended to assess for possible hepatic recovery and to preempt potential bleeding complications. Recommended targets are outlined in Table 87.3. Intravenous vitamin K is appropriate for all ALF patients and can be given on a daily basis. Although the evidence that clotting factor administration may precipitate a prothrombotic state is limited, it is sensible to limit therapy to situations where there is a clear indication, such as active bleeding in the setting of abnormal hemostatic test results.

Sepsis

Immune paresis is an important complication of ALF, and infection with bacterial or fungal pathogens is a common cause of death. Prophylactic antibiotics seem to offer no clear benefit, and there are concerns that resistance may be facilitated by their unnecessary use.[63] Vigilance with a low threshold to investigate for and empirically treat infection with broad-spectrum antimicrobials is a reasonable strategy. A typical septic workup should include imaging (e.g., chest x-rays) and surveillance cultures of blood, urine, and sputum. Standard markers of infection such as fever, leukocytosis, and biomarkers (e.g., C-reactive protein [CRP]) may not follow a typical pattern and should not be wholly relied upon.[64] There may be a role for empiric antifungal therapy if a patient remains critically ill or is deteriorating after several days of critical care support. Antimicrobial selection should be guided by knowledge of local resistance patterns and the avoidance of potential hepatotoxins.

Metabolic, Gastrointestinal, and Nutritional Support

Hypoglycemia is common in ALF patients with extreme hepatic insufficiency. It must be immediately corrected and a continuous infusion of concentrated dextrose (e.g., 25% dextrose via a central line) may be required, with a target blood glucose of between 6 and 10 mmol/L. Hyperglycemia is common during the recovery phase, and an insulin infusion may then be required to control elevations in blood glucose. Upper gastrointestinal bleeding may occur in ALF patients,[24] especially those with hypofibrinogenemia and thrombocytopenia, and use of H2 blockers or proton pump inhibitors is appropriate.

Nutritional support via the enteral route is preferred, and intubated patients will require a nasogastric feeding tube. There is scant evidence

on which to base recommendations for specific formulations; branched-chain amino acid–enriched preparations offer few additional benefits beyond standard options.

Emergency Liver Transplantation

ELT is the only single intervention proven to reduce mortality in ALF; however, it accounts for only a small proportion of liver transplants undertaken in jurisdictions where it is available. Although ELT for ALF has a slightly higher early mortality than transplantation undertaken for chronic liver disease, the outcomes are otherwise very good,[65] with rapid improvement in all aspects of critical illness over a short period after a successful procedure.[22] Developing reliable and generalizable selection criteria has proven challenging. The survival benefit of ELT in nonacetaminophen ALF seems clear; however, there is less certainty in the setting of ALF from acetaminophen overdose.[1,66,67] Other issues that require careful consideration include judging whether the patient has become too critically ill to survive major surgery and also complex ethical issues such as whether or not a patient who has deliberately overdosed in an act of self-harm should proceed to ELT.[68] Contraindications to ELT include known malignancy, irreversible neurologic injury, and uncontrolled sepsis. The most common surgical approach is orthotopic transplantation of a whole cadaveric organ; however, cadaveric split livers, living related partial donations, and the increasing use of marginal donors (including donation after circulatory death) increase the options available when organs are scarce. Another interesting approach is the use of auxiliary partial orthotopic liver transplantation (APOLT) in which a cut-down donor liver is transplanted orthotopically after partial hepatectomy of the native liver.[69] The transplanted donor tissue provides effective function for a bridging period until sufficient regeneration of the native liver can occur. When convincing evidence of recovered native liver function is evident, immunosuppression can be tapered to cessation, and a controlled chronic rejection of the transplanted tissue causes gradual atrophy.

The optimal approach to decision making uses predictive criteria as a preliminary screening assessment, which then informs the clinical interpretation of dynamic measures (such as INR, lactate, and indicators of shock and organ failure). It is usual practice to proceed to ELT in situations where death is likely in the absence of ELT, an organ is available, and there are no absolute contraindications. Frequent assessment and consultation between intensive care clinicians and transplant teams at the bedside are essential in order to make the best decisions possible under circumstances where certainty is so often impossible.

CONCLUSION

Although rare, ALF causes extreme critical illness to which patients often succumb. With optimal care, ELT-free survival is possible for many of those patients with favorable etiologies, and transplantation may be lifesaving for others.[70] Clinicians should be aware of the common causes in their region and know etiology-specific therapy and how to coordinate the complex supportive care that is often necessary. Early consultation with a liver transplant service is recommended so that transfer can be considered, even if ELT does not seem necessary on preliminary assessment. As with any complex critical illness, a proactive, coordinated approach to care is required, and frequent re-evaluation to assess the clinical course and detect complications is essential.

KEY POINTS

- ALF is defined by the triad of overt liver failure with jaundice occurring over a period of weeks, with encephalopathy and deranged hemostatic measures (usually INR or PT) in the absence of known chronic liver disease.
- Causes of ALF vary considerably by region, with acetaminophen and other drugs common in most developed countries, whereas viral hepatitis is much more frequent in many resource-limited and developing regions.
- Mortality is high, and ELT is the only single intervention proven to reduce mortality. Some etiologies have a more favorable outcome (e.g., acetaminophen overdose), whereas some are usually lethal without ELT (e.g., Wilson disease).
- Cerebral edema as a complication of hepatic encephalopathy is unique to ALF and rarely occurs in encephalopathic cirrhotic patients. The pathophysiology is complex, but hyperammonemia is a potent neurotoxin that drives many of the contributing processes and is a readily measured surrogate for other unmeasured toxins that accumulate in liver failure.
- For patients with high-grade hepatic encephalopathy, the early initiation of CRRT (e.g., with hemodiafiltration at an effluent dose of ≥40 mL/kg/hr), HTS administration (to achieve a serum sodium of 145–155 mmol/L), optimized mechanical ventilation ($PaCO_2$ lower of either low normal or that achieved by the patient before intubation), and targeted temperature management (core temperature 35°C and strict avoidance of fever) may limit the risk of intracranial hypertension. These interventions should be applied to all patients intubated for high-grade encephalopathy and continue until recovery is evident. Although it is widely used, invasive ICP monitoring does not improve outcomes, and its role remains unclear.
- The initiation of CRRT is neuroprotective and should not be delayed until overt renal failure is apparent. It effectively treats hyperammonemia and reduces levels to near normal, thereby reducing the risk of neurologic complications. Ammonia levels should be checked at least daily while encephalopathy persists. HTS should be used in conjunction with CRRT to avoid inadvertent reductions in serum osmolarity. Intermittent dialysis risks exacerbating cerebral edema and has an adverse impact on the systemic circulation.
- Elevations in the INR, although indicative of liver injury, are not especially predictive of bleeding risk. Administration of fresh frozen plasma to treat an isolated INR result or routinely before most procedures is not recommended. Hypofibrinogenemia and thrombocytopenia are associated with bleeding tendency, and the administration of cryoprecipitate and platelet transfusion is recommended for extremely low levels. Hemostatic parameters (especially INR, fibrinogen, and platelet count) should be checked at least daily.
- Various predictive scoring systems have been developed, and although they may assist with identifying many patients at high risk of death without ELT, none of the criteria developed so far should be wholly relied upon to determine listing for ELT. Clinicians must apply their own expertise and engage in repeated clinical assessment to ensure that patients capable of spontaneous recovery avoid ELT, whereas those who will likely die without it undergo transplantation.
- ELT should be considered early during the course of management for patients with unfavorable etiologies who are unlikely to achieve ELT-free survival (e.g., Wilson disease, idiosyncratic drug reactions, cryptogenic ALF).

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Calculous and Acalculous Cholecystitis

Samuel A. Tisherman

Evaluating the patient with a possible acute abdomen and intraabdominal sepsis in the intensive care unit (ICU) can be challenging. Patients frequently have multiple potential sources of sepsis and are often unable to describe symptoms or localize tenderness on physical examination. In addition, many imaging studies require transporting the patient to the radiology suite, which can be risky. These issues are especially troublesome for patients with the potential for acute cholecystitis.

Acute cholecystitis, frequently without gallstones, has long been recognized as a complication of surgery or acute critical illness.[1] The pathophysiology of cholecystitis in critically ill patients is different from that in the general population, as at least half of the patients have no gallstones.[2] Understanding the risk factors and pathogenesis of acute cholecystitis in the ICU can help increase the index of suspicion and lead to early diagnosis and treatment, which is necessary for good outcomes in the already critically ill patient.

RISK FACTORS AND PATHOPHYSIOLOGY

In the general population, acute cholecystitis is associated with the presence of gallstones, which develop as a result of decreased solubility of cholesterol and bile salts in bile. Risk factors for gallstones include age, female sex, recent pregnancy, positive family history for gallstones, and hemolysis. Patients with gallstones may develop acute cholecystitis at any time. Rarely, acute calculous cholecystitis can occur during hospitalization for other reasons.

Acalculous cholecystitis can occur spontaneously under certain circumstances. In outpatients, risk factors for acalculous cholecystitis include diabetes mellitus, vasculitis, older age, and male sex.[3]

Acute cholecystitis has been described as a complication of a variety of surgical procedures,[4,5] burns,[6] sepsis,[7] cardiovascular diseases, and malignancy.[8] Trauma patients are also at increased risk, perhaps because of the development of sludge over time, which may also increase the risk for pancreatitis.[9,10]

There is an association between total parenteral nutrition and biliary stasis.[11] Though lack of enteral feeding may play a significant role, parenteral nutrition can directly decrease bile production, worsening biliary stasis. Biliary sludge can be found in almost all patients on long-term parenteral nutrition.[11] Many go on to form gallstones. The fatty acid derivatives of lipid emulsions, large amounts of dextrose, and specific deficiencies, such as choline and taurine, may also play a role.[12]

Theories regarding the pathogenesis of acalculous cholecystitis in critically ill and postoperative patients have evolved over the years. Presumptive causes have included gastrointestinal hypomotility, biliary stasis, and lack of enteral feeding in the postoperative period, leading to increased concentrations of bile salts and cholesterol in bile.[13] The rarely observed acute onset of cholecystitis with refeeding suggests impaction of stones or viscous bile in the cystic duct with gallbladder contractions.

Gallbladder mucosal necrosis, arterial thrombosis, gangrene, and perforation suggest that hypoperfusion may be another critical mechanism for acalculous cholecystitis. Histopathologic studies confirm microvascular changes and ischemic cholecystitis histologically.[14] Hypoperfusion, particularly of the splanchnic circulation, is common in critically ill patients because of hemorrhage, dehydration, heart failure, and sepsis. Vasopressors can exacerbate the situation. Mechanical ventilation with positive end-expiratory pressure can increase hepatic venous pressure and thereby decrease portal perfusion.[15]

In addition to hypoperfusion, increased intraluminal pressure from biliary stasis secondary to fasting and narcotics may be a critical factor.[16] The combination of hypoperfusion and increased intraluminal pressure leads to a decrease in gallbladder perfusion pressure, wall ischemia, bacterial invasion, and cholecystitis.

INCIDENCE

The incidence of acute cholecystitis in the ICU is difficult to determine, given the great diversity in ICU patient populations and illness severity. Visceral hypoperfusion related to left ventricular dysfunction has been implicated as an etiologic factor, particularly in the cardiac surgery population. Early predictors of acute cholecystitis in these patients include arterial occlusive disease, low preoperative oxygen delivery, longer cardiopulmonary bypass times, need for surgical reexploration, cardiac arrhythmias, mechanical ventilation for $\geq$3 days, bacteremia, and nosocomial infections.[4] The common threads among these factors include decreased tissue perfusion and oxygenation, significant surgical trauma with the expected inflammatory response, and perhaps bacterial translocation from the gut lumen. Because of high risk, some have suggested ultrasound screening of patients who have had complicated courses after cardiovascular surgical procedures.[5]

In the general population of postoperative patients, acute cholecystitis appears to occur with or without gallstones. Among trauma patients, about 90% of the acute cholecystitis cases are acalculous.[9] Because the incidence of the disease is low but the many risk factors for the disease are common, it is difficult to identify specific groups of ICU patients who might benefit from selective screening for acute cholecystitis.

CLINICAL PRESENTATION

The signs and symptoms of acute cholecystitis do not generally differ between calculous and acalculous disease. Typically, patients with acute cholecystitis present with right upper quadrant or epigastric pain, often after ingesting a fatty meal. The pain may radiate to the back. Anorexia, nausea, and vomiting are common findings, as are fever and chills. If the patient is receiving enteral nutrition, the symptoms may be related to meals or tube feedings.

On examination, the most consistent finding is fever. Focal tenderness in the right upper quadrant or epigastrium is typically found, often with evidence of peritoneal irritation. Rarely, the gallbladder is palpable. There may be abdominal distention and loss of bowel sounds. In critically ill patients, symptoms and physical examination findings are frequently difficult to assess or absent because of alterations in the patient's mental status and concurrent disease.

The most consistent laboratory finding is a leukocytosis. Serum levels of liver enzymes and bilirubin are usually normal unless choledocholithiasis, Mirizzi syndrome (external compression of the common hepatic duct by a stone impacted in the cystic duct), or liver dysfunction from sepsis is present. Thus jaundice is rare. Clinical findings and laboratory studies are not very sensitive or specific for cholecystitis, even in the general population,[17] and are less so in critically ill patients.

Given that the underlying pathophysiology of cholecystitis in the ICU often involves gallbladder wall ischemia, there is significant risk for rapid progression to gangrene and perforation. Consequently, even though other causes of sepsis in the ICU are more common, one needs to have a low threshold for considering cholecystitis in the differential diagnosis of patients who may have intraabdominal sepsis. Imaging of the gallbladder should be the next step.

IMAGING STUDIES

Ultrasonography is usually the first test of choice for acute cholecystitis in the general population and in critically ill patients. In the ICU, the presence or absence of gallstones does not help with the diagnosis. The most useful ultrasonographic findings are thickening of the gallbladder wall and pericholecystic fluid (Fig. 88.1). These findings correlate well with operative findings. False-positive findings may occur with sludge, nonshadowing stones, cholesterolosis, ascites, hypoalbuminemia, and portal hypertension. Other ultrasonographic findings indicative of acute cholecystitis include the following: the "double wall sign," representing edema of the gallbladder wall; the "halo sign," representing sloughed gallbladder mucosa; intramural gas; distention of the gallbladder; and the "sonographic Murphy sign," demonstrating point tenderness by pressing the ultrasound probe directly over the gallbladder. The sensitivity of ultrasound for detecting acalculous cholecystitis is 81%–92%. The specificity is 60%–96%,[17,18] but these results are operator dependent.

One problem in the ICU is that the typical ultrasonographic findings of cholecystitis can be seen in ICU patients without the condition. For example, Boland and colleagues performed ultrasound examinations of the gallbladder twice a week in a variety of ICU patients.[18] Half of the patients without calculi developed at least one ultrasonographic finding of acute cholecystitis. Patients with several findings should undergo more aggressive diagnostic evaluation and, perhaps, therapeutic interventions. In equivocal cases, serial examinations may demonstrate increasing wall thickness, which should increase the suspicion for cholecystitis.[19]

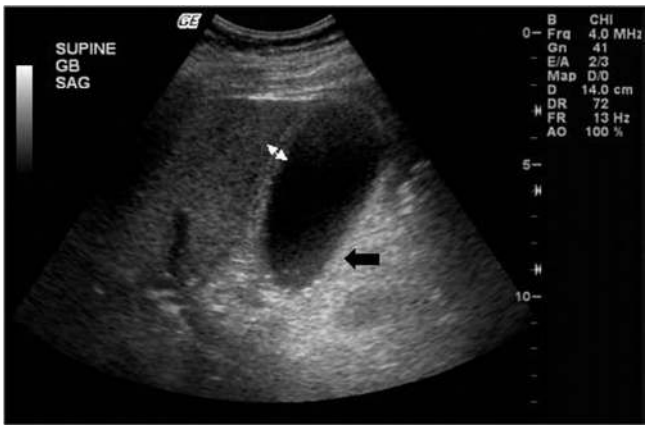

Fig. 88.1 Ultrasound of the gallbladder demonstrating wall thickening *(double arrows)* and sludge *(black arrow)*.

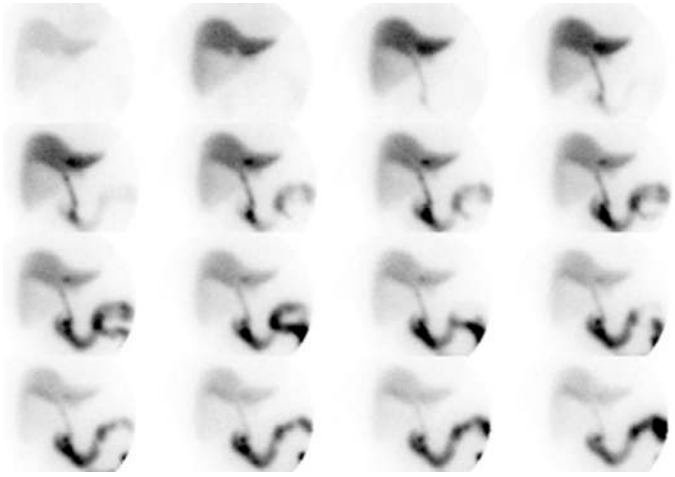

Fig. 88.2 Scintigraphy of the biliary tree demonstrating concentration of the tracer in the liver followed by flow into the biliary tree and small bowel. The gallbladder is not visualized.

Computed tomography (CT) of the abdomen can be used to make the diagnosis of acute cholecystitis.[20] The criteria for a positive study include wall thickness >4 mm, pericholecystic fluid, intramural gas, sloughed mucosa, or subserosal edema without ascites (Fig. 88.2). If intravenous contrast is administered, enhancement of the gallbladder wall may be seen. Although CT may not be as sensitive as ultrasound for determining the presence of gallstones or acute cholecystitis, it can help to detect or rule out other causes of intraabdominal sepsis. A great disadvantage of CT for critically ill patients, however, is the need to transport the patient to the scanner. In critically ill patients with suspected cholecystitis, ultrasound remains the first test of choice. Frequently, however, additional studies are necessary.

Scintigraphy of the gallbladder has been used when acute cholecystitis is suspected but findings from other tests such as ultrasound or CT are inconclusive or contradictory. Gallbladder scintigraphy is performed by administering technetium-labeled iminodiacetic acid (IDA). Cholecystitis is diagnosed if the radioactive tracer is visualized in the small bowel without visualization of the gallbladder within 4 hours, suggesting occlusion of the cystic duct (Fig. 88.3). Delayed visualization of the gallbladder may represent chronic cholecystitis. The rate of false-positive tests is significant in fasting patients, particularly those receiving parenteral nutrition, as the gallbladder may already be maximally filled. The use of intravenous morphine to increase tone in the sphincter of Oddi and thereby increase pressure within the biliary system can decrease the risk of a false-positive test.[21] In patients with severe liver disease, there may be inadequate uptake and excretion of the tracer to provide visualization of the biliary tree. Also, if a patient has had a biliary sphincterotomy, the tracer may pass too quickly through the biliary tree. Overall, the sensitivity of scintigraphy is 91%–97% and the specificity is 38%–99%.[21] Scintigraphy is a useful complement to ultrasonography for early decision making regarding intervention.

DIAGNOSIS

The differential diagnosis for patients with potential cholecystitis in the ICU includes peptic ulcer disease (particularly perforation), acute

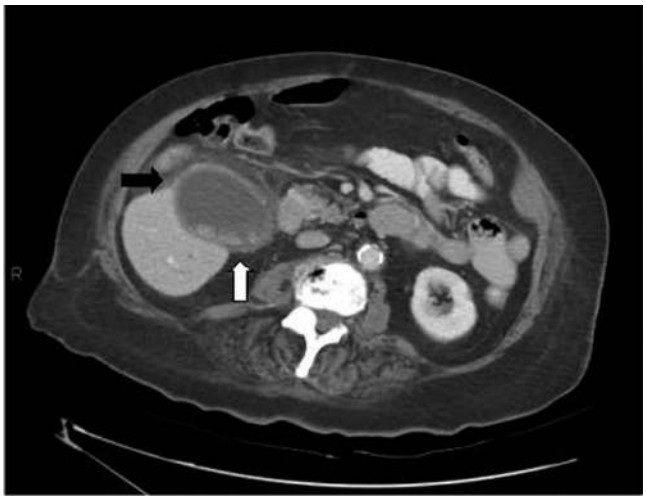

Fig. 88.3 Computed tomographic study of the abdomen demonstrating thickening of the gallbladder wall with infiltration of the pericholecystic fat *(black arrow)* and gallstones *(white arrow)*.

pancreatitis, hepatic or subphrenic abscess, pyelonephritis, right lower lobe pneumonia (although right lower lobe atelectasis is common with a subdiaphragmatic process), and practically any cause of sepsis. The clinical presentation, laboratory studies, and imaging studies all should be considered when making clinical decisions.

To help with confirming the diagnosis of acute cholecystitis, the Tokyo Guidelines for the management of cholecystitis from 2018 (TG18) include specific criteria.[22] Patients have suspected cholecystitis if they have signs of local inflammation (right upper quadrant pain, tenderness or mass, or a positive Murphy sign) and signs of systemic inflammation (fever, elevated C-reactive protein, leukocytosis). The diagnosis is definitive if the patient has positive imaging studies. The severity of cholecystitis is defined as grade I (mild: without any of the grade II or III criteria), grade II (moderate: white blood cell count $>18{,}000/mm^3$, palpable tender mass in the right upper quadrant, duration of symptoms >72 hours, or marked local inflammation), and grade III (severe: end-organ dysfunction). Markers of inflammation, such as Ôªøneutrophil-to-lymphocyte ratio, the Glasgow Prognostic Score (original or modified), and the C-reactive protein/albumin ratio, also correlate with severity and may complement the Tokyo guidelines severity grade.[23] The American Association for the Surgery of Trauma Emergency General Surgery grading system may also perform at least as well as the Tokyo guidelines.[24]

MANAGEMENT

The management of a patient with acute cholecystitis involves supportive care, antibiotics, and either drainage or removal of the gallbladder (Fig. 88.4). Even in equivocal cases, drainage of the gallbladder may be appropriate in critically ill patients.

The standard initial medical treatment for acute cholecystitis includes antibiotics, analgesia, and, at least during the early phase, bowel rest. For patients who are septic from cholecystitis, it is appropriate to follow the Surviving Sepsis Campaign guidelines regarding fluid resuscitation, use of vasopressors, and initiation of broad-spectrum antibiotics.[25]

Antibiotics for uncomplicated cholecystitis should cover enterococcal species and gram-negative rods, particularly *Escherichia coli* and *Klebsiella* spp.[26] Cultures are positive in about half of the cases, particularly beyond 72 hours after the onset of symptoms—more so if empyema of the gallbladder is present. In patients who have more severe illness, have previously received antibiotics, or are older, more resistant and unusual organisms may be cultured from gallbladder bile. These organisms can include *Staphylococcus* spp., resistant gram-negative bacilli, anaerobic bacteria, and fungi. Broader coverage may be required initially until cultures are obtained and coverage can be more tailored. Local antibiograms, particularly the proportion of extended-spectrum beta-lactamase–producing organisms can be helpful.

Optimal duration of antibiotic coverage for cholecystitis remains unclear. If patients undergo early cholecystectomy, continuing antibiotic coverage postoperatively may not be necessary. For patients who undergo cholecystostomy, 7 days or less of antibiotics seems to be as good as more prolonged courses.[27]

Nonsteroidal antiinflammatory drugs can be very effective for controlling the pain from cholecystitis. When narcotics are needed, the choice of narcotic analgesic is probably not as important as was once believed. All narcotics can increase the pressure of the sphincter of Oddi, potentially increasing pressure in the biliary tree.

The next question is whether to drain or remove the gallbladder acutely. For patients with septic shock, severity of illness and delay in source control, particularly greater than 16 hours after presentation, are associated with increased mortality.[28] There is a lack of prospective, randomized trials to help clarify this issue. Early surgical consultation is critical. The decision regarding drainage or removal of the gallbladder must be made with consideration of both the critical care and general surgical issues. If the patient can tolerate transport to the operating room and a general anesthetic, cholecystectomy remains the most definitive therapy, particularly in light of the risk of gallbladder gangrene and perforation. Patients with grade I or II cholecystitis and with good performance status based upon the Charlson Comorbidity

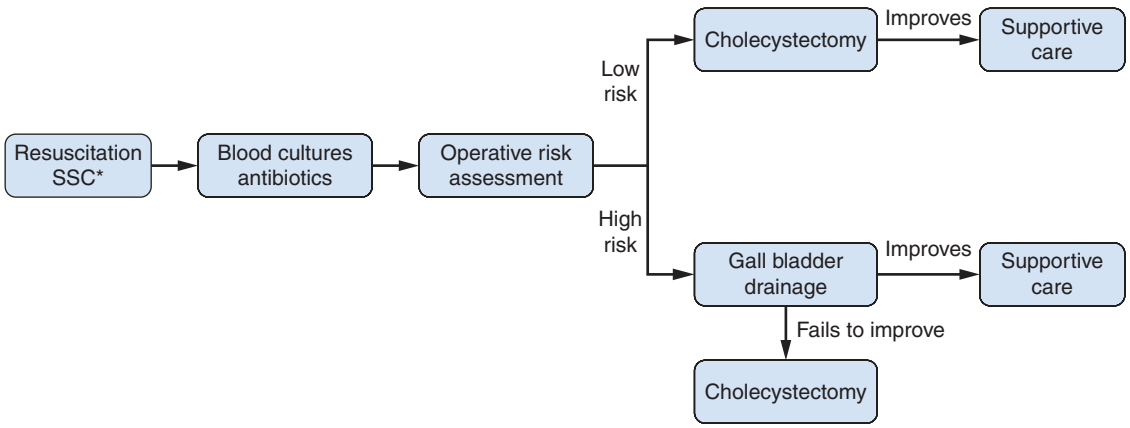

Fig. 88.4 Management of cholecystitis. **SSC,* Surviving Sepsis Campaign.

Index and American Society of Anesthesiologists physical status should undergo cholecystectomy.[29] Frequently, however, critically ill patients with acute cholecystitis, particularly those with significant respiratory dysfunction or hemodynamic instability, may be too ill for cholecystectomy. Patients with grade II cholecystitis and poor performance status or with grade III disease may be better managed with image-guided or endoscopic drainage to obtain source control.

Image-Directed Drainage

Image-directed cholecystostomy has become a relatively low-risk procedure for patients with acute cholecystitis.[30] Some physicians have used percutaneous cholecystostomy as a diagnostic and therapeutic maneuver in ICU patients with persistent, unexplained sepsis, though its role in this setting remains unclear. Because the risk of this procedure is low, percutaneous cholecystostomy should be considered when the index of suspicion for acute cholecystitis is high enough in a critically ill patient.

Percutaneous cholecystostomy is contraindicated if the patient has evidence of diffuse peritonitis, suggesting gallbladder perforation. On the other hand, if imaging studies suggest a pericholecystic abscess, concomitant drainage of the abscess or surgical exploration is indicated.

Percutaneous cholecystostomy is performed under ultrasound or CT guidance. A needle is inserted into the gallbladder, usually via a transhepatic approach. The tract is dilated using a standard Seldinger technique. A pigtail catheter is advanced over the wire into the gallbladder. Some use a trocar technique instead. The catheter is then attached to a drainage bag.

Studies suggest up to 100% success with tube placement and clinical improvement, but mortality remains high, particularly with multiple comorbidities.[31] Given the risk for catheter-related complications over time, interval cholecystectomy or removal of the catheter should be considered once safe to do so, which can be considered once symptoms have resolved.[32,33]

There has been concern that the presence of ascites may increase the risk of complications, such as bile peritonitis or catheter dislodgement, from percutaneous cholecystostomies. Duncan and colleagues found no difference in procedural complications between patients with or without ascites, though patients with ascites underwent fewer delayed cholecystectomies and had greater mortality.[34]

Overall mortality for percutaneous cholecystostomy is variable depending on the presence of shock and other comorbidities.[32,35] The limiting factor for success of percutaneous drainage is the viability of the gallbladder. Focal ischemia or necrosis is unlikely to improve without cholecystectomy and predisposes the patient to perforation. Cholecystectomy should be considered in patients who do not improve with cholecystostomy.

In many cases, cholecystostomy may provide definitive management without the need for interval cholecystectomy, particularly with acalculous disease and with elderly patients.[36,37] Patients with calculous disease should generally undergo interval cholecystectomy. Optimal timing is unclear. Performing the interval cholecystectomy too early (perhaps $<$10 days after cholecystostomy placement) may be associated with greater difficulty and more frequent complications.[38] Others have found that early cholecystectomy (within 5 days of drainage) after percutaneous cholecystostomy can be safe and even advantageous.[39]

In some cases, percutaneous, transhepatic gallbladder aspiration in elderly or otherwise high-risk patients can provide clinical improvement with few complications and allow safe, delayed cholecystectomy.[40,41] On the other hand, some patients, particularly those with calculous disease and/or purulence in the gallbladder, seem to be at higher risk for recurrent cholecystitis before cholecystectomy.[42]

Whether or not percutaneous cholecystostomy is superior to cholecystectomy has been difficult to determine. One systematic review did not demonstrate benefit and, in fact, suggested worse outcomes with cholecystostomy.[43] Patients who undergo a percutaneous cholecystostomy may have a more prolonged inflammatory response and higher mortality.[44]

ENDOSCOPIC DRAINAGE

A novel technique for drainage of the gallbladder involves a transpapillary endoscopic approach.[45] This approach may be helpful if other indications for endoscopic evaluation or intervention are present. It seems that the intervention is more successful if the ultrasound demonstrates that the gallbladder is not severely distended or thick. Endoscopic ultrasound can also be used for transgastric or transduodenal placement of a stent into the gallbladder. The success rate for this approach seems to be similar to that of percutaneous cholecystomy,[46] possibly with fewer complications and need for fewer repeat procedures.[47,48]

Surgical Management

Surgical options include cholecystostomy and cholecystectomy. Surgical cholecystostomy can be accomplished via a small right subcostal incision using local anesthesia or via laparoscopy. This procedure largely has been supplanted by image-guided, percutaneous or endoscopic drainage.

Cholecystectomy may be advantageous compared with cholecystostomy, because it allows one to examine the entire right upper quadrant for other pathology and to completely drain any fluid collections around the gallbladder. It also alleviates the risk of gallbladder perforation. When cholecystectomy is performed, a laparoscopic approach can usually be attempted, recognizing that one may need to convert to an open procedure because of difficulty with the dissection. The timing of cholecystectomy for acute cholecystitis remains controversial, but cholecystectomy within the first 3 days, even in patients with severe cholecystitis, seems to be safe if the patient does not have other risk factors for mortality.[49] In a study of patients over 65 years of age with cholecystitis in the National Inpatient Sample, cholecystostomy was associated with greater mortality and morbidity than cholecystectomy, suggesting that unless the risk of cholecystectomy is clearly prohibitive, cholecystectomy is indicated.[50] On the other hand, age alone may not be an independent risk factor for complications after cholecystectomy.[51] If the patient is not responding to nonoperative management, cholecystectomy needs to be considered.

Though rarely done, bedside laparoscopy can be performed for evaluation of the acute abdomen in critically ill patients. If acute cholecystitis is identified, a cholecystostomy can be performed readily, or the patient can be taken to the operating room for a cholecystectomy.[52] If the diagnosis of cholecystitis is excluded, the patient may be spared an unnecessary operation.

Summary of Management

The TG18 guidelines include management bundles for patients with acute cholecystitis.[53] The diagnosis should be made expeditiously with imaging. If the findings are equivocal, repeat assessment is indicated every 6–12 hours until cholecystitis or an alternative diagnosis is confirmed. Early supportive care for critically ill patients with cholecystitis should focus on fluid resuscitation, bowel rest, analgesia, and antibiotics. The next steps are based upon the severity of cholecystitis (see Fig. 88.4). For patients at low risk for an operation, early laparoscopic cholecystectomy is recommended. For patients at high risk, urgent gallbladder drainage is more appropriate, though it has been difficult to prove this.[43] If the patient fails to improve after drainage, operative intervention should be considered. Transfer to a higher level of care should be considered in appropriate cases.

COMPLICATIONS AND OUTCOME

Complications of acute cholecystitis are much more common in critically ill patients than in the general population. Elderly patients are particularly at risk. Among patients with acalculous cholecystitis, gangrene is common.[9,17] Compared with patients without gangrene, those with gangrene are at greater risk of perforation or of failure of percutaneous drainage. Some of these patients have emphysematous cholecystitis, a diagnosis that carries an even greater risk of perforation. Emphysema can be identified by plain abdominal radiographs, CT, or ultrasound. In these cases, antibiotics should cover gas-forming anaerobic organisms. Although percutaneous drainage may be effective, early cholecystectomy is indicated if the patient does not improve promptly.

Perforation of the gallbladder occurs in up to 10% of cases.[54] Usually, the resulting fluid collection is localized and amenable to percutaneous drainage. Free perforation also can occur, and when it does, the risk of mortality is markedly increased. The clinical problem, however, is that preoperative imaging may not demonstrate evidence of perforation. The risk of perforation increases with delay in drainage or operation. Cholecystectomy is indicated for free perforation.

Empyema of the gallbladder also greatly increases mortality. This complication may be amenable to percutaneous drainage, but the risks of failure or perforation are substantial.

The risk of mortality from cholecystitis in the ICU mainly reflects the underlying disease processes and comorbidities, but may be as high as around 30%.[7,9]

PREVENTION

No intervention has been shown conclusively to prevent development of cholecystitis in ICU patients. If the theories regarding the pathophysiologic mechanisms are correct, the incidence of the disease should be reduced by aggressively resuscitating patients with shock, avoiding biliary stasis by implementing early enteral feeding, and minimizing the use of narcotics.

SUMMARY

The diagnosis of acute cholecystitis in critically ill patients is difficult because patients frequently do not present with the usual symptoms and signs. Laboratory tests are nonspecific. The best initial radiographic study is ultrasound. Scintigraphy and CT also may be helpful. Management includes antibiotics and bowel rest. Image-guided or endoscopic gallbladder drainage may be performed in unstable patients, although cholecystectomy remains the most definitive treatment if this intervention can be accomplished safely.

KEY POINTS

- Critically ill patients frequently do not present with the usual symptoms and signs of cholecystitis.
- Laboratory tests for cholecystitis are not specific.
- The best initial imaging study is ultrasound, but scintigraphy or CT may be needed as well.
- Management begins with antibiotics and bowel rest.
- Although cholecystectomy is the most definitive procedure, image-guided or endoscopic gallbladder drainage is indicated for patients too unstable to undergo cholecystectomy.

References for this chapter can be found at expertconsult.com.

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The Tokyo Guidelines group has published several guidelines for the diagnosis and management of acute cholecystitis. This paper reviews the clinical criteria for making the diagnosis and proposes useful criteria for severity assessment.

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Acute Pancreatitis

Lillian L. Tsai and Pamela A. Lipsett

Acute pancreatitis is an inflammatory condition of the exocrine pancreas, the severity of which can range from mild edematous changes to severe acute necrotizing pancreatitis. Pancreatitis is one of the most common diseases requiring inpatient hospitalization with an incidence of 34 per 100,000 people worldwide.[1,2] In the United States the annual cost associated with treatment of acute pancreatitis has increased by 365% from 1997 to 2012, now accounting for more than $9.2 billion.[1,3] Mild acute pancreatitis is a self-limited process that usually resolves within several days to 1 week, rarely causes mortality, and is not associated with organ dysfunction or necrosis.[4,5] By definition, transient organ failure and local complications occur in moderately severe acute pancreatitis. Although 80% of patients have mild disease, 15%–20% develop severe pancreatitis, which is characterized by persistent organ failure.[5] Although the overall mortality rate for all patients with acute pancreatitis is very low, the mortality rate for severe acute pancreatitis can be over 30%.[1,6–9]

In the early phase of pancreatitis, which typically lasts about 1 week, pancreatic inflammation triggers cytokine cascades, which result in a systemic inflammatory response syndrome (SIRS). The late phase can last for many weeks to many months with persistence of multiple organ failure, local complications, and ongoing inflammation. A compensatory antiinflammatory response syndrome (CARS) is thought to contribute to the increased risk of infection.[4,9] There has been limited success in attempting to modify the course of the disease using agents such as protease inhibitors.[10,11]

Since the early 2000s, mortality associated with acute pancreatitis has decreased from 1.6% to 0.8%.[1,8] Most cases of pancreatitis that result in patient death are caused by infection of necrotic pancreatic tissue. Although there have been many improvements in management of pancreatitis, there remain many long-term sequelae of the disease. After an episode of acute pancreatitis, 40% of patients develop new-onset prediabetes or diabetes. Up to 25% develop exocrine pancreatic insufficiency and 8% chronic pancreatitis.[1] Therefore it is critical to optimize the prevention, diagnosis, and treatment of pancreatitis to improve patient outcomes.

This chapter delineates the etiology, pathophysiology, severity and staging, and current management of patients with acute pancreatitis.

ETIOLOGY AND EPIDEMIOLOGY

In the United States alone, pancreatitis accounts for over 270,000 hospital admissions annually.[12] It is the most common gastrointestinal discharge diagnosis and fifth leading cause of in-hospital mortality.[13] From 2002 to 2012 there has been a 16% increase in pancreatitis-related admissions.[8] The increasing incidence of pancreatitis, particularly in western countries, is conventionally thought to be associated with a rise in obesity and thus gallstone-related pancreatitis. To this point, recent studies have discovered more than a threefold increase in aspects of metabolic syndrome and morbid obesity among patients with pancreatitis.[8] However, in recent years the prevalence of chronic pancreatitis has increased markedly, suggesting that increasing hospitalization may be the result of recurrent flares of chronic pancreatitis.[8] Epidemiologically, the subgroup of acute pancreatitis patients with associated chronic pancreatitis had higher odds of alcohol and tobacco use, African American race, and lower socioeconomic background.[8] A greater proportion of these patients were admitted to urban teaching hospitals in the United States.

Risk factors for acute pancreatitis include smoking, alcohol use, age, family history, obesity, diabetes, inflammatory bowel disease, end-stage renal disease (ESRD), and possibly cannabis use.[13–18] Interestingly, there is a differential dose-response relationship between alcohol consumption and pancreatitis in women versus men. In men, the relationship between alcohol consumption and pancreatitis is linear, monotonically increasing with no threshold, whereas in women, the relationship is nonlinear and J shaped in which the risk of pancreatitis is increased only above 40 g per day of alcohol consumption.[13,16]

The most common etiology of acute pancreatitis is the result of gallstones, causing 40%–70% of cases.[5,8] Alcohol abuse accounts for 25%–35%, and hypertriglyceridemia causes 9% of cases of acute pancreatitis. The majority of alcoholic pancreatitis occurs in males.[19] Other causes of pancreatitis fall into several categories and are widely varied. These include trauma, medications, infectious agents, metabolic disorders, pancreaticobiliary tumors, genetic factors, autoimmune factors, and idiopathic factors. Traumatic insults to the pancreas can occur during procedures such as endoscopic retrograde cholangiopancreatography (ERCP), endoscopic ultrasound (EUS) with fine needle aspiration, aortic surgery, and pancreatic resection.[20] Medications known to cause pancreatitis include mercaptopurine, azathioprine, mesalamine, furosemide, and losartan.[1,5,21] Bacterial, viral, and parasitic infections can all trigger pancreatitis. Metabolic disorders of hypercalcemia and hyperparathyroidism are rare causes. In hypertriglyceridemia, only a triglyceride level above 1000 mg/dL has been found to be significant.[5] Tumors obstructing pancreatic drainage, including intraductal papillary mucinous neoplasms (IPMNs) and adenocarcinoma, also can cause pancreatitis. Genetic mutations in *PRSS1, SPINK, CFTR, CTRC,* and *CASR* have all been linked as well. Finally, anatomic anomalies of the pancreas such as pancreas divisum and sphincter of Oddi dysfunction predispose to pancreatitis. Identifying the etiology of acute pancreatitis is important to tailor diagnostic and treatment strategies.

PATHOGENESIS AND GENETIC SUSCEPTIBILITY

The main function of the exocrine pancreas is carried out by acinar cells, which are responsible for synthesizing, storing, and secreting digestive enzymes.[2] These enzymes are then transported to the small

intestine via ductal cells that secrete 2.5 L of alkaline, bicarbonate-rich fluid each day.[2,22] Although the pathogenesis of acute pancreatitis is complex and remains under active investigation, it is known that derangements in the molecular processes of these cells contribute to dysregulation. Normally, acinar cells secrete trypsinogen in an inactive precursor form that becomes activated to trypsin by serine protease enteropeptidases in the duodenum.[23,24] In turn, trypsin then activates chymotrypsinogens, proelastases, and carboxypeptidases and autoactivates additional trypsinogen. This process relies on normal functioning of cellular organelles.

Theoretically, premature activation of digestive enzymes is the inciting event that leads to pancreatitis.[25] Calcium signaling is tightly regulated by the endoplasmic reticulum of acinar cells because it serves as a messenger for the release of digestive enzymes.[2,23] Pathologic stimuli to the cell causes a transient spike in cytoplasmic calcium that becomes a sustained, global increase in calcium levels, replacing physiologic oscillations.[2,24,25] This calcium signal then activates calcineurin, which mediates activation of trypsinogen.[24] Simultaneously, the elevated calcium level affects mitochondrial membrane permeability, resulting in inability to produce adenosine triphosphate (ATP), increased reactive oxygen species, and triggering of apoptosis.[2]

Abnormal calcium signaling also precedes colocalization, or fusion, of lysosomal and zymogen components.[24] Trypsinogen is activated by the lysosomal enzyme cathepsin B in these intracellular vacuoles.[24,25] Impaired autophagy additionally leads to an imbalance between cathepsin B, which activates trypsinogen, and cathepsin L, which degrades trypsin.[2,24] The inappropriate activation of these digestive enzymes induces up-regulation and release of cytokines that contribute to local and systemic inflammation. Furthermore, activation of the NFκB pathway in acinar cells has recently been found to cause many downstream inflammatory effects.[22,25]

Certain proteins act to regulate trypsinogen and, when mutated, can predispose to pancreatitis. For instance, in normal pancreatic cells SPINK1 inhibits trypsin and CTRC mediates trypsinogen degradation.[23] Mutations in *PRSS1* prevent CTRC from functioning and thus cause hereditary pancreatitis. Although SPINK1 mutations have been found in many patients with pancreatitis, the expression and function of the protein do not seem to be affected in all variants.[23] Therefore the mechanism for predisposition to pancreatitis remains unclear.[26]

DIAGNOSIS

The diagnosis of pancreatitis can be made when two of the following three criteria are met: (1) abdominal pain, (2) serum amylase and/or lipase level over three times the upper limit of normal, and (3) imaging consistent with pancreatitis.[1,18,27] Symptoms of severe, persistent epigastric pain radiating to the back are most characteristic of pancreatitis. Oftentimes, this pain is associated with nausea and vomiting. Dull, colicky pain and lower abdominal pain are generally not consistent with pancreatitis and alternative diagnoses should be considered.[5]

On physical examination, upper abdominal tenderness is perceived and can be associated with guarding. Although not specific, Cullen and Grey Turner signs portend severe pancreatitis and high mortality rates up to 37%.[28,29] In both signs, pancreatic enzymes cause diffusion of fat necrosis that leads to inflammation and retroperitoneal hemorrhage. In Cullen sign, ecchymoses are seen in the periumbilical region via the round ligament, whereas in Grey Turner sign, ecchymoses are seen in the flanks via subcutaneous tissues.

Serum amylase and lipase are the most commonly used laboratory markers of acute pancreatitis. The upper limit of normal for amylase ranges from 100 to 300 U/L, and for lipase it ranges from 50 to 160 U/L.[1] Amylase levels usually elevate within the first few hours after onset of symptoms and return to normal in 3–5 days. However, serum amylase may remain normal in up to one-fifth of patients with pancreatitis and can be normal in those with alcohol abuse or hypertriglyceridemia.[5] Serum lipase is a more specific marker of pancreatitis and remains elevated for a longer period than does amylase.[5,27] After diagnosis, daily measurement of amylase or lipase has limited value.[27] Other disease processes that cause increased serum amylase include intestinal perforation or infarction, bowel obstruction, abdominal aortic aneurysm, appendicitis, cholecystitis, peptic ulcer disease, biliary obstruction, salivary gland diseases, and gynecologic conditions.[1,5] Serum lipase can also be elevated in intestinal pathologies, cholecystitis, peptic ulcer disease, and renal disease.[1,5] Additional laboratory values that can be useful in the clinical evaluation of acute pancreatitis include a complete blood count, electrolytes, blood urea nitrogen (BUN), creatinine, liver enzymes, coagulation tests, albumin, calcium, and triglycerides.[18,27]

Some studies have investigated the ability of urinary trypsinogen-2 to diagnose acute pancreatitis. Overall, dipstick urinary trypsinogen-2 has been found to rule out acute pancreatitis with high probability and identify patients who should be further evaluated. It may be useful as a screening test because of its reported high negative predictive value.[30–33]

SEVERITY AND SCORING

The ability to distinguish patients at high risk of morbidity and mortality from pancreatitis is important to guide management decisions. To this end, over 20 different scoring systems for acute pancreatitis have been developed.[34] One of the most commonly described scoring systems is the Ranson criteria, which have a sensitivity of 75%, specificity of 77%, positive predictive value of 49%, and negative predictive value of 91% for predicting severe acute pancreatitis (Table 89.1).[35] Ranson criteria assesses 11 factors (2 clinical components and 9 laboratory values) at the time of patient presentation and at 48 hours after admission. The score ranges from 0 to 11, with a score of <3 associated with a mortality of 0%–3%, a score of ≥ 3 associated with a mortality of 11%–15%, and a score of ≥ 6 conferring a 40% chance of mortality.[34,36] One major weakness of Ranson criteria is that the score can

TABLE 89.1 Pancreatitis Scoring Systems

Name of Scoring System	Number of Variables	Sensitivity	Specificity	PPV	NPV
Ranson Criteria	11	75%–82%	74%–77%	48%	93%
APACHE II	12	58%–81%	72%–78%	43%–63%	84%–86%
BISAP	5	51%–62%	72%–91%	25%	93%

From Refs. 35,37,38–40.
NPV, Negative predictive value; *PPV,* positive predictive value.

only be calculated after 48 hours, when many early interventions have already been determined.

The Acute Physiologic and Chronic Health Evaluation (APACHE) score originated as an intensive care unit (ICU) scoring method. Early iterations, APACHE II and III, have been used as established prognostic indicators in acute pancreatitis. The latest version, APACHE IV, is highly accurate in predicting ICU mortality. It takes 52 variables into consideration, including bilirubin, albumin, sedation status, and chronic health problems. Limited studies have validated APACHE IV as a valuable system to predict mortality associated with acute pancreatitis.[35,37] However, further investigation is needed, and the latest version is proprietary.

The Bedside Index for Severity in Acute Pancreatitis (BISAP) is a tool that evaluates and identifies patients who are at high risk of mortality within the first 24 hours of hospital admission.[38] It is scored out of 5 points, with each of the following variables conferring 1 point: BUN >25 mg/dL, impaired mental status, SIRS, age >60, and presence of a pleural effusion.[39] When compared with Ranson criteria and APACHE II, BISAP had higher specificity but lower sensitivity for mortality and severe acute pancreatitis.[39] BISAP is able to predict poor outcomes before the onset of organ failure.[38]

An imaging-based scoring system is Balthazar's computed tomography (CT) index that uses early scan characteristics such as pancreatic necrosis and peripancreatic inflammation to predict the severity of pancreatitis. A high index of 7–10 points confers a 92% morbidity and 17% mortality rate, whereas a low index of 0–2 points only had a 2% morbidity and no mortality.[40]

Various serum biomarkers have been suggested as predictors of severity for pancreatitis. In particular, increased admission hematocrit (≥44) and failure of hematocrit to decrease after 24 hours is thought to be associated with necrotizing pancreatitis. The third spacing of fluids caused by inflammation reduces intravascular volume and is reflected by the hematocrit.[36] Additionally, C-reactive protein (CRP) levels greater than 150 mg/L in the first 72 hours are associated with pancreatic necrosis, with a sensitivity and specificity of over 80%. Other laboratory values such as procalcitonin, trypsinogen-2, amyloid A, and urinary trypsinogen have also been investigated as predictive markers.[36]

The 2012 revision to the Atlanta Classification changed the definition of acute pancreatitis severity. In the updated version, pancreatitis is divided into mild, moderately severe, and severe.[4,9,18] Mild pancreatitis has no organ failure or complications, a self-limited course, and usually results in discharge within 7 days. Moderately severe pancreatitis shows transient organ failure, may have local and systemic complications, and has a greater risk of mortality. Severe acute pancreatitis is characterized by persistent organ failure (>48 hours), local and systemic complications, and a mortality of greater than 30%.[4,18] This classification recommends the modified Marshall scoring system to assess organ failure, which evaluates the respiratory, cardiovascular, and renal systems. Persistent organ failure is defined as a score of 2 or higher in any of the three organ systems for longer than 48 hours. The score is determined using laboratory and physiologic variables.[4,9] Although there are numerous scores aimed at identifying pancreatitis patients who are at high risk of mortality, early clinical recognition and treatment remains the cornerstone of prudent management.

IMAGING

Ultrasonography and Endoscopic Ultrasonography

Because of its noninvasive nature, transabdominal ultrasound is recommended in the first 24 hours for all patients with acute pancreatitis.[5,44–46] In acute pancreatitis, ultrasound examination can show diffuse enlargement and a hypoechoic echotexture from glandular edema. However, assessment of the pancreas is often limited as a result of overlying bowel gas. Therefore the primary function of ultrasound is in identification of gallstones and biliary ductal dilatation or choledocholithiasis. Ultrasound has a 70% sensitivity in detecting gallstones for patients with acute biliary pancreatitis, whereas it only has a 20% sensitivity in detecting choledocholithiasis. CT and magnetic resonance cholangiopancreatography (MRCP) have sensitivities of 40% and 80%, respectively.[45]

EUS is highly sensitive for the identification of choledocholithiasis, with accuracy similar to that of ERCP.[47] As a bedside procedure, EUS can be used to determine the need for ERCP in high-risk, pregnant, or critically ill patients and those with coagulopathy or unusual anatomy.[36]

COMPUTED TOMOGRAPHY

CT is the gold standard in the diagnosis of acute pancreatitis and its complications. When contrast is used, CT has over a 90% sensitivity and specificity for acute pancreatitis.[5] CT can reliably identify interstitial pancreatitis, necrotizing pancreatitis (Fig. 89.1), acute peripancreatic fluid collections, acute necrotic collections, walled-off necrosis (Fig. 89.2), and pseudocysts.[44] Interstitial pancreatitis

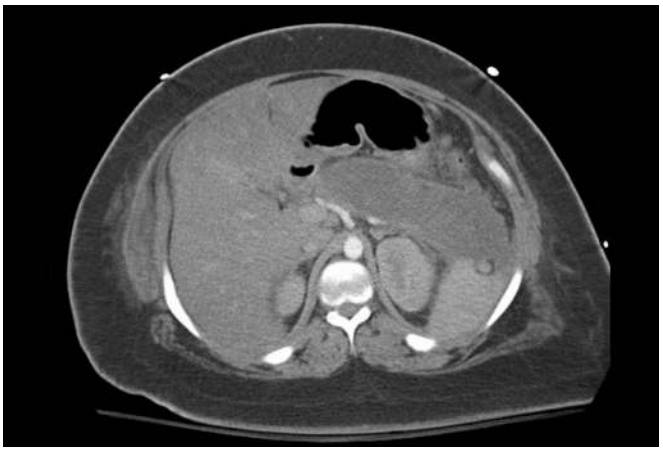

Fig. 89.1 Pancreatic necrosis.

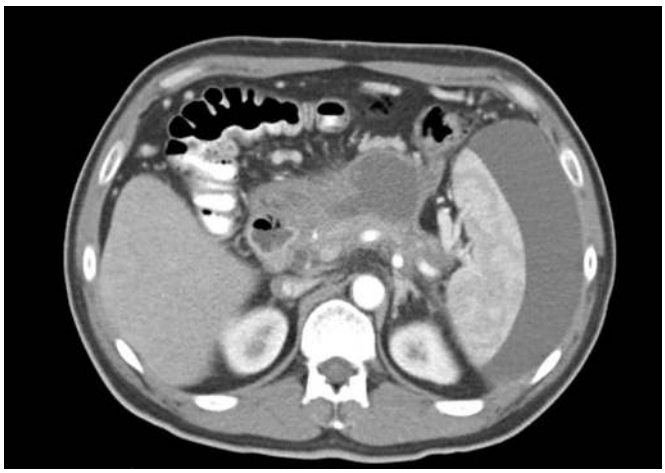

Fig. 89.2 Walled-off necrosis and perisplenic fluid.

shows uniform enhancement of the pancreas because of intact microcirculation, whereas necrotizing pancreatitis shows devitalized areas that do not enhance as a result of disturbances in the microcirculation.[36] Other complications visualized by CT include portal or splenic vein thrombus, abscess, pseudoaneurysm, colonic inflammation, and gastrointestinal (GI) tract obstruction from strictures or compression.[36,44]

Although CT is valuable in the assessment of acute pancreatitis, routine use is not recommended.[5,18,36,46] CT should be performed when the diagnosis is unclear to distinguish acute pancreatitis from other conditions causing abdominal pain, or when patients fail to clinically improve in the first 48–72 hours.[18,36,48] The best time for CT is after 72 hours to evaluate for local complications with additional scans if there is a change in clinical status.[21,47] CT is also recommended when patients older than 40 years present with a first episode of acute pancreatitis to exclude neoplasm. Patients exhibiting alarm signs of weight loss, recent diabetes diagnosis, and a history of tobacco use may also warrant a CT scan.[46]

ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY

ERCP is used in acute pancreatitis to treat common bile duct stones. Patients with acute cholangitis and severe pancreatitis should undergo ERCP in the first 24 hours. ERCP is also used in patients who are poor surgical candidates for cholecystectomy, certain cases post-cholecystectomy, and those with persistent biliary obstruction.[36] It is unnecessary to perform ERCP routinely before cholecystectomy. Because most gallstones causing pancreatitis pass naturally, ERCP is not recommended in biliary pancreatitis patients without laboratory and clinical evidence of ongoing obstruction.[5] Three recognized interventions decrease the risk of post-ERCP pancreatitis. The first is guidewire cannulation of the bile and pancreatic ducts to avoid hydrostatic injury from radiocontrast administration.[5] Other studied measures to reduce post-ERCP pancreatitis rates are insertion of pancreatic duct stents and rectal nonsteroidal antiinflammatory drugs (NSAIDs).

MAGNETIC RESONANCE CHOLANGIOPANCREATOGRAPHY

Magnetic resonance imaging (MRI) and cholangiopancreatography (MRCP) are comparable to CT when evaluating pancreatitis and offer certain advantages. MRCP has a sensitivity of 89%–100% and specificity of 83%–100% for gallstones, with an ability to detect choledocholithiasis down to a size of 3 mm.[5,44] Selective use of MRCP can thus decrease the need for ERCP. In addition, MRCP is excellent in delineation of fluid collection composition. MRCP has 100% sensitivity for the detection of solid debris and therefore can reliably distinguish between pseudocysts and necrotic or superinfected collections.[36,45,47,48] MRI is also more effective than CT in detecting pancreatic hemorrhage and pancreatic ductal anomalies, including anatomic variations, strictures, and disruptions.[46,49] MRCP with secretin administration improves image quality and allows for assessment of pancreatic excretory function.[50]

Further benefits of MRI include no radiation exposure and lack of nephrotoxicity from use of gadolinium. Patients who are pregnant, have a contrast allergy, or have renal insufficiency can undergo MRI safely.[5,36,44,45] However, there are disadvantages to MRI as well. There is a greater variation in image quality among different centers, difficulty managing critically ill patients during MRI, and relative lack of availability.

MANAGEMENT

General Support

Monitoring and Resuscitation

Upon admission for acute pancreatitis, hemodynamic and clinical status should be assessed for risk stratification.[5] Patients who meet one or more of the following parameters defined by the Society of Critical Care Medicine (SCCM) should be admitted to the ICU: heart rate <40 or >150 beats/minute, systolic arterial blood pressure <80 mm Hg, mean arterial pressure <60 mm Hg, diastolic arterial pressure >120 mm Hg, respiratory rate >35 breaths/minute, sodium <110 mmol/L or >170 mmol/L, potassium <2 mmol/L or >7 mmol/L, PaO_2 <50 mm Hg, pH <7.1 or >7.7, glucose >800 mg/dL, calcium >15 mg/dL, anuria, or coma.[12] Patients with persistent organ failure and thus severe acute pancreatitis as defined by the revised Atlanta Classification should also be admitted to the ICU.[5,12] Management in a high-volume institution with intensive care facilities, ability to carry out organ replacement therapy, daily access to interventional radiology, performance of EUS/ERCP, and surgical expertise is recommended for patients who may need those specialties and for those with severe acute pancreatitis.[12]

Fluid resuscitation is the foundation of acute pancreatitis management. Pancreatitis causes a state of hypovolemia caused by third spacing, emesis, reduced oral intake, and increased respiratory losses.[5,51] This leads to microangiopathic effects and glandular edema, which reduce blood flow and impair microcirculatory perfusion of the pancreas.[5,51,52] Tissue ischemia then triggers release of cytokines, increased capillary permeability, and endothelial damage, all ultimately resulting in cell death and necrosis.[5,52] Therefore the hypovolemic state is thought to play a major role in the transition from mild to severe acute pancreatitis with SIRS and organ failure.[52]

Early, goal-directed intravenous (IV) fluid resuscitation at a rate of 5–10 mL/kg/hr should be given initially.[12,21] In most patients, a total of 2.5–4 L in the first 24 hours will be sufficient to accomplish resuscitation goals. Fluid needs should be frequently assessed in the first 6 hours and for 24–48 hours after admission.[5,12,52] Patients with severe volume depletion who are tachycardic or hypotensive may need additional fluid boluses. Response to resuscitation should be monitored with noninvasive clinical parameters, including heart rate <120 beats/minute, mean arterial pressure of 65–85 mm Hg, and urine output >0.5–1 mL/kg/hr. Invasive clinical targets include stroke volume variation and intrathoracic blood volume assessment. Biochemical measurements should also be considered, with a hematocrit goal of 35%–44%, decreasing BUN, and normalizing creatinine as positive signs.[5,12,52] In elderly patients and those with cardiac or renal disease, fluid should be given more cautiously to avoid adverse effects of volume overload such as abdominal compartment syndrome and pulmonary edema.[5]

Although fluid resuscitation is vital and associated with decreased rates of organ failure and in-hospital mortality, overly aggressive therapy can be detrimental. One study compared fluid rates of 5–10 mL/kg/hr with 10–15 mL/kg/hr and found higher rates of infectious complications and mortality in the latter group.[12,53,54] Another study found that rapid hemodilution with a hematocrit of less than 35% was also more frequently associated with infection and mortality.[54,55]

Finally, there has been debate on the optimal fluid that should be used for resuscitation. The International Association of Pancreatology (IAP) and American Pancreatic Association (APA) recommend lactated Ringer's (LR), whereas the American Gastroenterological Association (AGA) makes no recommendation on normal saline versus LR.[12,21] Several studies suggest that LR may be preferred over normal saline.[5,56,57] A randomized controlled trial of 40 patients with acute pancreatitis showed that patients resuscitated with LR had a significantly

lower prevalence of SIRS and lower CRP levels (mean CRP 51 mg/L versus 104 mg/L) compared with those resuscitated with normal saline. Use of LR was associated with a smaller decrease in serum bicarbonate, suggesting a pH-mediated reduction of inflammation.[56] Other studies have suggested that LR has direct antiinflammatory properties via inhibition of macrophages and NFκB.[51,58] Hydroxyethyl starch is discouraged as a resuscitative fluid because of increased mortality and higher rates of renal failure.[12]

In a general critical care patient population, there is a theoretical concern that the high chloride level in normal saline may cause a greater risk of acute kidney injury. However, the SPLIT trial was a randomized double-crossover trial that showed no difference in acute kidney injury, failure, or mortality among patients receiving normal saline compared with buffered crystalloid.[59] The subsequent SALT trial similarly found no overall difference in acute kidney injury between critically ill patients receiving normal saline versus balanced crystalloids.[60] Interestingly, patients who required larger volumes of saline had an increased risk of major adverse kidney events, suggesting a possible dose-response relationship.

PULMONARY DYSFUNCTION

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) occur in 10%–25% of acute pancreatitis cases and are responsible for up to 60% of pancreatitis-associated mortality.[61–63] Pulmonary complications of acute pancreatitis are the most common and potentially the most perilous.[63,64] SIRS in acute pancreatitis causes increased pulmonary endothelial permeability, with leakage of exudate into the alveolar space and interstitial tissues.[61,62] This leads to alveolar damage, type I pneumocyte necrosis, release of cytokines, and leukocyte infiltration, all of which injure the lung parenchyma and compromise gas exchange.[61] Furthermore, pancreatic autodigestion releases phospholipase A2 into the circulation, where it travels to the lung and degrades surfactant.[62,64] Acute pancreatitis also increases production of platelet-activating factor, pancreatic elastase, and proteases that damage lung tissue. These multifactorial effects of acute pancreatitis on the lung cause hypoxia from a ventilation perfusion mismatch via right-to-left intrapulmonary shunting.[64]

In this setting of ALI, the addition of a secondary gram-negative infection serves as a predisposing factor for the development of ARDS. The compromised intestinal barrier in acute pancreatitis allows for translocation of gut bacteria and endotoxins.[61,62] Severe respiratory compromise and multiple organ failure can then occur. Other pulmonary complications include atelectasis, pleural effusion particularly on the left side from lymphatic obstruction, and pancreaticopleural fistulae from pancreatic duct disruption.[64]

PULMONARY MANAGEMENT

It is imperative to monitor oxygenation status and diligently observe for signs of respiratory failure in patients with acute pancreatitis. Supplemental oxygen should be provided as needed. Treatment of pleural effusions should be conservative unless symptomatic, in which case thoracentesis or tube thoracotomy may become necessary.[64] Some patients, particularly those who have developed ARDS, will require endotracheal intubation and mechanical ventilation.

Limited studies have shown that noninvasive positive-pressure ventilation (NIPPV) can be an effective option for the treatment of ARDS in the setting of acute pancreatitis.[65,66] One retrospective cohort study found that NIPPV was successful in all pancreatitis patients with mild ARDS, 49 of 64 patients with moderate ARDS, and 10 of 19 patients with severe ARDS.[65] There were significant improvements in oxygenation and decreases in heart rate and respiratory rate after NIPPV use in patients who did not require ventilation. Another study similarly suggested that NIPPV increases lung volume by re-expanding collapsed alveoli and redistributing extravascular fluid in the lung.[66] Together, these results suggest that NIPPV may decrease the need for intubation if administered early in the clinical course of respiratory distress. Success of NIPPV is dependent on clinician experience and patient compliance. In particular, one should cautiously use NIPPV in patients with nausea and vomiting for fear of aspiration. The positive pressure of NIPPV can also cause gastric distension, which reduces functional residual capacity of the lung.[67]

PAIN RELIEF

Pain is one of the main symptoms of acute pancreatitis and should be effectively controlled. There is very limited evidence to support the use of one type of analgesic over another. In a systematic review, buprenorphine, pentazocine, and metamizole showed relatively superior efficacy.[68] Buprenorphine was able to specifically reduce pain in acute pancreatitis. Morphine theoretically may cause spasms in the sphincter of Oddi, but there is no clinical evidence to recommend avoiding its usage.[54] NSAIDs have a favorable safety and efficacy profile. In a comparison of nine randomized controlled trials, there was no evidence to support the use of parenterally administered local anesthetics.[54] Patients with severe pain should be given IV analgesia. Patient-controlled analgesia and epidural analgesia are both viable options as well. A Cochrane review assessed multiple agents and concluded that opioids may decrease the need for supplementary analgesia. There was no difference in complications or adverse events between opioids and nonopioids.[51,69] One study found that opioid analgesia was associated with a significantly increased risk of GI dysmotility and cautioned overuse to prevent delays in oral intake.[51,70] Overall, there is no consensus on the optimal analgesic regimen, agent, or method of administration. Pain in acute pancreatitis should be treated adequately, with adjustments made as needed for patient comfort.[71]

SPECIFIC SUPPORT

Nutrition

Traditionally, it was thought that patients with pancreatitis should remain nil per os to allow for the inflamed organ to recover. However, recent studies suggest that maintenance of enteral nutrition can help protect the intestinal mucosal barrier. Current guidelines recommend early feeding in acute pancreatitis. The IAP/APA state that oral feeding can be started in mild pancreatitis once abdominal pain improves and inflammatory markers are down-trending, without a need to wait for normalization.[12,72] In mild pancreatitis, instituting a normal, solid diet is safe and has been shown to correlate with shorter hospitalizations.[73–75] The AGA recommends feeding within 24 hours of admission. Their review analyzed 11 randomized controlled trials comparing early versus delayed feeding and found a 2.5-fold increase in risk of interventions for necrosis in the delayed feeding group. There were also trends towards higher rates of organ failure and necrotizing pancreatitis.[76]

Multiple studies have shown that patients who initiate early enteral nutrition have improved outcomes.[77] In one study, delayed enteral nutrition was found to be associated with increased mortality and rates of infected necrosis, fluid collections, respiratory failure, and ICU admission.[78] Another study examined inflammatory markers in severe acute pancreatitis patients receiving enteral nutrition within 48 hours versus 8 days after admission. Laboratory CRP levels and CD4+

T-lymphocyte percentages were lower in the early feeding group, suggesting a moderating effect on the immune response. Clinical outcomes, including organ dysfunction, SIRS, and pancreatic infection, were all lower in the early enteral nutrition group.[79] A meta-analysis of 11 studies with 775 total patients similarly indicated that enteral feeding within 48 hours reduced the risk of infectious complications, catheter-related septic complications, hyperglycemia, length of stay, and mortality. A stratified analysis based on severity showed that early feeding was superior in severe pancreatitis as well.[80] Further, three additional studies showed gastrointestinal symptoms of feeding intolerance, nausea, and vomiting occurred at a lower rate among patients who received early feeding.[75]

Despite these studies, the recent Dutch PYTHON trial results do not support the current guidelines recommending early initiation of enteral feeding.[81] This was a multicenter randomized controlled trial of 208 patients at high risk for complications according to APACHE II, Imrie score, or CRP level. Patients were randomized to receive nasoenteric tube feeding within 24 hours or an oral diet 72 hours after presentation, with tube feeding if intolerant of an oral diet. There was no difference between the two groups in rates of major infection or death. A later study compared enteral nutrition within 24 hours with no nutritional support and found no reduction in SIRS, organ failure, or mortality.[82] There are many possible explanations for this discrepancy, and further studies may be needed to clarify the extent to which early feeding affects infection rates.

In pancreatitis patients who need nutritional support, enteral is recommended over parenteral feeding.[12,76,83] Parenteral nutrition causes gut atrophy and increased intestinal permeability. The lack of peristaltic action also leads to disturbances in the microflora.[77] All reviews and meta-analyses comparing enteral versus parenteral nutrition show that enteral feeding decreases rates of organ failure and infection.[12,71,76,77,84–87] Additionally, some studies showed a marked reduction in mortality, with a 4% rate in patients receiving enteral and 15.9% in those receiving parenteral nutrition.[77,85] A Cochrane review of eight trials comprising 348 patients showed reduced mortality, organ failure, systemic infection, need for operative intervention, and a trend towards shorter length of stay for pancreatitis patients receiving enteral nutrition.[71,84] Similar results are seen in the subset of critically ill patients with severe pancreatitis as well.[86] If oral and enteral tube feeding are not tolerated, parenteral nutrition should be used.

When enteral feeding is given, it may be administered using either a nasogastric (NG) or nasojejunal (NJ) route.[12,16,76] There have been three notable randomized controlled trials comparing NG and NJ feeds.[71,88–91] All of these have found that enteral nutrition is well tolerated via both NG and NJ routes in severe acute pancreatitis with no significant clinical differences. Neither route is associated with differences in pain, infectious complications, discharge, surgical need, or mortality.[89,90] A meta-analysis examining these three trials compiled a total of 157 patients and found no difference in tracheal aspiration, diarrhea, pain level, achievement of energy goals, or mortality.[88] One study showed that NG delivery of enteral feeds was efficacious, with 90% receiving only NG nutrition and 92% reaching nutritional targets. Patients receiving feeds via NG and NJ had similar rates of changing to parenteral nutrition. Vomiting and diarrhea were the most common adverse effects of NG feeds.[92] Caution should be taken in pancreatitis patients with delayed gastric emptying and intolerance of feeds to avoid aspiration risk.

PATHOGENESIS OF PANCREATIC INFECTION AND ANTIBIOTIC PROPHYLAXIS

Secondary infections cause over 80% of pancreatitis-related deaths.[93] Patients with infected pancreatic necrosis have double the risk of death, three times higher rate of organ failure, and are four times as likely to require ICU admission compared with patients with sterile necrosis.[94] The large majority of pathogens involved in pancreatic infection are gram-negative enteric bacteria such as *Escherichia coli, Pseudomonas, Proteus,* and *Klebseilla*.[93,95] Infection with gram-positive organisms, including *Staphylococcus aureus, Streptococcus faecalis,* and *Enterococcus,* anaerobes, and fungi have also been identified.

The pathogenesis of secondary infection is thought to occur either hematogenously, ascending from the duodenum and biliary system through the pancreatic duct, or via translocation of GI bacteria.[93] Impairment of the gut barrier from reduced intestinal blood flow, mucosal damage, and epithelial atrophy during acute pancreatitis leads to greater mucosal permeability.[95] In patients with severe acute pancreatitis, there are significant increases in intestinal permeability to both macromolecules and micromolecules. This change was found within 72 hours of onset and was correlated with poor clinical outcomes. In addition to facilitating bacterial translocation, intestinal permeability corresponded with systemic endotoxin levels. Endotoxin exposure has negative effects on immune function and causes release of cytokines. Together, these processes predispose patients to fatal secondary pancreatic infections.

There has been much debate and many conflicting studies on the use of prophylactic antibiotics to prevent infectious complications during acute pancreatitis. Currently, the guidelines from multiple organizations and studies do not recommend the routine use of antibiotic prophylaxis.[12,16,76] Some studies have found that early use of antibiotics, within 72 hours of symptom onset, reduces mortality and secondary infection.[96] However, multiple meta-analyses over the years have found no difference in outcomes.[97] One meta-analysis of 14 randomized controlled trials with a total of 841 patients showed that antibiotic prophylaxis was not associated with reduction in mortality, incidence of infected necrosis, nonpancreatic infections, or surgical interventions.[98] A more recent review examined 18 meta-analyses of randomized controlled trials between 1998 and 2015.[93] The authors found that 6 of 18 studies showed reduced mortality with prophylactic antibiotics, and 12 of 18 studies had no change in mortality. Based on these results, use of antibiotics is recommended only once there are clinical signs of infection or elevated inflammatory markers on laboratory testing.[93] Interestingly, a Cochrane meta-analysis of seven studies found that when imipenem specifically was used, there was a significant decrease in rates of pancreatic infection. When beta-lactams in general were used, there was a trend towards lower mortality (9.4% versus 15%) and infected pancreatic necrosis (16.8% versus 24.2%), but the results were not statistically significant.[99]

Overall, prophylactic antibiotics have no impact on mortality, risk of infection in pancreatic necrosis or nonpancreatic sites, rate of organ failure, and hospital length of stay.[76] When infection is suspected, antibiotics should be given promptly. Selective gut decontamination may be promising in preventing infectious complications, but further characterization is needed.[12] Probiotic prophylaxis is also not recommended.[12,100,101]

MANAGEMENT OF PANCREATIC NECROSIS AND ABSCESS

Infected pancreatic necrosis is suspected based on clinical and imaging signs. The demonstration of gas in pancreatic or peripancreatic collections on contrast-enhanced CT scan is the strongest indicator of infection.[102,103] Clinical deterioration, persistent fevers, elevated inflammatory markers, and bacteremia are all signs of infected necrosis as well.[12] When these elements are identified, broad-spectrum IV antibiotics

should be initiated. Agents with adequate pancreatic penetration include quinolones, metronidazole, carbapenems, and third-generation or higher cephalosporins.[103] Fine needle aspiration (FNA) can also be used to diagnose infected necrosis or to tailor antibiotic therapy to specific bacteria. However, routine use of FNA is unnecessary and not recommended. There is a high false-negative rate and a small risk of contaminating a previously sterile fluid collection.[102,103]

LABORATORY MARKERS OF INFECTED NECROSIS

Several laboratory values have been shown to provide prognostic value in pancreatic necrosis. CRP at 48 hours after admission is an indicator of severe acute pancreatitis, pancreatic necrosis, and in-hospital mortality.[104] Daily measurement of procalcitonin is used to predict infected pancreatic necrosis. The highest value, in addition to a sustained increase in procalcitonin on serial measurements, are able to identify patients who are likely to develop infected necrosis.[105] One study found that procalcitonin, hematocrit, BUN, and CRP all independently served as risk factors for infected pancreatic necrosis. Individually, these markers had high specificity but low sensitivity. When taken together, the maximum level at 48 hours of these four values had a sensitivity of 67.8% and specificity of 77.3% for infected pancreatic necrosis.[106]

INDICATION AND TIMING OF INTERVENTION

In necrotizing pancreatitis, intervention is indicated when there is suspicion or evidence of infected tissue and a decline in clinical status. Intervention may also be necessary in the absence of documented infection when there is prolonged organ failure.[12,102] In sterile necrotizing pancreatitis, intervention is warranted with (1) ongoing gastric, intestinal, or biliary obstruction; (2) persistent systemic symptoms such as weight loss, anorexia, and pain; and (3) disconnected pancreatic duct syndrome. Other rarer indications for intervention include abdominal compartment syndrome, bowel ischemia, and acute hemorrhage.

Generally, invasive measures should ideally be delayed until 4 weeks after initial onset of pancreatitis to allow for necrotic collections to liquefy and become encapsulated or walled off.[12,102,103,107] This reduces the risk of adverse events and has been shown to decrease morbidity and mortality.[103,107]

INTERVENTIONAL PROCEDURES

When intervention for infected necrosis becomes necessary, the step-up approach is currently the standard of care.[12] The optimal initial strategy is percutaneous catheter drainage followed by minimally invasive retroperitoneal necrosectomy if catheter drainage fails. In the landmark PANTER trial, 88 patients with suspected or confirmed infected necrotizing pancreatitis were randomized to receive either an open necrosectomy or the step-up approach.[108] The composite endpoint of major complications or death was lower in the step-up group (40% versus 69%). Patients in the step-up group also had a lower rate of multiple organ failure (12% versus 40%), incisional hernia (7% versus 24%), and new-onset diabetes (16% versus 38%). Notably, of the patients randomized to the step-up group, 35% were adequately treated with percutaneous drainage alone.[103,108]

A long-term follow up study of the PANTER trial reassessed all 73 patients who were alive at an average of 86 months after admission. At this time, the rate of death or major complications was 44% in the step-up group and 73% in the open necrosectomy group.[109] In the step-up group there was a lower incidence of incisional hernias (23% versus 53%), pancreatic exocrine insufficiency (29% versus 56%), and endocrine insufficiency (40% versus 64%). There was no significant difference in incidence of patients requiring pancreatic surgery, additional procedures, chronic pancreatitis, recurrent acute pancreatitis, pain scores, or medical costs. Thus the step-up approach with supportive management and percutaneous catheter drainage is recommended as the initial intervention for infected necrotizing pancreatitis.

When catheter drainage is unsuccessful, the tract can guide entry for video-assisted retroperitoneal debridement (VARD). In this procedure, laparoscopic instruments are used to access the retroperitoneal space and debride necrotic tissue under direct visualization. Minimally invasive necrosectomy has been found to decrease the incidence of multiple organ failure, complications, and mortality compared with open necrosectomy.[107]

NECROSECTOMY

The overarching goals of operative debridement in necrotizing pancreatitis are to achieve source control and to reduce the burden of necrotic tissue.[103] Classically, open surgical necrosectomy is performed via midline laparotomy or bilateral subcostal incisions. The greater omentum is opened to gain entry into the lesser sac and expose the pancreas. Blunt fragmentation is then used to remove necrotic tissue.[110] Cholecystectomy can be performed concurrently in cases of biliary pancreatitis. Large-bore drains are then left before closure.[103] Open necrosectomy has a complication rate of 34%–95% and a mortality rate of 11%–39%.[107] Patients undergoing this procedure often have more severe disease and a large amount of necrosis. Indications for open surgical intervention include failure of the step-up approach, abdominal compartment syndrome, bowel ischemia, and perforation.[102]

Endoscopic interventions can be done to drain collections transduodenally or transgastrically. Endoscopic ultrasound is used to guide transmural entry. Self-expandable metal stents or plastic stents may be placed into the necrotic cavity. Direct endoscopic necrosectomy involves using an endoscope to mechanically debride infected tissue.[103] Disadvantages to this approach include the risk of intracavitary bleeding, perforation, and air embolism. Antibiotic lavage and hydrogen peroxide irrigation are complementary therapies that can be used during endoscopic intervention as well.

In the recently conducted TENSION trial, 98 patients with suspected or confirmed pancreatic necrosis were randomized to a surgical or endoscopic step-up approach.[111] The endoscopic arm started with EUS-guided transluminal drainage followed by endoscopic necrosectomy. The surgical group received percutaneous catheter drainage followed by VARD. No patients underwent open necrosectomy. The primary endpoint of major complications or death occurred in 43% of the endoscopic group and 45% of the surgical group. The rate of pancreatic fistulae and hospital length of stay were lower in the endoscopic group. This study concluded that the endoscopic step-up approach was not superior to the surgical step-up approach. However, because of their less invasive nature, endoscopic approaches may be reasonable to consider as initial treatment options if local expertise is available to safely perform these interventions.

OUTCOME

With the increasing survival of acute pancreatitis patients, it has become important to analyze long-term outcomes and quality of life. One study examined 91 patients at 14 months after admission for acute pancreatitis.[112] Physical health–related quality of life was

significantly impaired after acute pancreatitis compared with control patients, independent of factors including age, gender, race, smoking status, alcohol consumption, body mass index (BMI), and comorbidities. The decrease in mental health–related quality of life normalized within 1 year of follow-up. Multiple organ failure during admission along with abdominal pain, analgesic use, and smoking at follow-up were all associated with decreased physical health–related quality of life.[112] Another study analyzed 113 patients with acute pancreatitis and found that 59% developed diabetes or impaired glucose tolerance. A smaller proportion developed exocrine pancreatic insufficiency, 6% severe and 29% mild to moderate.[113] These studies suggest that modifiable factors should be identified and optimized to improve long-term outcomes of acute pancreatitis.

SUMMARY

Acute pancreatitis is a disease of increasing incidence and cost. Although most cases of acute pancreatitis are mild and self-limited, the mortality in severe acute pancreatitis can be over 30%. Patients with severe acute pancreatitis often require intensive care, including aggressive fluid resuscitation, nutritional support, respiratory management, and therapy for multiple organ failure. In patients with declining clinical status, persistent fevers, and signs of SIRS, infected pancreatic necrosis should be suspected. The step-up approach should be used with percutaneous catheter drainage as initial treatment and escalation to minimally invasive debridement as needed. Endoscopic techniques have shown promise and may be considered in expert centers.

KEY POINTS

- Severe acute pancreatitis accounts for 15%–20% of patients with acute pancreatitis and has a mortality of over 30%.
- The early phase of severe acute pancreatitis is characterized by a pronounced SIRS response followed by organ failure, often requiring intensive support.
- The most common etiologies of acute pancreatitis are gallstones (40%–70%), alcohol abuse (25%–35%), and hypertriglyceridemia (9%).
- Acute pancreatitis is diagnosed when two of the following three criteria are met: (1) abdominal pain, (2) serum amylase and/or lipase level over three times the upper limit of normal, and (3) imaging consistent with pancreatitis.
- Ultrasound is recommended in all patients with acute pancreatitis. Contrast enhanced CT is the gold standard for the diagnosis of pancreatitis and its complications. However, its routine use is not recommended and should be performed in patients with unclear diagnoses or clinical worsening. ERCP should be performed in patients with acute cholangitis or evidence of ongoing obstruction. MRCP is useful in particular patient populations and for detailed imaging of the ductal system and for distinguishing composition of fluid collections.
- Fluid resuscitation is the cornerstone of acute pancreatitis management. Early, goal-oriented IV fluid resuscitation at a rate of 5–10 mL/kg/hr should be given, with heart rate, mean arterial pressure, and urine output used to measure adequacy of response.
- Early feeding should be instituted to protect the intestinal mucosal barrier once abdominal pain is improving and inflammatory markers are downtrending. Enteral feeding is recommended over parenteral feeding and may be administered via NG or NJ routes.
- Over 80% of pancreatitis-related deaths are attributable to secondary infections. Prophylactic antibiotics are not recommended because they do not improve mortality, risk of infection, or other clinical outcomes.
- When infected pancreatic necrosis is suspected or confirmed, IV antibiotics should be promptly initiated. Interventions should be delayed for 4 weeks after initial onset to allow for collections to become walled off. The step-up approach is standard of care, with percutaneous drainage as the initial therapy and minimally invasive retroperitoneal necrosectomy to follow as needed. Endoscopic interventions can also be performed in skilled centers and are being investigated as a safe alternative to classical surgical interventions.

References for this chapter can be found at expertconsult.com.

ANNOTATED REFERENCES

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Abdominal Sepsis

Scott Brakenridge and Ashley Thompson

INTRODUCTION

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection and accounts for approximately 20% of deaths worldwide.[1] Despite tremendous advancements in early diagnosis and both surgical and antimicrobial therapies, it remains a leading cause of in-hospital and intensive care unit (ICU) mortality.[2,3] Intraabdominal sepsis is the second most prevalent infectious etiology after pneumonia.[4,5] Similar to other etiologies of sepsis, early recognition, initiation of antimicrobial therapy, and expedient volume resuscitation are crucial components of initial management of intraabdominal sepsis. Uniquely, rapid and definitive source control is an additional early management priority that differentiates intraabdominal sepsis from other infectious etiologies and is crucial to survival. Failure to achieve early source control is more likely to cause death than refractory infection by a multidrug-resistant pathogen. Independent risk factors for 30-day mortality in severe intraabdominal sepsis include the extent of peritonitis, type of exudate (purulent, fecal or bile), and a nonappendiceal source of infection.[6] In those who require intensive care, studies have shown a mortality rate that exceeds 25%.[7] Recent trends indicate that although inpatient mortality after abdominal sepsis is declining, a large number of "sepsis survivors" develop a clinical trajectory of chronic critical illness (CCI) and suffer dismal long-term outcomes.

DEFINITIONS AND CLASSIFICATIONS

Intraabdominal infection (IAI) occurs when bacteria or yeast invade the normally sterile peritoneal cavity. This condition encompasses a variety of pathologic processes ranging from localized appendicitis to feculent peritonitis after colonic perforation. Both bacterial factors and the host innate immune response contribute to the subsequent clinical course and influence the transition from initial infection to sepsis. There is a wide range of disease severity based on the physiologic response of the patient, including systemic inflammatory response syndrome (SIRS), sepsis, and septic shock. These represent a physiologic continuum with a progressively worsening balance of proinflammatory and antiinflammatory responses. Multiple organ dysfunction syndrome (MODS) and multisystem organ failure (MOF) are terms used to describe the development of end-organ dysfunction in septic patients that leads to physiologic imbalances that are not maintainable without organ support interventions.[8]

Several classification systems exist to describe IAIs. These include (1) community acquired versus hospital acquired and (2) complicated versus uncomplicated infections. Complicated infections can be categorized as localized (such as an abscess) or diffuse (peritonitis). Diffuse peritonitis is further classified as primary, secondary, and tertiary. Each of these has a distinct spectrum of infectious organisms (Table 90.1). Therefore treatment regimens vary based on the etiology and extent of infection. Most IAIs (e.g., appendicitis, colitis) are community acquired and, if identified and treated promptly, do not require intensive care. However, some patients will go on to develop sepsis and become critically ill, usually because of delayed presentation or recognition, immunosuppression, or advanced age/frailty. The majority of these patients have polymicrobial intraabdominal infections as a result of inflammatory or ischemic bowel perforation or postoperative complications (i.e., enteric anastomotic leak).

Uncomplicated IAIs are those contained within a single organ (e.g., appendicitis, cholecystitis) and rarely lead to critical illness if addressed in a timely fashion. Definitive management is surgical, and antibiotics are not warranted after source control has been achieved. If the infection is contained by the initial host inflammatory response, an intraabdominal abscess will form, which depending on the size, accessibility, and patient status is best treated with abdominal-spectrum antibiotic therapy and image-guided percutaneous drain placement. Abscesses that are not amenable to percutaneous drainage and fail to resolve (or progress) on antibiotic therapy alone may require operative washout and drainage.

In contrast, complicated IAIs extend beyond the source organ into the peritoneal cavity, resulting in a much greater systemic inflammatory response. Complicated infections causing peritonitis can be classified as primary, secondary, or tertiary. In primary peritonitis, formerly referred to as "spontaneous" bacterial peritonitis, the infection does not arise from direct gastrointestinal (GI) tract spillage or contamination and rarely causes critical illness. Primary peritonitis most commonly occurs in patients with ascites caused by advanced cirrhosis, but can also be associated with collagen vascular disease or glomerulopathies. The diagnosis is made with a positive ascites bacterial culture and elevated fluid absolute polymorphonuclear leukocyte (PMN) count.[9] These cases are almost always monomicrobial (most commonly *Escherichia coli* [~70%] or *Klebsiella* [~10%]).[10] Treatment consists of antibiotic therapy, and there is no role for operative intervention. Drainage of diffuse ascites as a means of source control is not warranted unless loculated peritoneal fluid collections develop. Device-associated primary peritonitis can occur in patients on peritoneal dialysis. The incidence of these infections is relatively high, at approximately one episode per year of peritoneal dialysis. Peritoneal catheter-related infections are usually monomicrobial, and the most common pathogens are *Staphylococcus aureus, Pseudomonas,* and *Candida*. Although rare, these patients can develop methicillin-resistant *S. aureus* (MRSA), and vancomycin-resistant pathogens are emerging.[11] Treatment includes catheter removal and antibiotics.

Secondary peritonitis is by far the most common presentation in clinical practice and describes infections with an intraabdominal pathology. Causes of secondary peritonitis include perforation of a hollow viscus, bowel ischemic/necrosis, leak of surgical bowel anastomoses, and

TABLE 90.1 Microbiology of Intraabdominal Infection

Primary Peritonitis	Secondary Peritonitis	Tertiary Peritonitis
Escherichia coli	*Bacteroides fragilis*	*Enterobacter* spp.
Enterococcus spp.	*Escherichia coli*	*Enterococcus* spp.
Klebsiella spp.	*Klebsiella* spp.	*Acinetobacter* spp.
Streptococcus pneumoniae	*Clostridium* spp.	*Pseudomonas* spp.
	Other anaerobe spp.	*Staphylococcus* spp.
		Candida spp.

bowel injury after penetrating trauma. These infections are polymicrobial with, on average, five distinct organisms identified in a peritoneal fluid sample. Not surprisingly, common gut flora are the most frequently encountered bacteria (e.g., *E. coli, Klebsiella, Bacteroides*). Treatment includes percutaneous or operative source control and antibiotic therapy.

An infection that recurs or persists after a source control procedure has been performed is considered tertiary peritonitis. These infections are also polymicrobial, but can present an additional management challenge, as there is an increased likelihood of multidrug-resistant organisms (e.g., *S. aureus*/MRSA, *Enterococcus*/vancomycin-resistant *Enterococcus* [VRE], *Candida, Pseudomonas*). These patients may have an acute or chronic host defense impairment that has resulted in an inability to clear the index infection. Whether tertiary peritonitis represents a persistent invasive infection versus peritoneal cavity colonization remains controversial.

Regardless of the etiology of peritonitis, clinicians should be aware of the presence of adjuvant substances that decrease the bacterial threshold inoculum necessary to cause an infection and often require removal in order to clear the infection. The most common adjuvant is blood, but other examples include ascites, fibrin, bile, urine, chyle, pancreatic fluid, and platelets. Evacuation and ongoing drainage of these fluid adjuvants (via percutaneous or surgical drainage) are often required for adequate source control. Fibrin promotes bacterial trapping and can isolate bacteria from neutrophils. Iron present in hemoglobin is essential for bacterial growth and reduces phagocyte function. Foreign bodies are also a nidus for persistent infection and may be present in IAIs in the form of prosthetic mesh or nonabsorbable sutures. Clearance of infection most often requires explant of the infected material, especially when the formation of biofilms is suspected.

ENTERIC MICROBIOTA

Most of the bacteria in the gut are commensal flora that generally do not contribute to the pathogenesis of IAI. They play a fundamental role in immunomodulation, maintenance of barrier function, metabolism (enterohepatic circulation), and overgrowth prevention of pathogenic microbes. Loss of intestinal homeostasis, whether by disruption of the gut mucosal barrier or by depleting the normal flora with long-term antibiotic use, is the first step in the development of abdominal sepsis. The vast majority of cases of IAI are bacterial, although intraabdominal candidiasis is not uncommon in critically ill patients and those who are immunocompromised. The microbial density and composition vary across the digestive tract. Therefore the offending pathogens in an IAI can, to some degree, be anticipated if the inciting pathology is known.

The stomach was initially considered to be a "sterile organ" because of its high intraluminal acidity. *Helicobacter pylori* was discovered in 1982, and for the next few decades, it was believed to be the only bacteria capable of survival in such a low pH secondary to its ability to produce neutralizing urease. The development of culture-independent molecular methods has facilitated the identification and classification of additional gastric bacteria.[12] Although most gastric microbes originate from and are in transit from the oropharynx, the most abundant inhabitants are *Streptococcus, Propionibacterium,* and *Lactobacillus*.[13] These bacteria are more prevalent in patients with reduced gastric acidity. In addition to bacteria, *Candida* commonly colonizes the GI tract and has been associated with the development of gastric ulcers. However, there are relatively small numbers of gastric microbes ($<10^4$ colony-forming units [CFU]/mL) in healthy subjects.[14]

The proximal small bowel, because of the nearness to the stomach and outflowing acidic juices, contains many of the same bacteria in relatively small numbers. Duodenal bile and pancreatic secretions have additional antibacterial properties. Forward propulsion (peristalsis) also plays a key role in suppressing the flora of the upper GI tract. In the distal small bowel, the more alkaline conditions allow for the growth of enteric gram-negative rods. The terminal ileum represents a transition zone from the jejunum, containing predominantly aerobes, to the colon, containing predominantly anaerobes. There are typically $<10^9$ CFU/mL of microorganisms immediately proximal to the ileocecal valve.

In the colon, the concentration and variety of enteric flora changes dramatically. The number of anaerobic bacteria outnumber aerobic by a factor of up to 1000:1,[15] with the most abundant being members of the *Bacteroides* genus. As many as 10^{12} CFU/mL can be found, which contribute to 60% of fecal mass. The stability of the normal flora discourages infection by exogenous microbes and helps prevent overgrowth of pathogenic bacteria already present.

PATHOGENESIS

In general, the pathophysiology of intraabdominal sepsis is described as an initial hyperinflammatory phase that lasts several days followed by an immunosuppressive phase (Fig. 90.1). This pathophysiologic state is the result of opposing influences of the host defense and pathogen virulence. Multiple factors contribute to the inflammatory response. Host factors include patient age, functional status, comorbidities, medications (e.g., steroids, immunosuppressants), environment, and genetics.[16] Pathogen factors include the microbial load, virulence, and pathogen-associated molecular patterns (PAMPs). PAMPs are highly conserved molecules essential for bacterial survival that can be detected by the host innate immune response. Examples of PAMPs include lipopolysaccharide (LPS) and porins from gram-negative cell walls, peptidoglycans, lipoteichoic acids, flagellin in bacterial flagella, and bacterial/viral nucleic acids. PAMPs are recognized by Toll-like receptors (TLRs) and other pattern recognition receptors (PRRs) and trigger a robust innate immune response which can be beneficial to the host. However, this response can later be counterproductive if it is overly robust or fails to resolve and return to immunologic homeostasis.

Resident flora bacteria occupy the bowel lumen and adhere to the mucosa. Direct penetration of organisms through the mucosa is an abnormal event. However, pathogens such as *Shigella, Salmonella,* and *Campylobacter* can invade in this manner.[17] More commonly, bacteria are released in the peritoneal cavity as the result of a perforation of the GI tract. When this occurs, the bacteria must proliferate to cause a clinical infection. To assist with this process, they express specific adherence factors that ultimately make their eradication much more difficult. Adherence factors are one of the many mechanisms bacteria

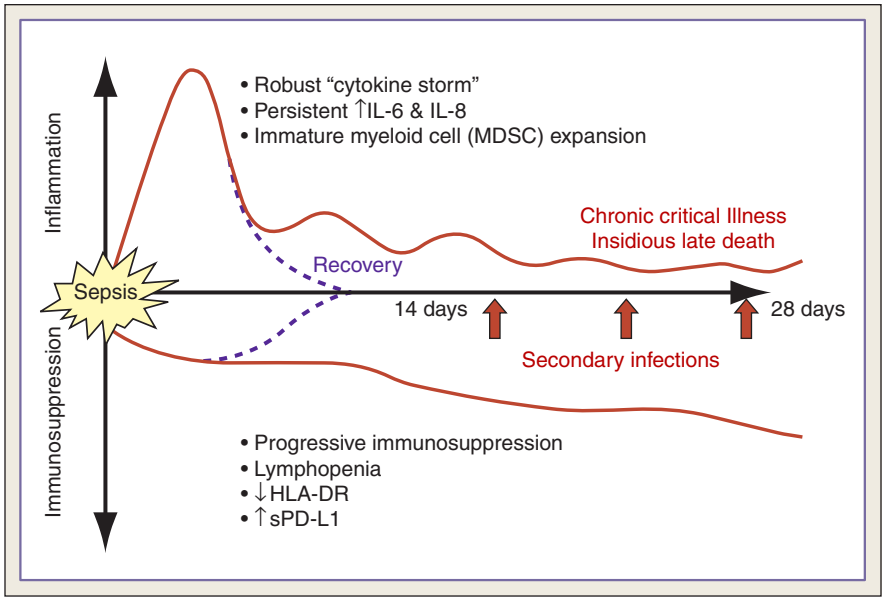

Fig. 90.1 Intraabdominal sepsis is driven by a dysfunctional host innate immune response to infection, with an early "cytokine storm" causing shock and organ dysfunction. Persistent inflammation and progressive immunosuppression lead to immune incompetence and recurrent infections. *HLA,* Human leukocyte antigen; *IL,* interleukin; *MDSC,* myeloid-derived suppressor cell.

use to achieve increased virulence. Endotoxins are LPSs in the outer membrane of gram-negative bacteria. They are large molecules that provide structural integrity and protect invading organisms from the host immune response. The lipid A domain of LPS is primarily responsible for the initial systemic toxicity in gram-negative bacterial infections. When bacterial cells are lysed, fragments containing lipid A are released into the host's circulation, causing systemic symptoms such as fever and potentially septic shock. In gram-positive bacteria, lipoteichoic acid and peptidoglycans in the cell walls play an important role in initiating the host innate immune response; however, they can cause an excessive response resulting in the inflammatory sequelae involved in sepsis.[18]

Once the inflammatory response has been initiated, proinflammatory cytokines (e.g., tumor necrosis factor alpha [TNF-α], interleukin [IL]-1, IL-6) are released, which have a multitude of effects. They cause production of toxic mediators such as prostaglandins, phospholipase A_2, platelet-activating factor, and others, which damage the endothelial lining and subsequently lead to increased capillary leakage.[19] They lead to increased production of adhesion molecules on neutrophils and endothelial cells, resulting in further endothelial injury from release of neutrophil components. These activated neutrophils release nitric oxide, a vasodilator that plays a key role in the development of septic shock. Proinflammatory cytokines from innate immune effector cells also disrupt activated protein C and antithrombin, modulators of coagulation. The culmination of these effects can result in extensive "third-spacing" of intravascular fluid, vasodilatory shock, and MODS/MOF.[20]

After the initial "cytokine storm" triggered by infection, there is a subsequent phase of profound and persistent immunosuppression, which manifests as secondary infections and "sepsis recidivism." This state of host immunoparalysis is the result of several mechanisms, including apoptotic depletion of immune cells, endotoxin tolerance/impaired cytokine response, the expansion of immature myeloid lineage cells (myeloid-derived stem cells [MDSCs]), and compromised T-cell function and exhaustion (see Fig. 90.1).[21–23] Apoptosis of lymphocytes and antigen-presenting cells (T cells, B cells, and dendritic cells) is considered a hallmark of immunosuppression in sepsis[24] and has shown promise as a new target for sepsis treatment in animal models.[25] Endotoxin tolerance is the severely reduced capacity of a cell to respond to LPS in a second exposure to a toxic stimulus and represents an immune amnesia instead of an antiinflammatory response.[26] T-cell exhaustion develops in the face of persistent antigen exposure and/or inflammation. This prolonged exposure leads to decreased expression of major histocompatibility complex (MHC) class II molecules (human leukocyte antigen [HLA]-DR) on antigen-presenting cells and increased expression of cell surface inhibitory receptors (such as programmed cell death-1 [PD-1]) on $CD4^+$ and $CD8^+$ T lymphocytes.[27] Studies have shown that increased expression of PD-1 in circulating T cells from patients with sepsis correlated with decreased T-cell proliferative capacity and mortality.[28]

More specific to abdominal sepsis is the concept of peritoneal compartmentalization. Based on findings of high concentrations of cytokines (IL-1, TNF-α, IL-6, IL10, interferon-gamma [IFN-γ]) in the peritoneal fluid of patients with peritonitis, studies have suggested that intraabdominal sepsis may result in a cytokine-mediated proinflammatory response that is initially localized to the abdominal compartment[29] and that plasma levels may increase only after saturation of tissues within the peritoneal cavity.[30]

SPECTRUM OF DISEASE CAUSING CRITICAL ILLNESS

Perforated Hollow Viscus

Loss of integrity of the GI tract is the most common cause of IAI and abdominal sepsis. Inciting disease processes range from perforated gastric ulcers to acute appendicitis, diverticulitis, and traumatic injuries. Each of these clinical conditions is discussed in further detail in their respective chapters; however, their significance as common etiologies of abdominal sepsis should be noted. The basic tenets of sepsis management should be applied regardless of the specific cause: timely identification, rapid intravascular volume resuscitation, early initiation of antimicrobial therapy, and definitive source control.

Solid Organ Abscess

Abscesses of solid organs are rare but can progress to expansive, potentially lethal IAIs if not diagnosed promptly. Most cases arise from bacterial translocation from another infected system. The most common site of solid organ abscess is the liver, followed by the spleen and kidney.

Pyogenic liver abscesses can develop from direct injury to the liver or from a disseminated IAI. The most common cause—approximately half of the cases—are secondary to cholangitis and direct extension from an infected biliary tract.[31] Less common causes include portal vein bacteremia from an enteric infection (usually diverticulitis), hepatic artery bacteremia, and devitalized liver secondary to trauma or angioembolization or ablation of neoplasms. The most common organisms identified in these lesions are *Klebsiella, E. coli, Streptococcus, Staphylococcus,* and anaerobic organisms, but they are usually polymicrobial. If *Staphylococcus* or *Streptococcus* are the sole isolates, there should be a high suspicion for another source of infection (endocarditis) that has spread hematogenously. *Entamoeba histolytica* is the most common anaerobic source and is acquired via ingestion of food or water contaminated by human feces. Ingestion initially causes an amebic colitis and seeds the portal system, ultimately resulting in an amebic liver abscess. Although these are quite rare in the United States, they are not uncommon among those who live or have recently traveled to developing countries. *Echinococcus granulosus* is a parasitic organism that causes hydatid cysts of the liver. These are most often acquired from dogs and are usually discovered incidentally or in the late stages.[32]

Patients with liver abscesses may present with a wide range of symptoms. Fever is present in 90%, and abdominal pain is present in 50%–75% of patients.[33] Approximately half of patients will have elevated liver transaminases and 90% will have elevated alkaline phosphatase.[34] An abdominal ultrasound is the initial test of choice, but computed tomography (CT) imaging of the abdomen is slightly more sensitive. Drainage of the abscess and antibiotics are the cornerstones of treatment. If the abscess is less than 5 cm, ultrasound or CT-guided needle aspiration may suffice. If the abscess is larger than 5 cm, consider percutaneous drainage with a pigtail catheter placement. Although rarely encountered, indications for surgical intervention include ruptured abscess with generalized peritonitis, thick-walled or multiple abscesses, and previously failed percutaneous drainage procedures. Antibiotics should be administered and may require up to 6 weeks of coverage. Metronidazole should be used for *E. histolytica.* Echinococcal treatment involves injection of the hydatid cysts before drainage, as rupture of the abscess may cause shock in addition to albendazole therapy, which may last for several years. In-hospital mortality of pyrogenic liver abscesses is estimated at 2.5%–19%.[35]

Abscesses of the spleen most commonly arise from hematologic seeding of bacteremia (most often from endocarditis) or as a result of devitalized tissue. Devitalization can result from trauma, angioembolization, or infarction secondary to systemic disorders such as hemoglobinopathies or sickle cell disease. Direct extension of an adjacent infection, such as from a gastric or colonic perforation, may also occur. The most commonly encountered pathogen is hematogenously spread *Staphylococcus*. CT imaging is the gold standard for diagnosis. Treatment includes empiric antibiotic therapy and abscess drainage. Percutaneous aspiration can be attempted as a temporary solution as a bridge to surgery, but splenectomy is often required as definitive treatment.[36]

Renal abscesses are the rarest solid organ abscess. They most commonly develop from obstruction and ascending infection from the lower urinary tract and, not surprisingly, are caused by the same pathogens as a urinary tract infection (*E. coli, Klebsiella,* and *Enterococcus*). Treatment includes urinary tract decompression and broad-spectrum antibiotics until speciation and susceptibility data are available.

Acute Acalculous Cholecystitis

Acute acalculous cholecystitis is inflammation of the gallbladder secondary to ischemia without evidence of gallstones or cystic duct obstruction. It is the cause of approximately 5%–10% of all cases of acute cholecystitis and occurs most commonly in critically ill patients after a major physiologic insult such as sepsis, severe burns, cardiopulmonary bypass, emergent aortic surgery, or significant trauma.[37,38] The etiology of this disease is thought to be biliary stasis. Critically ill patients and those on total parenteral nutrition (TPN) are more predisposed because of fever, dehydration, and prolonged absence of oral feeding resulting in a decrease of cholecystokinin-induced contraction of the gallbladder. The gallbladder becomes distended with increased wall tension and subsequent impaired lymphatic/venous drainage, progressive edema, and ultimately ischemic necrosis.

As patients with this condition are commonly intubated and sedated, pinpointing a diagnosis of acalculous cholecystitis can be challenging. Clinicians must carry a high index of suspicion and consider this possibility in any critically ill patient with fever or sepsis of unclear origin. Transaminases, bilirubin, and alkaline phosphatase may be elevated. Abdominal ultrasound is the imaging modality of choice,[39] and diagnosis can be confirmed by a gallbladder wall thickness greater than 3.5 mm and the presence of pericholecystic fluid.[40] Abdominal CT imaging is equally accurate, but hepatobiliary iminodiacetic acid (HIDA) imaging has a poor positive predictive value in this patient population, as patients are not generally receiving adequate alimentary stimuli for gallbladder contraction.

Once a diagnosis has been established, treatment most often includes antibiotics and percutaneous cholecystostomy. Although surgical evaluation is warranted, most of these critically ill patients are not candidates for definitive cholecystectomy, and temporizing percutaneous drainage is necessary. Percutaneous cholecystostomy has a >90% success rate for source control. Failure of cholecystostomy placement is usually secondary to catheter malposition or gallbladder necrosis and perforation. Once the patient has recovered from acute illness, interval cholecystectomy is the definitive treatment. However, many of these patients remain high-risk surgical candidates because of underlying comorbidities. In these cases, if a cholecystostomy tube study confirms the absence of gallstones and a patent biliary tree, the drain can simply be removed. Transpapillary drainage through an endoscopic retrograde cholangiopancreatography (ERCP) has been used with variable success but has high recurrence rates.[41] An emerging alternative for drainage is endoscopic placement of a lumen-apposing fully covered metal stent (LAMS) through the GI tract into the gallbladder. This procedure obviates the need for percutaneous drain placement, and studies are showing success rates similar to percutaneous cholecystostomy with few adverse events.[42,43]

Mesenteric Ischemia

Intestinal ischemia occurs when a patient has inadequate blood flow through the mesenteric vessels, resulting in ischemia and eventual gangrene of the bowel. If this condition occurs acutely, it can be a life-threatening surgical emergency that requires immediate intervention. Chronic mesenteric ischemia typically presents with vague, postprandial abdominal pain and rarely leads to bowel necrosis and abdominal sepsis unless a patient develops acute-on-chronic disease.

Acute mesenteric ischemia (AMI) can be subdivided into four categories based on the etiology: acute mesenteric arterial embolism (AMAE), acute mesenteric arterial thrombosis (AMAT), mesenteric venous thrombosis (MVT), and nonocclusive mesenteric ischemia (NOMI). An additional cause of acute bowel ischemia is that which occurs as a result of mechanical obstruction (e.g., intussusception, volvulus, internal hernia with strangulation). Each of these types of

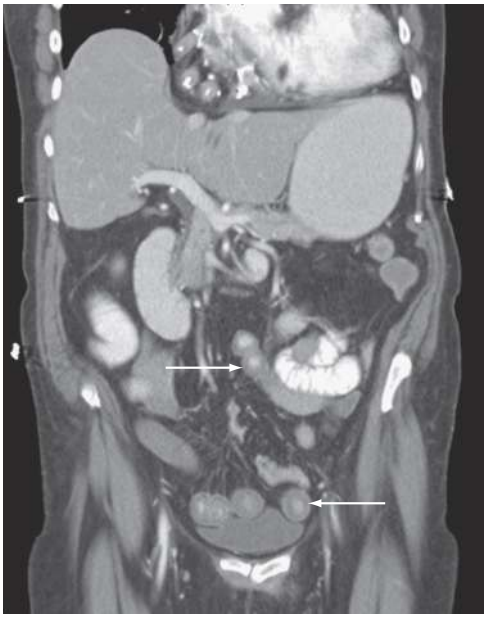

Fig. 90.2 Computed tomography with oral and intravenous contrast in a patient with embolic occlusion of the superior mesenteric artery and segmental ischemia of the small bowel and right colon *(arrows).* Bowel ischemia is evident from the marked thickening of the intestinal wall.

AMI has somewhat different predisposing factors and prognoses, but all share a final common pathway to bowel infarction and necrosis if not treated expeditiously.

Mesenteric ischemia caused by an arterial embolism is the most common subtype accounting for up to 50% of AMI cases.[44] In this type of AMI, an embolus (usually from a cardiac source) lodges in the mesenteric vasculature. Large emboli lodge in the superior mesenteric artery (SMA), most often 6–8 cm from the origin and distal to the middle colic artery.[45] Blood flow distal to the embolism will be interrupted, resulting in bowel ischemia (Fig. 90.2). If the entirety of flow through the SMA is compromised, the patient may have the devastating outcome of entire midgut necrosis. Smaller emboli are more likely to lodge in the more distal mesenteric circulation, resulting in smaller segments of affected bowel with a generally better prognosis.

AMAT is a similar phenomena, but abrupt cessation of flow is secondary to in situ thrombosis of the vessel rather than an embolus. This occurs in patients with underlying atherosclerotic disease who may have had progressively worsening abdominal pain over the weeks preceding presentation. Mesenteric (or portal) venous thrombosis occurs when a blood clot forms in one of the major veins carrying blood from the intestine and is usually in patients with either a hypercoagulable state or a local inflammatory process such as pancreatitis. Mesenteric or portal vein thrombosis is rarely associated with bowel necrosis and is usually successfully managed with systemic anticoagulation and bowel rest.

NOMI is a common complication of severe critical illness and is the result of a low-flow state to the splanchnic circulation, most notably when the cardiac index is less than 2 L/min/m^2.[46] There are numerous potential causes of the decreased flow, including hypovolemia, shock, and prolonged high-dose vasopressor use. Any segment of bowel can be affected; however, the most frequently affected are the cecum and splenic flexure. The cecum is the farthest from the inferior mesenteric artery (IMA) collaterals, and the splenic flexure is a watershed region of the superior and inferior mesenteric arteries. Of note, in patients with prior abdominal aortic operations, the IMA may have been ligated, and therefore the left colon is at higher risk for NOMI.

In patients that are communicative, abdominal pain out of proportion to examination is the hallmark symptom of AMI. In intubated, sedated patients, the diagnosis can be more challenging. Clinical features may include abdominal distention and a progressively worsening metabolic acidosis. Hematochezia can be seen as the vasculature to the mucosa is more vulnerable and the mucosa will begin to slough. Patients may develop sepsis or septic shock before transmural gangrene and perforation because of the compromised integrity of the mucosa leading to bacterial translocation and bacteremia. Blood per rectum after an abdominal aortic surgery is strongly suggestive of colonic ischemia.

Aortic angiography has traditionally been the most reliable method to diagnose AMI, but is now superseded by CT angiographic (CTA) imaging.[47] Bedside lower endoscopy can be used for a diagnosis of colonic ischemia, but may underestimate the extent of disease (Fig. 90.3). When AMI is suspected, goals of management are resuscitation, rapid diagnosis, early revascularization, and reassessment of the bowel.[48] Revascularization is generally performed via several endovascular strategies, including percutaneous aspiration embolectomy, balloon thrombectomy, catheter-directed thrombolysis, and stenting.[49] An exploratory laparotomy is generally performed in conjunction with revascularization to evaluate the bowel. Necrotic bowel is resected, but potentially viable bowel should be left for at least 30 minutes once perfusion has been established or reassessed at an interval repeat laparotomy 24 hours later. These patients are at risk for short bowel syndrome if a large resection is performed. Depending on the patient's physiologic status, the surgeon may consider a second-look laparotomy in 12–48 hours if there is questionable bowel viability or if a massive enterectomy would be needed.

Clostridium difficile Colitis

Clostridium difficile is a gram-positive, anaerobic, spore-forming bacteria that is the most common pathogen causing healthcare-associated infection in the United States, accounting for 15% of all such infections.[50] The incidence of *C. difficile* infections (CDIs) continues to rise, and cases of antibiotic resistance are becoming more common.[51–53] Risk factors for colonic CDI include advanced age, hospitalization, and antibiotic exposure. The prevalence of *C. difficile* spores in the environment is relatively high among hospitals and long-term care facilities. As such, it is not surprising that patients in these facilities carry a higher colonization rate (10%–25% among hospitalized patients,

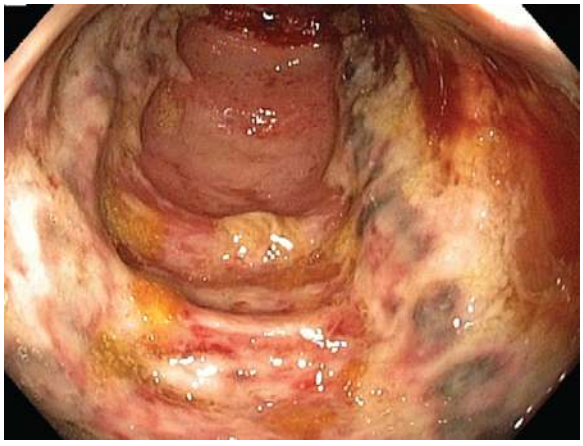

Fig. 90.3 Colonoscopy is the preferred modality to assess for colonic ischemia, but visualizes only the mucosa and may underestimate the extent of disease.

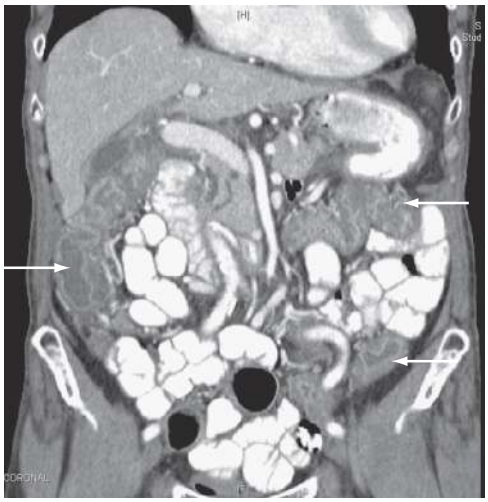

Fig. 90.4 Computed tomography with oral and intravenous contrast in a patient with *Clostridium difficile* colitis. Typical findings include colonic wall thickening *(arrows),* dilation, and thickened/edematous colonic wall.

4%–20% among residents of long-term care facilities) than healthy adults in the general population (2%–3% colonization rate).[54]

Clinical features of active CDI infection include crampy abdominal pain, diarrhea, fever, and leukocytosis in the setting of recent antibiotic use, generally within the previous 8 weeks. Peritonitis is generally not seen until advanced stages of infection with megacolon and/or perforation. The diagnosis is confirmed with a stool sample. Multiple tests are available, including polymerase chain reaction (PCR) assays, antigen detection tests, tissue culture cytotoxicity assays, enzyme immunoassays, and stool culture. PCR assays are the most effective diagnostic method for accurate and early diagnosis of CDI.[55] Imaging is not needed for diagnosis, but CT imaging may reveal colonic wall thickening, dilation, ascites, pericolonic stranding, and a characteristic "accordion sign" of thickened haustral folds containing trapped contrast material (Fig. 90.4). Visualization of colonic pseudomembranes on endoscopy is also diagnostic, though this procedure is not commonly used because of the risk of perforation in fulminant colitis.

Recommended treatment of CDI includes a 10-day course of oral vancomycin or fidaxomicin.[56] Metronidazole, previously the first-line drug for CDI, may be used as an alternative for an initial, nonsevere episode or in intravenous (IV) form as a secondary agent in a fulminant infection. Rectal vancomycin enemas may also be added, but are cumbersome, and their additional yield is unclear. Fecal microbiota transplantation is perhaps the most promising emerging therapy for refractory CDI, but there are logistical changes regarding stool donation, storage, and dissemination that remain problematic at this time.[57] Fulminant colitis has been broadly defined as *C. difficile* colitis with significant systemic toxic effects and shock and occurs in 3%–5% of patients with *C. difficile.* These patients develop a severely dilated toxic megacolon, which may progress to perforation. Treatment includes aggressive sepsis resuscitation and source control with a total abdominal colectomy. In-hospital mortality for fulminant *C. difficile* colitis is >30%.[58]

Acute Necrotizing Pancreatitis

Acute pancreatitis is an inflammatory condition of the pancreas that is characterized by premature activation of digestive enzymes within the pancreatic acinar cells resulting in autodigestion. There are many underlying causes of pancreatitis, but 60%–75% of all cases are caused by gallstone disease or alcohol abuse.[59] Most patients develop a mild, self-limited disease, but up to 30% develop a severe, life-threatening form that is associated with a mortality rate as high as 25%.[60] Severe pancreatitis is defined by single or multiple organ failure lasting >48 hours and can be complicated by the development of parenchymal/peripancreatic fluid collections and necrosis. Acute necrotizing pancreatitis is diagnosed when more than 30% of the gland is necrotic (Fig. 90.5). Two-thirds of necrotic pancreatic collections are sterile and will resolve with conservative management. The remaining minority that become infected or mature to a pancreatic pseudocyst require further intervention.[61]

The initial assessment of a patient with acute pancreatitis includes determining the etiology of the disease, as this may help direct management (e.g., ERCP for an obstructing gallstone). These patients generally require aggressive IV fluid resuscitation. Prophylactic antibiotics have no role in preventing infection of pancreatic necrosis, are associated with the development of antibiotic resistance, and do not improve clinical outcomes.[62] The timing of infection in pancreatic necrosis is variable and unpredictable, with peaks in the second to fourth week after the onset of pancreatitis.[63] Diagnosis of infected pancreatic necrosis remains a significant clinical challenge. The presence of retroperitoneal gas on contrast-enhanced CT imaging is considered indicative of infected pancreatitis but is only present in a limited number of patients. Fine-needle aspiration (FNA) culture remains the diagnostic "gold standard" but has largely been abandoned because of its high false-negative rate. Serum biomarkers such as procalcitonin may offer some diagnostic yield, but overall infected necrosis remains a clinical diagnosis.

Treatment for infected necrosis includes an appropriate antibiotic regimen, source control, and early enteral feeding. The antibiotic selected must provide both aerobic and anaerobic gram-negative and gram-positive coverage and provide adequate pancreatic penetration. Current treatment guidelines include use of a carbapenem, piperacillin/tazobactam, or a third-generation cephalosporin or fluoroquinolone combined with an antianaerobic drug such as metronidazole.[64,65] A Cochrane meta-analysis revealed enteral nutrition to be superior to TPN in severe acute pancreatitis, with reduction in infectious complications, length of hospital stay, and overall mortality.[66] Early institution of feeding (within 48 hours) is preferred, though the exact timing remains controversial.[67]

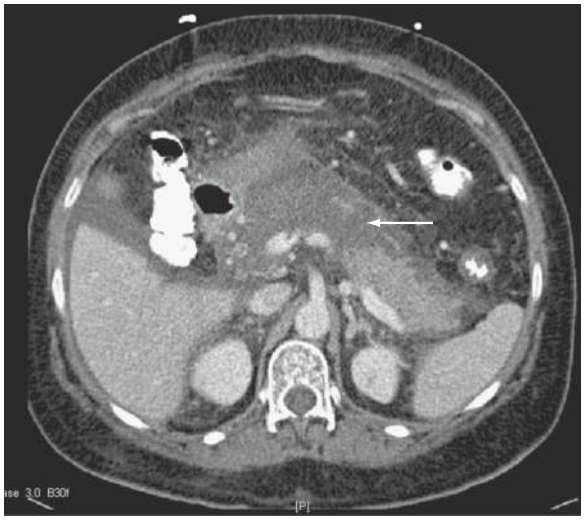

Fig. 90.5 Computed tomography with oral and intravenous contrast in a patient with necrotizing pancreatitis. There is significant peripancreatic inflammation, and the hypodense area in the body of the pancreas is an area of pancreatic necrosis *(arrow).*

The three well-established approaches for drainage of infected pancreatic necrosis are radiographically guided percutaneous, endoscopic, and surgical. Over the last two decades, the paradigm has shifted away from surgical intervention to less invasive approaches. Open necrosectomy is associated with high morbidity and mortality rates and the development of complications such as enterocutaneous and pancreatico-cutaneous fistula formation.[68] Percutaneous drain placement under ultrasound or CT guidance via a retroperitoneal approach is preferable to a transperitoneal approach and has fewer complications. Additionally, this facilitates a "step-up" approach in which the drain can be upsized and eventually used as a tract for laparoscopic-assisted retroperitoneal necrosectomy if necessary. The drain should be irrigated multiple times daily with sterile water. Endoscopic drainage and debridement is usually reserved after the formation of a defined pancreatic pseudocyst. The necrotic collection is punctured through the gastric wall under ultrasound guidance. The tract is then dilated and stented, allowing drainage of necrotic material into the GI tract.

DIAGNOSIS

The diagnosis of abdominal sepsis is based primarily on clinical assessment. The patient may present with abdominal pain or other GI complaints and show signs of a systemic inflammatory response such as fever, tachycardia, and tachypnea. In advanced cases, peritonitis may be present with abdominal distention or rigidity. Altered mental status, hypotension, and oliguria are signs that a patient is transitioning from sepsis to septic shock.

Recommended laboratory tests include a complete blood count with differential, basic metabolic panel, measurement of lactate and liver enzyme levels, coagulation studies, and blood cultures. Leukocytosis is often seen because of an early leukemoid reaction. However, leukopenia can also result secondary to an overwhelming infection causing bone marrow suppression. Cytokine production triggers the release of immature granulocytes from the bone marrow, resulting in a "left shift" or "bandemia" in the cell differential analysis.[69] Serum lactate is a sensitive but nonspecific indicator of metabolic stress.[70] As a product of anaerobic glycolysis, lactate is increased in hypoxia, systemic malperfusion, and many critical illnesses.[71] There is a clear association between higher lactate levels and increased mortality. Different thresholds have been recommended as an early aggressive resuscitation predictor and, as a result, early identification of elevated serum lactate can potentially lead to early identification of patients who are at high risk for poor outcomes.[72–74] Lastly, procalcitonin is a biomarker that has been evaluated for early detection of sepsis in addition to monitoring the antimicrobial treatment regimen but is limited because of its nonspecific nature in the setting of inflammation.

Radiographic imaging yields a definitive diagnosis in most patients with IAIs. Upright plain films may reveal intestinal obstruction, ischemia, or pneumoperitoneum (Fig. 90.6). They may also be used with water-soluble contrast injection to evaluate drains and/or fistulas. Ultrasound can be performed at the bedside and is useful in patients that are too unstable to leave the ICU. It is the imaging modality of choice for biliary sepsis and can also be used to detect and drain intraabdominal abscesses, particularly in the pelvis using transvaginal or transrectal probes. However, ultrasound is dependent on operator experience and patient body habitus. CT with IV (± oral [PO]) contrast is the test of choice in stable patients. Findings concerning for IAI include extraluminal air (Fig. 90.7), contrast extravasation, free fluid, mesenteric stranding, and the presence of a contrast-enhancing rim that is characteristic of an abscess (Fig. 90.8). In a patient with mesenteric ischemia, vascular thrombus may be identified in addition to pneumatosis or portal venous gas suggesting bowel ischemia. Obtaining CT imaging

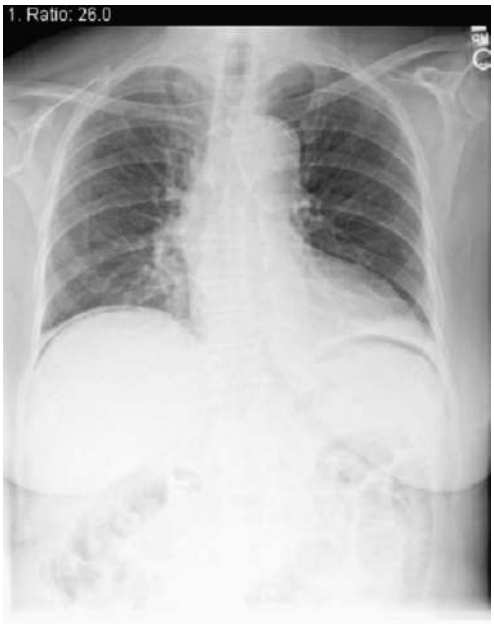

Fig. 90.6 Pneumoperitoneum under the right hemidiaphragm on an upright chest radiograph of a patient with perforated sigmoid diverticulitis. The crescent-shaped lucency under the left hemidiaphragm is the gastric bubble.

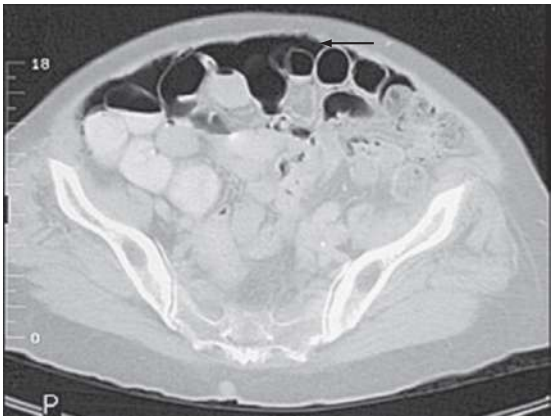

Fig. 90.7 Computed tomography with oral and intravenous contrast in a patient with perforated viscus and extraluminal gas *(arrow).*

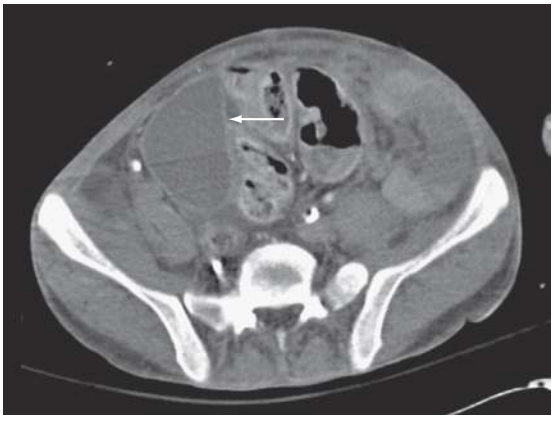

Fig. 90.8 Computed tomography with oral and intravenous contrast in a patient with a large pelvic abscess amenable to percutaneous drainage. There is classic "rim enhancement" of the abscess cavity *(arrow).*

requires transport, which can be challenging in an unstable patient and also carries the risk of contrast-induced nephropathy.

MANAGEMENT

Sepsis Resuscitation

Regardless of etiology, initial treatment principles are the same for all sepsis patients and include timely recognition, initiation of antimicrobial therapy, volume resuscitation to restore end-organ perfusion, and prompt source control. Sepsis is characterized by a state of systemic malperfusion caused by vasoregulatory dysfunction and myocardial depression. Increased venous capacitance and capillary leakage result in an overall hypovolemic state with decreased venous return to the heart. The resultant diminished cardiac function leads to tissue hypoxia, which causes overstimulated endothelial cell activity leading to a systemic inflammatory cascade.[20] The key contributor to the high morbidity and mortality rates associated with sepsis is the development of MOF driven by malperfusion and systemic inflammation.

Although the efficacy of individual components can be debated, the use of early goal-directed therapy protocols clearly reduce in-hospital mortality from sepsis.[75] Fluid resuscitation should be initiated as early as possible if clinical evidence of organ dysfunction exists, regardless of lactate level. There is no clear evidence from randomized controlled trials that support colloids over crystalloid solutions to reduce the risk of death in patients with trauma, burns, or sepsis.[76] Because of the increased expense of colloids, crystalloid solutions are recommended.[77] Intravascular volume status can be monitored and optimized during the initial resuscitation with point-of-care echocardiography. Pulmonary artery catheters have been shown to not improve outcomes and increase cost.[78] Experimental studies have correlated a positive fluid balance with more severe organ dysfunction and overall worse outcomes.[79] Volume overload can cause increased intraabdominal pressure, resulting in splanchnic hypoperfusion and increased bowel edema leading to bacterial translocation, cytokine release, and perpetuation of the inflammatory cascade. Patients should be monitored for the development of intraabdominal hypertension with repeated intravesical measurements of intraabdominal pressure.

Vasopressor support should be added when hypotension persists with restoration of adequate intravascular volume. Norepinephrine is recommended as the first-line vasoactive agent in septic shock.[77] Compared with dopamine, norepinephrine causes less tachycardia and is less arrhythmogenic. Vasopressin increases vasculature responsiveness to catecholamines and can be added as a second-line agent, if needed.[80] Epinephrine is a potent adrenergic agent that increases cardiac index and peripheral vascular tone through both alpha and beta stimulation. Because of its potential to reduce splanchnic blood flow, there are concerns regarding its use in septic shock, though no trials have shown worse outcomes with epinephrine compared with norepinephrine.[81] Dobutamine is rarely used in septic shock but may be considered only if the patient has a simultaneous myocardial dysfunction. The Surviving Sepsis Campaign (SSC) is a global initiative created in 2004 that designed evidence-based guidelines and bundles to help improve outcomes in sepsis. Resuscitation goals from SSC include central venous pressure (CVP) >8 mm Hg, mean arterial pressure (MAP) >65 mm Hg, central venous oxygen saturation ($ScvO_2$) of >70%, and urine output (UOP) of >0.5 mL/kg/h.

Empiric Broad-Spectrum Antibiotics

Timely antimicrobial administration is a key factor in the management of sepsis.[82,83] Initial empiric therapy used in abdominal sepsis should be broad spectrum but, if possible, take into account the presumed source, as the etiologic distribution varies according to the source site (Table 90.2). The upper GI tract has a prevalence of gram-positive

TABLE 90.2 Empiric Antimicrobial Regimens for Critically Ill Patients With Intraabdominal Infection

Hospital-Acquired IAI		Community-Acquired IAI	
Meropenem 1 g q8h or Doripenem 500 mg q8h or Imipenem/cilastatin 1 g q8h		Piperacillin/tazobactam 4.5 g q6h or Cefepime 2 g q8h + Metronidazole 500 mg q6h	
Carbapenem-sparing regimen:	Ceftolozane/tazobactam 1.5 g q6h + Metronidazole 500 mg q6h or Ceftazidime/avibactam 2.5 g q6h + Metronidazole 500 mg q6h + Vancomycin 25–30 mg/kg loading dose, then 15–20 mg/kg/dose q6h or Teicoplanin 12 mg/kg q12h × 3 loading dose, then 12 mg/kg q24h	If at risk for community-acquired ESBL-producing Enterobacteriaceae:	Meropenem 1 g q8h or Doripenem 500 mg q8h or Imipenem/cilastatin 1 g q8h
If at risk for vancomycin-resistant enterococci (VRE):	Linezolid 600 mg q24h or Daptomycin 6 mg/kg q24h	If at high risk for infection with enterococci:	Ampicillin 2 g q6h* *If not on piperacillin/tazobactam or imipenem/cilastatin
If at high risk for invasive candidiasis:	Caspofungin 70 mg loading dose, then 50 daily Or Micafungin 100 mg daily Or Amphotericin B liposomal 3 mg/kg/dose q24h		

ESBL, Extended-spectrum beta-lactamase; *IAI,* intraabdominal infection.

bacteria and *Candida* with a progressive increase of anaerobes and gram negatives in the lower GI tract. The patient should be reassessed when the results of microbiologic testing are available. Antibiotic de-escalation has been associated with lower mortality rates in ICU patients and is considered a key practice for antimicrobial stewardship.[84]

For patients with community-acquired IAI, a narrower spectrum of activity is recommended. There is an increased likelihood in hospital-acquired IAI to encounter pathogens with reduced susceptibility to traditional antibiotic regimens. With increasing prevalence of MRSA and extended-spectrum beta-lactamase (ESBL)–producing Enterobacteriaceae because of selection pressures related to cephalosporin overuse, their routine use is discouraged.[85] Carbapenem use has increased in recent years with the rise in ESBL infections; however, there is now an emergence of carbapenem resistance in *Pseudomonas aeruginosa.* With regard to gram-positive bacteria, enterococci play a significant role in IAIs, and hospitalized, critically ill patients are at risk of vancomycin-resistant enterococci (VRE) infection.[86] Options for treating VRE are linezolid or tigecycline.

Empiric antifungal therapy should be considered in patients with intraabdominal septic shock from community-acquired infections or in patients with postoperative infections where the presence of yeast is associated with a poor prognosis.[87] An echinocandin should be used as empirical antifungal therapy in critically ill patients having either community-acquired or hospital-acquired IAI.

In uncomplicated IAIs, once the source of infection (e.g., appendix or gallbladder) has been effectively treated by surgical therapy, postoperative antibiotics are not necessary.[88,89] In complicated IAIs in patients who are not severely ill and where source control has been obtained, a short course (3–5 days) of postoperative antibiotic therapy is suggested.[90] For severe bacterial hospital-acquired IAI in those who were severely ill, a duration of antibacterial therapy between 7 and 15 days may be necessary.[91] In a patient with intraabdominal candidiasis, a longer duration of antifungal coverage is recommended, up to 2–3 weeks, because of the high rates of recurrence.[92] For complicated patients with persistent IAIs, the decision to continue, revise, or stop antimicrobial therapy should be made based on the patient's clinical picture, available laboratory data, and clinician judgment.

Source Control

Early intervention and adequate source control are tenets to surviving intraabdominal sepsis. Source control encompasses all measures taken to reduce the bacterial load, including drainage of fluid collections, debridement of necrotic tissue, and resection or repair of perforated viscus. If the patient is stable and a fluid collection/abscess is accessible by percutaneous means, CT- or ultrasound-guided drain placement may be the optimal approach. Surgical intervention is indicated in the hemodynamically unstable patient with diffuse peritonitis, suspected perforated viscera, uncontrolled enteric spillage, or infected fluid collections not amenable to percutaneous drainage.

Objectives of surgical intervention include determination of the cause of peritonitis, drainage of fluid collections, and controlling the origin of abdominal sepsis. Intraoperatively, the entirety of the GI tract should be evaluated. Blood, purulent fluid, and any other contaminants should be removed to reduce the infectious burden and to help prevent or reduce fibrin formation. Careful attention should be given to the pelvis, paracolic gutters, and subphrenic spaces, as these are the most dependent areas of the abdomen and are therefore prone to fluid pooling and abscess development. Peritoneal lavage may help with removal of and dilution of contaminants by irrigating with large volumes of saline; however, its use remains controversial.

Damage control laparotomy was introduced in 1993 in the severely injured trauma population.[93] This technique involves performing a midline laparotomy to obtain initial control of contamination or hemorrhage in an unstable patient. The fascia of the abdomen is left open with a temporary closure device placed, and the patient is transferred to the ICU to facilitate the prioritization of resuscitation to normal physiology (Fig. 90.9). Once stabilized, patients are taken back to the operating room within 24–48 hours for re-exploration, definitive repair, and abdominal closure. The principle of damage control or "staged" laparotomy has since been applied to many other patient populations, including those with abdominal sepsis. The abdomen may be left open to prevent the development of abdominal compartment syndrome, allow for re-evaluation of adequate source control, and optimize conditions for definitive surgical reconstruction (e.g., bowel anastomosis or ostomy creation).[94,95] The patient managed by temporary abdominal closure should return to the operating room every 24 hours for re-evaluation and attempt at sequential or completion fascial closure. Failure to achieve primary fascial closure as a result of bowel edema and retracted fascia requires temporization with absorbable mesh and split-thickness skin grafting of the granulated exposed bowel. This commits the patient to a large planned ventral hernia, carries significant risk of enteroatmospheric fistula formation, and commits the patient to a 6- to 12-month course to definitive surgical repair.

Fig. 90.9 Management of the open abdomen after damage control surgery. A nonadherent plastic layer is placed over the abdominal contents below towels or commercial sponge dressings. Negative pressure is applied to the closure to drain fluid, prevent evisceration, and facilitate subsequent abdominal closure.

Adjunctive Therapies

Corticosteroids should only be considered for patients with clinical suspicion of relative adrenal insufficiency in the setting of vasopressor refractory shock.[77] If steroids are used, hydrocortisone 200 mg/day IV in four divided doses or as a 100-mg bolus followed by a continuous infusion of 10 mg/h is the recommended regimen.[96] The optimal duration of steroid taper remains unknown and therefore should be tailored to the physiologic status of the individual patient.

Nutritional support, preferably via the enteral route, should be initiated once initial resuscitation is complete and adequate perfusion pressure has been achieved.[97] Enteral nutrition maintains the integrity of the gut mucosa and helps prevent bacterial translocation. Some studies have shown early enteral feeding reduces the length of mechanical ventilation, ICU length of stay, and hospital length of stay but with no consistent mortality benefit.[98]

COMPLICATIONS

Outcomes after abdominal sepsis are directly related to early diagnosis, timely sepsis resuscitation, early source control, and contributing comorbidities. Most complications are a result of failed source control or the overwhelming physiologic response to sepsis. Abscess formation, anastomotic dehiscence, abdominal compartment syndrome, surgical site infection, "frozen" abdomen hindering return to the operating room, fistula formation, postoperative secondary nosocomial infection, MOF, and development of CCI are just a few of the potential complications that can arise. However, refractory or nonresolving MOF remains the leading cause of inpatient death.[99]

Enterocutaneous fistula is a dreaded complication of abdominal sepsis and can be significantly life-altering for the patient. After an IAI, this may be an occult source of sepsis before the tract drains through the skin. The tract can also contain an abscess cavity that requires drainage. Initial treatment is primarily supportive care with bowel rest, nutritional support, and skin care. The output should be monitored and controlled to avoid dehydration. Data on spontaneous closure rates are variable but most studies demonstrate 20%–30% of fistulas will close without operative intervention, usually within 3–4 weeks.[100] An elective fistula take-down procedure can be considered months later once the peritoneal cavity is less hostile.

The understanding of long-term outcomes after critical illness from abdominal sepsis has substantially evolved. Because of advances in sepsis detection, management, and critical care organ support, inpatient mortality rates have significantly declined over the past 20 years. However, there is an increasingly recognized cohort of "sepsis survivors" that overcome the initial septic insult to develop into a state of CCI.[101] Patients that develop CCI have an underlying pathophysiologic state of a persistent inflammation, immunosuppression, and catabolism syndrome (PICS), which manifests clinically as the development of recurrent nosocomial infections and multiple hospital readmissions because of "sepsis recidivism," and approximately 40% are dead at 1 year (see Fig. 90.1).[102–107] Risk factors for PICS-CCI include advanced age, severe comorbidities, and severity of shock. Therefore the prompt identification and treatment of intraabdominal sepsis of at-risk patients should be prioritized in order to improve the post-ICU outcomes for these patients.

KEY POINTS

- Timely diagnosis, initiation of antimicrobial therapy, volume resuscitation to restore end-organ perfusion, and definitive source control are essential in decreasing the mortality of intraabdominal sepsis.
- CT imaging of the abdomen/pelvis with IV (± PO) contrast is generally the imaging modality of choice in evaluating intraabdominal sepsis.
- The Surviving Sepsis initiative has helped improve outcomes in sepsis. Norepinephrine is recommended as the first-line vasoactive drug in septic shock.
- Empiric antimicrobial therapy in abdominal sepsis should be broad and include coverage for aerobic gram-negative bacilli, anaerobes, and possibly fungi. Antibiotics should be de-escalated after source control has been obtained and results of microbiologic testing are available.
- Source control encompasses all measures taken to reduce the bacterial load, including drainage of fluid collections, debridement of necrotic tissue, and resection or repair of perforated viscus.
- Studies have shown a cohort of "sepsis survivors" who overcome an initial septic insult but go on to develop into a state of CCI. These patients have an underlying pathophysiologic state of PICS, which manifests clinically as the development of recurrent nosocomial infections and multiple hospital readmissions because of "sepsis recidivism," and approximately 40% are dead at 1 year.

References for this chapter can be found at expertconsult.com.

ANNOTATED REFERENCES

Blot S, Antonelli M, Arvaniti K, et al. Epidemiology of intra-abdominal infection and sepsis in critically ill patients: "AbSeS", a multinational observational cohort study and ESICM Trials Group Project. *Intensive Care Med.* 2019;45(12):1703–1717.
Overall mortality of critically ill patients with intraabdominal sepsis is greater than 25%.

Gardner AK, Ghita GL, Wang Z, et al. The development of chronic critical illness determines physical function, quality of life, and long-term survival among early survivors of sepsis in surgical ICUs. *Crit Care Med.* 2019;47(4):566–573.
Chronic critical illness (CCI) is an emerging phenotype of sepsis survivors that can be clinically identified by prolonged intensive care unit stays with persistent yet sustainable organ dysfunction. Those who develop CCI demonstrate poor long-term outcomes, including high postdischarge healthcare resource use, significant physical function deficits, poor health-related quality of life, and higher long-term mortality as compared with those who rapidly recover.

McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clin Infect Dis.* 2018;66(7):987–994.
The recommended treatment of an initial episode of Clostridium difficile *infection (CDI) is a 10-day course of oral vancomycin or fidaxomicin. These agents have been shown to be superior to metronidazole; however, in settings where access to vancomycin or fidaxomicin is limited, metronidazole may be used for an initial episode of nonsevere CDI only.*

Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: International guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med.* 2017;43:304–377.
Administration of IV antimicrobials should be initiated as soon as possible after recognition and within 1 hour for both sepsis and septic shock. Routine microbiologic cultures (including blood) should be obtained before starting antimicrobial therapy in patients with suspected sepsis or septic shock as long as doing so results in no substantial delay in the initiation of antimicrobials.

Sartelli M, Chichom-Mefire A, Labricciosa FM, et al. The management of intra-abdominal infections from a global perspective: 2017 WSES Guidelines for management of intra-abdominal infections. *World J Emerg Surg.* 2017;12:29.
Key aspects of the management of intraabdominal infections include early and accurate diagnosis, prompt resuscitation, early and effective source control, and initiation of appropriate antimicrobial therapy.

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For complicated intraabdominal infections in patients who are not severely ill and where source control has been obtained, a short course (3–5 days) of postoperative antibiotic therapy is recommended.

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In patients with pancreatic necrosis, broad-spectrum antimicrobial therapy is recommended only if clinical or culture evidence of an established infection is present. Appropriate treatment regimens include single-agent therapy such as a carbapenem or piperacillin/tazobactam or combination therapy using a third-generation cephalosporin or fluoroquinolone combined with an antianaerobic drug such as metronidazole.

Waibel B, Rotondo M. Damage control in trauma and abdominal sepsis. *Crit Care Med.* 2010;38(Suppl. 9):S421–S430.
Damage control and open abdomen techniques from trauma have been adopted for emergency surgery. If repeat operations are needed for debridement or source control, significant visceral edema is present preventing closure without development of abdominal compartment syndrome (ACS), or patient instability requiring further resuscitation would have high risk of creating ACS, a temporary abdominal closure may be used.

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Mechanical Bowel Obstruction

Albert Hsu, Jens Flock IV, and Andrew J. Kerwin

Mechanical bowel obstruction occurs when there is an occlusion of the lumen of the intestine that causes a blockage of the normal flow of intraluminal contents through the gastrointestinal tract. As a common surgical emergency, 3.2 million cases of bowel obstruction occurred throughout the world in 2015 resulting in 264,000 deaths.[1,2] The small bowel is more much frequently affected compared with the large bowel and is involved in 80% of cases.[3] In the United States, small bowel obstruction (SBO) accounts for 15% of hospital admissions for patients presenting with abdominal pain and more than 300,000 annual hospitalizations.[4] Approximately 20%–30% of these patients will require operative management and contend with significant healthcare costs.[5,6]

ETIOLOGY

In developed countries, intraperitoneal adhesions that develop from prior abdominal surgery are the most common cause of mechanical SBO and account for 55%–80% of cases.[7] Patients who have previously undergone pelvic surgery, specifically colorectal resection, appendectomy, and gynecologic surgery; required prior adhesiolysis for bowel obstruction; or had resection for a malignancy are at increased risk for developing adhesive SBO.[5,8] Malignant neoplasms are responsible for 20% of cases and are most commonly intraperitoneal metastases from primary gastric, pancreatic, colonic, or ovarian malignancies. Hernias account for approximately 10% of cases and result from innate weak points in the abdominal wall or arise from previous surgical incisions.[9]

PATHOPHYSIOLOGY

An obstruction is classified as complete when the intestinal lumen is completely occluded and no amount of gas or fluid is able to pass through the site of obstruction. Intestinal obstruction can lead to severe life-threatening complications if bowel ischemia were to occur.[10] The progression to ischemia begins with bowel dilatation proximal to the site of obstruction, as intraluminal contents are unable to pass. As the bowel dilatation worsens, its absorptive function is lost and fluid and electrolytes accumulate in the intestinal lumen. These events result in an increase in the intraluminal pressure of the bowel that can cause a decrease in blood flow to the intestinal wall leading to ischemia. If malperfusion is severe enough, necrosis of the bowel wall and perforation can occur. The risk for bowel ischemia is greater in the setting of a complete bowel obstruction.

A closed loop bowel obstruction occurs when a segment of intestine is occluded at two different points along its course so that gas and fluid are trapped within this loop of bowel (Fig. 91.1). Because intraluminal pressures are much higher in a closed loop obstruction, there is increased risk for the development of bowel ischemia. This is most commonly caused by an abdominal wall hernia, internal hernia, or volvulus. Strangulation is another serious complication of bowel obstruction that can also lead to bowel ischemia and is more commonly seen with a closed loop obstruction. This occurs when the blood supply from the mesentery to the intestine is occluded, with rapid progression to bowel necrosis and perforation if left untreated.

CLINICAL PRESENTATION

Patients classically present with symptoms of crampy abdominal pain, nausea and vomiting, and constipation.[11] The addition of abdominal distension and obstipation should raise suspicion for the presence of a bowel obstruction. The severity of abdominal pain may be dependent on the degree of the obstruction. A partial obstruction may have an insidious onset over the course of hours or days accompanied by intermittent, crampy pain. A complete bowel obstruction tends to be acute with unrelenting abdominal pain. Fever; tachycardia; tachypnea; severe abdominal pain with involuntary guarding, rigidity, and rebound tenderness on examination; and the presence of leukocytosis or metabolic acidosis may be indicative of bowel ischemia. However, it should be noted that using clinical symptoms and signs has not been found to be accurate in predicting the presence of ischemic gangrenous bowel.[12]

EVALUATION

The evaluation for a mechanical bowel obstruction includes patient history, physical examination, and imaging. Patient history should focus on the severity, character, and duration of the patient's abdominal pain; time since last flatus and bowel movement; and changes in stool color or caliber. On the physical examination, it is important to detect signs of peritonitis; identify prior surgical incisions; and evaluate for ventral, incisional, inguinal, or femoral hernias. A digital rectal examination should be performed to evaluate for a rectal mass and blood per rectum.

It is extremely difficult to discern clinically whether a patient has a complete or partial obstruction. Therefore radiographic imaging is usually required for further evaluation. Radiographic imaging begins with abdominal upright and supine plain x-rays. This may show dilated loops of small bowel containing air–fluid levels. The colon may appear decompressed with an absence of air depending on the location of the obstruction. The presence of free air under the diaphragm indicates a hollow viscous perforation and mandates the need for immediate surgical consultation without the need for additional imaging.

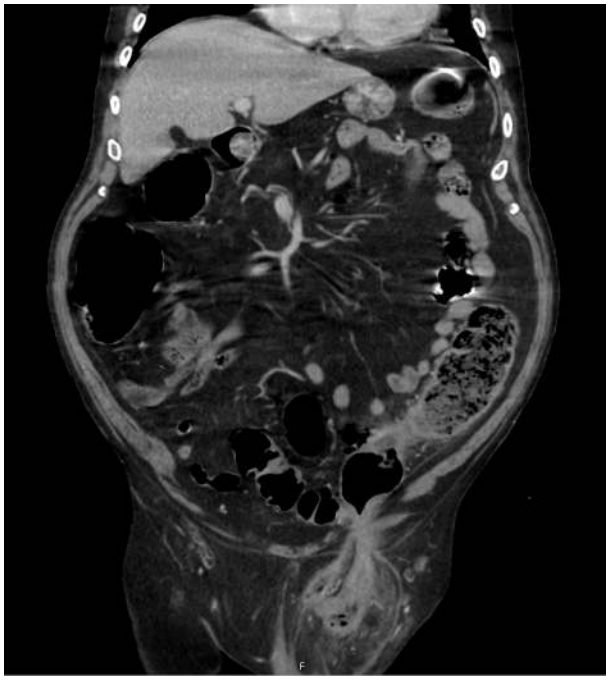

Fig. 91.1 A CT scan showing a closed loop obstruction involving the sigmoid colon caused by an incarcerated inguinal hernia.

Computed tomography (CT) of the abdomen and pelvis should be performed on all patients being evaluated for a bowel obstruction, as it is useful for characterizing the severity of the obstruction, determining the etiology, and revealing the presence of compromised bowel. The sensitivity and specificity of diagnosing a bowel obstruction with CT imaging is 94% and 97%, respectively.[13] CT scan is also fairly accurate in diagnosing a complete obstruction.[14] A common finding of an obstruction is a transition point with dilated bowel proximally and decompressed bowel distally. In postoperative patients, however, bowel dilatation is a common finding, and it may be difficult to differentiate between an ileus and an obstruction. Other findings on CT may include a target sign or mesenteric swirling suggestive of a volvulus or an internal hernia. Unlike plain x-rays, CT imaging with intravenous contrast can show signs that may indicate bowel ischemia. These findings include bowel wall thickening and edema, poor enhancement of the bowel wall, pneumatosis intestinalis, portal or mesenteric venous gas, and ascites.

MANAGEMENT

Patients commonly present with signs of dehydration and mild electrolyte abnormalities. A metabolic panel may show the depletion of sodium, chloride, or potassium, and a complete blood count may show leukocytosis and hemoconcentration. Isotonic fluid such as lactated Ringer's solution or 0.9% normal saline should be administered for resuscitation, and electrolyte abnormalities should be corrected if necessary. If operative intervention is indicated, patients should be resuscitated before surgery. A Foley catheter should be inserted so that urine output can be measured and used as a marker of end-organ perfusion to guide fluid resuscitation.

A subset of patients may present with more severe physiologic derangements in the form of hypovolemic shock, metabolic acidosis, or acute kidney injury. The development of sepsis and septic shock in a patient with presumed bowel obstruction is indicative of bowel ischemia and should prompt surgical intervention. Respiratory compromise can occur with severe bowel distension elevating the diaphragm and abdominal pain and discomfort limiting inspiratory effort. Depending on the severity of the acute physiologic derangements, patients may require admission to an intensive care unit (ICU) for hemodynamic monitoring and aggressive fluid resuscitation before operative intervention. Potassium repletion should be done judiciously with close monitoring in the setting of acute kidney injury. In addition, the pH of 0.9% normal saline is around 5.5, and caution should be taken with its use in resuscitation, as infusing large amounts can cause or worsen metabolic acidosis.[15]

Patients should be made nil per os. A nasogastric tube should be placed for gastric decompression to improve patient comfort and reduce the risk of vomiting and aspiration. The nasogastric tube can also evacuate swallowed air, limiting further bowel distension. Antibiotics are not routinely administered for uncomplicated mechanical bowel obstruction. They should be administered in the perioperative setting if operative intervention is warranted and concern for sepsis caused by bowel ischemia, necrosis, or perforation exists. Severe sepsis and septic shock can also occur after surgery for strangulated gangrenous bowel, as relieving the strangulation can cause the release of endotoxin and other inflammatory mediators into the bloodstream.[16] These patients should be admitted to the ICU and receive treatment based on the Surviving Sepsis Guidelines.[17]

The decision for operative versus nonoperative management of a patient with a mechanical SBO is a challenging one largely based upon clinical judgment. The morbidity and mortality risks associated with an operation are weighed against the likelihood of worsened outcomes caused by a delay in appropriate management. Patients with peritonitis on physical examination, systemic toxicity, an acutely incarcerated or strangulated hernia, and findings of pneumatosis or perforation on imaging studies should undergo emergent surgery. There is a low threshold for operative intervention when CT scan findings are suggestive of possible bowel ischemia and closed loop obstruction.

Patients without clinical or radiologic signs of bowel compromise are managed nonoperatively with close clinical monitoring that comprises serial abdominal examinations. Nonoperative management is overall successful in 65%–80% of patients. Any clinical deterioration should prompt urgent operative intervention. Traditional surgical dogma has endorsed immediate surgery for patients with a complete SBO. Recent practice guidelines have recommended that patients without signs of bowel ischemia can safely undergo initial nonoperative management while cautioning that complete obstruction has a higher risk of failure.[18] The four concerning signs of bowel ischemia are fever, leukocytosis, tachycardia, and localized abdominal tenderness. Patients with SBO often present with mild tachycardia and leukocytosis, but these should resolve with hydration and pain relief. If one or more of these signs progress, concern for bowel ischemia should prompt the need for operative intervention. A hypertonic water-soluble contrast agent should be administered to patients being observed, as it can be therapeutic by accelerating the resolution of adhesive bowel obstruction.[19,20] Additionally, the lack of contrast in the colon by 24 hours after administration is predictive of failure of nonoperative management and should prompt early operative intervention.[21] Nonoperative management should not extend beyond 3–5 days, as the obstruction is unlikely to resolve at this point. An exception is early postoperative SBO (without obvious sign of ischemia), which can generally be managed conservatively for up to 2 weeks.[22] The risk of surgery during this postoperative time is significant because of the nature of abdominal adhesions that increases the risk for iatrogenic injury.

KEY POINTS

- Patients may present with severe physiologic derangements in the form of metabolic acidosis, acute kidney injury, and hypovolemic shock.
- Patients with peritonitis on physical examination, systemic toxicity, an acutely incarcerated or strangulated hernia, and findings of pneumatosis or perforation on imaging studies should undergo emergent surgery.
- A CT scan should be obtained in all patients suspected of having a bowel obstruction.
- Patients without clinical or radiologic signs of bowel compromise may safely undergo nonoperative management of mechanical SBO.
- Nonoperative management consists of fluid resuscitation, correction of electrolyte disturbances, close monitoring of resuscitative efforts. and nasogastric tube decompression.
- Administration of hypertonic water-soluble oral contrast is both diagnostic and therapeutic for the management of adhesive SBO.
- Delay in appropriate management in the setting of bowel compromise is associated with increased morbidity and mortality.

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92

Toxic Megacolon and Ogilvie's Syndrome

Chasen Ashley Croft and Maria Estela Alfaro-Maguyon

Acute megacolon refers to a syndrome defined by abnormal colonic distention in the absence of mechanical obstruction. Megacolon may be a manifestation of Ogilvie's syndrome or toxic megacolon. The sequelae of these disorders results in diffuse colonic dysmotility. Ogilvie's syndrome is an eponym for acute colonic pseudo-obstruction (ACPO).[1,2] Critical illness–related colonic ileus (CIRCI) is characterized by constipation for several days without marked colonic distention and may herald development of Ogilvie's syndrome.[3] Ogilvie's syndrome is believed to be a functional disturbance of colonic motility often observed in hospitalized patients as a result of hemodynamic, metabolic, pharmacologic, inflammatory, or postoperative conditions.[4] In toxic megacolon, the distention is caused by severe colitis and is associated with systemic manifestations or toxicity. Although usually attributed to inflammatory bowel disease (IBD), most notably ulcerative colitis (UC), toxic megacolon may manifest in the critically ill as a complication of severe infectious colitis, most frequently caused by *Clostridium difficile*. Both Ogilvie's syndrome and toxic megacolon are medical emergencies that, if left untreated, result in intestinal barrier failure, colonic ischemia, perforation, and multiple organ failure (MOF). This chapter focuses on toxic megacolon and Ogilvie's syndrome in critically ill patients admitted to the intensive care unit (ICU) and provides management and prevention strategies for each disease process.

CLINICAL FEATURES

Ogilvie's or Acute Colonic Pseudo-Obstruction

The clinical features of Ogilvie's syndrome include abdominal distention, with or without abdominal pain, in hospitalized or institutionalized patients with serious underlying medical and surgical conditions.[2,5,6] Patients usually present with constipation; however, passage of flatus or stool is reported in up to 40% of patients.[2] Bowel sounds may be normal, diminished, or hyperdynamic. Leukocytosis and fever are more common in patients with ischemia or perforation, but also occur in those who have not developed these complications. According to Laplace's law, the pressure required to stretch the walls of a hollow viscus decreases in inverse proportion to diameter.[7] Therefore progressive colonic distention causes the highest tension in the wall of the cecum and is most likely to be the site of perforation. The risk of cecal perforation increases sharply when cecal diameter is greater than 12 cm and when this distention has been present for longer than 6 days.[8] A diameter of 9–12 cm has been suggested as a sign of impending perforation.[2,4] Institutionalized patients with chronic constipation or chronic dysmotility can have a chronically distended cecum with diameter over 12 cm without clinical manifestation. The 12-cm diameter warning must therefore be individualized. If the diagnosis and treatment are delayed, progressive distention may cause peritoneal signs, abdominal compartment syndrome, respiratory compromise, sepsis, ischemia, perforation, MOF, and death.

Toxic Megacolon

Toxic megacolon is the late, life-threatening complication of inflammatory or infectious colitis. Patients present with fever, leukocytosis, abdominal distention, and tenderness, with or without signs of local or generalized peritonitis. Both IBD and infectious colitis classically present with diarrhea, but constipation may herald the onset of megacolon, delaying diagnosis. In addition to these findings, patients may present with dehydration, altered consciousness, electrolyte disturbances, hypoalbuminemia, and hypotension. In severe cases, septic shock and MOF may ensue.[9,10] Factors that may trigger or predispose to the development of toxic megacolon have been identified; these include severe hypokalemia; discontinuation or rapid tapering of corticosteroids, sulfasalazine, or mesalazine; use of antidiarrheal agents; and use of antidepressants.[11] Barium enema and colonoscopy may cause worsening distention that further impairs colonic blood supply, leading to worsening ischemia and perforation. Colonoscopy and barium enema are contraindicated in patients with clinical or radiographic features of toxic megacolon because of the risk of perforation.

PATHOGENESIS OF ACUTE MEGACOLON

Colonic Ileus and Ogilvie's Syndrome

The pathophysiology of Ogilvie's syndrome is not fully understood. Current literature suggests an imbalance in autonomic regulation of the colonic motor function, leading to excessive parasympathetic suppression and sympathetic stimulation. This results in an aperistaltic colon.[12,13] In addition to autonomic dysregulation, neurotransmitters (e.g., substance P and vasoactive intestinal polypeptide [VIP]), inflammatory mediators (e.g., tumor necrosis factor [TNF], interleukin-1 [IL-1]), metabolic derangements, and pharmacologic interventions also play a crucial role in the development of Ogilvie's syndrome.[14] Electrolyte disturbances are common and often multifactorial. For example, the inflamed colon loses its capacity to reabsorb salt and water, and the rate of potassium excretion into the lumen may be markedly increased because of inflammatory diarrhea. Metabolic alkalosis secondary to volume depletion and potassium loss is associated with poor prognosis. Metabolic acidosis suggests the presence of ischemic colitis.

Postoperative motility disturbances are inevitable after abdominal surgery and result from a complex interaction of neurogenic and inflammatory mechanisms. The extent of parasympathetic suppression and sympathetic activation depends on the amount of surgical stimulation, as demonstrated by Bueno and colleagues in experimental studies in dogs.[15] Surgical manipulation triggers two different, distinct phases of postoperative ileus. The first or early phase is neurally mediated and is activated during and immediately after surgery. During this phase, intestinal manipulation initiates release of norepinephrine via the sympathetic nerves from the spinal cord, in addition to nitric oxide

(NO) and VIP release via vagal nerve stimulation, abolishing the motility of the entire gastrointestinal tract.[16,17] This phase ceases once the abdomen is closed. The second, long-lasting phase of postoperative ileus involves the inflammation of the intestinal muscularis. During this phase, activation of peritoneal mast cells triggers release of vasoactive and proinflammatory substances, such as histamine and proteases, which recruit leukocytes and temporarily increase mucosal permeability. This allows luminal bacteria or bacterial products to enter the lymphatics. This likely represents the key event that triggers the next stage of the inflammatory cascade: activation of resident macrophages. Once activated, resident macrophages release cytokines such as TNF and subsequent upregulation of inducible nitric oxide synthetase (iNOS) and cyclooxygenase-2 (COX-2), further blunting the contractile response of the inflamed tissues.[18] In addition, in vivo animal studies have demonstrated that endogenous opioids released peripherally can modulate gastrointestinal (GI) motor and secretory functions.[19] Opioid receptors are stimulated by endogenous opioids, which are secreted locally upon stress. Once activated, they inhibit acetylcholine release from motor neurons and promote transmitter release from inhibitory neurons.[20] In addition to stimulation by endogenous opioids, exogenous opioids, commonly used for analgesia, also act upon peripheral opioid receptors in the GI tract, inhibiting GI motility.

CIRCI may be related to circulating bacteria or bacterial products and/or proinflammatory cytokines, following a similar mechanism as previously described. Colonic ileus also has been associated with ischemia-reperfusion injury, causing energy deficit, functio laesa, and oxidant-mediated tissue damage. Finally, distal colonic distention induces inhibition of proximal colonic motility, the so-called *colo-colonic reflex,* thereby perpetuating a vicious cycle.[21]

BOX 92.1 Clinical Factors Predisposing to Ogilvie's Syndrome or Acute Colonic Pseudo-Obstruction

Cardiovascular
- Heart failure, stroke
- Gut ischemia

Critical Illness
- Severe sepsis
- Acute pancreatitis
- Shock or hypoxemia

Postoperative State or Trauma
- Intestinal manipulation
- Peritonitis
- Immobility and dehydration
- Vertebral, pelvic, or hip fracture/surgery
- Retroperitoneal hematoma

Metabolic Factors
- Hypokalemia and hyperglycemia
- Hypothyroidism, diabetes mellitus
- Liver or renal failure
- Amyloidosis

Drugs
- α-Adrenergic agonists, dopamine[18]
- Clonidine and dexmedetomidine[36]
- Opioids
- Anticholinergics, calcium channel antagonists
- Antipsychotics[39,40]
- Antidepressants
- High-dose phosphodiesterase inhibitors

Gastrointestinal Infections
- Cytomegalovirus, herpes zoster
- Tuberculosis

Neurologic
- Transection of the spinal cord
- Low spinal cord disease
- Parkinson disease

Obstetric
- Cesarean section
- Normal delivery

PREDISPOSING FACTORS

Ogilvie's Syndrome

ACPO was first described by Sir William Heneage Ogilvie's in two patients who had retroperitoneal tumors invading the celiac plexus, which led him to suggest sympathetic deprivation as the etiology of the massive distention.[5] The vast majority of patients presenting with Ogilvie's syndrome have the syndrome in association with a predisposing factor. Clinical factors predisposing to Ogilvie's syndrome are summarized in Box 92.1.[1,2,6] In a large retrospective series of 400 patients, Vanek and Al-Salti reported the most common predisposing conditions associated with Ogilvie's syndrome were nonoperative trauma (11%), infections (10%), and cardiac disease (10%).[6] Although nonsurgical factors predisposing to Ogilvie's syndrome are frequent, surgical operations remain the most common cause of this syndrome. Of these, Ogilvie's syndrome is most likely to occur after obstetric/gynecologic, abdominal/pelvic, trauma, orthopedic/spine, and cardiac procedures. These procedures account for 50%–60% of all Ogilvie's cases.[22] Exogenous catecholamines have dose-dependent effects on intestinal motility; low doses promote and high doses suppress motility. α-Adrenergic agonists and dopamine are stronger inhibitors of acetylcholine release than β-adrenergic agents. Dopamine, in addition to inhibiting upper GI motility, inhibits distal colonic motility. Antipsychotic agents such as clozapine, haloperidol, and olanzapine have been associated with life-threatening forms of Ogilvie's syndrome.[23] One explanation of these gastrointestinal side effects is their antimuscarinic properties. Opioids suppress GI motility through activation of mu-opioid receptors, which inhibit the release of acetylcholine from the myenteric plexus. The outcome of this interaction is the decreased levels of cyclic adenosine monophosphate (cAMP) and calcium with a reduction in excitatory neurotransmitter release that ultimately leads to decreased peristalsis.[12,20] Opioid agonists inhibit GI wall motility, impair reabsorption of fluid from the lumen, and impair relaxation of the internal anal sphincter.[24] Additional predisposing factors such as severe metabolic derangements, sepsis, GI infections, and spinal cord injuries have also been implicated in the development of Ogilvie's syndrome.

Toxic Megacolon

Acute toxic megacolon was originally described in 1950 as a complication of IBD. Currently, the incidence of toxic megacolon in IBD has substantially decreased with advances in the management of severe colitis. Over the course of the last decade, the list of etiologic factors was expanded by a vast array of inflammatory and infectious conditions: bacterial colitides such as *C. difficile*, *Staphylococcus* spp., *Salmonella* spp., *Shigella* spp., and *Campylobacter* spp.; in addition, viral (e.g., cytomegalovirus [CMV], human immunodeficiency virus [HIV] and herpesvirus) and parasitic *(Entamoeba)* infections have been associated with toxic megacolon.[25,26] However, the most common cause of acute toxic megacolon in the critically ill is pseudomembranous colitis caused by *C. difficile*. Although many conditions have been associated with the development of toxic megacolon, the precise pathophysiology is not fully understood. Causes of toxic megacolon are summarized in Box 92.2.

Clostridium Difficile Infection

C. difficile is a gram-positive, spore-forming, toxin-producing, anaerobic rod bacterium. Less than 5% of the healthy adult population is colonized with this bacterium (see Chapter 135 for more details).[27] An estimated 30% of hospitalized patients become colonized with *C. difficile,* although most of these patients remain asymptomatic. Pathogenic strains produce two major exotoxins: toxin A (enterotoxin/Tcd A) and toxin B (cytotoxin/Tcd B).[28] Purified toxin A possesses potent enterotoxic and proinflammatory activities. Toxin B has been previously reported to exhibit no enterotoxic activities; however, recent studies have described enterotoxic and proinflammatory activities in human intestinal xenografts in mice.[29] It has been postulated that toxins A and B act synergistically to activate

BOX 92.2 Disorders Associated With Toxic Megacolon

Inflammatory Bowel Disease
- Ulcerative colitis
- Crohn disease

Infectious Colitis
- *Salmonella, Shigella,* amebic colitis
- *Clostridium difficile*
- Cytomegalovirus colitis
- HIV infection

Cancer Chemotherapy

Ischemia

HIV, Human immunodeficiency virus.

cell-signaling molecules, including transcription factor, nuclear factor kappa B (NF-κB), and mitogen-activated protein kinases in monocytes, leading to production and release of proinflammatory cytokines. Toxin A leads to an increased secretion of fluid within the digestive tract, mucosal inflammation, and structural damage. Toxin B, in most cases, is responsible for the major problems associated with infection and is estimated to have 10 times more impact on the gastrointestinal tract than toxin A.[30] Recently, a hypervirulent strain has been identified. This strain, referred to as *NAP1/BI/027,* is responsible for the outbreaks of highly virulent pathogens. A deletion in this strain's *tcdC* gene, which is a negative regulator of toxin production, causes production of both toxins A and B to increase by 16-fold to 23-fold.[27,31] This strain is also more resistant to fluoroquinolones, has hypersporulation capacity, and produces an additional toxin, toxin C. The hypersporulation capacity potentially accounts for the enhanced transmission in hospitals compared with previous strains.

Colonic proliferation of *C. difficile* is thought to occur when the bacterial environment has been altered by current or previous exposure to antibiotics.[27] Historically antibiotics such as clindamycin, cephalosporins, and certain penicillins were most commonly associated with *C. difficile* colitis. More recently, fluoroquinolones have been implicated as a more frequent cause of this infection. The risk of acquiring the organism increases with prolonged hospital stay and institutionalization, and may be spread by nosocomial transmission. It has been postulated that susceptibility is further increased with the concurrent use of gastric acid–inhibiting drugs by facilitating increased survival of *C. difficile* spores. A complete list of factors associated with *C. difficile* infection can be found in Box 92.3.

DIAGNOSIS OF ACUTE MEGACOLON

The diagnosis of acute megacolon is suggested by the clinical presentation. Thorough history and physical examination should be obtained for all patients with acute abdominal distention and may help identify the underlying cause (see Boxes 92.2 and 92.3). Mild cases typically present with abdominal pain and cramping, constipation or diarrhea, and low-grade fever. More severe cases may present with significant abdominal tenderness and signs of systemic inflammation, such as fever, leukocytosis, and electrolyte abnormalities. Plain abdominal radiography is essential in the diagnostic workup, which will show varying degrees of colonic dilation. Dilation is most pronounced in the cecum, ascending, and right transverse colon. The cecal diameter may range from 6 to 20 cm. "Cutoffs" are common at the splenic flexure and descending colon (Fig. 92.1). Dilation of the left colon may occur as

BOX 92.3 Factors Associated With Colonization and Subsequent Infection With *Clostridium difficile*

Disruption of Indigenous Microflora
- Antibiotics suppressing indigenous microflora
- Cancer chemotherapeutics with antimicrobial activity
- Preoperative bowel preparation

Opportunity of Infection
- Prolonged hospital stay

Microbial Factors
- Toxigenicity and adhesion

Diminished Gastrointestinal Defense
- Reduced or suppressed gastric acid secretion
- Parenteral nutrition
- Postpyloric enteral nutrition
- Gastrointestinal surgery

Antibody Response of the Host

Poor Underlying Condition
- Old age
- Cancer
- Renal insufficiency
- Long-term use of corticosteroids
- Bedridden state

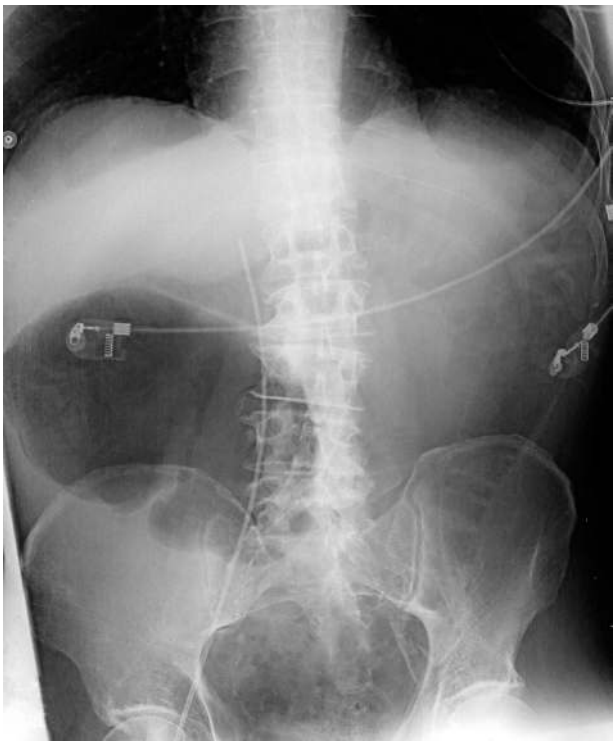

Fig. 92.1 Plain abdominal radiograph of patient with respiratory insufficiency caused by severe emphysema and Ogilvie's syndrome 10 days after dynamic hip screw implantation for femoral fracture. Dilatation is most pronounced in the cecum and ascending colon. Gas and fecal pattern in the distal colon is normal. The patient was successfully treated with intravenous neostigmine.

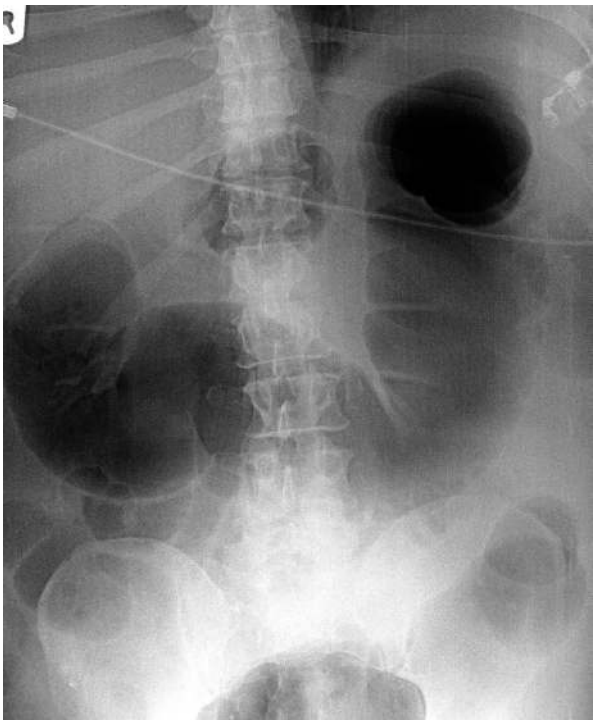

Fig. 92.2 Plain abdominal radiograph of a patient with Ogilvie's syndrome 11 days after surgery for a ruptured aneurysm of the abdominal aorta. Dilatation (probably the result of ischemia) is present in both the right and left colon. The syndrome was resolved with vasodilators and intravenous neostigmine.

well (Fig. 92.2). The distribution of colonic dilation may be caused by different origins of the proximal and distal parasympathetic nerve supply of the colon. Air/fluid levels may be seen in the small bowel, indicating a paralytic ileus. The differential diagnosis of acute colon distention in a critically ill patient should include mechanical obstruction, infectious colitis with toxic megacolon, and Ogilvie's syndrome. Prompt evaluation of a patient with acute megacolon should involve excluding mechanical obstruction and other causes of toxic megacolon, such as *C. difficile* colitis, and assessment for signs of peritonitis or perforation, which indicates a surgical emergency. Mechanical obstruction is excluded if air is visible in all colonic segments, including the rectosigmoid junction. If the diagnosis is in question, mechanical obstruction can be excluded by performing a computed tomography (CT) scan. The clinical or radiographic features of a toxic megacolon are an absolute contraindication to barium enema or the administration of laxatives. Toxic megacolon is diagnosed based on clinical signs of systemic toxicity combined with radiographic evidence of colonic dilation (diameter >6 cm).[32] Pneumatosis of the bowel wall or free intraperitoneal air on CT scan indicates the need for urgent surgical consultation.

If toxic megacolon is suspected, fresh stool should be submitted for laboratory culture, and stool should be screened for the presence of toxigenic *C. difficile*. Commercially available nucleic acid amplification tests (NAATs) such as polymerase chain reaction (PCR) for the rapid detection of *C. difficile* infection (CDI) are inexpensive, highly sensitive, and allow results to be available within hours. These tests should only be used in patients with documented diarrhea. An alternative method for the detection of CDI requires a two-step procedure. The patient should first be screened for the presence of glutamate dehydrogenase (GDH), an enzyme produced by *C. difficile* in relatively large amounts compared with toxins A and B. Although GDH testing is sensitive, it is not as specific for CDI, because this enzyme is produced by both toxigenic and nontoxigenic organisms. GDH-negative specimens require no further testing. GDH-positive specimens must undergo additional screening either by NAAT or by toxins A and B enzyme immunoassay (EIA) testing, followed by NAAT if the EIA results are discordant.[33] Final results take 2–5 days. After an initial negative result, repeat testing within 48 hours should be discouraged, as conversion to a positive result occurs in less than 5% of patients.[34] Studies have shown that both toxins A and B EIA and toxigenic cultures may remain positive for as long as 30 days in patients who have resolution of symptoms. Therefore "test for cure" studies may complicate clinical care, resulting in unnecessary prolongation of treatment, and should not be performed. Surveillance cultures of feces are advocated to detect other pathogens such as enterotoxin-producing *Clostridium prefringens, Staphylococcus aureus,* and *Klebsiella oxytoca*. Blood cultures should be obtained in any patient presenting with toxic megacolon.

Limited endoscopy (e.g., flexible sigmoidoscopy) with biopsy may be valuable in differentiating etiologic causes; however, full colonoscopy bears the high risk of perforation and is therefore contraindicated. IBD is characterized by diffusely abnormal crypt structure, whereas normal crypt architecture is seen in bacterial colitis. Mild cases of *C. difficile* colitis are associated with nonspecific findings of colitis, such as friability of the mucosal surface. In severe cases, focal ulcerations covered by purulent material, or pseudomembranes, interspersed with normal intervening mucosa, may be seen. Although pathognomonic for CDI, these lesions are not uniformly present and may not be present throughout the entire colon.

MANAGEMENT

Ogilvie's Syndrome

Medical Management

An essential concept to the management of Ogilvie's syndrome is prevention. Many hemodynamic, surgical, and metabolic derangements have been implicated with the development of Ogilvie's syndrome. Strategies to prevent this condition in the critically ill are highlighted in Box 92.4. Life-threatening complications may occur if treatment is delayed. Supportive therapy is the preferred initial management and should be instituted in all patients with uncomplicated ACPO (absence of ischemia, peritonitis, cecal diameter >12, and/or significant abdominal pain).[35] Concomitantly, conditions that impair colonic motility must be corrected. Patients should be made nil per os (NPO) and intravenous fluids administered to restore euvolemia. Nasogastric decompression should be initiated in patients with concomitant paralytic ileus. Electrolyte and metabolic abnormalities, including phosphorous,

BOX 92.4 Strategies to Prevent Ogilvie's Syndrome in the Critically Ill

- Early resuscitation of the circulation
- Minimizing prolonged infusion of high doses of α-adrenergic drugs
- Minimizing the use of dopamine
- Minimizing the prolonged use of opioids
- Use of thoracic epidural anesthesia
- Minimally invasive or laparoscopic surgery
- Selective decontamination of the digestive tract
- Avoiding antibiotics that disrupt the growth of anaerobic fecal bacteria
- Early oral or enteral feeding
- Avoidance of proton pump inhibitors
- Early mobilization and ambulation
- Promoting timely defecation

magnesium, calcium, and thyroid functions, should be corrected via parenteral administration. Blood cultures and empiric antibiotics should be administered if sepsis is clinically suspected. Offending medication use, such as opioids, anticholinergic agents, norepinephrine, and dopamine, should be minimized or discontinued if possible. Optimal body positioning, such as prone positioning with the hips elevated on pillows or the knee-chest position with the hips held high, often aids in spontaneous evacuation of flatus.[2,5] These positions should be alternated with right and left lateral decubitus positions regularly, when feasible. Use of a rectal tube may also aid in decompression. Serial abdominal examinations, assessing for signs of peritonitis or free perforation, should be performed and plain abdominal radiographs should be obtained every 12–24 hours. Osmotic laxatives lead to increased gas formation in the colon and should be avoided.[36] The reported success of conservative management is variable, with rates from 77% to 96%.[32,37] Deterioration or nonresolution of symptoms despite maximal medical therapy within 48–72 hours of initiating therapy should prompt reconsideration of the management plan.

If these measures are ineffective beyond 48–72 hours, either pharmacologic therapy or endoscopic decompression should be considered as the next step in the treatment algorithm.[32] Intravenous neostigmine is the drug of choice. Neostigmine is a short-acting anticholinesterase parasympathomimetic agent commonly used for postoperative reversal of nondepolarizing neuromuscular blockade and in the treatment of myasthenia gravis. Parasympathetic stimulation can result in bradycardia, asystole, hypotension, bronchospasm, and hypersalivation. Coadministration of glycopyrrolate may be useful in preventing the side effects of the medication, including hypersalivation and bronchospasm.[38] Close observation and monitoring with telemetry in a controlled setting are warranted. In a double-blind, randomized placebo-controlled trial of 21 patients with a cecal diameter of at least 10 cm despite 24 hours of conservative therapy, 10 out of 11 patients randomized to receive an infusion of 2 mg neostigmine had prompt colonic decompression, and 1 responded after subsequent retreatment.[39] None of the 10 patients randomized to placebo experienced resolution, but all 7 in whom neostigmine was openly administered subsequently responded. In a double-blind, placebo-controlled prospective study in critically ill, ventilated patients with CIRCI, continuous infusion of neostigmine at 0.4–0.8 mg/h resulted in defecation in 80% of patients, with no reported adverse events.[3] Continuous-infusion neostigmine is associated with greater bowel diameter reduction at 24 hours and may be associated with decreased side effects compared with bolus dosing.[40] The 2019 American Society for Gastrointestinal Endoscopy guidelines recommend pharmacologic therapy with neostigmine (2 mg over 3–5 minutes) with appropriate cardiovascular monitoring. For patients who do not respond to a first dose of neostigmine, a second dose is recommended. For those patients refractory to bolus dosing of neostigmine, alternative routes of neostigmine administration, including subcutaneous or continuous intravenous infusion, are recommended.[32,41] Contraindications to the use of neostigmine include intestinal or urinary obstruction, presence of ischemia or perforation, pregnancy, uncontrolled cardiac arrhythmias, severe active bronchospasm, known hypersensitivity reaction, and renal insufficiency.[2,3,32] Unfortunately, relapse of Ogilvie's syndrome after the initial response to medical therapy occurs in 40% of patients, and more invasive therapies may be required.[42]

Invasive Interventions

Once medical management has failed, endoscopic decompression is the initial invasive procedure of choice for patients with marked cecal distention (>10 cm) of significant duration (>3–4 days), not improving after 24–48 hours of supportive therapy, and who have contraindications to or fail neostigmine treatment.[4] Colonoscopy should be performed by an experienced endoscopist without the administration of bowel preparation using water infusion and minimal to no insufflation. If insufflation is required, the use of carbon dioxide rather than air is the preferred gas agent, as liberal use of air insufflation may lead to perforation.[35] Advancing the scope to the level of the proximal hepatic flexure is usually sufficient to obtain adequate decompression.[7] Gas should be aspirated and the viability of the mucosa assessed during slow withdrawal of the scope. If signs of ischemia are present, the procedure should be aborted. Successful decompression has been achieved in 70%–80% of patients; however, the recurrence rates are as high as 50%.[2,43] To increase therapeutic benefit, decompression tube placement at the time of colonoscopy may reduce recurrence, but controlled trials with this intervention are not available. It is important to exclude perforation before performing endoscopic decompression, with a plain abdominal x-ray performed within several hours before the procedure, especially in patients with fever, leukocytosis, or worsening abdominal pain.[35] Studies comparing endoscopic decompression and pharmacologic treatment are limited.

Surgical management is rarely necessary and should be reserved for patients who have failed pharmacologic and endoscopic management or those who have clinical signs of colonic ischemia or perforation. Surgical options include a venting stoma (cecostomy) or colectomy.[6] Ogilvie's syndrome is one of the few conditions where cecostomy is indicated in patients with prohibitive morbidity. Tube cecostomy should be performed only in patients without evidence of ischemia or perforation. It can be performed laparoscopically or through a limited right lower quadrant incision. A large Foley catheter is left in place for 2–3 weeks to allow venting of the colon. Cecostomy is an effective treatment and can be performed under local anesthesia, but is associated with significant morbidity.[44] In cases of ischemia or perforation, laparotomy is indicated. Segmental or subtotal resection may be performed, as dictated by the extent of colon involvement. In the event a colectomy is needed, an end stoma and mucous fistula should be performed and anastomosis avoided.

An alternative method of decompression includes percutaneous endoscopic colostomy of the cecum (PEC-cecum). PEC-cecum tubes can be placed radiographically or endoscopically with reported success rates up to 100%.[35] However, PEC-cecum is not recommended as a routine option and should only be used in select cases after multidisciplinary assessment of inoperable candidates.[45] Complications associated with PEC-cecum include wound infection, bleeding, hematoma, perforation, granuloma, or buried bumper.

Toxic Megacolon

Medical Management

The initial goal of treatment is to reduce the severity of colitis so as to restore normal colonic motility and decrease the likelihood of perforation.[25] Patients should be monitored closely in an ICU with frequent examinations to assess for clinical deterioration. A surgical consultation should be obtained on admission, although medical treatment is successful in about 50% of patients. Complete blood counts, electrolyte panels, and serial plain abdominal films are reviewed every 12 hours initially, until clinical improvement has been observed. Conditions impairing colonic motility must be corrected (see Box 92.1). In general, patients will require adequate resuscitation, electrolyte and vitamin replacement, early optimization of circulation, and, if necessary, mechanical ventilation. A nasogastric tube should be placed to decompress the GI tract. Early total parenteral nutrition has shown no survival benefit and should be reserved for patients who have evidence of long-standing malnutrition in the absence of bacteremia, especially if they are likely to undergo surgery. However, enteral nutrition should be initiated as soon as possible and tolerance of enteral feeds monitored by

gastric volume residuals. Antimotility agents should be discontinued, and antiperistaltic agents for diarrhea are absolutely contraindicated.

Systemic antibiotics, administered empirically, are necessary to reduce septic complications and peritonitis. Empiric antibiotics should cover both gram-negative and anaerobic species, as guided by local susceptibility patterns and fecal surveillance cultures. It is important to select antibiotics that least inhibit the indigenous colonic flora, and in the case of *C. difficile,* the offending antibiotic should be discontinued. De-escalation of antibiotics should ensue, without delay, once final microbiologic data are obtained.

Patients with toxic megacolon caused by IBD should be treated with high-dose intravenous corticosteroids. Steroid treatment should be started immediately and not be delayed pending microbiologic results. Most authors recommend hydrocortisone 100 mg or equivalent every 6 hours or by continuous infusion. Steroid use should be reevaluated on a regular basis and discontinued once an exclusively infectious etiology of toxic megacolon has been established. Patients with IBD-related toxic megacolon who do not respond to intravenous glucocorticoids within 3 days should receive infliximab as the second-line therapy, and cyclosporine should be reserved for those who cannot tolerate infliximab.[46,47]

In patients with toxic megacolon caused by severe *C. difficile* colitis, the first step is to stop the offending antibiotic and to give vancomycin 125 mg orally, four times a day.[33] Treatment should not be delayed while awaiting microbiologic confirmation of CDI. Findings suggestive of severe, *complicated* CDI include admission to the ICU, hypotension with or without required use of vasopressors, fever ≥38.5°C, mental status changes, white blood cell count ≥35,000 or <2000 cells/mm^3, serum lactate levels >2.2 mmol/L, or evidence of end-organ failure. If any of these finding are present, the vancomycin dosing should be increased to 500 mg orally four times a day with the addition of metronidazole 500 mg intravenously every 8 hours. Vancomycin retention enemas (vancomycin 500 mg in 500 mL saline per rectum four times a day) should also be administered.[33] Fecal microbial transplant has been used successfully in *C. difficile* patients with severe colitis, including toxic megacolon, but the indications, outcomes, and risks of this approach are not well defined.[48–51]

Surgical Management

Patients unresponsive to medical treatment should undergo prompt surgical resection. Surgical intervention should be considered if a patient has progressive signs of organ failure despite optimal medical therapy; CT scan findings suggestive of worsening disease; or signs of peritonitis, abdominal compartment syndrome, colonic necrosis, full-thickness ischemia, or perforation. However, because of a lack of prospective randomized studies, it is difficult to identify the optimal point for surgical intervention in patients with severe, fulminant CDI, and mortality ranges from 35% to 80%.[52] Subtotal colectomy with end ileostomy is considered the procedure of choice when urgent or emergent surgery is required. More recently, Neal and colleagues published their experience with an alternative surgical approach: diverting loop ileostomy and colonic lavage.[53] In this technique, an ileostomy is created and intraoperative colonic lavage is performed with a warmed polyethylene glycol (PEG) solution via the ileostomy. Postoperatively, the patients received antegrade vancomycin flushes (500 mg in 500 mL lactated Ringer's) every 8 hours for a duration of 10 days. Mortality was reduced from 50% to 19% among patients treated using this novel technique. There are not currently enough data to support the routine use of this procedure; however, it remains an alternative approach for the treatment of fulminant *C. difficile* colitis.

SUMMARY

Ogilvie's syndrome manifests with massive dilation of the colon in the absence of mechanical obstruction. Evaluation involves exclusion of mechanical obstruction, cessation of offending agents, and selective use of neostigmine and colonic decompression. With appropriate management, colonic pseudo-obstruction usually resolves within several days. Toxic megacolon is a diagnosis based on clinical signs of systemic toxicity in combination with radiographic evidence of colonic dilation. The goal of treatment is to reduce the effects of colonic inflammation and prevent perforation. Timely treatment with broad-spectrum antibiotics combined with cessation of causative agents will help minimize the morbidity associated with this disease process. Surgery should be reserved for those patients who fail to respond to medical management or show signs of ischemia or perforation. A high index of suspicion and early recognition of both Ogilvie's syndrome and toxic megacolon are crucial to optimal management.

KEY POINTS

- Ogilvie syndrome, or acute colonic pseudo-obstruction (ACPO), is a syndrome of massive colonic dilation in the absence of mechanical obstruction that develops in critically ill patients with serious underlying medical and surgical conditions.
- Conservative therapy is the initial preferred management.
- Numerous contributory metabolic, infectious, and pharmacologic factors are associated with Ogilvie's syndrome. These factors should be identified and corrected early in the treatment.
- Neostigmine is effective in a majority of cases of Ogilvie's syndrome. Colonic decompression may be required.
- Toxic megacolon is a syndrome of nonobstructive colonic dilation associated with systemic toxicity.
- Empiric antibiotics with gram-negative and anaerobic coverage should be initiated early in the course of treatment.
- Surgical intervention should be reserved for those patients who fail optimal medical management or show clinical signs of colonic ischemia or perforation.

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Severe Gastrointestinal Bleeding

Tyler J. Loftus and Martin D. Rosenthal

Gastrointestinal bleeding is common, and severe bleeding often requires intensive care unit admission. Optimal management requires hemostatic resuscitation, management of antiplatelet and anticoagulant agents, acid suppression, and a multidisciplinary approach to localization for hemorrhage control, summarized in Fig. 93.1.

RESUSCITATION

For patients with acute upper gastrointestinal bleeding, restrictive transfusion strategies (i.e., red cell transfusion when hemoglobin falls below 7 g/dL) decreases mortality and morbidity relative to liberal transfusion strategies.[1,2] It is reasonable to maintain a higher threshold (e.g., hemoglobin 9 g/dL) in patients with ischemic cardiovascular disease.[3] Although there is a lack of high-level evidence to inform decisions regarding red cell transfusion strategies specifically for acute lower intestinal bleeding, it seems prudent to adopt a restrictive transfusion strategy for these patients as well.[4,5] In cases of hemorrhagic shock, hemostatic resuscitation should proceed with balanced administration of red cells and plasma, in addition to platelet transfusions for patients with thrombocytopenia or the use of antiplatelet medications.[6]

MANAGEMENT OF ANTIPLATELET AGENTS

Management of antiplatelet therapy for patients with severe gastrointestinal bleeding depends on the indication for and type of antiplatelet therapy. When the indication is primary prevention of cardiovascular events, antiplatelet therapy should be discontinued.[7] When the indication is secondary prevention of cardiovascular events in patients with known cardiovascular disease, low-dose aspirin monotherapy should be continued, and for patients receiving dual antiplatelet therapy, aspirin should be continued and the nonaspirin antiplatelet agent should be held for up to 1 week.[8–10] If dual antiplatelet therapy is indicated for cardiac percutaneous intervention within the prior 30 days or an acute coronary syndrome within the prior 90 days, it is reasonable to continue dual antiplatelet therapy, given the high risk of myocardial infarction and death associated with discontinuation of dual antiplatelet therapy.[11]

MANAGEMENT OF ANTICOAGULANTS

When severe gastrointestinal bleeding occurs in the context of therapeutic anticoagulation, the anticoagulant should be discontinued, and reversal should be considered. Intravenous administration of vitamin K and prothrombin complex concentrates effectively reverses warfarin. Increasingly, direct thrombin inhibitors (e.g., dabigatran) and factor Xa inhibitors (e.g., rivaroxaban, apixaban, edoxaban, and fondaparinux) are used to prevent embolic stroke in nonvalvular atrial fibrillation and to prevent and treat venous thromboembolism. When patients present within 2–3 hours of ingesting anticoagulants, administration of activated charcoal may decrease their intestinal absorption, but will also impair endoscopic visualization of the gastrointestinal mucosa. Hemodialysis can remove dabigatran from the bloodstream, but is ineffective in removing factor Xa inhibitors because they are highly protein-bound.[12] Idarucizumab, a specific monoclonal antibody, also reverses dabigatran.[13] Fresh frozen plasma and cryoprecipitate have limited efficacy in reversing direct thrombin inhibitor and factor Xa inhibitors.[14] For cases of severe bleeding, prothrombin complex concentrates and the antifibrinolytic agent tranexamic acid may be considered, though evidence supporting their use specifically for gastrointestinal bleeding is limited, and they are associated with thromboembolic complications.[12] It seems prudent to perform rapid thromboelastography and administer tranexamic acid if pathologic thrombolysis is identified, though this area remains controversial. Emerging evidence suggests that andexanet alfa effectively reverses factor Xa inhibitors with an acceptable safety profile, but further investigation is required before routine clinical use can be recommended.

LOCALIZATION AND TREATMENT

Clinical assessment often allows differentiation between upper gastrointestinal bleeding proximal to the ligament of Treitz and lower intestinal bleeding. Brisk upper gastrointestinal bleeding presents with hematemesis or hematochezia (maroon or red blood passed through the rectum), whereas slower upper gastrointestinal bleeding allows oxidation of blood products, resulting in coffee-ground emesis or melena (black, tarry stools).[15] In cases of melena, gastric tube placement can help differentiate between upper and lower etiologies. Gastric fluid containing bile and no blood effectively rules out upper gastrointestinal hemorrhage. In addition, blood urea nitrogen–to–serum creatinine ratios greater than 30:1 suggest upper gastrointestinal sources of hemorrhage, likely related to heme absorption and metabolism.[16] Further diagnosis and management are typically guided by initially upper or lower endoscopy.

UPPER GASTROINTESTINAL BLEEDING

Upper gastrointestinal bleeding occurs in 60–160/100,000 people in the United States annually and is associated with 4%–10% mortality.[17–20] The differential includes esophageal variceal hemorrhage—accounting for approximately 10%–20% of all cases and more prevalent among patients with portal hypertension—and nonvariceal hemorrhage, usually caused by peptic ulcer disease, esophagitis, gastritis, and Mallory-Weiss tears.[21] Rare causes include Dieulafoy lesions, tumor, vascular malformation, hemobilia, and aortoenteric fistula. Etiologies of gastrointestinal bleeding are listed in Table 93.1. When upper gastrointestinal bleeding is suspected and nasopharyngeal and

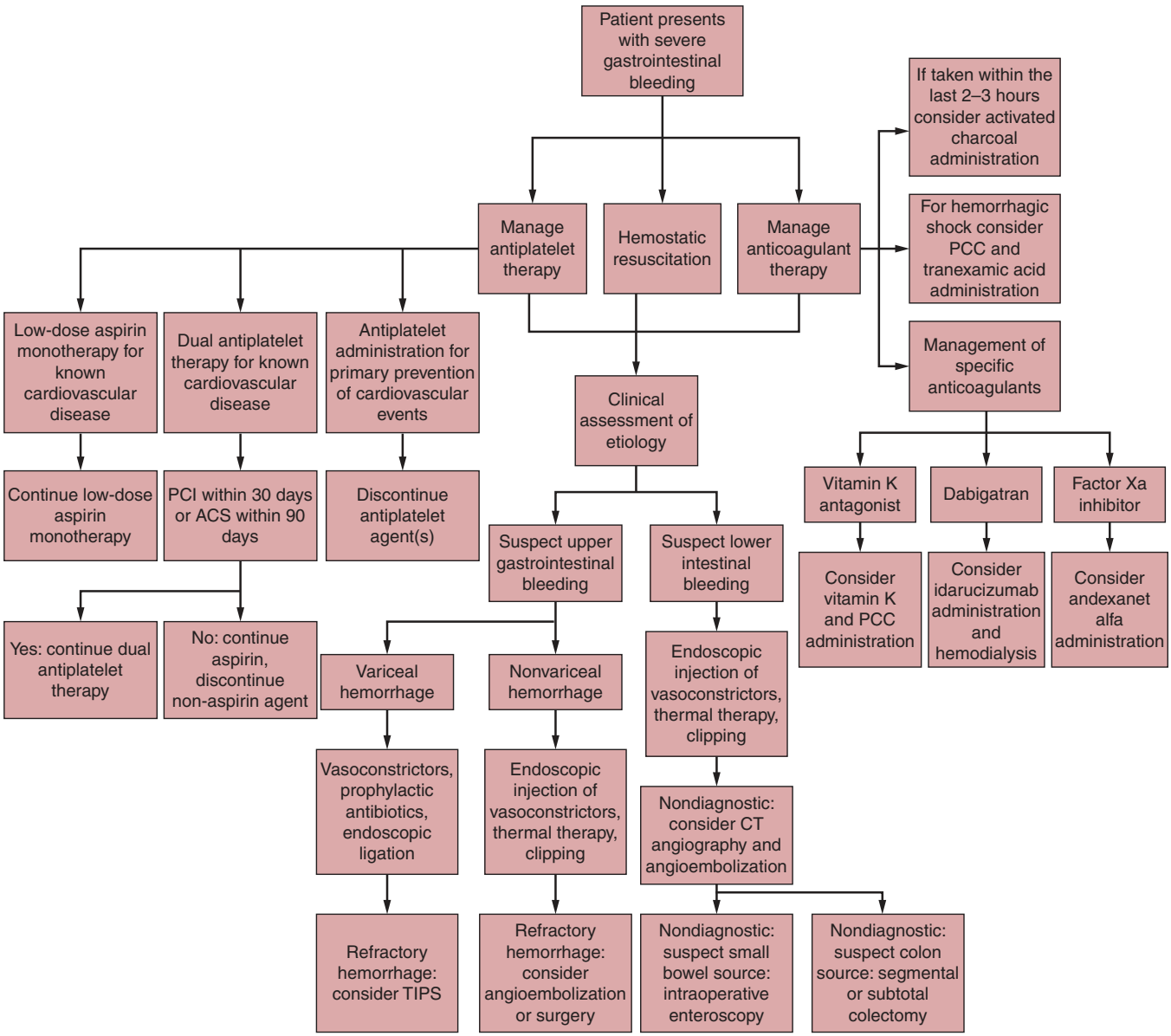

Fig. 93.1 Severe Gastrointestinal Bleeding Management Algorithm. *ACS,* Acute coronary syndrome; *CT,* computed tomography; *PCI,* percutaneous coronary intervention; *PCC,* prothrombin complex concentrate; *TIPS,* transjugular intrahepatic portosystemic shunt.

oropharyngeal sources have been ruled out, upper endoscopy establishes the etiology.

Management of variceal hemorrhage in patients with cirrhosis should ideally include splanchnic vasoconstrictors (e.g., terlipressin/vasopressin or octreotide), prophylactic antibiotics (e.g., norfloxacin or ceftriaxone), acid suppression with proton pump inhibitors, and endoscopic variceal ligation.[22,23] If these measures fail to resolve hemorrhage, transjugular intrahepatic portosystemic shunt placement should be performed early, ideally within 24–48 hours of admission.[24] If these measures are not feasible, a Sengstaken-Blakemore tube can be used to temporize massive bleeding from esophageal varices through balloon compression. For patients with isolated gastric varices, gastric devascularization and splenectomy should be considered.[25] Management of portal vein thrombosis should be determined on a case-by-case basis, weighing the risks and benefits of anticoagulation in terms of worsening portal hypertension and recurrent variceal hemorrhage versus bleeding complications.

Management of nonvariceal upper gastrointestinal hemorrhage depends on the etiology. Most can be managed endoscopically with injection of vasoconstrictors, thermal therapy with electrocoagulation or argon beam coagulation, and clipping. If endoscopic therapy is not feasible, fails once in the context of an ulcer greater than 2 cm or associated hypotension during rebleeding, or fails twice, surgical management and angiographic embolization should be considered.[26,27] Angiographic embolization is most likely to be successful in cases of discrete, localized arterial hemorrhage. Surgical management of refractory hemorrhage from a gastric ulcer typically includes ulcer excision and closure of the gastric defect, with intraoperative biopsy to assess for the presence of malignancy.[28]

Surgical management of refractory hemorrhage from a prepyloric or duodenal ulcer may consist of oversewing the ulcer plus vagotomy or performing a formal gastric resection, including the antrum, with reconstruction by Billroth I, Billroth II, or Roux-en-Y gastrojejunostomy techniques plus vagotomy. Between these options, the latter has the

TABLE 93.1 Principal Causes of Upper and Lower Gastrointestinal Bleeding, Approximating Descending Order of Prevalence

Upper Gastrointestinal Bleeding	Lower Intestinal Bleeding
Variceal hemorrhage	Diverticulosis
Peptic ulcer disease	Hemorrhoids
Esophagitis	Ischemic colitis
Gastritis	Colorectal polyps or neoplasms
Mallory-Weiss tears	Angiodysplasia
Dieulafoy lesions	Postpolypectomy bleeding
Tumor	Inflammatory bowel disease
Vascular malformation	Infectious colitis
Hemobilia	Stercoral ulceration
Aortoenteric fistula	Colorectal varices
	Radiation proctopathy
	NSAID-induced colopathy

NSAID, Nonsteroidal antiinflammatory drug.

advantage of including both antrectomy and vagotomy to reduce gastrin and acetylcholine stimulation of hydrochloric acid production by parietal cells, and is associated with a lower incidence of recurrent bleeding, with similar mortality rates.[29,30] However, when discrete bleeding from the gastroduodenal artery at the base of a posterior duodenal ulcer can be identified though a pyloromyotomy or duodenotomy, hemorrhage can be effectively managed with three-point ligation of the gastroduodenal artery—cephalad, caudad, and medial, to ligate proximally, distally, and the transverse pancreatic branches, respectively—with vagotomy.[28,31]

LOWER INTESTINAL BLEEDING

Lower intestinal bleeding occurs in approximately 36/100,000 people in the United States annually and is associated with 2%–9% mortality.[17,20,32,33] Common causes of acute lower intestinal bleeding, in descending order of prevalence, include diverticulosis, hemorrhoids, ischemic colitis, colorectal polyps or neoplasms, angiodysplasia, postpolypectomy bleeding, inflammatory bowel disease, and infectious colitis; rare causes include stercoral ulceration, colorectal varices, radiation proctopathy, and nonsteroidal antiinflammatory drug (NSAID)–induced colopathy. Etiologies of gastrointestinal bleeding are listed in Table 93.1. Lower intestinal bleeding usually resolves spontaneously, and is thus less likely to require emergency interventions. For most patients presenting with lower intestinal bleeding, colonoscopy is the initial diagnostic and therapeutic procedure of choice.[3]

Early colonoscopy (i.e., within 12–24 hours of presentation) is associated with greater likelihood of obtaining a definitive diagnosis and shorter hospital length of stay.[34–36] Preparation with polyethylene glycol or a similar solution is ideal, although the cathartic effects of intraluminal blood products along with cleaning of colonic mucosa during the procedure can provide adequate visualization.[37] Similar to upper gastrointestinal hemorrhage, most cases can be managed endoscopically with injection of vasoconstrictors, thermal therapy with electrocoagulation or argon beam coagulation, and clipping.[38]

When colonoscopy is nondiagnostic or hemorrhage is brisk, computed tomography (CT) angiography is useful for localization, detecting bleeding as slow as 0.3 mL per minute.[37] This can facilitate targeted, selective interventional angiography and embolization.[39] Provocative angiography with administration of heparin, nitroglycerin, or thrombolytics may increase the likelihood of identifying the origin of hemorrhage, but also risks worsening hemorrhage.[40] This technique should only be attempted when a surgical team and operating room are available.

In contrast to upper gastrointestinal bleeding—with rich collateral circulation—lower gastrointestinal angiographic interventions target end arteries, and are thus more likely to lead to ischemia requiring surgical resection. Video capsule endoscopy can noninvasively identify small bowel sources of bleeding. When the etiology of bleeding cannot be identified by other means, laparotomy and intraoperative enteroscopy can identify the source in approximately 80% of all cases.[41] Lower intestinal hemorrhage secondary to ischemic colitis, inflammatory bowel disease, and tumors is less likely to respond well to endoscopic and angiographic management.[3] In such cases, surgical resection of the involved bowel should be a primary consideration. It is important to localize the site of hemorrhage as precisely as possible before proceeding with bowel resection. When upper gastrointestinal and small bowel hemorrhage have been ruled out and a discrete source of lower intestinal bleeding cannot be identified, it is acceptable to perform subtotal colectomy, but this approach is associated with increased mortality and morbidity relative to targeted, segmental colectomy, particularly in elderly patients with multiple comorbidities and increased risk for dehydration secondary to high ileostomy output.[42,43]

PROGNOSIS

For patients with upper gastrointestinal hemorrhage, the Glasgow Blatchford score accurately predicts requirements for endoscopic interventions and mortality.[44] Endoscopic visualization of pathology can estimate the likelihood of recurrent bleeding based on visualization of active bleeding (high risk), visible nonbleeding vessels or adherent clot on an ulcer (intermediate risk), or clean ulcer base (low risk). Among patients with lower intestinal bleeding, risk factors for recurrent bleeding or death include tachycardia, hypotension, ongoing hematochezia, age greater than 60 years, serum creatinine greater than 1.7 mg/dL, and unstable or clinically significant comorbidities.[45]

KEY POINTS

- Hemostatic resuscitation should proceed with restrictive transfusion strategies when possible.
- Management of antiplatelet agents depends on the indication for antiplatelet therapy.
- Management of anticoagulants depends on the type of agent and urgency of reversal.
- Variceal hemorrhage is managed with vasoconstrictors, prophylactic antibiotics, and endoscopic ligation, with salvage by TIPS.
- Nonvariceal upper gastrointestinal hemorrhage is managed primarily with endoscopic techniques and secondarily by angioembolization or surgery.
- Lower intestinal hemorrhage is initially managed with endoscopic techniques, then with angiography, and then with intraoperative enteroscopy for small bowel sources and subtotal or segmental colectomy for colorectal sources.

References for this chapter can be found at expertconsult.com.

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Core Principles of Renal Physiology and Pathophysiology in Critical Illness

Emily J. See, Daniel Leisman, Clifford Deutschman, and Rinaldo Bellomo

INTRODUCTION

The kidney plays a key role in maintaining solute, water, and acid-base homeostasis. Some or all of these roles may be impaired in critically ill patients because of processes that disrupt glomerular, tubular, or interstitial function. This chapter will cover the core principles of renal physiology and pathophysiology relevant to the intensive care setting.

STRUCTURES OF THE NEPHRON

The Glomerulus

The glomerulus is the filtering unit of the kidney (Fig. 94.1). Located in the renal cortex, it is composed of a tuft of capillaries that filter plasma across a semipermeable barrier. The glomerular filtration barrier consists of three layers: the fenestrated endothelial cells of glomerular capillaries, the glomerular basement membrane, and specialized epithelial cells called *podocytes.* Mesangial cells surrounding the glomerular capillaries have contractile properties that alter the surface area available for filtration. After passing through the barrier, the filtrate collects in the Bowman space, encased by the Bowman capsule, before it passes into the renal tubule.

Proximal Tubule

The proximal tubule is a hollow structure outlined by a single layer of epithelial cells that extends from the Bowman space to the loop of Henle (see Fig. 94.1). It is a key site for the reabsorption of sodium, water, bicarbonate, phosphate, potassium, calcium, and organic solutes (e.g., glucose, citrate, urea, and amino acids; Table 94.1). Transport occurs either paracellularly (across tight junctions) or transcellularly (across the apical and basolateral membrane of the epithelial cells). The resorptive function of the proximal tubule is enhanced by amplification of the luminal cell membrane into a "brush border" and by densely packed mitochondria on the basolateral cell surface, which supply energy for the active transport of solutes.

The Loop of Henle

The loop of Henle is divided into three segments: the thin descending limb, the thin ascending limb, and the thick ascending limb (see Fig. 94.1). Its primary function is to concentrate the urine by the countercurrent system. The countercurrent system is responsible for generating the osmotic gradient within the interstitium that increases from the renal cortex (~290 mOsm/kg) to the inner medulla (~1200 mOsm/kg). This is achieved by means of its U-shaped configuration and variable permeability to sodium and water.[1] The thin descending limb is highly permeable to water but impermeable to sodium, whereas the thin and thick ascending limbs are impermeable to water but permeable to sodium, which is reabsorbed passively in the thin ascending limb and actively in the thick ascending limb. The thick ascending limb is also a primary site for magnesium reabsorption and urea secretion (see Table 94.1).

Macula Densa

The macula densa lies at the apex of the nephron between the thick ascending limb and the distal convoluted tubule, adjacent to the parent glomerulus. The cells of the macula densa detect the composition of the tubular fluid and provide feedback to the afferent and efferent arterioles to control renal blood flow (RBF) and glomerular filtration rate (GFR) in a process called *tubuloglomerular feedback* (TGF).

Distal Convoluted Tubule

The distal convoluted tubule is a short nephron segment located between the thick ascending limb and the collecting duct (see Fig. 94.1). The early distal convoluted tubule participates in the reabsorption of sodium, potassium, calcium, and magnesium (see Table 94.1). It is impermeable to water, making it the final diluting segment of the kidney. The late distal convoluted tubule contains three cell types. Principal cells reabsorb sodium and water and secrete potassium under the control of antidiuretic hormone (ADH) and aldosterone, respectively. Alpha-intercalated cells secrete hydrogen ions, reabsorb bicarbonate, and either reabsorb or secrete potassium, depending on the plasma concentration. Beta-intercalated cells secrete bicarbonate and reabsorb hydrogen ions.

Collecting Duct

The collecting duct connects the distal convoluted tubules of individual nephrons to calyces or directly to the renal pelvis (see Fig. 94.1). Like the late distal convoluted tubule, the collecting duct contains principal and alpha- and beta-intercalated cells. Collecting ducts are classified as cortical or medullary ducts; the proportion of intercalated cells (which are responsible for acid-base balance) decreases as the collecting duct enters the medulla. Urea is reabsorbed in the medullary collecting duct in response to ADH, which up-regulates urea transporters, increasing interstitial osmolality and enhancing the osmotic gradient of the countercurrent system.

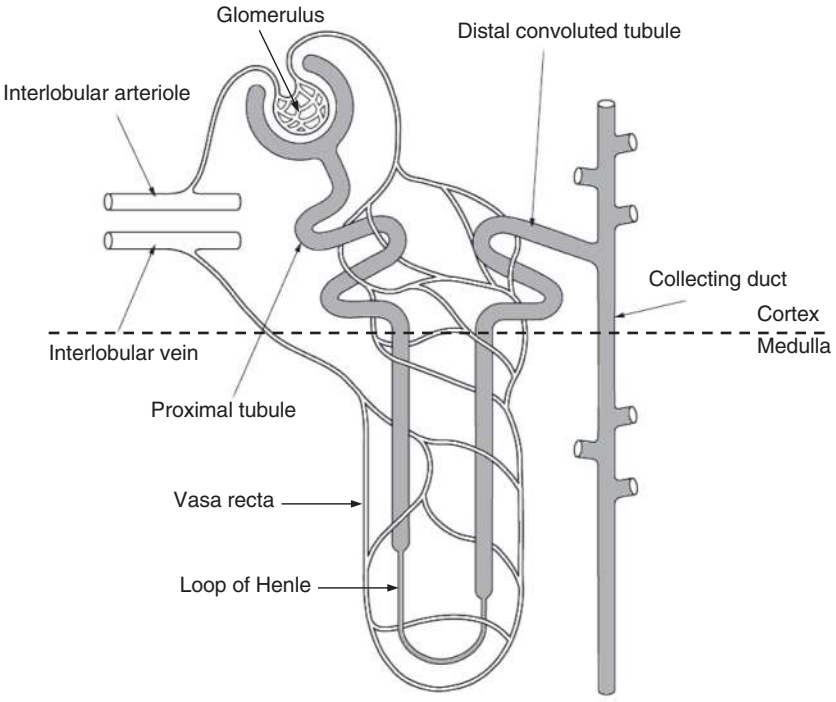

Fig. 94.1 Structures of the nephron.

Renal Vasculature

Blood is delivered to the glomerular capillaries via the renal artery, interlobar artery, arcuate artery, interlobular artery, and afferent arteriole. Glomerular capillaries are composed of a single layer of endothelial cells, encased by the glomerular basement membrane and interdigitating podocyte processes. Capillaries drain into the efferent arteriole, which gives rise to the peritubular capillaries and vasa recta. The vasa recta are a series of vascular loops that supply oxygenated blood and nutrients to the cortex and medulla and return reabsorbed water and solutes to the circulation. The vasa recta converge to form the interlobular vein, arcuate vein, interlobar vein, and renal vein before emptying into the inferior vena cava.

The arrangement of vasa recta capillaries within the medulla is an important determinant of medullary oxygen delivery. The U-shaped configuration of these vessels ensures that the medullary osmotic gradient is maintained, such that solute entry and water loss in the descending branches is balanced by solute loss and water entry in the ascending branches ("countercurrent exchange"). Like solutes and water, oxygen can also diffuse directly from descending to ascending branches of the vasa recta, creating an environment of low oxygen tension in the medulla. This mode of oxygen shunting, coupled with low oxygen delivery and high metabolic activity, makes the medulla particularly prone to hypoxemia.

GLOMERULAR FILTRATION, RENAL BLOOD FLOW, AND METABOLISM

Glomerular Filtration Rate

The glomerulus initiates the formation of urine by producing a filtrate that enters the tubular lumen. The rate of filtrate production, the GFR, is determined by hydrostatic and oncotic pressure gradients between the glomerular capillary and Bowman space, in addition to the ultrafiltration coefficient, according to the equation:

$$GFR = k_f(P_{GC} + \pi_{BS}) - (P_{BS} + \pi_{GC})$$

where

P_{GC} = the hydrostatic pressure in the glomerular capillary
P_{BS} = the hydrostatic pressures in Bowman spaces
π_{GC} = the oncotic pressure in the glomerular capillary
π_{BS} = the oncotic pressure in Bowman spaces
k_f = the ultrafiltration coefficient, which reflects the permeability of the glomerular filtration barrier

In healthy young adults, the normal GFR is approximately 120–130 mL/min/1.73m^2. The proportion of plasma filtered across the glomerulus (the GFR divided by the plasma flow rate) is referred to as the *filtration fraction*. Under normal conditions, it is roughly 0.2.

The previous equation provides important insight into the manner in which different renal pathologies can all reduce GFR. For example, urinary obstruction leads to congestion in the tubular lumen, which increases P_{BS}. Hypovolemic shock decreases RBF, which lowers P_{GC}. Direct damage to the filtration barrier, such as from immunologic injury, initially causes the filtration barrier to become leaky, which increases k_f, but with time, the filtration barrier becomes occluded secondary to thrombosis, which reduces k_f. RBF does not directly determine GFR, but contributes indirectly by influencing P_{GC}. Increases in P_{GC}, π_{BS}, or k_f all raise the filtration fraction.

Renal Blood Flow

To maintain a stable RBF across a range of systemic arterial pressures, the kidney employs two main autoregulatory mechanisms: the myogenic reflex and TGF. The myogenic reflex arises from the physical properties of smooth muscle: increased intravascular volume stretches

TABLE 94.1 Site of Reabsorption of Water and Solutes Along the Nephron

	Site of Reabsorption	Contribution to Reabsorption
Sodium	Proximal tubule	60%–70%
	Loop of Henle	20%–30%
	Distal tubule	5%–10%
	Collecting duct	3%–5%
Water	Proximal tubule	60%–70%
	Loop of Henle	10%–20%
	Collecting duct	10%–20%
Bicarbonate	Proximal tubule	80%–90%
	Loop of Henle	10%–15%
	Collecting duct	0%–5%
Potassium	Proximal tubule	60%–70%
	Loop of Henle	20%–30%
	Distal tubule	0%–10%
	Collecting duct	0%–30%
Calcium	Proximal tubule	60%–70%
	Loop of Henle	20%–30%
	Distal tubule	5%–10%
	Collecting duct	5%–10%
Magnesium	Proximal tubule	20%–30%
	Loop of Henle	50%–60%
	Distal tubule	5%–10%
Phosphate	Proximal tubule	80%–90%
	Loop of Henle	5%–10%
	Distal tubule	0%–5%
Glucose	Proximal tubule	100%
Amino acids	Proximal tubule	100%
Urea	Proximal tubule	50%–60%
	Loop of Henle	(Secretion 50%)
	Collecting duct	50%–60%

TABLE 94.2 Effect of Vascular Mediators on Renal Blood Flow and Glomerular Filtration Rate

	Action	Effect	Δ RBF	Δ GFR
Sympathetic nervous system	Afferent > efferent arteriole vasoconstriction	↓ P_{GC}	↓	↓
	Decreased glomerular capillary surface area	↓ k_f		
Catecholamines[1]	Afferent arteriole vasoconstriction	↓ P_{GC}	↓	↓
	Efferent arteriole vasoconstriction	↑ P_{GC}		
Angiotensin-II[1]	Efferent > afferent arteriole vasoconstriction	↑ P_{GC}	↓	↔
	Mesangial cell contraction	↓ k_f		
Adenosine	Afferent arteriole vasoconstriction	↓ P_{GC}	↓	↓
	Efferent arteriole vasodilatation	↓ P_{GC}		
	Inhibition of renin release			
Natriuretic peptides	Afferent arteriole vasodilatation	↑ P_{GC}	↑	↑
	Efferent arteriole vasoconstriction	↑ P_{GC}		
Nitric oxide	Afferent arteriole vasodilatation	↑ P_{GC}	↑	↑
	Efferent arteriole vasodilatation	↓ P_{GC}		
PGE_2 and PGI_2 Histamine	Afferent > efferent arteriole vasodilatation	↑ P_{GC}	↑	↑
	Afferent arteriole vasodilatation	↑ P_{GC}	↑	↔
	Efferent arteriole vasodilatation	↓ P_{GC}		
Bradykinin	Afferent > efferent arteriole vasodilatation	↑ P_{GC}	↑	↔

GFR, Glomerular filtration rate; k_f, ultrafiltration coefficient of the glomerular filtration barrier; P_{GC}, hydrostatic pressure in the glomerular capillary; *PGE_2,* prostaglandin E_2; *PGI_2,* prostacyclin; *RBF,* renal blood flow.
[1]In states of vasodilatation and/or shock, these agents counteract alterations in vascular tone to restore RBF and preserve GFR.

arteriolar walls, which increases vascular smooth muscle contractile force to promote vasoconstriction. TGF responds to chemical stimuli. Increased renal perfusion pressure increases sodium delivery to the macula densa, which triggers the release of adenosine triphosphate (ATP) into the extracellular space and conversion of ATP to adenosine.[2,3] Adenosine causes vasoconstriction of the afferent arteriole and inhibits the release of renin from the juxtaglomerular apparatus. A reduction in renin reduces angiotensin II levels, inducing efferent arteriolar relaxation and reducing RBF and GFR. TGF is impaired by loop diuretics, renin-angiotensin-aldosterone system (RAAS) inhibitors, and in the setting of chronic kidney disease (CKD). Either the myogenic reflex or TGF may be overcome in the setting of critical illness with low renal perfusion pressure.

Autoregulatory mechanisms leverage the ability of the glomerular microcirculation to alter resistance in preglomerular and postglomerular vessels independently (Table 94.2). If afferent arterioles preferentially constrict, RBF, P_{GC}, GFR, and filtration fraction fall. If efferent arterioles preferentially constrict, RBF decreases but P_{GC}, GFR, and filtration fraction will increase because vascular resistance increases distal to the glomerulus. This is a key concept: net constriction or dilatation of afferent arterioles changes RBF and GFR in the same direction, whereas net changes in efferent arteriolar tone change RBF and GFR in opposite directions.

Renal Metabolism

The high metabolic demand of the kidney is driven by the active reabsorption of filtered solutes via the Na^+-K^+-ATPase pump. The density of these pumps is particularly high in the proximal tubule and thick ascending limb of the loop of Henle. The proximal tubule is dependent on aerobic metabolism (using fatty acids, ketone bodies, and amino acids as substrates) and is susceptible to hypoxia. The cells in this region generate glucose from lactate to provide substrate for the loop of Henle, where glycolytic capacity is high as a result of low ambient oxygen.

Disruption of bioenergetics and mitochondrial function is a major pathophysiologic event in the development of renal injury.

Measuring Glomerular Filtration Rate

GFR can be estimated by examining the clearance of any substance that is produced at a constant rate, only metabolized by the kidney, freely filtered at the glomerulus, and neither secreted nor reabsorbed along the tubule. The gold standard for measuring GFR is urinary inulin clearance (an exogenous filtration marker). However, this measurement requires continuous intravenous infusion, which is impractical in most clinical settings. Other exogenous filtration markers (e.g., Tc-DPTA) are available but are equally cumbersome. Although the clearance of the endogenous filtration marker creatinine is the most widely used approach to GFR in clinical practice, the physiology of critical illness may render it invalid for several reasons. First, creatinine is not produced at a constant rate in most critical illness states, and its concentration may be diluted by fluid resuscitation. Second, certain medications (e.g., sulfonamide antibiotics) alter tubular creatinine secretion, which affects creatinine concentration without reducing GFR. Third, equations to estimate GFR from plasma creatinine are not valid in critically ill patients. Cystatin-C, another endogenous marker, may perform better during acute illness because it is not dependent on muscle mass or metabolic activity. Cystatin-C is a plasma protein synthesized by nucleated cells at a constant rate and is almost completely filtered at the glomerulus. Older age, female sex, steroid use, and hyperthyroidism are associated with lower synthesis rates. However, the higher cost of cystatin-C and the lack of standardized assays limit its wider use.

Renal Functional Reserve

In states of increased stress and intact nephron mass, the kidney is capable of augmenting GFR and tubular function through nephron recruitment and increased RBF.[4] The difference between maximal capacity and baseline function is termed the *renal functional reserve.* Glomerular reserve can be quantified by measuring GFR at baseline and after an oral or intravenous protein load (1–1.2 g/kg) that stimulates RBF.[5] Tubular reserve can be assessed by administering intravenous furosemide ("furosemide stress test"), which is actively secreted in the proximal tubule. Natriuresis and increased urine flow confirm the integrity of tubular function.[6] In critically ill patients, this test has been used to predict progression of early acute kidney injury (AKI) and successful discontinuation of renal replacement therapy.[7] The role of recruitable renal functional reserve as a potential therapeutic target is being explored.[8]

PHYSIOLOGIC FUNCTIONS OF THE KIDNEY

Regulation of Sodium Reabsorption

Sodium is the principal determinant of extracellular volume. Almost all filtered sodium is reabsorbed along the course of the nephron. Sodium reabsorption is driven by the Na^+-K^+-ATPase on the basolateral membrane.[9] The enzyme maintains a low intracellular sodium concentration by moving sodium into the interstitium. This effect creates a gradient for the entry of sodium from the tubular lumen via transporters on the apical membrane (Fig. 94.2). The main site of sodium reabsorption is the proximal tubule, where apical sodium reabsorption occurs via solute-specific symporters (cotransport with glucose, amino acids, phosphate, citrate) and antiporters (cotransport with hydrogen ions). In the thick ascending limb, apical sodium is transported via the Na^+-K^+-$2Cl^-$ cotransporter, which is a key component of the countercurrent system. This cotransporter is the site of action for loop diuretics; mutations in this cotransporter are found in Bartter syndrome. Apical sodium reabsorption in the distal convoluted tubule occurs via the thiazide-sensitive Na^+-Cl^- cotransporter.[10,11] That cotransporter is the site of action of thiazide diuretics; mutations at that site are found in Gitelman syndrome.[12] In principal cells of the distal convoluted tubule and collecting duct, sodium is reabsorbed apically via the epithelial sodium channel (ENaC), which is the site of action of potassium-sparing diuretics.

Regulation of Water Reabsorption

Water is passively reabsorbed with sodium by specialized membrane channels called *aquaporins.* Aquaporin-1 channels are constitutively expressed on the apical and basolateral membranes of the proximal tubule and thin descending limb, making them highly permeable to water. The thick ascending limb and distal convoluted tubule have no aquaporin channels and are impermeable to water. In principal cells, apical aquaporin-2 channels (under the control of ADH) and basolateral aquaporin-3 and -4 channels absorb water.

Regulation of Free Water and Isotonic Fluid Volume

To maintain sodium and water balance, the kidney regulates two interdependent but distinct compartments: free water and isotonic fluid. Free water refers to water that is not associated with a dissolved particle. Isotonic fluid refers to fluid with a physiologic osmolarity of roughly 280–300 mOsm/L. Modelling free water and isotonic fluid as distinct components of total body fluid is useful to distinguish two physiologic states: dehydration and volume depletion. Dehydration refers to loss of free water. Volume depletion refers to loss of total body fluid, which can occur regardless of free water balance.

The free water compartment is primarily controlled by ADH release from the posterior pituitary in response to increased plasma osmolality or reduced mean arterial pressure. ADH exerts three main actions on the kidney: up-regulation of Na^+-K^+-ATPase activity in the loop of Henle, increased permeability of the inner medullary collecting duct to urea (reducing inner medullary osmolarity to as low as 600 mOsm/L), and increased insertion of aquaporin-2 channels into the apical membrane of the cells of the distal nephron. At very high levels, ADH is also a potent vasoconstrictor (i.e., vasopressin). Inappropriately high ADH secretion (i.e., syndrome of inappropriate ADH secretion) is a common cause of hypotonic hyponatremia. Reduced ADH secretion (i.e., central diabetes insipidus) or resistance to the action of ADH at the kidney (i.e., nephrogenic diabetes insipidus) leads to hypertonic hypernatremia. Because renal reabsorption of free water is almost exclusively driven by ADH, and because urine osmolarity has a reciprocal relationship with free water content, the urine osmolarity can be taken as a direct measure of renal ADH activity.

Isotonic fluid volume is regulated by the opposing actions of the RAAS and the natriuretic peptides. RAAS activation initiates with the release of renin from the juxtamedullary apparatus in response to three stimuli: decreased afferent arteriolar distention, decreased delivery of sodium to the macula densa, or increased renal sympathetic nervous system activity. Renin converts angiotensinogen (released from the liver) to angiotensin I, which is then converted to angiotensin II by the primarily endothelial-bound angiotensin-converting enzyme 1 (ACE 1). Angiotensin II induces vasoconstriction of efferent and afferent arterioles and contraction of mesangial cells, which reduces RBF. It acts directly on the early proximal tubule to increase sodium resorption via the Na^+-H^+ antiporter, which functionally represents the resorption of isotonic volume. Angiotensin II also promotes volume retention indirectly by stimulating aldosterone release by the adrenal granulosa. Aldosterone acts in the late distal convoluted tubule and collecting duct to increase sodium reabsorption by up-regulating the synthesis and membrane insertion of apical ENaC and

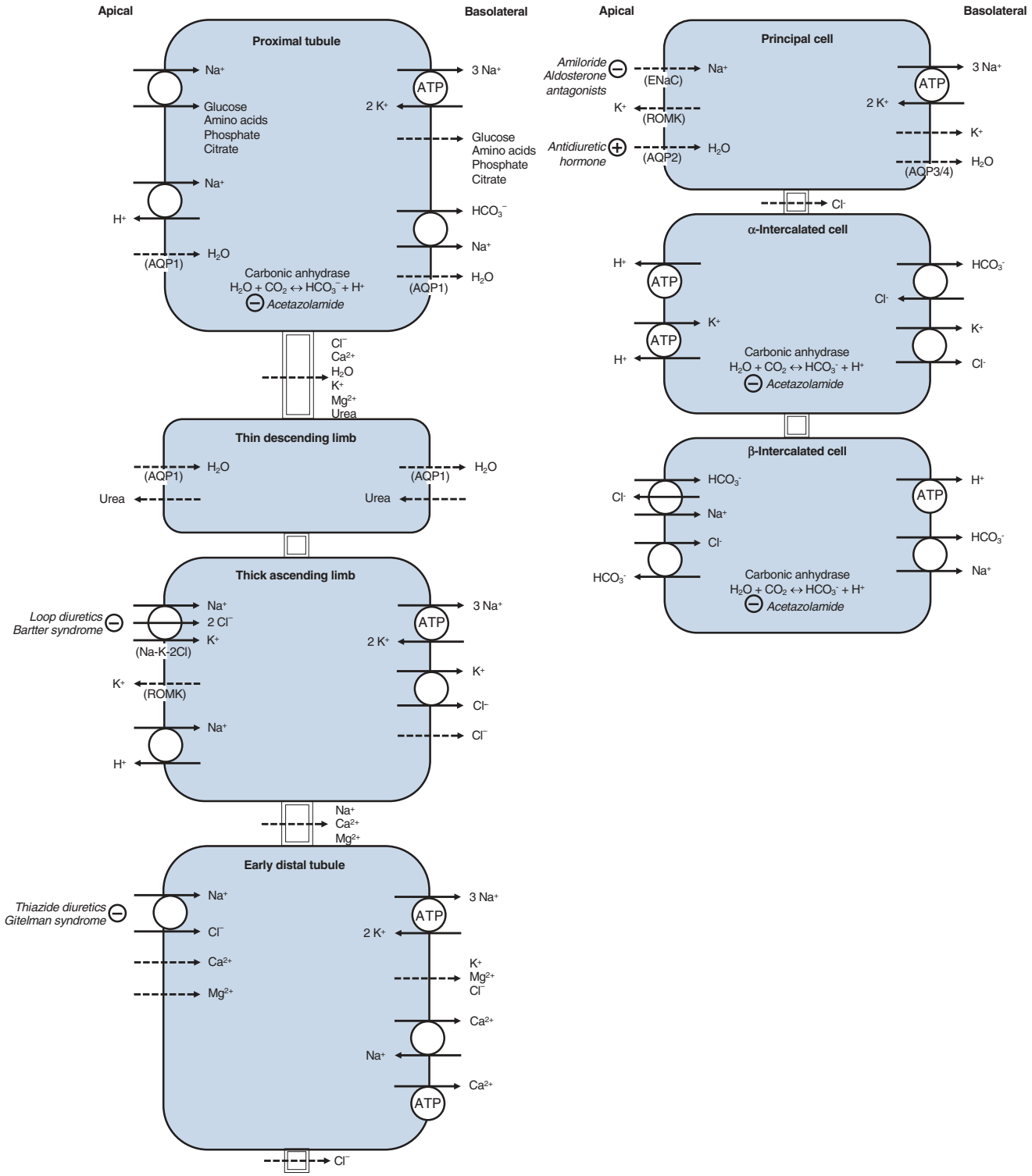

Fig. 94.2 Basolateral and apical receptors responsible for coordinating reabsorption of solutes and water along the course of the nephron.

enhancing the activity of the basolateral Na^+-K^+-ATPase. The net effect of RAAS activation in the kidney is therefore volume retention. Estimating RAAS activity is more complex than estimating ADH activity. Urinary sodium was classically felt to represent RAAS activation. However, this has many limitations in the intensive care setting and is unlikely to be reliable.

The volume-retaining properties of angiotensin II and aldosterone are opposed by the actions of the natriuretic peptides, such as atrial natriuretic peptide (ANP). These peptides have vasodilatory properties and reduce the total volume of body fluid by inducing natriuresis. Release of ANP is triggered by increased atrial stretch from volume expansion. At the glomerulus, ANP constricts the efferent arteriole,

dilates the afferent arteriole, and relaxes the mesangium, which increases RBF and GFR. In the proximal tubule, ANP reduces sodium reabsorption by inhibiting the Na^+-HCO_3^- cotransporter. In the late distal convoluted tubule, it directly inhibits the ENaC. ANP also reduces RAAS effects by inhibiting renin release. The net effect of ANP is therefore volume excretion.

To estimate the comparative excretion of free water and isotonic fluid, free water clearance can be calculated according to the equation:

$$ClH_2O = V - (U_{osm} \times V/P_{osm})$$

Where
V = urinary flow rate
U_{osm} = urinary osmolarity
P_{osm} = plasma osmolarity

When ClH_2O is positive, free water is being excreted in excess of isotonic fluid. When ClH_2O is negative, free water is being retained. This information can be used to diagnose inappropriate fluid retention or excretion, including occult diuretic resistance in patients who produce large urine volumes without significant natriuresis.

Regulation of Bicarbonate and Hydrogen Ion Movement

The kidney contributes to acid-base balance on many levels, the full biology of which is beyond the scope of this chapter. Central to this role, however, is its regulation of the movement of bicarbonate and hydrogen ions. The proximal tubule is the main site of bicarbonate reabsorption in the nephron. Intracellular water dissociates into hydrogen ions and OH^-. The electrochemical gradient generated by the Na^+-K^+-ATPase encourages secretion of hydrogen ions into the tubular lumen via the apical Na^+-H^+ exchanger. After entering the tubular lumen, hydrogen ions combine with filtered HCO_3^- to form carbonic acid (H_2CO_3). Carbonic acid dissociates into CO_2 and H_2O (under the action of luminal carbonic anhydrase), and both are passively reabsorbed into the cell. The OH^- generated by the dissociation of intracellular water combines with the reabsorbed CO_2 to form HCO_3^- (under the action of intracellular carbonic anhydrase), which is reabsorbed into the interstitium via the basolateral Na^+-HCO_3^- cotransporter. Impairments in Na^+-HCO_3^- transporter function produce type 2 renal tubular acidosis.

The alpha-intercalated cells of the distal convoluted tubule are the primary site for acid excretion. The apical H^+-ATPase drives secretion of hydrogen ions into the tubular lumen, where it combines with the remaining 10% of filtered HCO_3^-. Under the action of luminal and intracellular carbonic anhydrase, HCO_3^- is reabsorbed into the interstitium by the basolateral Cl^--HCO_3^- exchanger. Impaired function of the apical H^+-ATPase pump or basolateral Cl^--HCO_3^- transporter produce type 1 renal tubular acidosis. Luminal hydrogen ions also combine with urinary buffers (NH_3 to form NH_4^+ and HPO_4^{2-} to form $H_2PO_4^-$). Acid excretion in the distal nephron is further enhanced by the apical H^+-K^+-ATPase pump.

Regulation of Potassium

Potassium is reabsorbed passively via a paracellular mechanism in the proximal tubule and by paracellular and transcellular (Na^+-K^+-$2Cl^-$ and K^+-Cl^- cotransporter) pathways in the thick ascending limb. In the distal convoluted tubule and collecting duct, potassium can either be actively reabsorbed by intercalated cells (H^+-K^+-ATPase and K^+-Cl^- cotransporter) or secreted by principal cells. Secretion occurs under the control of aldosterone, which increases basolateral Na^+-K^+-ATPase activity and augments the number of open apical ENaC and potassium channels. Excessive renal potassium loss occurs in the setting of increased luminal flow to the distal nephron (e.g., loop or thiazide diuretics), volume depletion with activation of RAAS, Bartter or Gitelman syndromes, hyperaldosteronism, and types 1 and 2 renal tubular acidosis. Hyperkalemia caused by reduced renal excretion occurs with AKI, CKD, acidemia, potassium-sparing diuretics, RAAS inhibitors, or type 4 renal tubular acidosis.

Other Roles

The kidney is also involved in erythropoiesis and vitamin D metabolism. Erythropoietin is produced by peritubular fibroblasts in the juxtamedullary cortex in response to low oxygen tension and extracellular volume to achieve a hematocrit of ~45%.[13] Renal vitamin D metabolism involves the conversion of 25-hydroxyvitamin D (calcidiol) to 1,25-dihydroxyvitamin D (calcitriol) in the proximal tubules. Calcitriol acts on the gut, bone, and kidney to increase intestinal absorption of calcium, increase bone resorption, and reduce calcium and phosphate excretion. These functions are commonly compromised in the setting of CKD.

DIURETICS

The site of action, molecular target, and physiologic effect of commonly used diuretics in the intensive care unit (ICU) are summarized in Table 94.3.

TABLE 94.3 The Site of Action, Molecular Target, and Physiologic Effect of Commonly Used Diuretics

	Site of Action	Molecular Target	Physiologic Effect	Comments
Loop diuretics *Furosemide, bumetanide*	Thick ascending limb	Na^+-K^+-$2Cl^-$	Natriuresis 20%–25%	Highly protein-bound Enter tubule by secretion in proximal tubule Increase calcium excretion
Thiazide diuretics *Chlorothiazide, hydrochlorothiazide, chlorthalidone*	Distal tubule	Na^+-Cl^- cotransporter	Natriuresis ~5%	Partial inhibition of carbonic anhydrase and Cl^--HCO_3^- exchanger Increase calcium reabsorption
Potassium-sparing diuretics *Amiloride, spironolactone, eplerenone*	Distal tubule and collecting ducts	ENaC	Natriuresis 1%–2%	Amiloride directly blocks ENaC Spironolactone/eplerenone block the mineralocorticoid receptor, reducing synthesis of ENaC and Na^+-K^+-ATPase Hyperkalemia and mild metabolic acidosis
Carbonic anhydrase inhibitor diuretics *Acetazolamide*	Proximal tubule	Carbonic anhydrase	Minimal natriuresis	Reduced reabsorption of bicarbonate, sodium, and chloride Useful for correction of metabolic alkalosis

DISORDERS OF FUNCTION: ACUTE KIDNEY INJURY

Epidemiology

AKI is a clinical syndrome that describes the abrupt loss of GFR over 7 days or less. It affects as many as two-thirds of critically ill patients, of whom 10%–15% require renal replacement therapy. AKI is associated with early and late adverse outcomes.[14–16]

Etiology

AKI can be caused by processes that induce glomerular, tubular, or interstitial injury. In critically ill patients, common causes include shock, sepsis, trauma, cardiac or major noncardiac surgery, burns, cardiorenal or hepatorenal syndrome, or exposure to nephrotoxic agents. Injury is generally mediated by ischemia or direct toxicity.[17] Ischemic injury occurs in the context of sustained and significant alteration in RBF.[18] Reduced oxygen delivery disrupts mitochondrial function, which depletes cellular ATP. Nephron segments at greatest risk of ischemic injury include those with a high metabolic activity (e.g., proximal tubule and thick ascending limb) and those with lower physiologic oxygen tension because of their location in the medulla (e.g., thick ascending limb). Nephrotoxic injury occurs after exposure to exogenous or endogenous compounds that are directly toxic to the kidney or that alter renal hemodynamics.[19] Exogenous nephrotoxins include aminoglycosides, amphotericin, nonsteroidal antiinflammatory drugs (NSAIDs), and radiocontrast media. Endogenous nephrotoxins include hemoglobin or myoglobin.

Epithelial Cell Injury

Tubular epithelial cell injury arises because of ischemia, restoration of RBF (i.e., reperfusion), or direct cytotoxicity. It manifests as effacement and loss of the proximal tubule brush border, sloughing of tubular cells into the lumen, formation of casts from cell debris, obstruction and dilatation of the tubule, and back-leak of filtrate into the interstitium because of loss of adhesion molecules.[20,21] These changes impair solute reabsorption and increase the delivery of sodium chloride to the macula densa, leading to activation of the TGF mechanism with afferent arteriolar vasoconstriction and reduced GFR.[22] Increased sympathetic nervous activity and release of vasoconstrictors increase renal vascular resistance and further impair GFR.[23,24] Therapies aimed at reversing vasoconstriction (e.g., administration of low-dose dopamine or ANP) have failed to consistently influence AKI outcome.[25,26]

Endothelial Cell Injury

Injury to vascular endothelial cells impairs GFR via multiple mechanisms. Decreased production of nitric oxide synthase and prostaglandin impairs autoregulation; endothelial cell swelling and outer medullary congestion lead to hypoxia; dysregulation of the coagulation cascade damages the endothelial barrier function; and up-regulation of leukocyte adhesion molecules promotes neutrophil recruitment, release of proinflammatory mediators, and oxidative stress.[27,28] Cumulatively, these changes disrupt microcirculatory flow and further compromise oxygen delivery.

Oxidative Stress and Mitochondrial Injury

Oxidative stress and mitochondrial injury have emerged as important contributors to injury in AKI.[29,30] In highly oxidative states, such as in ischemia-reperfusion injury or after exposure to pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), the formation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) exceeds the capacity of counteractive antioxidant systems, which creates an environment of oxidative stress. High levels of oxidative stress damage the outer mitochondrial membrane, resulting in membrane permeabilization and the efflux of mitochondrial contents (including calcium, proapoptotic proteins, ROS, and RNS) into the cytoplasm. Release of ROS and RNS causes direct damage to lipids, proteins, and DNA. Influx of water and solutes from the cytoplasm into the mitochondrial matrix also occurs after membrane permeabilization. This promotes osmotic swelling and can lead to mitochondrial fragmentation and rupture.

The mitochondrial response to oxidative stress is to coordinate metabolic reprogramming: oxygen consumption is decreased, energy allocation is reprioritized, and mitophagy and cell-cycle arrest are initiated.[31] Clearance of damaged mitochondria by mitophagy is an adaptive change that may enhance cell survival.[32] Entering cell-cycle arrest is similarly protective because it prevents division of potentially damaged cells. Biomarkers of cell-cycle arrest (including TIMP-2 and IGFBP-7) have been proposed as early indicators of "renal stress" that could be used to detect the impending onset of AKI before creatinine elevation.[33] If oxidative stress is sustained and/or severe, programmed cell death may be initiated (i.e., apoptosis).[31]

Recovery After AKI

Renal injury activates a series of intrinsic repair processes, which may be adaptive or maladaptive. Adaptive repair involves cellular dedifferentiation, proliferation, migration, and differentiation to re-establish the structural integrity of the nephron and restore its function.[34] The capacity for adaptive repair is dependent on the availability of progenitor cells and surviving tubular epithelial cells, which are determined by the duration and severity of insult, and by baseline renal status.[35] Maladaptive repair describes a state of persistent inflammation with release of profibrotic cytokines, proliferation of myofibroblasts, deposition of extracellular matrix, and the development of interstitial fibrosis and tubular atrophy.[36] Vascular rarefaction and chronic ischemia culminate in glomerulosclerosis, loss of renal functional reserve, glomerular hypertension, and the development of acute kidney disease (AKD) and CKD.[37] AKD is the term used to describe the course of disease after AKI in patients in whom pathophysiologic processes in the kidney are ongoing or recurrent. It has been defined by the Acute Dialysis Quality Initiative (ADQI) group as a condition in which AKI is present for between 7 and 90 days after an inciting event. Studies suggest that the outcomes after AKD are at least as poor as after AKI.[38]

SPECIFIC ACUTE KIDNEY INJURY SYNDROMES

The purpose of this section is to provide an overview of key pathophysiologic processes for the most commonly encountered AKI syndromes in the ICU. A detailed description of the pathophysiologic processes underlying these syndromes, and within the context of the disorder as a whole, is outside the scope of this chapter.

AKI in Cardiac Surgery

The pathophysiology of AKI in cardiac surgery is multifactorial. Cardiopulmonary bypass induces injury through aortic cross-clamping (ischemia and reperfusion), loss of pulsatile flow, systemic inflammation, and hemolysis. Arterial cannulation can destabilize atherosclerotic plaques leading to embolism. Hemodynamic changes relating to cardiac dysfunction, severe bleeding, and administration of potent vasopressors worsen ischemia and oxidative stress. Perioperative administration of radiocontrast dyes, aminoglycoside antibiotics, loop diuretics, NSAIDs, and RAAS inhibitors may cause direct nephrotoxicity or impair autoregulation of renal blood flow.

AKI in Sepsis

Sepsis-induced AKI (SIAKI) is a specific pathophysiologic entity arising from the direct effect of sepsis on the kidney. Sepsis can also, however, cause AKI indirectly, through hypotension or therapies administered during resuscitation (e.g., antimicrobials, normal saline, or high-dose

vasopressors). The traditional paradigm of sepsis-induced renal ischemia caused by hypotension and vasoconstriction has been challenged by several pieces of emerging evidence. First, septic patients without hemodynamic instability still develop AKI. Second, plasma from septic patients induces cellular changes indicative of AKI in vitro. Third, RBF has been observed to increase (rather than decrease) in both animal and human studies.[39,40]

Recent evidence suggests that SIAKI reflects a complex interaction of renal macrocirculatory and microcirculatory dysfunction, increased inflammation and oxidative stress, activation of the coagulation cascade, and disordered cellular energetics. Despite an increase in cardiac output and RBF, vasodilatation of the efferent arteriole (possibly driven by inadequate angiotensin signaling) creates a condition of low postglomerular pressure, which reduces GFR.[41,42] Blood flow to the kidney is also believed to be more heterogeneous in sepsis, with variable expression of inducible nitric oxide synthase promoting intrarenal shunting of blood from the ischemia-prone medulla to the cortex.

Release of PAMPs and DAMPs by pathogens and injured cells, and their recognition by Toll-like receptors, triggers proinflammatory mediator release, leukocyte adhesion, platelet activation, and initiation of the clotting cascade. Enhanced ROS generation coupled with antioxidant depletion contributes to oxidative stress and uncoupling of mitochondrial respiration in the proximal tubule and its surrounding microvasculature. Although apoptosis can occur, it is not a prominent histologic feature of SIAKI.[43]

AKI in Rhabdomyolysis

AKI is a common complication of rhabdomyolysis. After muscle injury, myoglobin is released from skeletal muscle, freely filtered by the glomerulus, and metabolized by epithelial cells. When the capacity for metabolism is exceeded, myoglobin appears in the urine, becomes concentrated along the nephron, and precipitates with the Tamm Horsfall protein in the distal convoluted tubule. Experimental models suggest that renal injury is mediated by hypovolemia from sequestration of fluid in injured muscles, intrarenal vasoconstriction from activation of the RAAS, direct injury to proximal tubule cells from free chelatable iron, and obstruction of the distal convoluted tubules by casts.[44] An acidic urine promotes proximal tubule injury and cast formation.[45] Although weakly correlated to creatinine kinase level, the risk of AKI appears to be low when peak levels are below 15,000–20,000 U/L.[46]

AKI Resulting From Drug Toxicity

Many drugs commonly used in critically ill patients can cause AKI. Aminoglycosides are filtered by the glomerulus and enter proximal tubule cells by endocytosis. Cytoplasmic aminoglycoside acts directly and indirectly on mitochondria to disrupt ATP production and initiate apoptosis.[47] NSAIDs can contribute to renal injury by causing interstitial nephritis or by reducing production of prostaglandins, which reduces renal perfusion and is especially relevant in states of reduced RBF.[48] Amphotericin B is believed to cause both toxic and ischemic injury.[49] It creates pores in the cell membrane of proximal tubular cells, which allows back-diffusion of hydrogen ions (which impairs urinary acidification) and triggers apoptosis (which decreases renal concentrating ability and increases potassium wasting). Afferent arteriolar vasoconstriction mediated by TGF reduces RBF and GFR and causes medullary hypoxia. Vasoconstriction may be attenuated by salt loading, which reduces the sensitivity of the TGF system. Administration of contrast media can cause AKI by increasing the concentrations of adenosine, endothelin, and intracellular calcium, which cause afferent arteriolar vasoconstriction.[50] In the past, use of high-osmolality compounds also induced diuresis and natriuresis by activating the TGF mechanism. In hospitalized patients, AKI occurring shortly after administration of iodinated contrast may or may not be causally related.

AKI in Cardiorenal Syndrome

Cardiorenal syndrome describes the bidirectional interaction between the function of the heart and kidney. Of its five subtypes, type 1 cardiorenal syndrome describes the processes through which acute heart failure can precipitate AKI. Right heart dysfunction leads to increased renal venous pressure, whereas left ventricular dysfunction is associated with a low cardiac output state. These hemodynamic derangements trigger a variety of compensatory mechanisms, including activation of the RAAS and sympathetic nervous system and increased release of ADH (i.e., vasopressin) and endothelin. The result is vasoconstriction, sodium and water retention (with urinary sodium generally <25 mEq/L), decreased renal perfusion, and ischemia. In some patients, diuretic therapy may decrease GFR because of a decline in ventricular preload, whereas in other patients, diuretic therapy may increase GFR by reducing renal venous pressure.

AKI in Hepatorenal Syndrome

Hepatorenal syndrome represents an end-stage complication of cirrhosis with severe portal hypertension. Portal hypertension creates significant hemodynamic derangement, characterized by marked splanchnic arterial vasodilation, a progressive rise in cardiac output, and a fall in systemic vascular resistance. These changes trigger intense activation of the RAAS and sympathetic nervous system, leading to intrarenal vasoconstriction, a decline in GFR, increased sodium resorption, and the development of ascites. Although cardiac output initially increases, eventually the cardiac output is insufficient to compensate for the degree of vasodilation. Hepatorenal syndrome is frequently accompanied by electrolyte and acid-base disturbances, including hypervolemic hyponatremia, hypokalemia, and an anion gap metabolic acidosis.

KEY POINTS

- The functional unit of the kidney, the nephron, is composed of a filtering unit (glomerulus), several specialized segments for the reabsorption of solutes and water (proximal tubule, loop of Henle, and distal convoluted tubule), and a collecting duct.
- Blood flow to the kidney is tightly controlled by sophisticated autoregulatory mechanisms, which preserve the GFR and renal oxygen delivery across a range of systemic arterial pressures.
- Sodium is the principal determinant of extracellular volume, and its reabsorption is regulated by the opposing actions of the RAAS and natriuretic peptides.
- Because energy is required for the active reabsorption of solutes, renal function is dependent on metabolism and the kidney is prone to hypoxic, ischemic, and oxidative injury.
- AKI describes the abrupt reduction in GFR that occurs because of one or more insults that damage tubular epithelial and vascular endothelial cells and disrupt mitochondrial function.

References for this chapter can be found at expertconsult.com.

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Chawla LS, Davison DL, Brasha-Mitchell E, et al. Development and standardization of a furosemide stress test to predict the severity of acute kidney injury. *Crit Care.* 2013;17:207.

This cohort study of critically ill patients investigated the impact of administering a dose of furosemide to individuals with early AKI to assess their progression to stage 3 AKI. They found that the furosemide stress test performed well as an assessment of tubular function and had reasonable predictive capacity to identify patients with severe and progressive AKI.

Gottschalk CW, Mylle M. Micropuncture study of the mammalian urinary concentrating mechanism: Evidence for the countercurrent hypothesis. *Am J Physiol.* 1997;196:927–936.

This basic science study described the differences in fluid osmolality between each nephron segment and vasa rectas of various rodents, confirming the hypothesis that the mammalian nephron functions as a countercurrent multiplier system.

Langenberg C, Bellomo R, May C, et al. Renal blood flow in sepsis. *Crit Care.* 2005;9(4):363–374.

This systematic review of studies describing changes in renal blood flow in human and experimental sepsis identified that cardiac output was a key determinant of renal blood flow during sepsis. In the setting of decreased cardiac output, renal blood flow was typically decreased, whereas in the setting of increased cardiac output, renal blood flow was maintained or increased. This provides important insight into the nature of renal blood flow in sepsis.

Sun D, Samuelson LC, Yang T, et al. Mediation of tubuloglomerular feedback by adenosine: Evidence from mice lacking adenosine 1 receptors. *Proc Natl Acad Sci U S A*. 2001;98:9983–9988.

Using mice lacking adenosine 1 receptors, this study demonstrated the central role of adenosine in juxtaglomerular signalling through the tubuloglomerular feedback mechanism in response to an increase in loop of Henle flow rate.

Tumlin JA, Murugan R, Deane AM, et al. Outcomes in patients with vasodilatory shock and renal replacement therapy treated with intravenous angiotensin II. *Crit Care Med*. 2018;46:949–957.

A post hoc analysis of the ATHOS-III randomized trial of angiotensin II in catecholamine-resistant vasodilatory shock provided important insight into the role of angiotensin signaling in SIAKI. The authors observed that patients with an elevated serum angiotensin I/angiotensin II ratio were more likely to have AKI, that patients receiving continuous renal replacement therapy (CRRT) at enrollment who received angiotensin II had a greater than 20% absolute survival advantage, and that markedly elevated serum renin levels appeared to identify a subset of treatment responsive vs. nonresponsive patients.

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Clinical Assessment of Renal Function

Jason Kidd, Kate S. Gustafson, and Todd W.B. Gehr

Five to fifteen percent of patients in intensive care units (ICUs) experience acute deterioration in renal function.[1,2] Renal dysfunction substantially adds to the morbidity and mortality of critically ill patients. Moreover, changes in renal function directly affect drug clearance. Thus a means to assess renal function is essential for the optimal management of patients with critical illness. This chapter reviews selected aspects of renal physiology with an emphasis on measurement of renal function, consequences of altered function, and approaches to improving renal function. The focus is on measurement and optimization of glomerular filtration rate (GFR) and renal blood flow (RBF).

RENAL BLOOD FLOW

Under physiologic conditions, blood flow to the kidneys is approximately 20% of the cardiac output. This high rate of blood flow (1–1.2 L/min) is particularly remarkable because the kidneys make up just 0.5% of the total body weight. The high blood flow rate is caused by, at least in part, the unique anatomic arrangement of the renal vasculature, with the interlobar and arcuate vessels offering little resistance to flow. The interlobular arteries originate from the arcuate vessels in a parallel arrangement, and the afferent arterioles also arise in a parallel arrangement from the interlobular vessels. It is this parallel arrangement that accounts for the low resistance in the RBF because the total resistance of n equals parallel paths, each with a resistance R, which is R/n^3. The major resistance vessels in the kidney are the afferent and efferent arterioles that bind the glomerular capillary network. Although total resistance is a function of resistance across each of these vessels, it is a unique feature of the kidney that variations in individual resistances across the afferent and efferent arterioles may lead to alterations in glomerular capillary pressure and, hence, the GFR.[3]

Despite a wide range of perfusion pressures, under most conditions, the RBF and GFR are relatively constant, a process described as autoregulation. The term *autoregulation* generally refers to the relative constancy of the GFR over a range of perfusion pressures and to the regulation of RBF. Emphasis has been placed on the preglomerular vasculature, mainly the afferent arterioles, as the major site at which renal perfusion is regulated. However, studies also suggest that the larger vessels, such as the interlobular vessels, respond to a variety of vasoactive stimuli and participate in an autoregulatory phenomenon. A variety of hypotheses have been generated to explain the autoregulatory response of the kidney with respect to the RBF. There is evidence to suggest that neural, humoral, or intrarenal factors are involved in the regulation of renal circulation.[4]

The renin–angiotensin pathway has a significant effect on renal hemodynamics. Renin, which is elaborated in the juxtaglomerular cells, is released in response to a decrease in renal perfusion pressure and to altered sodium chloride delivery to the ascending limb and macula densa cells. Increased renin secretion leads to augmented angiotensin II (AII) formation at the local nephron level. AII affects renal vascular resistance through modulation of both afferent and efferent arterioles, with the major effect being on the efferent arterioles.

Renal eicosanoids affect renal hemodynamics. Eicosanoids are biologically active fatty acid products of arachidonic acid and are synthesized in the kidney in response to a variety of stimuli, with local release and effect on the renal vasculature. Stimulation of the cyclooxygenase pathway and prostaglandin synthetases leads to the formation of endoperoxides (PGG_2 or PGH_2), prostaglandins (PGD_2, PGE_2, $PGF_{2\alpha}$, or PGI_2), and thromboxane A_2 (TXA_2). Leukotrienes are synthesized through a pathway involving the enzyme lipoxygenase. In the kidney, the major products of arachidonic acid metabolism are PGE_2 and PGI_2 and, to a lesser extent, $PGI_{2\alpha}$. These compounds have a predominant effect of relaxing renal vascular smooth muscle and lead to vasodilatation, whereas TXA_2 is a vasoconstrictor prostanoid. It is believed that in disease states, endogenous vasodilator prostaglandins have a protective function to maintain renal perfusion and the GFR in response to vasoconstrictor stimuli, including AII and enhanced sympathetic nervous system activity. In contrast, release of vasodilatory prostaglandins is inhibited by nonsteroidal anti-inflammatory drugs.

Other vasoactive compounds that affect renal circulation include plasma and glandular kallikreins and kinins and endothelium-derived vasoactive factors, such as nitric oxide and endothelin.[4] Among the catecholamines, α- and β-adrenergic agonists are known to affect renal vascular tone by causing vasoconstriction and vasodilatation, respectively. In addition, dopamine in low doses leads to renal vasodilatation. Atrial natriuretic peptide and purinergic agents, such as adenosine, have also been shown to participate in modulating renal circulation.

The effect of vasoactive mediators on renal circulation is likely to be influenced by changes in salt intake and extracellular fluid (ECF) volume and by hydration status. For example, the influence of AII on renal hemodynamics is greater in sodium depletion, which activates the sympathetic nervous system. In response to mild nonhypotensive hemorrhage, renal hemodynamics are relatively well maintained. However, with further reductions in volume associated with more severe hemorrhage, renal ischemia mediated by activation of the renin–angiotensin system, renal efferent adrenergic nerves, and circulating catecholamines may occur.[4]

Modification of dietary protein and amino acid intake may affect renal hemodynamics. Dietary protein intake in excess of 1 g/kg/day has been associated with renal vasodilatation, as have infusions of casein hydrolysates and amino acids.[5,6] Conversely, chronic consumption of a low-protein diet may be associated with renal vasoconstriction.

Measurement of Renal Blood Flow

The RBF is measured conventionally by the clearance of infused para-aminohippurate (PAH), which is cleared almost totally from the

arterial plasma by both filtration and secretion. Thus its clearance approximates the rate of renal plasma flow (RPF):

$$RPF = U_{PAH} \bullet V/P_{PAH}$$

where U_{PAH} and P_{PAH} refer to urine and plasma PAH concentration, respectively, and V is the urine flow rate in milliliters per minute.

The RBF can be estimated by correction for hematocrit (Hct):

$$RBF = RPF/[1-Hct]$$

Although available, this test is rarely used in clinical practice. In fact, direct quantitation of the RPF and RBF is rarely indicated outside research studies; however, sometimes it is necessary to document that the kidneys are being perfused. In this case, one of three additional methods may be used: (1) selective arteriography, including computed tomography (CT) angiography and magnetic resonance (MR) angiography, (2) Doppler ultrasonography, and (3) external radionuclide scanning. Because the latter two methods are noninvasive, they are preferred. With respect to the nuclide study, until recently, scanning was usually performed using ^{125}I-iodohippurate sodium; however, the poor radiologic characteristics of ^{131}I limit its use in renal imaging.[7] More recent evidence suggests that other agents, such as ^{127}I-orthoiodohippurate and ^{99m}Tc-L,L-ethylenedicysteine, are superior to ^{125}I-iodohippurate sodium.[7,8]

Clinical Correlates

Although a significant amount of data has been obtained to indicate a complex relationship between neurocirculatory factors and renal hemodynamics, several points can be made from a clinical perspective. Optimization of cardiac output and ECF volume, including the intravascular space, is essential for the maintenance of renal perfusion. In particular, because the effects of vasoactive compounds such as AII and catecholamines are accentuated in the presence of renal hypoperfusion and volume contraction, attention should be given to the assessment of ECF volume, with correction of any deficits, and to optimize cardiac function. Frequently, pharmacologic agents have been employed to maintain renal perfusion in situations in which this may be compromised. Specifically, there has been widespread use of the so-called *low-dose* or *renal-dose dopamine infusions.* This is based on the observation that in low doses (<3 μg/kg/min), dopamine leads to renal vasodilatation.[9] At higher doses, renal vasoconstriction may occur.

The beneficial effects of dopamine infusion have not been documented in patients who exhibit evidence of intravascular volume depletion, and the use of dopamine has been shown to be ineffective beyond a short period of infusion.[9–11] Thus although infusions of renal-dose dopamine for 24–36 hours may be beneficial under the appropriate circumstance, there is no evidence supporting the long-term use of this agent. Furthermore, reports suggest that adverse outcomes are associated with the use of dopamine.[11] In patients with acute decompensated heart failure and renal dysfunction, the addition of low-dose dopamine did not enhance decongestion or improve renal function when added to diuretic therapy.[12] Continuous infusions of fenoldopam mesylate, a potent dopamine A_1 receptor agonist, have been employed in an attempt to preserve renal function in a variety of clinical settings. A meta-analysis of 16 randomized trials in critically ill patients showed that fenoldopam significantly reduced the risk of acute kidney injury, need for renal replacement therapy, and in-hospital death.[13]

Beyond anecdotal evidence, there are no compelling data to support the use of other potential vasodilator substances such as prostaglandins. Although high-protein feeding and amino acid infusions may increase the RBF by undefined mechanisms, there is no justification in using these therapies solely from a hemodynamic point of view.[5,6]

GLOMERULAR FILTRATION RATE

Of the 500–700 mL of plasma delivered per minute to the kidneys (corresponding to an RBF of 1–1.2 L/min), 20%–25% is filtered. Glomerular filtration is a major function of the kidney and averages approximately 130 mL/min/1.73 m^2 in normal males and 120 mL/min/1.73 m^2 in normal females. Estimation or direct assessment of the GFR remains one of the most important measurements of renal function and is widely used in clinical practice.

Measurement of Glomerular Filtration Rate

The GFR is classically measured as the clearance of inulin (C_{In}), a fructose polymer with a mean molecular weight of approximately 5 κDa. Because this substance is not present endogenously, it must be given by constant infusion after a loading dose. Inulin is available commercially but is expensive, often difficult to obtain, and cumbersome to use. As a result, the C_{In} is rarely used in clinical practice except for research protocols. Although the C_{In} is generally measured chemically, ^{3}H- and ^{14}C-labeled inulins are also available but are expensive.

Other radiolabeled nuclides have been found to be satisfactory substitutes for inulin and have advantages in the measurement of GFR.[7,8,14,15] In particular, ^{99m}Tc-labeled diethylenetriamine pentaacetic acid (DTPA) and ^{125}I- or ^{131}I-labeled iothalamate clearances closely approximate C_{In}.[16,17] ^{99m}Tc-DTPA has been used and found to give values that correlate closely with the C_{In} in ICU patients.[18,19] In addition, the clearance of gentamicin has been used in a limited fashion to measure GFR.[20,21] At the present time, it is not common for the GFR to be measured directly. Rather, the GFR is estimated by endogenous creatinine clearance (C_{Cr}) or serum creatinine determination (see later discussion).

The normal values for the GFR obtained previously apply for individuals from teenage years through approximately 35 years. Thereafter, the GFR declines in most individuals. Although this decline was formerly thought to occur at a relatively constant rate of approximately 10 mL/min per decade,[22–24] more recent data obtained in a longitudinal manner indicate that this reduction is not so predictable.[25] In addition, a circadian rhythm for GFR has been described.[26,27] GFR is maximal in the day, whereas a minimal value during the night has been found in normal individuals. It is not known whether this circadian pattern of GFR occurs in critically ill hospitalized patients.

CREATININE CLEARANCE AND SERUM CREATININE

Creatinine Clearance

The C_{Cr} enjoys widespread use as a reasonable gauge of GFR when great precision is not demanded, which it rarely is in clinical practice. The use of creatinine as a marker of the GFR has the advantage that creatinine is endogenously produced and easily measured by inexpensive methods. Creatinine, like inulin, is freely filtered and absorbed minimally, if at all, by the tubules. However, creatinine is secreted, and the contribution of secretion to total excretion is greater as the GFR decreases and serum creatinine rises. At GFRs below 40 mL/min, the C_{Cr} exceeds the C_{In} by 50%–100%.[16,28] When GFR is significantly depressed and it is deemed important to get a more precise measurement of GFR, one of the previously mentioned methods to estimate the GFR directly might be used. Additionally, because the C_{Cr} overestimates the GFR and the clearance of urea underestimates the GFR, the mean value of simultaneously obtained creatinine and urea clearances has been shown to provide a close estimation of the C_{In} when the latter is below 20 mL/min.[29]

Because cimetidine competes with creatinine for tubular secretion (see later), administration of cimetidine may increase the accuracy of both creatinine clearance in 24-hour collections (when given for several days beforehand) and 4-hour, water-loaded clearances.[30–32] Taking advantage

of this effect results in a more accurate estimate of the GFR. Specifically, the C_{Cr} obtained in the presence of cimetidine (400 mg as a priming dose followed by 200 mg every 3 hours) yielded values that closely approximate C_{In}.[30,31] Volume expansion in humans causes a small rise in the GFR, whereas volume depletion, severe heart failure, hypotension, anesthesia, surgery, trauma, sepsis, and even mild intestinal bleeding without frank hypotension may depress the GFR substantially.

Various methods are available to measure creatinine. Creatinine is frequently measured using the Jaffé alkaline picric acid reaction. Although this method is widely used, this reaction also measures other chromogens, which may lead to a false elevation in the estimated serum creatinine (S_{Cr}) measurement. Substances such as acetoacetate (in ketoacidosis), pyruvate, ascorbate, 5-flucytosine, certain (but not all) cephalosporin antibiotics, and very high urate artifactually raise S_{Cr} in normal subjects by 0.5–2 mg/dL.[33–39] These substances are excreted into the urine but contribute trivially compared with overall urine creatinine (U_{Cr}). Thus noncreatinine chromogens affect the S_{Cr} but have little effect on the U_{Cr}.

In individuals with normal renal function, the contribution of serum noncreatinine chromogens in raising the S_{Cr} is approximately equal to the contribution of secretion to creatinine excretion, such that the C_{Cr} closely approximates the GFR. As the GFR decreases, the contribution of noncreatinine chromogens to the total measured S_{Cr} becomes less than the secreted moiety, and the C_{Cr} overestimates GFR to a greater extent. Direct enzymatic creatinine measurements are not affected by noncreatinine chromogens. Very high levels of serum glucose (>1000 mg/dL) and 5-flucytosine may interfere with the enzymatic reaction, whereas high levels of bilirubin (>5 mg/dL) affect the autoanalyzer method[37] and lead to falsely low S_{Cr} values. The use of catecholamines—particularly dopamine and dobutamine—can underestimate serum creatinine concentrations by some enzymatic methods.[38] It is therefore important to know the method by which a given laboratory measures S_{Cr}. Competing for the same proximal tubular organic base secretory site as creatinine, certain pharmacologic agents may suppress this process and lead to a rise in the S_{Cr}. Trimethoprim, probenecid, dronedarone, pyrimethamine, salicylate, antiretroviral agents, cobicistat, many chemotherapeutic agents (olaparib, rucaparib, imatinib, bosutinib, sorafenib, sunitinib, crizotinib, gefitinib, pazopanib), and cimetidine, but not ranitidine, are organic bases that inhibit creatinine secretion competitively and can result in a mild elevation in the S_{Cr}, usually 0.5 mg/dL or less.[39–43]

As with all clearance methods, the C_{Cr} is subject to errors that may amount to as much as 10%–15%. In addition to potential problems in estimating the S_{Cr} and U_{Cr}, errors in timing of urine collection, incomplete collection, and inaccurate measurement of urine volume are other factors that contribute to errors.[44] Although 24-hour U_{Cr} clearances have been widely used, no specified period is required for the clearance to be obtained. In fact, shorter collection periods of several hours may be more accurate in patients passing adequate amounts of urine (not oliguric), particularly if the patient is not in a steady state (see later). To reduce errors in volume measurement, one can induce water diuresis in stable subjects before beginning the test,[45] although this is rarely practical in the ICU setting. Nevertheless, because many ICU patients have indwelling Foley catheters, it should be possible for accurately timed urine collections to be obtained and for the C_{Cr} to be measured with reasonable accuracy.

Serum Creatinine

Because of the practical and technical problems in obtaining estimates of the GFR by clearance methods, renal function is most commonly estimated by following the S_{Cr} in hospitalized patients. Creatinine is formed nonenzymatically from creatine and phosphocreatine in skeletal muscle cells and is normally present in the serum at a concentration of 0.8–1.4 mg/dL in adults and 0.3–0.6 mg/dL in children and pregnant subjects. This process is irreversible, is temperature and pH dependent, and occurs at a constant rate. The measured S_{Cr} depends on the method of measurement, as discussed previously, the GFR, rate of creatinine production, volume of distribution (e.g., S_{Cr} is lower in anasarca), and extent of its tubular secretion and intestinal degradation.[3] Because creatinine production is closely related to muscle mass, the S_{Cr} is generally less in females than in males and decreases as muscle mass is lost with aging or debilitating illnesses.

The relationship between the S_{Cr} and C_{Cr} (and hence GFR) can be described by a rectangular hyperbola[44]; however, this relationship applies in the steady state and assumes a constant rate of creatinine production (Fig. 95.1). Thus a doubling of the S_{Cr} reflects a 50% decrease in C_{Cr}, a fourfold increase in the S_{Cr}, a 75% drop in the GFR, and so on. Because creatinine production may not remain constant, the S_{Cr} may underestimate the decrease in GFR in critically ill patients who have a decrease in muscle mass secondary to an ongoing catabolic state. Moreover, it should be appreciated that the S_{Cr} is an insensitive marker of change early in the course of renal disease. Thus a 33% fall in the GFR may raise the S_{Cr} from 0.8 to 1.2 mg/dL, a value still within the normal range. If the prior value is not known, this fall in the GFR may go unrecognized.

The S_{Cr} provides a close estimate of the GFR only in the steady state. With an abrupt decrease in the GFR, as may occur in acute renal failure, creatinine production would be expected to continue unchanged, but because of the decrease in the GFR, creatinine excretion will be impaired. As a result, the S_{Cr} increases until a new steady state is obtained, at which time the amount of creatinine produced equals the amount filtered (GFR − S_{Cr}) and excreted (U_{Cr} − V). Depending on the extent of damage and decrease in the GFR, it may take several days for a new steady state to be achieved. Therefore after an insult leading to an abrupt decrease in the GFR, the S_{Cr} rises progressively over the next several days. This should not be interpreted as a new insult each day, but rather that a steady state has not yet been obtained. While the S_{Cr} is changing, its absolute value cannot be used as an accurate measure of the decrease in the GFR. If an accurate measurement of the GFR is needed during this time, a short C_{Cr} can be obtained.

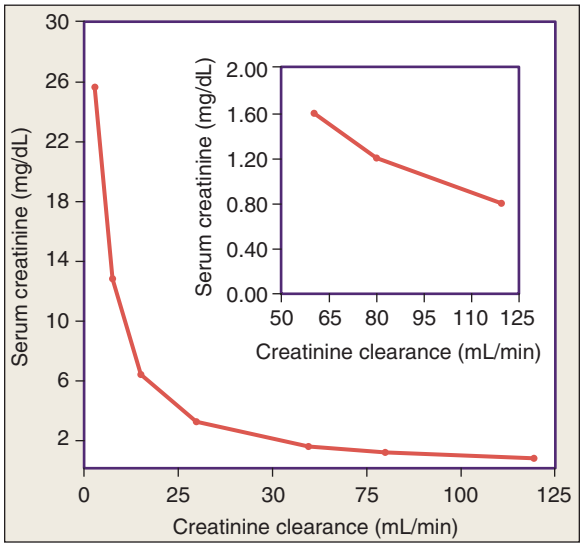

Fig. 95.1 Relationship Between Creatinine Clearance and Serum Creatinine. In steady state, serum creatinine should increase twofold for each 50% reduction in creatinine clearance. *Inset* represents enlarged view of changes in serum creatinine as creatinine clearance decreases from 120 to 60 mL/min. If serum creatinine is 0.8 mg/dL when creatinine clearance is 120 mL/min, creatinine clearance can decrease by 33% such that increased serum creatinine is still within normal range.

Many equations have been developed to estimate the C_{Cr} based on the S_{Cr} without collection of urine.[46,47] Box 95.1 is a compilation of the more commonly used equations.[48] These equations generally take into consideration muscle mass (estimated as body weight), sex (males having a higher GFR than females), and age. Aging, hepatic diseases, excessive muscle wasting, severe muscular atrophy or dystrophy, hyperthyroidism, paralysis, and chronic glucocorticoid therapy are associated with reduced creatinine generation.[18] In addition, particularly at low levels of GFR, correction for nonrenal creatinine metabolism is recommended.[49,50] One of the most commonly used equations is that developed by Cockcroft and Gault[51]:

$$C_{Cr} = \frac{(140 - \text{age}) \bullet \text{lean wt in kg}}{72 \bullet S_{Cr}}$$

where age is expressed in years. The preceding expression is used for men. The formula for women is the preceding formula multiplied by 0.85.

The reliability of the Cockcroft-Gault equation as a measure of the GFR has been assessed in patients with diabetes, pregnant women with renal disease,[52] obese individuals,[53] elderly individuals,[54,55] and African Americans with hypertensive renal disease.[56] It has also been assessed in critically ill patients.[57] These studies have indicated that the accuracy of GFR estimates using the Cockcroft-Gault equation is similar to or greater than 24-hour C_{Cr} and that the precision is better. This equation seems to be most accurate for estimating the GFR when the latter is in the range of 10–100 mL/min.[53,56,57] The advantage of this formula is that it is simple and underscores the essential determinants of C_{Cr}.

The Modification of Diet in Renal Disease (MDRD) study equation previously gained widespread acceptance by most clinical laboratories, which now routinely report estimated GFRs across populations when serum creatinine testing is ordered.[58–60] Major limitations included imprecision and underestimation of the measured GFR at high GFRs (GFR >60 mL/min/1.73 m^2). The MDRD equation is generally more precise than the Cockcroft-Gault equation.[61]

Limitations at higher GFRs prompted a further modification by the Chronic Kidney Disease Epidemiology Collaboration Research Group.[62] This equation offers improved precision, especially with higher GFRs up to 90 mL/min/1.73 m^2.

Serum Cystatin C

Because of the limitations in using creatinine as a marker for the GFR, there has been an ongoing search for alternative GFR markers. To this end, cystatin C has emerged as a possible candidate biomarker. Cystatin C is a low-molecular-weight protein of 13.3 kDa and is expressed by all nucleated cells. It is cleared by glomerular filtration and metabolized in the kidney. And it is not secreted by the tubules like creatinine. Serum cystatin C levels are minimally affected by demographics such as race and muscle mass. Although initially thought to be an ideal GFR marker, a number of factors may influence cystatin C levels other than GFR. These include hyperthyroidism, malignancy, corticosteroid use, diabetes mellitus, leukocyte count, albumin concentration, and C-reactive protein levels. Despite such limitations, cystatin C use is increasing and analytical methods are standardized. Cystatin C, like creatinine, has been employed in equations that more accurately estimate the GFR. By using both creatinine and cystatin C, even more accuracy in determining the GFR can be obtained, especially in populations with higher baseline levels for GFR. Cystatin C will likely continue to emerge as an important biomarker for the estimation of GFR and the CKD-EPI cystatin C calculation became more commonly used.[63]

BOX 95.1 Common Equations for Estimating Glomerular Filtration Rate or Creatinine Clearance

Cockcroft-Gault (C_{Cr} • BSA/1.73 m^2)

For men: $C_{Cr} = [(140 - \text{age}) \bullet \text{weight(kg)}]/S_{Cr} \bullet 72$

For women: $C_{Cr} = ([(140 - \text{age}) \bullet \text{weight (kg)}]/S_{Cr} \bullet 72) \bullet 0.85$

Jellife (1) (C_{Cr} • BSA/1.73 m^2)

For men: $(98 - [0.8 \bullet (\text{age} - 20)])/S_{Cr}$

For women: $(98 - [0.8 \bullet (\text{age} - 20)])/S_{Cr} \bullet 0.90$

Jellife (2)

For men: $(100/S_{Cr}) - 12$

For women: $(80/S_{Cr}) - 7$

Mawer

For men: $\text{weight} \bullet [29.3 - (0.203 \bullet \text{age})] \bullet [1 - (0.03 \bullet S_{Cr})]$

For women: $\text{weight} \bullet [25.3 - (0.175 \bullet \text{age})] \bullet [1 - (0.03 \bullet S_{Cr})]$

Bjornsson

For men: $[27 - (0.173 \bullet \text{age})] \bullet \text{weight} \bullet 0/S_{Cr}$

For women: $[25 - (0.175 \bullet \text{age})] \bullet \text{weight} \bullet 0.07/S_{Cr}$

Gates

For men: $\left(89.4 \bullet S_{Cr}^{-1.2}\right) + \left(55 - \text{age}\right) \bullet \left(0.447 \bullet S_{Cr}^{-1.1}\right)$

For women: $\left(89.4 \bullet S_{Cr}^{-1.2}\right) + \left(55 - \text{age}\right) \bullet \left(0.447 \bullet S_{Cr}^{-1.1}\right)$

Salazar-Corcoran

For men: $[137 - \text{age}] \bullet [(0.285 \bullet \text{weight}) + (12.1 \bullet \text{height}^2)/(51 \bullet S_{Cr})]$

For women: $[146 - \text{age}] \bullet [(0.287 \bullet \text{weight}) + (9.74\ \text{height}^2)/(60 \bullet S_{Cr})]$

CKD-EPI 2021 eGFRcr equation

$$\text{eGFRcr} = 142 \times \min(\text{Scr}/\kappa, 1)a \times \max(\text{Scr}/\kappa, 1) - 1.200 \times 0.9938^{\text{Age}} \times 1.012 \text{ [if female]}$$

where: Scr = serum creatinine in mg/dL
κ = 0.7 (females) or 0.9 (males)
a = −0.241 (female) or −0.302 (male)
min(Scr/κ, 1) is the minimum of Scr/κ or 1.0
max(Scr/κ, 1) is the maximum of Scr/κ or 1.0
Age (years)

CKD-EPI 2021 eGFRcr-cys equation

$$\text{eGFRcr-cys} = 135 \times \min(\text{Scr}/\kappa, 1)a \times \max(\text{Scr}/\kappa, 1) - 1.200 \times \min(\text{Scys}/0.8, 1) - 0.323 \times \max(\text{Scys}/0.8, 1) - 0.778 \times 0.9961^{\text{Age}} \times 0.963 \text{ [if female]}$$

where: Scr = serum creatinine in mg/dL
κ = 0.7 (females) or 0.9 (males)
a = −0.219 (female) or −0.144 (male)
min(Scr/κ, 1) is the minimum of Scr/κ or 1.0
max(Scr/κ, 1) is the maximum of Scr/κ or 1.0
Scys = serum cystatin C in mg/L
Age (years)

New Equations Used to Estimate eGFR without the use of Race

Equations for estimating glomerular filtration rate using serum creatinine or cystatin previously incorporated age, sex and race to estimate measured eGFR, however, race is a social and not biologic construct. Recently, a new eGFR equation without race has been developed and is now in the process of being implemented widely.[64-65]

CKD-EPI 2021 eGFRcr equation

$$eGFRcr = 142 \times \min(Scr/\kappa, 1)a \times \max(Scr/\kappa, 1)\text{-}1.200 \times 0.9938^{Age} \times 1.012 \text{ [if female]}$$

where: Scr = serum creatinine in mg/dL
κ = 0.7 (females) or 0.9 (males)
a = −0.241 (female) or −0.302 (male)
min(Scr/κ, 1) is the minimum of Scr/κ or 1.0
max(Scr/κ, 1) is the maximum of Scr/κ or 1.0
Age (years)

CKD-EPI 2021 eGFRcr-cys equation

$$eGFRcr\text{-}cys = 135 \times \min(Scr/\kappa, 1)a \times \max(Scr/\kappa, 1)-1.200 \times \min(Scys/0.8, 1)-0.323 \times \max(Scys/0.8, 1)-0.778 \times 0.9961^{Age} \times 0.963 \text{ [if female]}$$

where: Scr = serum creatinine in mg/dL
κ = 0.7 (females) or 0.9 (males)
a = −0.219 (female) or −0.144 (male)
min(Scr/κ, 1) is the minimum of Scr/κ or 1.0
max(Scr/κ, 1) is the maximum of Scr/κ or 1.0
Scys = serum cystatin C in mg/L
Age (years)

Serum Urea Nitrogen

Less accurate as a marker of GFR than the S_{Cr}, serum urea nitrogen (SUN) (or blood urea nitrogen [BUN]) is still used extensively in clinical practice to estimate renal function. Although this was the earliest available indicator of renal function, several other factors should be appreciated regarding the use of this substance. Urea, like creatinine, is freely filtered and is retained in the blood as the GFR falls. However, in contrast to creatinine, urea may be reabsorbed to a significant extent. The excretion of urea tends to be increased with increasing urine flow rates, whereas its excretion is reduced when tubular fluid reabsorption is enhanced. Of greater importance, urea production is more variable than that of creatinine. Produced in the liver, urea increases with high protein intake, amino acid infusions, and hypercatabolic states. In addition, endogenous sources of protein, such as absorbed hemoglobin from gastrointestinal bleeding, may contribute to increased urea synthesis. Even at a constant GFR, SUN may rise in subjects on high-protein intake and fall with protein restriction or on refeeding of previously starved, nonhypercatabolic subjects.

Several pharmacologic agents may also affect urea nitrogen formation. Tetracyclines may lead to an increase in SUN by an antianabolic effect without any detectable change in the GFR, whereas glucocorticoids and severe illnesses or trauma do the same by inducing endogenous protein hypercatabolism. Because of the widespread use of hyperalimentation in ICU patients, impairment in renal function is often associated with a marked disproportion in the elevation of SUN compared with S_{Cr}. For this reason, an issue is raised as to whether SUN elevation itself poses an important threat to patients if the GFR is in a range that should not lead to enhanced morbidity by itself. In those circumstances, it is useful to measure the rate of urea appearance (or generation) to estimate whether other factors such as gastrointestinal bleeding, excessive amino acid infusions, and protein administration are contributing to the increase in SUN above that expected by a decrease in the GFR.[48,49] Urea nitrogen (UN) appearance can be determined from urine urea nitrogen (UUN), SUN, and body weight as follows:

$$UN = UUN \bullet V + \Delta \text{body pool UN}$$

where UUN • V is the 24-hour UN excretion, and Δ body pool UN = 0.6 − nonedematous weight (kg) • Δ SUN/day.

If the weight is changing[48,49]:

$$\Delta \text{ body pool UN} = \left(0.6 \bullet \text{nonedematous weight} \bullet \Delta \text{SUN}\right) + \left(\Delta \text{ weight} \bullet \text{final SUN}\right)$$

Nitrogen balance (BN) is equal to:

$$BN = IN - UN - NUN$$

where IN is the urea nitrogen intake and NUN is nonurea nitrogen excretions.[49]

NUN, which includes fecal nitrogen, urinary creatinine, uric acid, and unmeasured nitrogen, averages 0.031 g nitrogen/kg/day.[49] Data obtained from the measurements just described may be quite useful in evaluating the cause of disproportionate elevations in SUN. If a patient is in the steady state (with a stable weight and SUN), BN = 0, and IN can be estimated from UN + NUN.[49] Because catabolism, except for *severe* trauma and burns, is usually 2–4 g nitrogen per day, additional conclusions can be drawn if the patient is not in the steady state. For example, if it is known that IN is less than UN + NUN, gastrointestinal bleeding with or without excess catabolism would be suggested. Similarly, one can evaluate if an increase in SUN is a reflection of excessive exogenous protein and amino acid administration (usually >1.5 g/kg/day; g UN 0.16 = g protein or amino acids). If the IN is above the UN, such as in severe liver disease, the clinician might more carefully evaluate changes in weight and SUN in addition to clearances because the latter may be more severely depressed than initially suspected.

FUTURE METHODOLOGIES

A number of emerging methods and technologies are currently under investigation for measuring GFR. ProEnkephalin A 119-159 is a precursor peptide (5 κDa) found in the adrenal medulla, nervous and immune systems, and kidney. Its concentration is inversely proportional to GFR, and it is a novel and useful predictor of acute kidney injury (AKI).[66] Real-time measurement of GFR is also on the horizon using 3,6-diamino02,5-bispyrazine as a tracer measurement via transdermal patch shows good correlation with GFR.[67] Another novel method uses two visible fluorescent injectates to simultaneously measure plasma volume and GFR.[68] These methods will hopefully allow the clinician to estimate GFR on a real-time basis in order to aid in the diagnosis of chronic kidney disease (CKD) and AKI.

SODIUM BALANCE AND EXTRACELLULAR FLUID VOLUME

Sodium is the primary cation of the ECF, present at a concentration of 140–142 mmol/L. The volume of the ECF is approximately 20% of the total body weight and represents one-third of the total body water. Regulation of ECF volume is governed by factors regulating sodium balance and sodium excretion.[69]

Under physiologic conditions and in the steady state, sodium balance is maintained because the amount of sodium excreted equals that which enters the body by oral and intravenous routes. The excretion of sodium excretion and fraction of filtered sodium that is excreted (FE_{Na}) can be readily determined. Absolute sodium excretion

is measured as the product of urine sodium concentration and urine volume:

$$Na^{+}\ \text{excretion} = (U_{Na} \bullet V)$$

The FE_{Na} can be determined as follows:

$$FE_{Na} = U_{Na} \bullet V/GFR \bullet S_{Na}$$

For practical reasons, C_{Cr} ($= U_{Cr} \cdot V/S_{Cr}$) is used to estimate the GFR, such that:

$$FE_{Na} = U_{Na} \bullet V/U_{Cr} \bullet V/S_{Cr} \bullet S_{Na}$$

Because V in the numerator and denominator cancels out:

$$FE_{Na} = U_{Na}/S_{Na} \bullet S_{Cr}/U_{Cr}$$

Thus the FE_{Na} can be calculated from sodium and creatinine determined in a random urine sample and serum (or plasma) simultaneously. The resulting calculation is expressed as a percentage by multiplying by 100. This test is of value in the setting of acute renal failure to aid in distinguishing a prerenal from a renal parenchymal etiology.[70] It is not usually helpful in aiding in the diagnosis of urinary tract obstruction or in the presence of underlying chronic renal insufficiency. The reason for the difficulty in interpreting chronic renal insufficiency can be illustrated by the following considerations. At a GFR of 130 mL/min and a dietary sodium intake of 3 g of sodium (130 mmol), an individual in sodium balance will excrete 0.5% of the filtered load ($FE_{Na} = 0.5\%$). For sodium balance to be maintained at lower levels of the GFR with the same sodium intake, the FE_{Na} must be increased progressively. Successive decreases in the GFR by 2 from 130 would result in FE_{Na} of 1%, 2%, 4%, and 8%, respectively. Thus interpretation of the FE_{Na} in a patient with acute renal failure superimposed on chronic renal insufficiency is problematic unless the prior steady-state FE_{Na} is known, but this is rarely the case.

The fractional excretion of chloride (FE_{Cl}) has been suggested to be more accurate than that of sodium in helping to distinguish prerenal from parenchymal causes of acute renal failure.[71] This is particularly so in the situation in which acute renal failure occurs with simultaneous metabolic alkalosis. If the urine contains substantial amounts of bicarbonate urinary pH ($U_{pH} > 7$), sodium excretion increases to maintain electroneutrality. Under these circumstances, the FE_{Na} may give misleading information, but the FE_{Cl} can be used to obtain the same information.

Although urinary sodium excretion can be used to help make determinations with respect to the ECF volume under certain circumstances, this may be fraught with potential errors. No laboratory test is available to provide this information. Rather, an astute clinician must rely on bedside evaluation complemented, where appropriate, with measurements of central venous pressure and pulmonary capillary wedge pressure to assist in making determinations with respect to the ECF volume status. For example, a low FE_{Na} (<1%) in the setting of acute renal failure usually indicates a decrease in renal perfusion but does not provide information on the status of the patient's ECF volume. Because a low FE_{Na} can be seen with either ECF volume contraction or severe congestive heart failure, these conditions must be distinguished at the bedside. Moreover, sometimes a low FE_{Na} exists even in the presence of parenchymal renal disease, such as acute glomerulonephritis, severe burns, and radiocontrast nephropathy. Finally, administration of potent diuretic agents can alter the FE_{Na} and may result in misleading interpretations. For this reason, urine samples should be obtained before diuretics are administered. However, it may not be possible to obtain urinary sodium or chloride values while a patient is not receiving diuretics. In this setting, the fractional excretion of UN has been employed to distinguish prerenal from renal causes of AKI. In a well-hydrated individual, the Fe_{UN} is 50%–65%,[72] whereas in the oliguric prerenal azotemic individual, the Fe_{UN} is below 35%. The use of Fe_{UN} in the setting of AKI has not attained widespread acceptance because of variable results in comparative trials.[72,73]

There is now ample evidence that in a patient in positive sodium balance, diuretic therapy should not be used without simultaneously restricting sodium intake, including intravenous saline, if negative sodium balance and reduction in edema fluid are desired.[74] In general, this requires restriction of dietary sodium intake, usually to less than 2 g of sodium per day (0.88 mmol) if the patient is in an edema-forming state. Although diuresis can be affected even with liberal sodium intake, this requires higher doses of diuretics and more frequent administration of these agents. The coexistence of hyponatremia should not deter clinicians from restricting sodium intake, but rather should cause them to address solute-free water intake as well. Under certain circumstances, obligatory intakes make it difficult to achieve optimal restriction to assist diuresis. That is, with various pharmacologic drips, blood products, and feeding regimens necessary in acutely ill patients in the ICU, restricting sodium intake may become a difficult problem. Under those circumstances, increasing doses of diuretics, including continuous infusions of loop diuretics, may be required.

KEY POINTS

- Acute deterioration of renal function is common in the ICU and contributes significantly to overall morbidity and mortality.
- The serum creatinine concentration often underestimates the decrease in GFR and may be abnormal only after marked reductions in GFR.
- Using equations to estimate renal function should be routine in the ICU.

References for this chapter can be found at expertconsult.com.

ANNOTATED REFERENCES

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Biomarkers of Acute Kidney Injury

Anja Haase-Fielitz and Michael Haase

EPIDEMIOLOGY OF ACUTE KIDNEY INJURY IN THE INTENSIVE CARE UNIT

Acute kidney injury (AKI) is a significant problem in intensive care unit (ICU) patients and carries a high mortality rate and long-term morbidity. AKI is defined according to the Kidney Diseases Improving Global Outcomes (KDIGO) criteria,[1] including three alternatively applied components: (1) serum creatinine increase (from baseline of >27 micromol/L or >0.3 mg/dL within a maximum of 48 hours or >50% within a maximum of 7 days), (2) reduced urine output (<0.5 mL/kg/hr over 6 hours), or (3) initiation of acute renal replacement therapy. Incidence of AKI in the ICU has been reported to be about 50%,[2] with 32% at stage 1, 16% at stage 2, and 52% at stage 3. In 13.5% of patients treated in the ICU, renal replacement therapy is initiated. AKI requiring renal replacement therapy in the ICU has a high mortality rate, often reaching over 50%. The most common causes of AKI in the ICU include sepsis/septic shock, major surgical procedures, acute cardiac decompensation/cardiac shock, and nephrotoxins.[2,3] Approximately 30% of patients have preadmission chronic kidney disease.

A major obstacle to the development of improved treatment strategies for AKI in critically ill patients is the absence of sensitive and specific biomarkers available to the clinician with a short laboratory turn-around time.[4] Therapeutic measures are sometimes started late in the course of AKI. The optimum time to start renal replacement therapy in the ICU is unknown. Therefore there is a need to understand whether and how novel kidney biomarkers with short turn-around time may be able to complement clinical decisions in ICU patients.

This chapter briefly highlights biologic characteristics of current tools in AKI diagnosis and of novel kidney biomarkers with short turn-around times and test results available to the clinician within 2 hours. This is followed by information on clinical characteristics of such biomarkers of AKI. Biologic and clinical characteristics of other published novel kidney biomarkers are summarized at the end of the chapter.

BIOLOGIC CHARACTERISTICS OF CURRENT TOOLS IN AKI

Serum creatinine (SCr) and urine output are used to diagnose AKI. Creatinine is generated in muscles from the nonenzymatic conversion of creatine and phosphocreatine. SCr concentrations carry the highest validity under stable physiologic conditions, but SCr is not sensitive or specific in the setting of AKI. SCr may change because of nonrenal factors independent of kidney function (e.g., age, gender, race, muscle mass, nutritional status, total parenteral nutrition, and infection).[5,6] Also, inhibition of tubular secretion (e.g., during intake of piperacillin/tazobactam) may increase SCr concentrations.[7] Moderate to severe abnormalities of thyroid or adrenal gland function may affect SCr independent of kidney function, with lower SCr concentrations in the setting of hyperthyroidism or hypercortisolism. SCr is not sensitive to the loss of kidney function reserve, as evidenced by the small change in SCr after the loss or donation of a kidney with one normal remaining kidney.[8] Alterations in SCr may lag several days behind actual changes in glomerular filtration rate (GFR).[6,9]

Both a decrease and lack of decrease of urine output are frequently not helpful in diagnosing or ruling out AKI. Urine output and urine output–modifying circumstances (e.g., hypovolemia) and treatments (fluids, diuretics) carry inherent impediments, limiting their sensitivity and specificity in AKI diagnosis. Specifically, diuretic administration in the setting of hypervolemia management or fluid administration in the setting of hemodynamic instability might limit the use of urine output for diagnosing or ruling out AKI. However, diuretic administration applied in euvolemic patients as a tubular stress test[10] may assess kidney tubular responsiveness.[11]

A biomarker independent of SCr and urine output limitations or a biomarker that is released into the blood or urine by the injured kidney may be a more sensitive and specific marker of AKI. In addition, earlier detection of AKI with a kidney-specific biomarker may result in earlier nephrology consultation, more optimal dosing of antibiotics in ICU patients, avoidance of nephrotoxic agents, and even patient-individualized timing of initiation of renal replacement therapy (RRT).

BIOLOGIC CHARACTERISTICS OF NOVEL AKI BIOMARKERS WITH SHORT TURN-AROUND TIMES

Recently, clinically available biomarkers of AKI with short laboratory turn-around times to the clinician have been described, including cystatin C, neutrophil gelatinase–associated lipocalin (NGAL), and cell-cycle arrest markers (TIMP-2/IGFBP7). All of those are available on clinical laboratory platforms or point-of-care devices with biomarker measurements of less than 60 minutes. Cystatin C, NGAL, and cycle arrest markers have CE marking, making the tests commercially available in Europe for supporting the clinician estimating AKI risk in critically ill patients. Cystatin C measurements are approved by the Food and Drug Administration (FDA) as an aid in the diagnosis and treatment of renal diseases. Cell-cycle arrest markers (TIMP-2/IGFBP7) have also been approved by the FDA to be used in conjunction with clinical evaluation in patients 21 years of age or older who currently have or have had within the past 24 hours acute cardiovascular and/or respiratory compromise and are ICU patients as an aid in the risk assessment for moderate or severe AKI within 12 hours of patient assessment. Renal handling of these biomarkers is shown in Fig. 96.1.

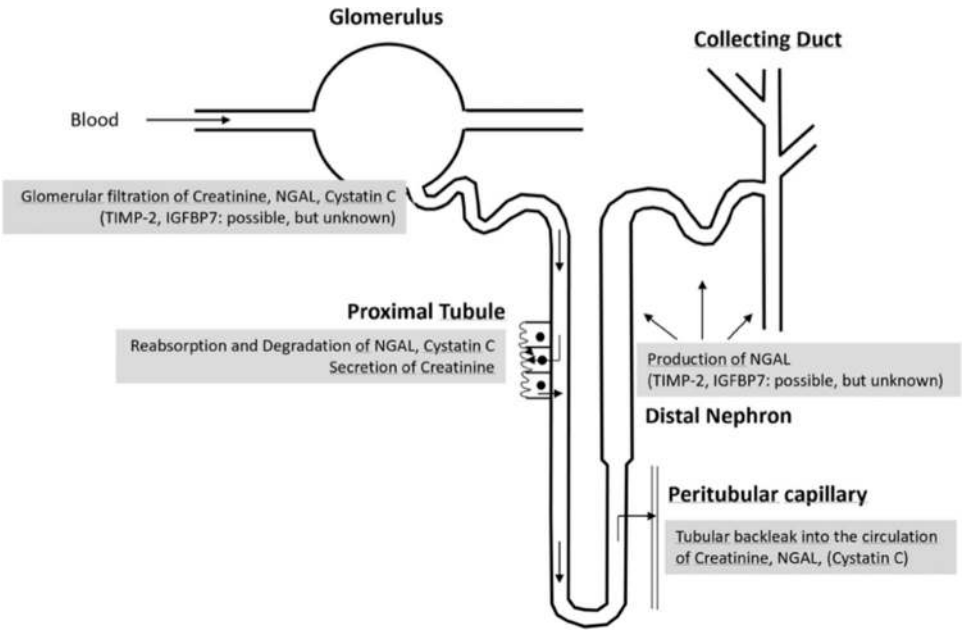

Fig. 96.1 The processing of AKI biomarkers cystatin C, NGAL, and cycle arrest markers by the kidneys.

Novel biomarkers of AKI that are not clinically available within a short turn-around time are summarized next, including IL-6, IL-18, KIM-1, and L-FABP.

Serum Cystatin C

Cystatin C is a 13-kDa protein produced by all nucleated cells at a constant rate. It is freely filtered by the glomerulus, completely reabsorbed by the proximal tubules, and is not secreted by the renal tubules.[12] Thus some of the limitations of SCr—for example, the effect of muscle mass, diet, gender, and tubular secretion—may not be a problem with cystatin C. Cystatin C is a better marker of GFR than SCr.[13–15] Increases in cystatin C occur sooner after changes in kidney function than change in SCr.[8,16] In critically ill patients, serum cystatin C correlated better with GFR than did creatinine and was diagnostically superior to creatinine.[16] Serum cystatin C was found to be better than SCr in the detection of AKI in critically ill children.[17]

There are limitations to the use of cystatin C as a marker of GFR. Abnormalities of thyroid function[18] and glucocorticoid therapy[19,20] may affect cystatin C independent of kidney function, with higher serum cystatin C concentrations in the setting of hyperthyroidism or prednisolone intake >10 mg/d. However, in critically ill patients, the effect of thyroid function appears to be nonclinically relevant.[21] The evidence regarding the impact of inflammation is limited; however, in a study with 327 ICU patients, the impact of sepsis on the levels of serum cystatin C in AKI and non-AKI patients was determined.[22] The change in cystatin C or creatinine did not differ significantly between the septic and nonseptic patients with or without AKI. Similarly, in a study with critically ill children, levels of cystatin C were not substantially increased in the setting of sepsis.[23]

Neutrophil Gelatinase–Associated Lipocalin

NGAL was originally isolated from the supernatant of activated neutrophils and identified as a polypeptide covalently bound to gelatinase.[24] It is expressed in a variety of human tissues, including lung, liver, and kidney, in various pathologic states. Human NGAL is a polypeptide with a molecular weight of 25 kDa covalently bound to gelatinase from human neutrophils. Although the majority of NGAL is in a monomeric form, NGAL also occurs as dimers and trimers and in a complex with neutrophil gelatinase. The 25-kDa monomeric NGAL form is secreted by injured kidney tubule epithelial cells, whereas the dimeric form is predominantly secreted by neutrophils.[25] The major ligands for NGAL are siderophores,[26] which are ferric ion-specific chelating compounds.[27] The iron status of NGAL is a critical determinant of biologic activity. Iron-containing NGAL binds to cell surface receptors such as megalin, gets internalized, and releases its bound iron. The increased intracellular iron concentration drives the regulation of iron-dependent genes. NGAL has been implicated in the differentiation of renal tubule epithelial cells and nephrons.[28] Preclinical studies identified NGAL to be one of the most up-regulated genes and proteins in the kidney early after AKI in animal models.[29a] NGAL protein expression was detected predominantly in tubule epithelial cells that were undergoing proliferation and regeneration, suggesting a role in the repair process. NGAL protein was also detected in the urine and plasma in animal models of AKI, where it preceded the increase in plasma creatinine concentrations. Urine NGAL is derived predominantly from epithelial cells of the distal nephron, although a fraction may come from the systemic pool escaping reabsorption because of proximal tubular injury.[29] Plasma NGAL originates not only from the damaged kidneys (via tubular backleak) but also from extrarenal organs. Recent evidence has emerged to implicate a potentially important pathophysiologic link between NGAL and cardiorenal syndrome. NGAL induces cardiomyocyte apoptosis by increasing intracellular iron accumulation.[30] Renal NGAL expression rapidly increased after acute inflammation and/or injured renal tubular epithelia, in particular after damage from ischemia-reperfusion injury (IRI) and toxin exposure. A reporter mouse responsive to ischemia/reperfusion or toxic stimuli allowed detection of NGAL expression in "real time" in vivo.[31] Volume depletion did not cause NGAL expression in the kidney or in the urine, thus indicating that NGAL can be an important clinical tool to discriminate patients with "prerenal azotemia" from those with AKI and therefore "true" structural damage. Finally, NGAL levels peak approximately 6 hours after tubular injury and follow a dose-response curve with respect to severity of injury.[32,33]

Cell-Cycle Arrest Markers

Replication is one of the most energy-consuming processes cells undergo. If, during the cell cycle, the cell will have not sufficient energy to replicate, the cell will undergo cell-cycle arrest to avoid cell death as a result of energy failure.[34] Therefore cell-cycle arrest is considered to be a major mechanism of down-regulation of energy expenditure that tubular epithelial cells may use to resist or recover from different insults. Even if insults may not actually destroy cells, tissue inhibitor of metalloproteinase-2 (TIMP-2) and insulin-like growth factor binding protein-7 (IGFBP7) may signal in autocrine and paracrine fashions. Therefore TIMP-2 and IGFBP7 have been recently described as an "alarm" spreading to adjacent cells, although this has not yet been shown for the kidney.[34] The cellular source and pathophysiologic role of these markers in AKI are unknown' however, one study showed that nonrenal organ failures in sepsis did not result in increased [TIMP-2]·[IGFBP7],[34] and other studies showed no increase of [TIMP-2]·[IGFBP7] in critically ill patients without AKI.[35] TIMP-2 and IGFBP7 have been found to be predictors of the development of human AKI.[35] Both cell-cycle arrest markers are inducers of G1 cell-cycle arrest occurring during the early phases of cellular stress,[36,37] a key mechanism implicated in AKI. TIMP-2 and IGFBP7 may increase in response to inflammation, oxidative stress, ultraviolet radiation, drugs, and toxins.[34,36,37] Sustained cell-cycle arrest will result in a senescent cell phenotype and lead to fibrosis. In turn, urine TIMP-2 and IGFBP7 values were not elevated in patients with stable chronic morbidities who did not have AKI.[38]

CLINICAL CHARACTERISTICS OF AKI BIOMARKERS WITH SHORT TURN-AROUND TIMES

Serum Cystatin C

The performance of serum cystatin C and SCr as biomarkers of GFR in 47 critically ill patients was compared with GFR measured using urine clearance of iohexol.[39] The areas under the ROC curve (AUCs) to detect a GFR of less than 60 mL/min were 0.80 and 0.94 for SCr and serum cystatin C, respectively. It was concluded that serum cystatin C outperforms SCr for the detection of an impaired GFR in critically ill patients.[39]

Serum cystatin C rapidly detects AKI in the ICU.[40] In a meta-analysis including data from 11 countries involving 3336 patients, serum cystatin C was reported to be predictive of AKI with an AUC of 0.84 if measured within 24 hours after ICU admission. Most studies in this meta-analysis found serum cystatin concentration >1.1 mg/L to be predictive.[41] Another meta-analysis including 2332 predominantly critically ill patients reported a 4.4 times increased risk of initiation of RRT if baseline serum cystatin C was increased.[42]

In another meta-analysis with 1079 ICU patients, cystatin C was predictive of the need for initiation of RRT, with AUC of 0.77, similar to the predictive value of contemporaneous serum creatinine with AUC 0.76.[43] In turn, serum cystatin C concentrations <2.5 mg/L with an AUC of 0.74 were predictive of successful 60-day discontinuation of RRT in critically ill patients.[44] Serum cystatin C was an independent risk factor for AKI, with an odds ratio of 4.5 per mg/L increase in 624 neurosurgical critically ill patients.[45]

In a study of 198 patients without known chronic kidney disease who underwent noncardiac major surgery and developed new-onset AKI in the first 48 hours after admission to the ICU, cystatin C predicted nonrecovery from AKI (within 7 days), with an AUC of 0.68, and improved a related statistical model enriched with clinical variables to AUC 0.80.[46]

Use of a vancomycin dosing algorithm according to estimated GFR (eGFR) using both an SCr and serum cystatin C–based CKD-EPI equation improved goal steady-state vancomycin trough concentrations compared with creatinine clearance based on the Cockcroft-Gault formula.[47]

Although SCr and cystatin C increase subsequent to a loss of renal filtration function, markers of acute tubular injury or cell stress may indicate structural kidney damage.

NGAL

NGAL is an early biomarker of AKI in critically ill patients. In 140 pediatric patients on mechanical ventilation,[48] the mean and peak urine NGAL concentrations increased with maximum AKI severity. Urine NGAL concentration rises in AKI 2 days before a 50% or greater rise in SCr. In a meta-analysis including more than 13,000 patients,[49] irrespective of meta-analytic approach, AKI definition, or subgroup assessment and considering several known NGAL confounders, NGAL diagnostic accuracy for the prediction of SCr-based AKI in adult critically ill patients was moderate to good (for overall AKI, moderate to severe AKI, RRT: AUC 0.73/0.78/0.75 for urine NGAL and AUC 0.77/0.82/0.87 for plasma NGAL) (Table 96.1). The estimated time from NGAL sampling to diagnosis of AKI was 69 hours (interquartile range (IQR) 33–107).[49] Moreover, in this meta-analysis, AUC values, classification, and test performance indices (sensitivity, specificity, predictive values) of NGAL for severe AKI were similar to those previously reported for the cell arrest markers TIMP-2 and IGFBP7.[50,51]

The optimal cutoff points of urine and plasma NGAL for the prediction of moderate to severe AKI in 245 critically ill patients were >80 ng/mL (sensitivity 70%, specificity 77%) and >150 ng/mL (sensitivity 79%, specificity 73%).[52] In this study, NGAL was also shown to be a marker of persistence of AKI for 48 hours or longer. Accordingly, the optimal cutoff points of urine and plasma NGAL (measured at the start of AKI stage 2/3) for the prediction of persistent AKI were similar with >80 ng/mL and >150 ng/mL. The ability of plasma NGAL to predict AKI in adult ICU patients was confirmed in another study.[53] In a prospective cohort study of NGAL in the ICU, using a cutoff of >155 ng/mL, the sensitivity and specificity of plasma NGAL to predict AKI were 82% and 97%, respectively (AUC 0.92). Of the patients who required RRT, all of them had plasma NGAL of >300 ng/mL. Plasma NGAL increased 48 hours before AKI was diagnosed. The study concluded that plasma NGAL at ICU admission was an early biomarker of AKI in adult ICU patients.[53]

TABLE 96.1 NGAL as a Biomarker of AKI in the ICU

		AKI		MODERATE TO SEVERE AKI		RRT
Covariate	N	AUC (95% CI)	N	AUC (95% CI)	N	AUC (95% CI)
Plasma NGAL	10	0.77 (0.76–0.78)	8	0.82 (0.81–0.83)	6	0.87 (0.86–0.87)
Urine NGAL	6	0.73 (0.72–0.75)	5	0.78 (0.78–0.81)	4	0.75 (–)

AKI, Acute kidney injury; *AUC,* area under the curve; *CI,* confidence interval; *RRT,* renal replacement therapy.
(From Albert C, Haase M, Albert A, Zapf A, Braun-Dullaeus RC, Haase-Fielitz A. Biomarker-Guided Risk Assessment for Acute Kidney Injury: Time for Clinical Implementation? Ann Lab Med. 2021 Jan;41(1):1-15. doi: 10.3343/alm.2021.41.1.1.)

A multicenter study of serum NGAL was performed in 143 critically ill children with systemic inflammatory response syndrome (SIRS) or septic shock during the first 24 hours of admission to the pediatric ICU.[54] There was a significant difference in the serum NGAL between healthy children, critically ill children with SIRS, and critically ill children with septic shock. Serum NGAL was significantly increased in critically ill children with AKI compared with those without AKI. Thus serum NGAL is a highly sensitive but nonspecific predictor of AKI in critically ill children with septic shock. Another study of NGAL in the ICU determined the influence of sepsis on NGAL in adult critically ill patients admitted with normal SCr.[55] Data from patients with SIRS, severe sepsis, or septic shock without AKI and patients with septic shock and concomitant AKI were analyzed. Peak levels of plasma NGAL were not significantly different between septic shock patients with and without AKI. Urine NGAL was a good predictor (AUC 0.86), whereas plasma NGAL was a poor predictor (AUC 0.67) of AKI within the next 12 hours in patients with septic shock.[55] The authors concluded that plasma NGAL is raised in patients with SIRS, severe sepsis, and septic shock and should be used with caution as a marker of AKI in ICU patients with septic shock. Urine NGAL was more useful for predicting AKI, as the levels were not elevated in septic shock patients without AKI.

The predictive value of urine NGAL, plasma NGAL, and serum cystatin C to differentiate among sustained, transient, and absent AKI was compared in 700 ICU patients in a prospective cohort study.[56] Urine NGAL was the only biomarker that could significantly differentiate sustained from transient AKI on ICU admission. The study concluded that urine NGAL measured on ICU admission can be used to differentiate patients with sustained AKI from patients with transient AKI or without AKI.

In a prospective study of serum NGAL in 109 critically ill patients at the initiation of RRT, serum NGAL was a strong independent predictor for 28-day survival.[57]

The diagnostic accuracy of plasma NGAL for the early detection of AKI and the need for RRT in an adult ICU was examined in a study of 307 consecutive adult patients admitted to a general medical/surgical ICU.[58] Peak plasma NGAL concentrations increased with worsening AKI severity.[58]

In a prospective observational study, 106 ICU patients were included to determine whether a panel of novel and traditional renal markers is superior to conventional renal markers in predicting RRT requirements.[59] Urine NGAL, serum cystatin C, and Acute Physiology and Chronic Health Evaluation (APACHE) II score were significant independent predictors of RRT. The combination of serum cystatin C and APACHE II score proved to be the best for detecting patients without AKI on ICU entry (AUC 0.78). The study concluded that the combination of a marker of GFR with one of tubular injury was the best predictor of RRT.

The ability of plasma NGAL and urine NGAL compared with SCr-based eGFR to predict severe AKI was determined in patients on ICU admission.[60] Urine and plasma NGAL performed better than SCr or eGFR (AUC 0.79/0.75 vs. 0.65/0.67) for the prediction of moderate to severe AKI in 498 critically ill patients with eGFR >60 mL/min/1.73 m^2.

It has become apparent that using clinical adjudication in conjunction with routine laboratory parameters may be insufficient in complex acute conditions such as AKI. In this regard, a recent prospective observational study found that a clinician's risk assessment for major adverse kidney events or AKI alone using information of NGAL test results measured on ICU arrival after cardiac surgery in addition to all other clinical information available was superior to clinical risk assessment without information of the NGAL test result.[61] Parikh and colleagues also reported cost savings in favor of biomarker measurement and adjustment of treatment.[62]

Finally, a systematic review and meta-analysis comparing a watchful waiting strategy with early initiation of RRT in critically ill patients found that randomized controlled trials (RCTs) that enrolled a surgical population and a population with high plasma NGAL had favorable outcomes in the early RRT initiation group compared with the late RRT initiation group. The authors concluded that results should be interpreted with caution and that further information from large-scale, well-designed RCTs should be obtained to provide a more definitive answer regarding biomarker-complemented, optimal timing of RRT initiation and optimal RRT duration.[63]

In summary, NGAL appears to be a potentially useful biomarker of AKI and the need for RRT. However, there is variation among studies, and conditions such as sepsis, chronic obstructive pulmonary disease, cardiac dysfunction, age (NGAL seems superior in children), sex, and baseline renal function may affect the sensitivity and specificity of NGAL as a biomarker of AKI in the ICU.[64] Thus there are limits in the interpretation of NGAL in AKI. In addition, plasma NGAL and urinary NGAL assays have detected different molecular forms of NGAL, and these various molecular forms have different predictive values as biomarkers of AKI.[65] Before NGAL is routinely and cost-effectively used in the ICU, further work is needed to describe the natural history of AKI and NGAL physiology in the ICU. Future studies should focus on accurate, early identification of AKI and the identification of new therapies.[66]

Cell-Cycle Arrest Markers

In one study, 340 candidate biomarkers were measured in the urine of critically ill ICU patients with sepsis or one or more risk factors for AKI such as hypotension and major trauma. In the initial analysis, the biomarkers were ranked by their ability to predict moderate to severe AKI within 12–36 hours. The two best biomarkers were the cell-cycle arrest proteins IGFBP7 and TIMP-2, which are both inducers of G1 cell-cycle arrest, a key mechanism implicated in AKI.[35] In a validation study ("Sapphire study") in 728 critically ill patients, the primary endpoint was moderate to severe AKI (KDIGO stage 2–3) within 12 hours of sample collection.[35] The combination of TIMP-2 and IGFBP7 ([TIMP-2]•[IGFBP7]) demonstrated an AUC of 0.80 (0.76 and 0.79 alone) for the primary endpoint. Urine concentrations of [TIMP-2]•[IGFBP7] were significantly superior to previously described markers of AKI, none of which achieved an AUC of more than 0.72 for the endpoint defined. Hoste and colleagues reported in the Opal study an AUC of 0.79 for moderate to severe AKI using [TIMP-2]•[IGFBP7].[50]

Several studies focused on identification and characterization of cutoff concentrations for AKI (Table 96.2). In the Topaz study, in 420 ICU patients, a predefined cutoff value of [TIMP-2]•[IGFBP7] was prospectively validated for risk assessment in AKI diagnosed by a clinical adjudication committee.[51] Critically ill patients with urinary [TIMP-2]•[IGFBP7] >0.3 had seven times the risk of AKI compared with critically ill patients with a test result <0.3. Sensitivity for the designated "high sensitivity cutoff" (0.3 ng/mL^2/1000) was 89% in both Sapphire[35] and Opal[50] studies, and specificity was 50% and 53%, respectively. For 2.0 ng/mL^2/1000 (which designated a high specificity cutoff), sensitivity was 42% and 44% and specificity was 95% and 90%, respectively. A recent meta-analysis[49] on the diagnostic performance of [TIMP-2]•[IGFBP7] for AKI reported a sensitivity for the 0.3 ng/mL^2/1000 cutoff of 0.76 and specificity of 0.48 within 12 hours of ICU admission. The sensitivity and specificity for the 2.0 ng/mL^2/1000 cutoff were 42% and 94%, respectively.

In addition, urinary [TIMP-2]•[IGFBP7] is associated with an increased risk of 9 months mortality or dialysis after AKI.[67] Furthermore,

TABLE 96.2 TIMP-2/IGFBP7 as a Biomarker of AKI in the ICU

Endpoint	Biomarker	Criterion	Cutoff	Sensitivity, % (95% CI)	Specificity, % (95% CI)	LR+ (95% CI)	LR− (95% CI)	DOR¶	Prevalence, %	PPV,%	NPV%	Adjusted Prevalence, %*	Adjusted PPV, %*	Adjusted NPV, %*
Severe AKI Sapphire and Opal Cohort, Hoste et al. [51]	[TIMP-2]• [IGFBP-7]	90% sensitivity	0.3 (ng/mL) 2/1000	89	51.5†	1.79 (1.63–1.97)	0.22 (0.11–0.35)	8.1	17.6‡	18 (17–20)	97 (96–99)	21.0	32 (29–35)	96 (94–97)
		Youden	0.7 (ng/mL) 2/1000	70	76	2.92 (2.44–3.44	0.39 (0.28–0.51)	7.5	17.6‡			21.0		
		95% specificity	2.0 (ng/mL) 2/1000	43†	92.5†	7.69 (5.57–10.88)	0.62 (0.51–0.71)	12.4	17.6‡	27 (41–58)	95 (92–94)	21.0	45 (40–49) 69 (63–75)	92 (90–94) 88 (86–89)
Severe AKI Topaz Cohort, Bihorac et al. [52]	[TIMP-2]• [IGFBP-7]	90% sensitivity	0.3 (ng/mL) 2/1000	92 (85–98) 70 (59–80)	46 (41–52) 82 (78–86)	1.7 (1.5–1.9)	0.18 (0.06–0.33)	5.5	17.4‡	27 (21–32)	96 (93–99)	21.0	31.17	95.58
		Youden	1.0 (ng/mL) 2/1000	37 (26–47)	95 (93–97)	3.9 (3.0–5.1)	0.37 (0.24–0.50)	10.5	17.4‡	45 (36–54)	93 (90–96)	21.0	50.83	91.14
		95% specificity	2.0 (ng/mL) 2/1000			7.7 (4.5–14.1)	0.67 (0.55–0.78)	11.5	17.4‡	62 (48–76)	88 (84–91)	21.0	66.30	85.01

(From Albert C, Haase M, Albert A, Zapf A, Braun-Dullaeus RC, Haase-Fielitz A. Biomarker-Guided Risk Assessment for Acute Kidney Injury: Time for Clinical Implementation? Ann Lab Med. 2021 Jan;41(1):1-15. doi: 10.3343/alm.2021.41.1.1.)

AKI, Acute kidney injury; *CI,* confidence interval; *DOR,* diagnostic odds ratio; *LR,* likelihood ratio; *NGAL,* neutrophil gelatinase–associated lipocalin; *NPV,* negative predictive value; *PPV,* positive predictive value; *RRT,* renal replacement therapy; *[TIMP-2] • [IGFBP7],* tissue inhibitor of metalloproteinases and insulin-like growth factor binding protein.

The following recommendations by Hoste and colleagues [51], PPV and NPV for severe AKI, were adjusted for the prevalence reported by Hoste and colleagues [51] and Bihorac and colleagues [52] in critically ill patients.

† Mean approximation from sensitivity and specificity reported for Sapphire and Opal Cohort [51].

‡ Derived from data reported for the Sapphire, Opal, or Topaz cohorts, respectively [51, 52].

¶ Calculated as LR+/LR−.

in several studies the combination of urinary [TIMP-2]•[IGFBP7] was examined to predict renal recovery in critically ill patients with AUC 0.68,[68] AUC 0.62,[69] and AUC 0.79,[70] with the latter study demonstrating eGFR improvement to be the best predictor of renal recovery (AUC 0.87). A proteome analysis exploring novel kidney markers in the urine of critically ill patients with AKI and early recovery ($n = 12$) compared with late recovery ($n = 12$) identified eight candidates, among them NGAL and IGFBP7.[71] In a validation study ($n = 28$), AUC for AKI recovery was 0.74 for urine IGFBP7 and 0.70 for urine NGAL. AUC for prediction of mortality was 0.68 for IGFBP7 and 0.81 for NGAL.

In several studies, the combination of TIMP-2 and IGFBP7 was used for clinical decision making. In a study cohort of 276 patients undergoing cardiac surgery, Meersch and colleagues[72] found that implementation of an AKI care bundle according to the KDIGO practice guidelines compared with standard care reduced the frequency and severity of AKI in high-risk patients identified by [TIMP-2]•[IGFBP7] >0.3 ("high sensitivity cutoff"). Likewise, using the same cutoff, Göcze and colleagues[73] identified patients at risk after major abdominal surgery and used the KDIGO care bundle in identified patients (intensified care group) compared with standard care in the control group. They found reduced AKI severity, postoperative SCr increase, length of ICU, and hospital stay in the intensified care group compared to control. Göcze and colleagues also reported cost savings in favor of biomarker measurement and adjustment of treatment, accordingly.[73]

BIOLOGIC AND CLINICAL CHARACTERISTICS OF OTHER NOVEL AKI BIOMARKERS

Interleukin-6

Interleukin (IL)-6 is a proinflammatory cytokine and has been studied as a predictor of AKI. In one clinical trial, 547 patients from the placebo group of the Prospective Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) data set were studied.[74] Of these 547 patients, 127 (23.2%) developed AKI. Using multivariate Cox regression, the predictors of AKI were log IL-6 and the APACHE II score. Similarly, IL-6 is a proinflammatory acute phase response cytokine that has been found to be elevated in the urine of pediatric[75] and adult[76,77] patients with acute tubular injury.

The Program to Improve Care in Acute Renal Disease (PICARD) was a prospective multicenter cohort study designed to examine the natural history and outcomes of critically ill ICU patients with established AKI.[78] Among other cytokines, IL-6 was determined in a subset of 98 patients from the PICARD study at the time of enrollment and then weekly for the duration of their hospital stay. Patients were enrolled into PICARD at the time of their nephrology consultation and thus had established AKI. IL-6 was significantly elevated compared with those in healthy controls. Increased serum levels of IL-6 at baseline were significantly correlated with increased in-hospital mortality in AKI patients. Thus the cytokine response in patients with AKI is significantly dysregulated. When cytokine values were further adjusted for the severity of illness (APACHE III scores), only IL-6 remained an independent predictor of mortality. Thus IL-6 may be an important biomarker of outcomes in patients with AKI.

In summary, in both patient and animal studies, early AKI is associated with a proinflammatory burst that is characterized by early increases in serum IL-6. Such a proinflammatory burst may also be linked with other complications in the ICU, such as acute lung injury.[79]

Interleukin-18

IL-18 is a proinflammatory cytokine that plays a role in both innate and acquired immune response.[80–82] Studies in humans have demonstrated that urinary IL-18 is an early predictive biomarker of AKI in the ICU.[83] On multivariable analysis, urinary IL-18 values predicted the development of AKI (defined as a 50% increase in SCr) 24 and 48 hours later. On diagnostic performance testing, urinary IL-18 demonstrated an AUC of 73% to predict AKI in the next 24 hours. The presence of sepsis in both control and AKI patients did not have a significant effect on urinary IL-18. On multivariate analysis, the urinary IL-18 value on the day of initiation of mechanical ventilation for acute respiratory distress syndrome was a strong predictor of mortality.[83] The finding that urinary IL-18 is an early biomarker of AKI in critically ill adults was reproduced in children.[84] Urinary IL-18 rises before SCr does in nonseptic critically ill children, predicts the severity of AKI, and is an independent predictor of mortality.[84]

The ability of urinary IL-18, measured within 24 hours of ICU admission, to predict the need for acute dialysis in 451 ICU patients was prospectively investigated.[85] The highest median urinary IL-18 levels were observed in patients with sepsis at enrollment, those receiving acute dialysis, and those who died within 28 days of ascertainment. After adjustment for a priori selected clinical predictors, urinary IL-18 was an independent predictor of a composite outcome of death or acute dialysis within 28 days. The study concluded that urinary IL-18 predicted poor clinical outcomes in a broadly selected critically ill adult population.

In a study with 101 critically ill patients with AKI, the APACHE III score had an AUC 0.87 and serum IL-18 had an AUC 0.85 in terms of in-hospital mortality.[86] However, after cardiac surgery, IL-18 measured at ICU admission appears not to be predictive of AKI.[87] Urinary IL-18 as a biomarker of AKI in various clinical settings was analyzed in a meta-analysis of prospective studies.[88] Subgroup analysis showed that the AUC of urinary IL-18 to predict AKI was 0.66 in ICU or coronary care unit patients.

Kidney Injury Molecule-1

Kidney injury molecule-1 (KIM-1) is a putative epithelial cell adhesion molecule containing a novel immunoglobulin domain. KIM-1 mRNA and protein are expressed at low levels in normal kidneys but are increased in postischemic kidneys.[89] Both KIM-1 and NGAL concentrations gradually increased until AKI diagnosis in 700 adult critically ill patients. KIM-1 was a good discriminator at the time of AKI only (AUC 0.73).[90] However, KIM-1 remains to be proven as an early biomarker of AKI and prognosis in the ICU.

Liver Fatty Acid–Binding Protein

Fatty acid–binding proteins (FABPs) are a family of carrier proteins for fatty acids and other lipophilic substances, including eicosanoids and retinoids. FABPs also transport lipophilic molecules from the outer cell membrane to intracellular receptors such as peroxisome proliferator-activated receptors.

Urinary and serum liver-FABP (L-FABP) were measured in 80 critically ill patients.[91] Urinary L-FABP levels in patients with septic shock were significantly higher than those in patients with severe sepsis without shock, patients with AKI, or healthy subjects. Serum L-FABP levels showed no significant differences between patients with septic shock, patients with severe sepsis, patients with AKI, and healthy subjects.

The diagnostic and prognostic abilities of urinary L-FABP in heterogeneous critically ill patients were determined.[92] Urine NGAL and L-FABP were measured in 145 medical and surgical patients at the time of ICU admission. AKI patients had significantly higher levels of urinary NGAL and L-FABP and higher mortality rates than non-AKI patients. The AUC was 0.77 for NGAL and 0.78 for L-FABP for the diagnosis of AKI. On multivariate Cox analysis, urinary L-FABP was an independent predictor for 90-day mortality. Thus urinary L-FABP

is promising both for the diagnosis of AKI and for the prediction of prognosis in heterogeneous ICU patients.[92]

Of 152 critically ill adults with early AKI, urine L-FABP demonstrated an AUC of 0.79 for injury progression, dialysis, or death within 7 days, which improved to 0.82 when added to the clinical model (AUC 0.74).[93]

Combinations of AKI Biomarkers

The classical biomarker paradigm is that one test detects one disease—for example, troponin for acute myocardial infarction and prostate-specific antigen for prostate cancer. However, AKI is a complex disease with multiple causes, and it is possible that a panel of biomarkers may be necessary. In summary, more than one biomarker may be necessary to obtain sufficient sensitivity and specificity for AKI screening.

CONCLUSION

The clinical application of biomarkers is difficult in critically ill patients because the timing of the renal insult is often unknown, sepsis may lead to false positives, and the pathophysiology of AKI in sepsis patients is complex and not caused only by ischemia and hypotension. Plasma biomarkers may be an indication of the severity of disease rather than of true AKI. Finding the ideal biomarker of AKI and prognosis in the ICU is a subject of intense investigation. Problems and prospects related to biomarker investigation in ICU patients have been reviewed in depth. However, despite the issues mentioned earlier, there are multiple promising serum and urinary biomarkers of AKI for refinement of risk assessment in the ICU, including cystatin C, NGAL, or the combination of TIMP-2 and IGFBP7, all of them detecting AKI before the rise in SCr and predicting the outcome in patients with AKI. Also, these biomarkers have already proven in initial studies to contribute to improved care and outcome. Ultimately, larger disease control and outcome studies are necessary to determine the impact of biomarker screening on reducing the burden of disease.

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KEY POINTS

- Accurate risk assessment and early recognition of AKI in critically ill patients is still a pressing issue.
- During the past several years, the evidence for novel AKI biomarkers with test results available within a short time, including cystatin C, NGAL, and the combination of cell-cycle arrest markers TIMP-2 and IGFBP7, has increased.
- There is evidence that serum cystatin C is a more accurate and earlier marker of kidney filtration function in critically ill patients compared with SCr. Limitations of serum cystatin C are few.
- NGAL and the combination of TIMP-2 and IGFBP7 predict AKI and initiation of RRT 12 hours to 2 days before the event occurs.
- Novel kidney biomarker–complemented clinical decision making has been tested in a few RCTs achieving amelioration of AKI.
- There is a cacophony of other novel kidney biomarkers with their test results not yet available within a short time, including cytokines, L-FABPs, KIM-1, and many more.

References for this chapter can be found at expertconsult.com.

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Water Metabolism

Elchanan Fried and Charles Weissman

Water is the body's most abundant component. Without ingesting sufficient fresh water, humans can survive for just a few days. Ingested water, plus water produced endogenously, must be appropriately excreted to maintain homeostasis. In the human body, water has many functions: intracellular, intravascular, and extracellular carrier of essential substances; body coolant, lubricant, reactant, and product in metabolic reactions; and shock absorber (e.g., cerebrospinal fluid [CSF] surrounding the brain). In critically ill patients, water metabolism and balance present special challenges. Patients are often admitted to the intensive care unit (ICU) with disordered water homeostasis, yet it can also be disturbed by ICU treatments.

Water accounts for 50%–67% of an average person's weight. Because fat has a lower percentage of water and women tend to have more fat, their proportion of water is lower (52%–55%) than that of men (60%). Water percentage is lower in the elderly and obese. A 70-kg man has ~40 L of water: ~25–27 L intracellularly, ~7 L extracellularly, and ~4 L intravascularly. Liquid water is the body's most common molecule, although some water is found in hydrated compounds. Hypovolemia and hypervolemia significantly threaten life. Therefore the body defends fluid volume and osmolarity within very narrow ranges.

WATER INGESTION AND PRODUCTION

Water is ingested via the gastrointestinal tract or infused via venous or interosseous routes. Water intake is regulated by thirst, although normally humans sufficiently self-regulate their intake so that thirst is only occasionally activated. Thirst is also activated by salty food, hot weather, and exercise. The latter two cause sweating and increased respiratory water loss. Adequate water intake is ~3 L/day for men and ~2.2 L/day for women.

Thirst. Thirst, the neurally induced motivation to find and consume water, is vital for defending against hypovolemia. Hypovolemic thirst is triggered when body water levels decrease by ~2%–3%. Hypertonic thirst occurs when osmolality increases to >290 mOsm/kg. Hypotension and hemorrhage also stimulate thirst. Peripheral and central mechanisms detect and react to these physiologic perturbations, leading organisms to seek and ingest appropriate fluids and fluid volumes. Drinking stimulates oral and pharyngeal receptors, thereby providing hypothalamic input to end the thirst sensation. Thirst ends even before plasma tonicity is reduced, likely preventing water overingestion. Thirst sensation is so powerful that normal subjects do not become hypernatremic if they have access to water. The inability to find, detect, react, request, or drink water adequately can cause severe illness and even death. The inability to self-regulate water intake—for example, during anesthesia and critical illness—makes patients totally dependent on caregivers to prevent and treat water disorders.

In the elderly, decreased kidney function, physical and cognitive problems, blunted thirst, and polypharmacy increase dehydration risk. There is also reduced renal sodium conservation (altered renal tubular function, greater peripheral atrial natriuretic peptide [ANP] concentrations but with reduced renal effects, lower renin–angiotensin–aldosterone secretion), decreased renal water excretion (lower renal blood flow, glomerular filtration rate, and distal renal tubular diluting capacity; greater renal passive water reabsorption and antidiuretic hormone [ADH] secretion), and reduced solute delivery caused by poor nutrition, limiting free water excretion. However, during dehydration, ADH secretion is often reduced, causing increased urinary output, and thus worsening the dehydration. A water-loss dehydration prevalence of up to 30% is observed in the elderly with concomitant morbidity.[1] A positron emission tomography study revealed age-associated changes in central nervous system (CNS) satiation patterns in response to hyperosmolarity, which were associated with inadequate hydration.[2] Paradoxically, elderly patients with worsening heart failure have increased thirst.[3]

Metabolic water production. Water is the principal end product of nutrient oxidation (Table 97.1). Although more water molecules are produced per mole of fat than per mole of glucose (129 vs. 36) per kilocalorie, overall, aerobically oxidized carbohydrates contribute to ~15% more water molecules than lipids.[4] An increased metabolic rate increases metabolic water production.

Water Loss

Water is lost through many routes, but mainly through the kidneys. Urine volume and composition depend on hydration status and the osmole load. Fecal losses are generally small, whereas sweating can cause large losses.

Renal function. Renal function, the major mechanism defending against disordered water balance, protects blood osmolarity within a narrow range by altering urine osmolarity over a wide range (50–1200 mOsm/L). Concentrated urine is formed by creating an osmotic gradient that progressively increases from the corticomedullary border to the tip of the inner medulla.[5] When the body must rid itself of excess water, urine can be diluted to as low as 50 mOsm/L.

Aging reduces the maximum urine-concentrating ability. Compared with younger individuals, those aged 60–79 years had a ~20% reduction in maximum urine osmolality, a ~50% decrease in the ability to conserve solute, and a 100% increase in minimum urine flow rate.[6]

Insensible losses. Insensible losses include transepidermal diffusion and evaporation of solute-free water plus evaporative water loss from the respiratory tract. Total insensible losses, ~800 mL/day in unstressed adults, are equally divided between skin and respiratory tract losses. Activity increases respiratory water losses so that active adults

TABLE 97.1 Water and the Human Body

Water Balance

Water balance = (water intake + metabolic water production) − water loss
~5%–10% of body water turns over daily
Total body water (estimate): Children = 0.6 × (wt, kg)
Adult men = 0.6 × (wt, kg)
Adult women = 0.5 × (wt, kg)

Recommended Water Intake

Average energy expenditure (EE) and environmental exposure = 1.0 mL/kcal EE
Increased activity, sweating, and solute load = 1.5 mL/kcal EE

Metabolic Water

Water produced by metabolism (usually oxidation) of endogenous substrates. Approximately 250–350 mL water/day (3–4 mL/kg/day).
Example: Glucose oxidation:

$$C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O$$

Metabolism produces ~110 g water/100 g fat, 41 g water/100 g protein, and 55 g water/100 g starch
~3 g water released per gram metabolized glycogen

Water Loss

Respiratory water loss (250–350 mL water/day) is influenced by temperature and humidity of inspired air
Urinary loss depends on water and solute intake
Insensible losses—skin and respiratory system = 0.7 L/day
Fecal loss—0.1 L/day
Sweating—0.1 L/day
Disease-associated losses—nasogastric drainage, vomiting, diarrhea

Water and Heat Loss

Heat exchange = radiation ± conduction ± convection (+ evaporation)
Heat gain via radiation, conduction, and convection plus endogenous body heat production
Heat loss via radiation, conduction, convection, and evaporation
Sweat evaporation
Heat of water vaporization = 580 calories/g at normal skin temperature
580 calories/g = heat loss to cool down 580 g of water 1°C
Evaporation rate influenced by
- Water temperature at air-water interface
- Air temperature
- Humidity of surrounding air—higher humidity lowers evaporation rate
- Area of air-water interface
- Water's chemical composition—vaporization rate decreases as salt content increases
- Wind speed
- Sweat that drips or is wiped off does not contribute to cooling
- Burn patients lose much water and heat through evaporation from open wounds; therefore they should be treated in warm humid environments and burned areas covered

can lose up to 50 mL/h. Age reduces transepidermal water losses.[7] In febrile patients, insensible losses can increase by fourfold to sixfold.[8]

Respiratory water losses are affected by many factors (see Table 97.1). In normal subjects, mouth breathing resulted in 42% greater water loss compared with nose breathing.[9] Cold exposure increases the need to humidify and warm inspired gases, thus increasing water losses. Using heat-and-moisture-retaining face masks during sleep reduced these losses.[10] In critically ill patients, rapid spontaneous respiratory rates increase respiratory water losses, whereas endotracheal tubes bypass the natural warming and humidifying mechanisms, requiring inspiratory gases to be artificially humidified and warmed.

Sweating. Sweating is mainly a mechanism of thermoregulation, although it also occurs in response to psychologic stress (see Table 97.1). Sweating involves the secretion of water-rich liquid by the eccrine glands located throughout the body surface and secretion of protein-, lipid-, and steroid-containing sweat by the apocrine glands found in the axilla, mammary, perineal, and genital areas. Thermoregulatory sweating mainly involves eccrine secretion occurring in response to intrinsic (fever, exercise) and extrinsic stimuli (elevated environmental temperatures). Maximum adult sweat rates can be 2–4 L/h during intense exercise.

Regulation of Water Balance

Regulating water balance involves central and peripheral volume and osmolarity sensors, providing neural input to the brain and other organs, thereby activating a cascade of endocrine and local activity.

Antidiuretic hormone (ADH)/arginine vasopressin (AVP). ADH is a peptide produced by the neurons of the hypothalamic paraventricular and supraoptic nuclei as a prohormone, prepropressophysin (preprovasopressin), comprising ADH, neurophysin II, and copeptin.[11] Neurons containing osmoreceptors have excitatory synapses with prohormone neurosecretory cells. ADH, bound to the carrier protein neurophysin II, then travels down the pituitary stalk (infundibulum) axons to the posterior pituitary, where it is stored and secreted into the circulation. Plasma osmolarity and plasma ADH concentration have a linear relationship above the osmoregulatory threshold for ADH secretion. This threshold determines when decreased intravascular volume and blood pressure effect ADH release. The threshold is more permissive during hypovolemia. As the hypovolemia worsens, nonosmotically regulated ADH release can persist despite significant hyponatremia.[11]

ADH production and secretion are also stimulated by angiotensin II and decreased blood volume detected by atrial stretch-sensitive low-pressure/vascular volume baroreceptors. A 5%–10% blood volume decrease is necessary for substantial ADH release. ADH is also secreted when carotid sinus and aortic arch baroreceptors detect a 10% blood pressure drop. Copeptin, the C-terminal fragment of the prohormone, is more stable than ADH. Copeptin plasma concentrations are often used as an ADH surrogate.

ADH levels increase the water permeability of distal renal tubules and collecting ducts, thus increasing water reabsorption and resulting in greater urine osmolarity and reduced renal water excretion. ADH binds to vasopressin-2 receptors on renal epithelial cells. These G-protein–coupled receptors activate adenylyl cyclase, converting adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP). Increased cAMP increases the transcription of the aquaporin-2 gene (Aqp2), increasing aquaporin-2 in collecting duct cells and triggering the fusion of aquaporin-2 water channels to the apical membranes of distal tubule and collecting duct epithelial cells, allowing water to move down an osmotic gradient into the nephron.[12] Aquaporin-3, located on the opposite side of the nephron, permits water leaving the nephron to be reabsorbed into the blood. ADH also upregulates aquaporin-3.

cAMP also activates protein kinase A, leading to protein phosphorylation (aquaporin-2 and thiazide-sensitive sodium chloride cotransporter) and upregulating expression of urea transporters, thereby increasing urea permeability of the collecting duct. There is also greater sodium absorption across the ascending loop of Henle. These

two effects further increase distal tubular and collecting duct water reabsorption, resulting in concentrated/hyperosmotic urine, which facilitates body water conservation.

Renin–angiotensin–aldosterone system (RAAS). RAAS is a hormonal system stimulated by changes in renal blood flow. When renal blood flow or blood pressure decreases, juxtaglomerular (JGE) cells in the renal afferent arterioles activate prorenin, which is cleaved to the protease renin (also called *angiotensinogenase*). The renin-producing JGE cells also have β_1-adrenoreceptors, which, when activated by catecholamines, rapidly and significantly stimulate renin release.[13] Renin is secreted into the circulation, where it converts angiotensinogen, an α_2-globulin synthesized by the liver, to angiotensin I. Plasma renin activity plays a major role in determining the rate that angiotensin I is formed from the large amount of angiotensinogen circulating in the plasma.[14] Angiotensinogen production is enhanced by estrogen, thyroxin, and glucocorticoids. There is evidence that cytokines (e.g., interferon-γ, interleukin [IL]-6) also induce angiotensin production, a possible mechanism for maintaining blood pressure during sepsis[15,16]

Angiotensin I is then converted to angiotensin II by angiotensin-converting enzyme (ACE), a glycoprotein found mainly in the lungs but also in endothelial cells and plasma. ACE also breaks down the potent vasodilator bradykinin, providing another mechanism for increasing blood pressure. Angiotensin II, a potent vasoconstrictor, increases systemic blood pressure and decreases renal medullary blood flow and glomerular filtration by vasoconstricting afferent and efferent arterioles. These changes increase sodium and water reabsorption in the loop of Henle. Hydrogen ions are excreted, coupled with bicarbonate reabsorption. Angiotensin II's effects are attributable to its enhancing proximal and distal sodium/hydrogen ion exchanger, basolateral membrane sodium/bicarbonate ion cotransporter, sodium/potassium ion ATPase activity, and distal tubular epithelial sodium channel. Angiotensin II also stimulates posterior pituitary ADH release, further causing water retention.

Angiotensin II's major actions occur via the stimulation of AT1 receptors located in the kidney, brain, heart, blood vessels, and adrenal cortex. The activated receptor couples to G proteins, activating phospholipase C and generating diacylglycerol and inositol trisphosphate. The latter increases cytosolic Ca^{2+} concentrations, which then activate intracellular kinases such as protein kinase C and tyrosine kinases. The activated AT1 receptor also inhibits adenylate cyclase. Angiotensin II also stimulates lower-affinity AT2 receptors, leading to effects opposite those caused by AT1 receptor stimulation. AT2 receptors lower blood pressure by increasing nitric oxide production, enhancing sodium excretion, and inhibiting renin production.[17] The latter action is a feedback loop designed to limit further angiotensin II production.

Angiotensin II also stimulates adrenal cortical aldosterone synthase, which synthesizes aldosterone from deoxycorticosterone. Aldosterone regulates blood pressure by binding to the mineralocorticoid receptors of the renal distal tubular and collecting duct epithelial cells, thereby increasing expression and activity of ion channels in the distal nephron. By upregulating and activating the basolateral Na-K-ATPase pumps, aldosterone increases renal tubular sodium and water reabsorption while boosting the excretion of hydrogen ions and potassium, thereby increasing body fluid volume and blood pressure.

The endocrine RAAS system is augmented by an RAAS with intrarenal paracrine, autocrine, and intracrine activity. Angiotensinogen produced intrarenally is converted by local renin to angiotensin I, which is then metabolized by ACE to angiotensin II and by ACE2 to angiotensin I–VII.[18] ACE is secreted by proximal and distal tubules, collecting ducts, and renal endothelial cells. Although most local effects are attributed to angiotensin II operating through AT1 receptors, angiotensin I–VII, operating through Mas receptors, counteract many of the

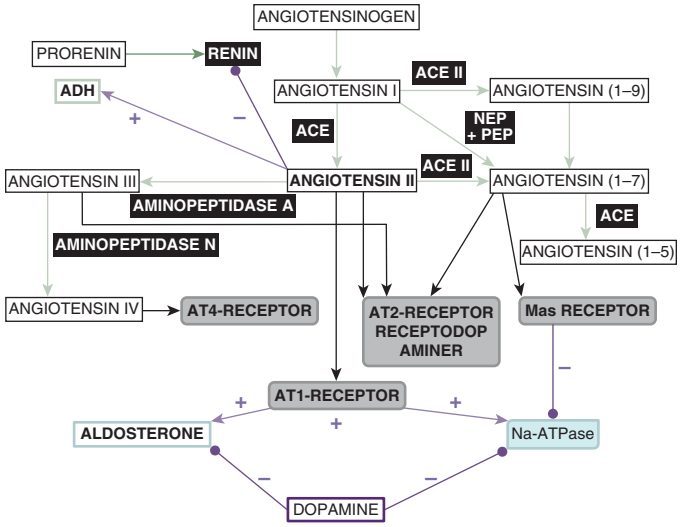

Fig. 97.1 RAAS System Plus Its Interactions with ADH and Dopamine.
ACE, Angiotensin-converting enzyme; *ADH,* antidiuretic hormone.

effects of angiotensin II/AT-1, leading to diuresis, natriuresis, and renal vasodilation (Fig. 97.1). Other local mediators include angiotensin III (angiotensin II–VIII) working via the AT1 receptors and angiotensin IV through the AT4 receptors.[19] Intrarenal angiotensin IV increases cortical blood flow and decreases sodium transport. In addition to the extracellular processing of these mediators, there is evidence that angiotensin II and angiotensin 1–7 also exist intracellularly.[20]

Natriuretic factors (peptides). Natriuretic factors consist of a peptide family involved in water and sodium homeostasis that counteract RAAS effects. A-type natriuretic peptide (ANP), released by atrial myocytes in response to atrial distention secondary to elevated blood volume,[21] is also secreted in response to sympathetic stimulation (α- and β-stimulation), angiotensin II, and endothelin. Cardiac ventricles, brain, adrenal glands, and kidneys (where it also acts as an autocrine/paracrine factor) are additional synthesis sites. ANP decreases circulating water and sodium, reducing atrial distention, and ultimately, lowering blood pressure. Another family member is brain natriuretic peptide (BNP), a peptide so named because it was first identified in porcine brain, although in humans it is mainly released by the cardiac ventricles in response to excessive cardiomyocyte distention. Biologically inactive circulating N-terminal fragments of ANP and BNP prohormones are used as biomarkers.

ANP and BNP increase glomerular filtration rates, reduce sodium and water reabsorption, inhibit renin release, and in proximal tubules, inhibit angiotensin II activity. The natriuretic peptides bind to natriuretic peptide receptor-A (NPR-A), which are membrane guanylate cyclases characterized by a single protein containing both a receptor and enzyme that produce cyclic guanosine monophosphate (cGMP).[22] cGMP targets cGMP-dependent protein kinases, cGMP-gated ion channels, and cGMP-regulated cyclic nucleotide phosphodiesterases [23] Changes in these enzymes and channels cause vasorelaxation, inhibit medullary collecting duct sodium reabsorption, and increase the glomerular filtration rate by dilating afferent and constricting efferent arterioles. This leads to greater glomerular capillary hydraulic pressure that enhances ultrafiltration. ANP, more effectively than BNP, stimulates cGMP production. ANP-induced diuresis and natriuresis occur, in part, by the V2 receptor–mediated action of ADH in the collecting ducts. Natriuretic peptide–induced increases in water and sodium excretion protect the body from overhydration. In pathologic conditions, such as congestive heart failure, ANP and BNP are stimulated by atrial overload secondary to the heart's inability to adequately empty.

Dopamine. The importance of dopamine in water homeostasis remains unclear, although renal production is increased by volume expansion, leading to natriuresis and water loss. Dopamine, synthesized in the renal proximal tubule from circulating L-dopa by L-amino acid decarboxylase, increases the glomerular filtration rate and diminishes sodium reabsorption in proximal tubules and collecting ducts. Dopamine, via D1 receptors, increases cAMP generation by stimulating adenyl cyclase and, via D1/D5 receptor heteromers, stimulates phospholipase C, inhibiting both the Na-K-ATPase pump and sodium/hydrogen ion exchanger-3. D2-like receptors (D2, D3, and D4), which inhibit adenyl cyclase, also inhibit Na^+-H^+ exchanger 3, although the effects of D1 receptors are more dominant. Caveolin-1, a membrane scaffolding protein, helps organize the D1-receptor signaling pathway and intracellular effects.[24, 24a] Renal dopamine production increases as dietary salt intake increases. Renal dopamine is thought to be responsible for regulating over 50% of net renal salt and water excretion when salt intake is increased. Dopamine also decreases aldosterone secretion[25] and inhibits the antinatriuretic effects of angiotensin II.[26] Dopamine is metabolized by the enzymes catechol-O-methyltransferase and monoamine oxidase. Some of the effects of ANP are likely mediated by dopaminergic mechanisms.[15]

Prostaglandins. Local renal prostaglandin (PGE_1 and PGE_2) generation occurs mainly in the distal nephron and is associated with increased basolateral membrane Na-K-ATPase.[27] This leads to greater renal blood flow, often despite decreased effective circulating volume. PGE_2 counteracts excessive sodium and water reabsorption by inhibiting the Na^+K^+-$2Cl^-$ cotransporter in the thick ascending loop of Henle, leading to natriuresis.

Endothelin. Endothelin-1 is a 21–amino acid, predominantly endothelium-derived peptide that operates via autocrine and paracrine mechanisms. In normal subjects, its plasma concentrations are inversely related to glomerular filtration rate (GFR).[28] Endothelin-1 inhibits Na^+ and water reabsorption, thus reversing ADH-mediated osmotic water permeability.[29] This occurs via intrarenal ET_B receptors located in vascular endothelium, vascular smooth muscle, and tubular epithelial cells lining the length of the nephron (with high density in the medullary collecting ducts).[30] Activation of these receptors induces vasorelaxation through the production of nitric oxide and prostacyclin, in addition to direct inhibition of renal tubular sodium uptake and increased urinary water excretion.[31]

Evaluating Water Balance

There are various ways to evaluate water balance (Table 97.2). In the ICU, water balance is generally assessed using body weight and fluid input-output. However, both methods have limitations.

WATER METABOLISM DISORDERS

Abnormal (hypervolemic or hypovolemic) water balance attributable to various intrinsic and extrinsic etiologies results in ICU admissions when the physiologic derangement endangers survival and/or requires treatment under close monitoring.

Hypervolemic Disorders

Hypervolemic disorders are caused by excessive water ingestion and/or the inability to excrete excess body water.

Water intoxication. The classic example of abnormal positive water balance is water intoxication (water poisoning or hyperhydration), where an individual consumes very large volumes of water. Such excess water intake overwhelms the kidney's capacity to excrete water (maximum daily renal capacity ~15 L), despite maximal dilution (urine osmolarity of ~50 mOsm/L).[32,33] This situation results in hyponatremia, hypochloridemia, and hypokalemia. Brain edema occurs secondary to the extracellular to intracellular concentration gradient, leading to headache, delirium, seizures, coma, and death. Other symptoms include nausea, vomiting, twitching, and muscle weakness.

Water intoxication (psychogenic polydipsia) is largely observed in psychiatric patients (predominantly in schizophrenia but also in anorexia nervosa). It is hypothesized that schizophrenics who develop water intoxication have impaired hippocampal regulation, resulting in increased ADH secretion in response to psychological stimuli.[34] Another cause might be the drugs used to treat schizophrenia.[35] Forced water intake in children (such as that associated with suspected child abuse) can also lead to water intoxication, as can excessive drinking in marathon runners and military trainees.[36] Excessive water drinking among users of the recreational drug ecstasy (3,4-methylenedioxymethamphetamine) can cause water intoxication.[37]

Iatrogenic causes of water intoxication include excessive, rapid water ingestion before pelvic ultrasound examinations and transurethral resection of the prostate syndrome. The latter occurs when a large volume of nonconducting (electricity) water plus glycine irrigation solution is absorbed through the prostatic veins and sinuses. The amino acid glycine is rapidly metabolized, causing water overload, hypoosmolarity, and hyponatremia. The introduction of bipolar cautery, which does not disperse electric current, permits using electrolyte-containing irrigation solutions (e.g., normal saline), thereby preventing hypoosmolarity and hyponatremia but not fluid overload. The absorption of water-glycine distention medium during operative hysteroscopy can also lead to intravascular volume overload and water intoxication.

Treatment of water intoxication involves water restriction and loop diuretics. Hypertonic saline is rarely required and should only be considered in cases of severe hyponatremia. Too rapid a correction of hyponatremia can result in central pontine myelinosis.

Syndrome of inappropriate antidiuretic hormone secretion (SIADH). SIADH causes hyponatremia and hypoosmolality because of impaired water excretion secondary to inappropriate, continued secretion or action of ADH despite normal or increased plasma volume. ADH promotes water reabsorption without affecting sodium reabsorption, leading to dilutional hyponatremia because of water excess rather than sodium deficiency.

Excessive water reabsorption activates volume receptors, causing the secretion of natriuretic peptides and natriuresis. Eventually, a steady state is reached with urinary sodium excretion matching sodium intake. Therefore only when water intake exceeds the reduced urine output does hyponatremia develop. Importantly, hyponatremia does not occur with severely restricted water intake. In addition to inappropriate ADH secretion, SIADH may include inappropriate thirst sensation, leading to water intake in excess of free water excretion. This increased water intake helps maintain hyponatremia.

SIADH includes hyponatremia, inappropriately elevated urine osmolality (>100 mOsm/kg), and reduced serum osmolality in a euvolemic patient (Fig. 97.2). SIADH should be considered when these findings occur in the setting of otherwise normal cardiac, renal, adrenal, hepatic, and thyroid function; absence of diuretic therapy; and absence of other factors that stimulate ADH secretion such as hypotension, severe pain, nausea, and stress.

Impaired ADH regulation in SIADH:

- Type A—erratic, unregulated ADH release unrelated to plasma osmolality.
- Type B—modest, constant ADH secretion.

TABLE 97.2 Evaluating Water Balance

Quantifying Input and Output

Clinical computation

Fluid balance = input (all intravenous and enteral intakes) − output (urine, GI, other drainages)

Often does not include

Intake: Accurate quantification of blood products, irrigation fluids

Output: Diarrhea, fluid lost into linens and bandages, insensible losses (skin, respiratory), sensible losses (sweating caused by fever, surface exudation from burns)

Body Weight

Fluid balance = Δ body weight

Requires accurate scale and bed taring

Tare weight = weight of bed without patient but with sheets, pillows, etc.

Net weight (patient weight) = gross weight (total weight) − tare weight

Urine Specific Gravity

U_{sg} = density of urine/density of water

Range: 1.003–1.035

Euhydration: 1.010–1.026

High-molecular-weight substances (e.g., glucose, protein, and radiographic contrast) can increase U_{sg} >1.035.

Serum and Plasma Osmolality/Osmolarity

Osmolarity = osmoles of solute/liter solution

Osmolality = osmoles of solute/kilogram solvent

Urine and plasma osmolalities should be measured but can be estimated

Calculated serum osmolarity (when using SI units [mmol/L])

Calculated serum osmolarity = $2(Na^+) + 2(K^+)$ + glucose + urea (BUN)

OR

Calculated serum osmolarity = $2(Na^+)$ + glucose + urea (BUN)

Calculated serum osmolarity (when Na^+ is mEq/L and glucose and BUN are [mg/dL])

Calculated serum osmolarity = $2[Na^+]$ + [glucose]/18 + [BUN]/2

Normal serum osmolality: 275–290 mOsm/kg; 295–300 mOsm/kg indicates impending dehydration; >300 mOsm/kg indicates dehydration

Urine: specific gravity vs. osmolality

Unlike specific gravity, osmolality is unaffected by the number and size of particles in solution; urine containing glucose and/or protein will have a specific gravity greater than osmolality

U_{sg} = 1.020–1.030 corresponds to osmolality of 800–1200 mOsm/kg H_2O

U_{sg} = 1.005 is an osmolality <100 mOsm/kg H_2O

Normal kidneys can concentrate urine to an osmolality four times greater than serum and dilute urine to 25% of serum osmolality.

Electrolyte–Free Water Clearance

Electrolyte–free water clearance ($T^e_{H_2O}$) − amount of water in urine free of solutes

$T^e_{H_2O} = V([U_{NA} + U_K]/P_{NA}) - 1$

V = total urine volume

U_{NA} = urine (Na^+)

U_K = urine (K^+)

P_{NA} = plasma (Na^+)

Positive $T^e_{H_2O}$ = water is being excreted (e.g., causing hypernatremia)

Negative $T^e_{H_2O}$ = water is being reabsorbed (e.g., causing hyponatremia)

Free Water Deficit

In hypernatremia, estimated free water deficit

$$\text{Water deficit} = \text{TBW} * (\{\text{serum[Na]}/140\} - 1)$$

TBW = estimated total body water: men, 0.6*Wt (kg); women, 0.5*Wt (kg); in the elderly and those significantly dehydrated: men, 0.5*Wt (kg); women, 0.4*Wt (kg)

This estimate does not account for ongoing water (i.e., insensible, urine, GI tract) or isoosmotic fluid (i.e., osmotic diuresis, diarrhea) losses that continue to contribute to water deficit.

Bioelectric Impedance

Noninvasive method used to estimate total body water based on the assumption that only body water conducts electricity, whereas fat, which has little water content, restricts the flow of current. However, this technique is limited by the assumptions used, such as assuming that fat-free mass has a constant hydration of 73%.[67]

BUN, Blood urea nitrogen; *GI,* gastrointestinal.

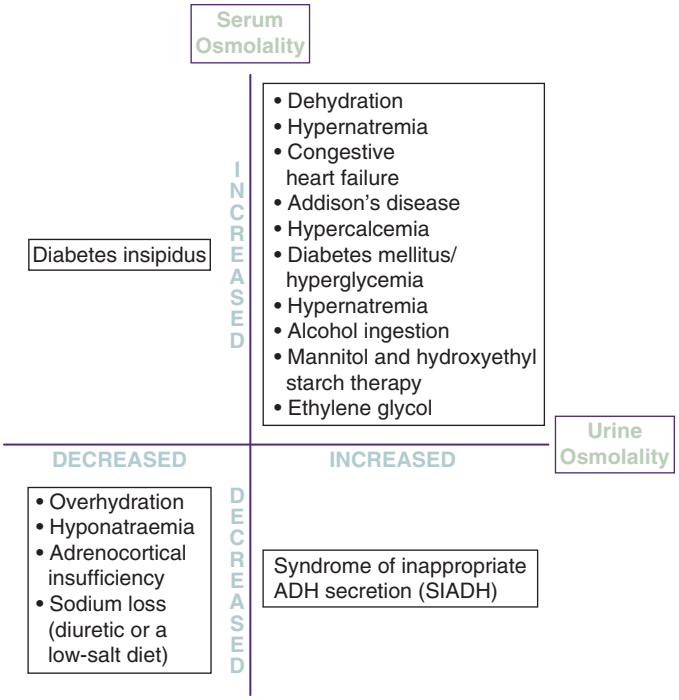

Fig. 97.2 Relationships Between Serum and Urine Osmolality.

- Type C—("reset osmostat")—downward resetting of the osmostat. Plasma sodium concentrations are regulated at a lower level and continue to fall without therapy.
- Type D—normal osmoregulation. ADH secretion varies appropriately with the plasma osmolality, but urine is concentrated even if ADH release is suppressed (e.g., vasopressin receptor is constituently activated, production of antidiuretic compound other than ADH, postreceptor defect in transferring aquaporin-2 water channels).

Classification of SIADH etiology:

- CNS disorders (e.g., stroke, hemorrhage, infection, inflammation, trauma, neurosurgery, acute intermittent porphyria). Must differentiate SIADH from cerebral salt wasting (ADH secretion is secondary to reduced extracellular fluid volume).
- Ectopic (paraneoplastic) ADH production by tumors (small cell lung carcinoma in 75% of cases).
- Pulmonary diseases (pneumonia, asthma, atelectasis, pneumothorax).
- Drugs that mimic ADH, stimulate ADH release, potentiate ADH effects, or have unclear mechanisms (e.g., exogenous ADH analogs such as vasopressin, desmopressin, selective serotonin reuptake inhibitors [SSRIs], phenothiazines, tricyclics, carbamazepine, cyclophosphamide, vincristine).
- Hormonal deficiency (hypothyroidism, hypopituitarism, Addison disease).
- Postoperative (likely mediated by pain afferents), transsphenoidal surgery.
- Symptomatic HIV infection.
- Hereditary/genetic—(e.g., gain-of-function mutation of arginine vasopressin receptor type 2—nephrogenic syndrome of inappropriate antidiuresis—causing constitutive receptor activation).
- Aging.
- Unknown origin/idiopathic.

Acute treatment includes water restriction and treating the underlying cause (e.g., stopping the offending drug, treating pneumonia, meningitis). In severe symptomatic cases associated with neurologic complications, hypertonic saline is administered to gradually correct hyponatremia. Loop diuretics can be useful by aiding water excretion. However, too rapid correction of serum sodium concentrations, especially in asymptomatic patients, can result in neurologic impairment from central pontine myelinolysis. Another complication of aggressive sodium correction is severe hypernatremia.

Pharmacologic treatment for SIADH includes vasopressin receptor antagonists (vaptans), which competitively bind to V2 receptors. An advantage of these agents is their ability to reduce the need for severe fluid restriction, while correcting hyponatremia within a short time. During the initial 24 hours of administration, it is critical to prevent overly rapid correction of hyponatremia. Discontinuing vaptan therapy for more than 5–6 days requires monitoring for hyponatremic relapse. Therefore it is prudent to taper the vaptan dose while restricting fluid intake. Side effects include thirst, polydipsia, and urinary frequency. Vaptans are ineffective in inappropriate antidiuresis caused by constitutive activating mutations of V2 receptors.

Oral urea is a new-old therapy that is now more available and that serves as an osmotic agent to increase urinary free water excretion. European clinical guidelines recommend the use of urea and discourage the use of vasopressin receptor antagonists (vaptans).[38,39]

Another treatment for SIADH is demeclocycline, a macrolide antibiotic, which induces nephrogenic diabetes insipidus by reducing adenylate cyclase expression, cAMP generation, AQP2 gene transcription, and AQP2 abundance in the renal medulla. Its frequent side effects include nausea and skin photosensitivity.

Cerebral (renal) salt-wasting syndrome (CSW). CSW is the extracellular volume depletion caused by abnormal sodium transport in patients with intracranial disease (but can also occur in patients without cerebral disease) and normal adrenal and thyroid function.[40] CSW usually develops in the week after brain insult. Its duration is usually brief (2–4 weeks) but can last for several months. Both SIADH and CSW present with low serum osmolality, elevated urine osmolality, and high urinary sodium concentrations. The basic difference is that in CSW, there is hypovolemia, whereas in SIADH, there is euvolemia or mild hypervolemia. Urinary sodium concentrations are elevated in SIADH and CSW (>40 mEq/L). However, urinary sodium excretion (urinary sodium concentration [mEq/L] × urinary volume [L/24 h]) is much higher than sodium intake in CSW but usually equals sodium intake in SIADH. Therefore net sodium balance is negative in CSW. Failure to distinguish CSW from SIADH in hyponatremic brain-injured patients can lead to inappropriate therapy with fluid restriction.

In CSW, excessive sodium is lost in the proximal tubule, leading to reduced effective circulating volume. The two proposed mechanisms are the excessive secretion of natriuretic peptides (BNP and C-type natriuretic peptide [CNP]) and the loss of renal sympathetic stimulation. Both the mechanisms reduce proximal and possibly distal sodium transport. The ensuing hypovolemia leads to baroreceptor activation increasing ADH secretion and water conservation in an attempt to return to a euvolemic state. In contrast, SIADH is caused by an inappropriate euvolemic increase in ADH secretion. Depressed sympathetic drive and increased BNP concentrations are also associated with decreased renin and aldosterone concentrations, further inhibiting sodium retention.

The decreased serum sodium concentration associated with CSW reduces serum osmolality, and a tonicity gradient develops across the blood-brain barrier, causing or exacerbating cerebral edema. Symptoms include lethargy, agitation, headache, altered consciousness, seizures, and coma. Treatment involves correcting intravascular volume depletion and hyponatremia, plus replacing persistent urinary sodium loss with intravenous normal or hypertonic saline solutions. Saline infusion corrects the hypovolemia, removing a potent stimulus for ADH secretion, increasing free water excretion, and correcting the

hyponatremia. There are reports of favorable responses to mineralocorticoid therapy. Once the patient is stabilized, enteral salt supplementation should be considered.

Hepatic cirrhosis. Regardless of etiology (alcoholic, chronic hepatitis, autoimmune, genetic, cryptogenic), cirrhosis involves the loss of normal hepatic architecture and irreversible liver damage. Cirrhosis changes splanchnic circulation, causing mechanical obstruction to the portal flow and portal hypertension. Ascites occurs when portal pressures of >12 mm Hg cause intrahepatic sinusoidal hypertension. If portal pressure decreases to <12 mm Hg (e.g., after portosystemic shunt), ascites usually disappears. Presinusoidal portal hypertension (e.g., portal vein thrombosis) does not cause ascites in the absence of another predisposing factor.

In addition to the mechanical obstruction to portal flow, cirrhosis is associated with an increased portal venous inflow secondary to splanchnic arterial vasodilation and the opening of portosystemic collaterals. The latter, because of increased circulating vasodilators, such as nitric oxide and prostacyclin, reduces systemic vascular resistance and arterial pressure. Cardiac output increases in compensation. This hyperdynamic pattern can be found in cirrhotic patients even before ascites develops. In response to cirrhosis-associated vasodilation, endogenous vasoconstrictors and sodium-retaining neurohumoral mechanisms activate (RAAS, sympathetic nervous system, ADH) in an attempt to normalize perfusion pressure. The net effect is sodium and water retention. However, cirrhotics are effectively intravascularly volume depleted despite increased extracellular sodium stores, plasma volume, and cardiac output. As the disease progresses, solute-free water excretion is increasingly impaired because of the increased ADH secretion. Reduced water excretion plus ascites accumulation adds to total body fluid overload. The intravascular depletion leads to further "compensation," including nonosmotic ADH secretion, worsening excess water retention, hypoosmolality, and dilutional hyponatremia. Nonosmotic ADH secretion is mediated via atrial, ventricular, aortic arch, and carotid sinus baroreceptors, which stimulate hypothalamic ADH release. This ADH secretion is paradoxical because serum osmolarity is low. The net result is enhanced sodium and water retention, which attempts to correct the depleted circulatory volume. Sodium retention occurs despite increased total body extracellular sodium concentrations. RAAS activation encourages water retention, which contributes to the development of hypervolemic hyponatremia. However, hypovolemic hyponatremia secondary to diuretic treatment is more common than hypervolemic hyponatremia.[41] Hyponatremia severity correlates with worsening survival and morbidity. Hyponatremia is an important prognostic marker before and after hepatic transplantation.

Other factors implicated in the development of hyponatremia and associated with cirrhosis include decreased renal PGE_2 production and slower ADH metabolism. Resistance to the natriuretic action of ANP may play a role in sodium retention. Renal perfusion in cirrhosis with ascites depends on a delicate equilibrium between the degree of stimulation of vasoconstrictor systems (sympathetic nervous system, RAAS) and the activity of intrarenal vasodilator compounds (prostaglandins and nitric oxide). Imbalance between systemic vasoconstriction and local renal vasodilation can result in progressive renal failure (hepatorenal syndrome).[42,43]

Stressed states. Exudation of protein-rich intravascular fluid from plasma to the extracellular space resulting in relative intravascular hypovolemia is the hallmark of stressed states (sepsis, pancreatitis, burns). It also occurs in ovarian hyperstimulation syndrome, anaphylaxis, viral hemorrhagic fevers, influenza, snakebite envenomation, ricin poisoning, and some immunotherapies including chimeric antigen receptor (CAR) T-cell therapy (cytokine release syndrome). Such exudation leads to sequelae, including acute respiratory distress syndrome, diffuse edema, and abdominal compartment syndromes. Plasma ADH, angiotensin, and aldosterone are usually increased during the initial phase of septic shock and burns and decrease later in the course.[44] Extravascular fluid shifts diminish as the patient convalesces. The greater the fluid accumulation, the greater the morbidity and mortality. There is currently no direct treatment for this condition.

The endothelium tightly controls intravascular fluid exchange from the circulation to the tissues. Dysfunction of this barrier causes fluid exudation and edema. Various mechanisms appear involved in increasing membrane permeability. The main function of vascular endothelial (VE)-cadherin, a cell adhesion molecule localized to endothelial cell junctions, is regulating and forming a homophilic calcium-dependent bond with a twin on an adjacent cell. The cytoplasmic domain of VE-cadherin is bound to catenins, which attach to the cytoskeletal structure. When endothelial cells are exposed to permeability factors, they contract via myosin-actin crossbridge cycling, resulting in the dissociation of VE-cadherin from its adjacent homolog, forming gaps between the endothelial cells. In addition, the endothelial glycocalyx, a carbohydrate-rich layer lining the luminal surface of the entire vascular endothelium, is thinned, contributing to capillary permeability. Permeability factors include proinflammatory cytokines (tumor necrosis factor [TNF], IL-6, IL-8, interferon-γ, IL-1β), nuclear transcription factors (high-mobility group box 1 [HMGB1]), transforming growth factor, and vascular endothelial growth factor (VEGF). These factors likely operate through the MyD88-ARNO-ARF6-signaling axis while also diminishing VE-cadherin expression.[45] VE-cadherin is internalized by VEGF-induced signaling through VEGF receptors and undergoes tyrosine phosphorylation, leading to greater VE cell detachment and transendothelial permeability. Matrix metalloproteases (e.g., MMP-9, gelatinase b) have been implicated as degrading interendothelial adherens junction proteins. An associated mechanism is activation of Rho-A GTPase, which increases actomyosin contractility, inducing intercellular junction breakdown and enhancing permeability.[46]

Hypovolemic Disorders

Diabetes insipidus (DI). DI, polyuria (defined as a urine output exceeding 3 L/day in adults and 2 L/m^2 in children) caused by plasma ADH deficiency or renal resistance to ADH's effects, is characterized by the failure to appropriately concentrate urine.

In the absence of ADH (<0.5 pg/mL), renal collecting duct membranes become impermeable to water (fewer aquaporin-2 water channels), thereby allowing the formation of dilute filtrate in proximal nephrons. This results in the excretion of relatively large urine volumes of low osmolality (≥100 mOsm/kg), causing hypovolemia and even hypotension. These stimulate hypothalamic osmoregulators, encouraging water intake via thirst. With normal thirst and access to water, fluid intake increases to compensate for most of the water loss. Consequently, even in the complete absence of vasopressin, urine output and fluid intake increase in parallel, maintaining plasma osmolality within the normal range. Severe dehydration and hypernatremia occur when access to water or intravenous fluids is lacking or there is coexisting thirst deficiency.

The most common cause of DI is inadequate neurohypophyseal ADH secretion, resulting in partial or complete central DI. Nephrogenic DI is characterized by normal ADH secretion with varying degrees of renal resistance to its antidiuretic effect. Another mechanism is the suppression of ADH secretion by excessive water intake, as seen in primary polydipsia. ADH insufficiency can rarely result from increased metabolic clearance during pregnancy because of the placental production of the aminopeptidase vasopressinase, which rapidly

degrades ADH, causing a fourfold to sixfold increase in ADH metabolism. In most women, the pituitary compensates by producing more ADH. In some women, presumably those with diminished ADH secretory reserves, polyuria develops. This usually occurs during the third trimester and spontaneously resolves after placental delivery.

Central DI can be caused by defects along the ADH neurosecretory pathway, including genetic mutations affecting ADH synthesis and packaging, damage to ADH-producing magnocellular neurons or the supraopticohypophyseal tract, and disorders of neurohypophyseal hormone release. Five percent of central DI cases are familial/genetic; >50 mutations have been identified in the AVP-neurophysin II gene (chromosome 20), and other loci have been described. Thirty to fifty percent of cases are considered "idiopathic" (autoimmune, aberrant posterior pituitary blood supply). Other causes include neoplasms involving the hypothalamus (craniopharyngiomas, germinomas, metastatic disease of the posterior pituitary [breast or lung cancer]) and granulomas (sarcoidosis, tuberculosis, granulomatosis with polyangiitis, Langerhans cell histiocytosis [histiocytosis X]). In the ICU, common causes are trauma—for example, closed head injury, postcraniotomy, anterior communicating artery (ACA) aneurysmal rupture causing subarachnoid or intracerebral hemorrhage (ACA aneurysms and their treatment can compromise hypothalamic blood supply), brain abscess, subdural hemorrhage (DI persisted for 3 months in 8% of survivors), and ischemic brain injury.[47] Transient or permanent DI occurs in 8%–9% of endoscopic transsphenoidal surgeries.

Nephrogenic DI may reflect an intrinsic renal defect, a congenital condition (primary nephrogenic DI caused by mutations of the genes encoding vasopressin V2 receptor [*AVPR2*] and aquaporin [*AQP2*]), or may be acquired secondary to metabolic disease or medication. It is characterized by complete or partial deficiency to the renal antidiuretic response to normal or increased ADH concentrations. Adults generally have an acquired form. Normal aging can also result in partial nephrogenic DI. In terms of drugs inducing nephrogenic DI, lithium is the most common offender, with nephrogenic DI reported in 25%–55% of patients receiving lithium. With long-term use, lithium-induced DI can become irreversible. Hypercalcemia and hypokalemia can partially block renal ADH action. Hereditary forms of nephrogenic DI are caused by defective renal ADH V2 receptor (males with X-linked recessive defect in chromosome region Xq28) or aquaporin-2 genes.

Adipsic DI is a condition where impaired thirst complicates deranged water balance. It is closely associated with ACA aneurysm clipping and is characterized by dramatic increases in plasma ADH concentrations during nonosmotic stimuli such as hypotension. This situation reflects intact supraoptic and paraventricular nuclei and the posterior pituitary with abnormalities of the anterior pituitary osmoreceptors. Vascular supply to this latter area is from small arterioles supplied by the ACA. Disrupting this blood supply causes infarction that impairs ADH secretion response to thirst or hyperosmolarity.

A diagnosis of DI is made when urine volume is markedly increased and urine osmolality is very low (<100 mmol/kg), which is associated with elevated plasma osmolality (>300 mmol/kg) and serum sodium concentrations (>145 mmol/L). However, other causes of polyuria must be excluded—for example, excessive fluid resuscitation, osmotic diuresis, hypertonic saline infusion, and so on. When basal plasma osmolality and sodium are within normal ranges, osmotic stimulation with a formal water deprivation test or hypertonic saline infusion (if necessary) to achieve plasma osmolality of >295–300 mOsm/kg is indicated. If there is no change in the water loss despite fluid deprivation, the type (central or nephrogenic) of DI should be determined by monitoring the response to administered ADH or 1-deamino-8-D-arginine vasopressin (DDAVP-desmopressin), a synthetic ADH analog. A significant increase in urine osmolality 1–2 hours after subcutaneously or intravenously injecting 1 μg of DDAVP indicates insufficient endogenous ADH and probable central DI. Little or no increase in urinary concentration indicates renal resistance to ADH and severe nephrogenic DI. Some cases are not as straightforward and require further evaluation with a 2-day therapeutic trial of DDAVP, magnetic resonance imaging (MRI) of the hypothalamus and pituitary, and plasma ADH and copeptin measurements.

While diagnosing and identifying the cause of the DI, it is imperative that adequate fluid intake is maintained. The treatment for central DI is either intravenous ADH (vasopressin) or oral, intranasal, or parenteral DDAVP. DDAVP is a synthetic ADH analog with a longer half-life than the native hormone. In nephrogenic DI, therapeutic options are only partially effective: a low-sodium diet, thiazide diuretics, prostaglandin E synthetase inhibitors, and nonsteroidal antiinflammatory drugs may partially decrease urine volume. The potassium-sparing diuretic amiloride is used in lithium-induced nephrogenic DI (it induces natriuresis and reduces lithium uptake in the distal tubules and collecting ducts, blunting lithium's inhibition of water reabsorption). Pregnancy-associated DI can be controlled with vasopressinase-resistant DDAVP but not ADH.[48]

Osmotic diuresis. Osmotic diuresis is characterized by increased urination caused by nonreabsorbed solutes (e.g., glucose and urea) in renal proximal tubules. Increased osmotic pressure within the tubule causes luminal water retention, reducing water reabsorption and increasing urine output. When blood glucose exceeds 160–180 mg/dL, the proximal tubule is overwhelmed, causing glycosuria. Osmotic urea diuresis is common in the ICU, associated with high-protein nutrition, high corticosteroid doses, and resolving acute renal failure. Hypernatremia ensues because of the greater urinary loss of water than electrolytes.[49]

Therapeutic agents (e.g., mannitol) are used to increase urine output and decrease extracellular fluid volume. Mannitol, freely filtered by the glomerulus and not reabsorbed, acts as an osmotic diuretic, increasing urinary losses of electrolyte-free water. Osmotic substances increase blood osmolarity, thereby pulling water from the interstitial space and increasing GFR and urine output. Failure to replace fluid losses can lead to volume depletion and hypernatremia. However, if very high doses of hypertonic mannitol are infused, or if it is administered to patients with preexisting renal failure, mannitol is retained in the circulation. The resulting plasma osmolality increase, like that produced by hyperglycemia, causes osmotic movement of water out of cells, leading to extracellular fluid volume expansion and dilutional hyponatremia. This can result in intravascular fluid overload, especially if the excess fluid and osmotic substances cannot be excreted.

Osmotic diuresis generally leads to significant free water losses and can cause or contribute to hypernatremia. However, with glycosuria secondary to uncontrolled diabetes mellitus, diabetic ketoacidosis, and hyperosmolar hyperglycemic state, most patients are mildly hyponatremic. The serum sodium concentration reflects the balance between the dilutional effect of water moving out of cells in response to the hyperglycemia-induced increase in serum osmolality (dilutional hyponatremia—i.e., true hypertonic hypervolemic hyponatremia) and the increased water excretion due to glycosuria-induced osmotic diuresis.

Treating water losses secondary to osmotic diuresis involves reducing the nonreabsorbed solute either by stopping its administration (e.g., mannitol) or treating the underlying pathologic condition (e.g., reduce blood glucose concentrations). Furthermore, excessive dehydration should be treated and prevented by administering sufficient fluid with close monitoring of serum and urine electrolytes plus urine output.[50]

Cold diuresis. Cold or cold-induced diuresis occurs during exposure to a hypothermic environment and during mild to moderate

accidental and therapeutic hypothermia. During therapeutic hypothermia, cold diuresis is most apparent during the induction phase.[51] Cold diuresis is characterized by increased sodium and chloride excretion, leading to enhanced water loss, decreased blood volume, and increased blood viscosity. The latter augments the increased viscosity secondary to the hypothermia. Vasoconstriction and hypovolemia caused by hypothermia are most problematic; thus vasodilation during rewarming must be countered by fluid resuscitation to avoid hypotension.

Possible causes of cold diuresis include the redirection of blood from vasoconstricted extremities to the core, leading to increased core fluid volume. The latter leads to increased renal blood flow and diuresis. ADH appears to be involved in cold diuresis. Some investigators report decreased ADH, whereas others report that although ADH concentrations are elevated, cold exposure inhibits renal V2 receptors, decreasing V2 receptor mRNA expression and inducible renal medullar AQP-2 water channel protein expression.[52] ANP does not appear to be involved in cold diuresis.

Heat and exercise-induced disorders. Sweat is hypoosmotic relative to plasma; hence, excessive sweating can lead to significant water loss, reaching >2.5 L/h during strenuous exercise.[53] Sweat sodium concentrations range from 15 to 90 mmol/L, with an average of 40 mmol/L. As sweating increases, sodium secretion rates proportionally increase. However, heat acclimatization lowers sodium chloride concentration. The rate of sweat potassium losses appears to be indirectly related to the sweat flow rate.[54] Maintaining normal hydration during exercise maintains cardiovascular and thermoregulatory responses. Whenever possible, oral, rather than intravenous (IV), rehydration should be performed. Although IV fluids rehydrate faster, the benefits are often transient, with the major limitation being the bypassing of the oropharynx. Oropharyngeal stimulation influences thirst sensation, ADH release, cutaneous vasodilation, and mean arterial pressure.[55] Therefore drinking water plus electrolyte solutions to minimize dehydration is necessary during and after significant exercise and heat exposure. To maintain adequate hydration, elite athletes, ingest ~200–800 mL/h. Less acclimatized participants should not drink as much as possible, but according to the stimulation of thirst and no more than 400–800 mL/h.

In collapsed marathon runners, there are significant incidences of both hypernatremia with hyperosmolality and hyponatremia with hypoosmolality. The latter is often the result of hyperhydration, caused by considerable water ingestion, and may be exacerbated by nonosmotic ADH secretion.[56] Hypernatremia results when water loss via sweating is associated with a low or insufficient fluid intake.[57] Hyponatremia, hyperthermia, hypertonic hypernatremia, orthostatic hypotension caused by decreased peripheral resistance, and dehydration can each contribute to cerebral dysfunction.[58,59] Moreover, it is crucial to differentiate between hypernatremia and hyponatremia because the immediate management differs. Administering hypotonic fluids to severely hyponatremic patients may cause fatal cerebral edema, evidenced by seizures and/or coma. Therefore laboratory testing to determine serum sodium concentration is vital to direct therapy.

Heat stress illness (HSI), also called *heat-related illness,* includes benign rash, heat syncope, heat cramps, heat exhaustion (most common HSI), and heat stroke (most severe form). During 2001–2010, ~28,000 HSI hospitalizations occurred in 20 states.[60] HSI occurs during heat exposure with and without exercise, with greater thermoregulatory heat strain occurring during high humidity because of decreased environmental evaporative capacity. Obesity, heart failure, preexisting neuropsychiatric disorder, psychotropic drug intake (e.g., phenothiazines, cocaine), and strenuous outdoor work[61] are associated with increased HSI risk. HSI development and severity are significantly related to hydration status and ability to sweat.[62,63] HSI is exacerbated by hypovolemia and plasma hyperosmolality, which inhibit thermoregulatory responses, such as cutaneous vasodilation and sweating.[64] Elevated core temperature does not stimulate ADH secretion except with increased serum osmolality.[65] HSI treatment includes rapid cooling, fluid replacement, and physiologic support.

CONCLUSION

Maintaining homeostatic water balance is a vital body function commonly disordered in critically ill patients because of combinations of their acute illness, underlying chronic diseases, treatments, and aging. Modern critical care medicine needs to better understand water metabolism, especially the microcirculatory consequences of edematous and overhydrated states. Such a better understanding should influence treatment—for example, whether to treat with saluretic diuretics that enhance sodium excretion or with aquaretics that increase water excretion.[66]

KEY POINTS

- Water, the liquid of life for all organisms, has many functions: carrier of essential substances; body coolant, lubricant, reactant, and product in metabolic reactions; and shock absorber.
- Water homeostasis is controlled by thirst, the ability to find and ingest water, kidney function, sweating, and endogenous systems.
- Endogenous systems active in water metabolism include ADH, the RAAS system, natriuretic peptides, dopamine, and renal intracrine mechanisms.
- Environmental conditions—extreme heat and cold—can cause disordered water homeostasis, as can diarrhea, drugs, excessive water ingestion, and disorders of endogenous systems (DI, SIADH).
- In stressed states (e.g., sepsis, burns, and trauma), plasma ADH and aldosterone are increased during the initial phase, accompanied by extravascular exudation of protein-rich fluids.
- Critically ill patients are totally dependent on their care providers for maintaining water homeostasis and for preventing and correcting disordered homeostasis.

References for this chapter can be found at expertconsult.com.

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Advanced Techniques in Blood Purification

Antoine Streichenberger, Pauline Sambin, Celine Monard, and Thomas Rimmelé

INTRODUCTION

During the last decade, several blood purification techniques have been developed. Blood purification techniques are extracorporeal treatments that can either be combined with renal replacement therapy (RRT) or used as standalone methods. Their common objective is to remove from the blood proteins or cells that may have deleterious effects. These techniques are mostly used in septic shock, targeting endotoxins, cytokines, proinflammatory cells, or even bacteria and viruses.

Most randomized controlled trials (RCTs) have failed so far to demonstrate an improved survival with the initiation of extracorporeal blood purification sessions in sepsis. Numerous biases from published trials have been underlined, including the heterogeneity of studied populations, timing of treatment initiation, dose, and duration of the therapy. This was specifically reinforced in the 2016 Surviving Sepsis Campaign. Given the lack of positive RCTs, no recommendations relating to blood purification techniques in sepsis could be made, and further research was encouraged.[1] The same reservations apply to artificial liver support systems that are not routinely implemented in intensive care units (ICUs) because of the lack of conclusive RCTs.

This chapter will first describe the dysregulated immune response observed in sepsis and the potential targets of extracorporeal blood purification in this specific context. Second, the main blood purification techniques and related literature will be presented. Finally, we will review the indications for blood purification outside sepsis and the liver support technology.

PATHOPHYSIOLOGY OF DYSREGULATED IMMUNE RESPONSE IN SEPSIS AND TARGETS FOR BLOOD PURIFICATION TECHNIQUES

The Dysregulated Immune Response in Sepsis

Pathophysiology of the immune response in septic shock is usually described in two phases. During the first phase, a massive dysregulated proinflammatory component, also called a *cytokine storm,* is associated with tissue damage, organ injuries, and early mortality. During the second phase, the predominant antiinflammatory component, triggering immunoparalysis, is responsible for nosocomial infections, viral reactivations, and late mortality.[2]

During pathogen invasion (either bacteria, viruses, fungi, or parasites), numerous molecular signals are activated, driving the immunoinflammatory response. These alerts are triggered by pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs)[3,4]. PAMPs are described as the "molecular signature" of pathogens. They are not produced by the host, but they are expressed at the pathogen surface and include endotoxins at the surface of gram-negative bacteria, double-stranded ribonucleic acid (RNA) produced by most viruses, and beta-glucans and mannans found in fungi. DAMPs are endogenous molecules, such as high-mobility group box 1 or extranuclear deoxyribonucleic acid (DNA), released during tissue damage.[5,6] DAMPs are released during sepsis but also during specific conditions such as burns, trauma, surgery, or acute pancreatitis, triggering a sterile inflammatory response.[7–10] Both PAMPs and DAMPs are recognized by pattern recognition receptors (PRRs), which are ubiquitous on the surface of innate immune cells. Importantly, activation of PRRs by PAMPs or DAMPs leads to the appropriate synthesis of cytokines and the immune response. However, in septic shock, the inflammatory response is dysregulated and leads to a massive release of cytokines (interleukin [IL]-1, IL-17, IL-6, tumor necrosis factor [TNF]-alpha) and an intense activation of complement.

Concomitantly, immunosuppressive patterns also appear, mainly consisting of a reduced antigen-presenting cell function and reduced human leukocyte antigen–DR isotype (HLA-DR) expression on monocytes (mHLDA-DR), which correlates with mortality and lymphocyte apoptosis.[11–13] Lymphopenia is also a marker of immunosuppression in sepsis and has a poor prognosis. The massive production of the antiinflammatory IL-10 cytokine participates in sepsis-induced immunosuppression as well.[14]

Immunomodulatory Therapies and Targets for Extracorporeal Blood Purification

Along with antibiotics, controlling the site of infection, and symptomatic treatment, numerous intravenous treatments targeting specific pathways such as IFN-γ, rhIL-7, and TNF-alpha have been tested to modulate the immunoinflammatory cascade in sepsis.[15] Unfortunately, all these treatments have failed to demonstrate any benefits on morbidity and mortality.[15] Again, some authors have highlighted sepsis "heterogeneity" with regard to the site of infection, pathogens, genetic background, and premorbid conditions. Other experts have argued that all these molecules target a specific pathway of the immune response, whereas a more global approach might be more efficient. Based on this second hypothesis, extracorporeal blood purification techniques have been developed to control the dysregulation of the immune system with the removal from the blood a large panel of components that participate in the inflammatory response.

Several extracorporeal techniques have been developed during the last two decades. They target different mediators of the immunoinflammatory response, which can be endotoxins, cytokines, proinflammatory cells, or pathogens such as bacteria and viruses. Most techniques are developed towards one particular target, but some are able to remove two or more mediators (e.g., cytokines and endotoxins) (Fig. 98.1). Contrary to intravenous treatments, blood purification techniques are nonselective.

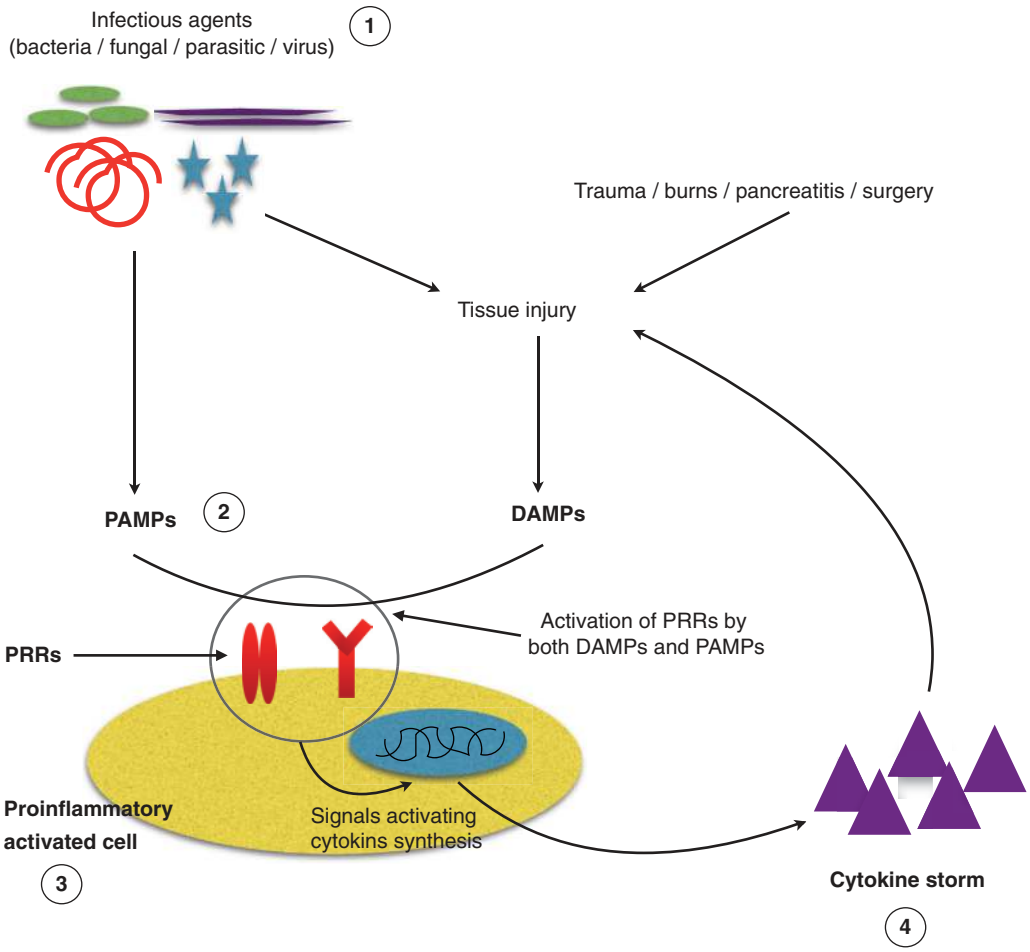

Fig. 98.1 The immunoinflammatory response to sepsis and targets for extracorporeal blood purification. Blood purification targets shown include (1) Removing pathogens from the blood; (2) Removing endotoxins and other PAMPs from the blood; (3) Removing proinflammatory cells from the blood; and (4) Removing cytokines from the blood. *DAMPs,* Damage-associated molecular patterns; *PAMPs,* pathogen-associated molecular patterns; *PRRs,* pattern recognition receptors.

As this immunoinflammatory response seems to represent a "final common pathway," these techniques may be proposed in sepsis, but also in trauma, burns, pancreatitis, and other inflammatory situations causing a dysregulated immunoinflammatory response (see Fig 98.1).

BLOOD PURIFICATION TECHNIQUES FOR SEPSIS

Most of the techniques described subsequently refer to hemoperfusion. Its principle is as follows: the blood runs through a cartridge, and some blood components are fixed on an adsorbent material. Adsorption relies on binding chemical interactions between the targeted circulating molecule and the sorbent. The purpose of these is to remove a significant proportion of the targeted molecule from the blood compartment. We describe next each technique with the details of its targets and its mechanisms of action (Fig. 98.2).

Endotoxin Removal

Two major hemoperfusion devices are available for endotoxin removal. First, the adsorption properties of polymyxin-B have been used in a hemoperfusion cartridge named Toraymyxin (Toray, Tokyo, Japan) since 1993. Polymyxin-B is an antibiotic with great affinity for endotoxin, thanks to ionic and hydrophobic interactions. However, its intravenous use is impossible because of renal and neurologic toxicities. In this hemoperfusion cartridge, polymyxin-B is covalently bound to the fibers. The clinical effects of a polymyxin-B hemoperfusion treatment (typically two 2-hour hemoperfusion sessions 24 hours apart) have been widely studied over the last two decades. Interestingly, this technique represents the current standard of care for abdominal septic shock in Japan. In 2007 Cruz and colleagues reviewed the performance of this hemoperfusion cartridge on septic patients, based on evidence gathered from 1998 to 2006.[16] They found a positive effect on mean arterial pressure (MAP), oxygenation, and a decrease in vasopressor use, to the point that the risk ratio for mortality was 0.53 (95% confidence interval [CI] 0.42–0.65) in the polymyxin-hemoperfusion group. This study was an incentive for further RCTs, mainly focusing on gram-negative abdominal sepsis because of likely high levels of circulating endotoxin in this clinical context. The EUPHAS trial showed encouraging results, consistent with those previously reported by Cruz and colleagues' meta-analysis. This study was even stopped early because of a significant improvement in 28-day mortality (adjusted hazard ratio [HR], 0.36; 95% CI 0.16–0.80; $P = 0.01$) after the intermediate analysis.[17] The ABDOMIX trial was conducted subsequently and included a greater number of patients with similar inclusion criteria.[18] However, it did not find such promising outcomes, with, conversely, a nonsignificant increase in 28-day mortality (odds ratio [OR], 1.5872; 95% CI 0.85–2.93; $P = 0.14$) in the intervention group. Importantly, the

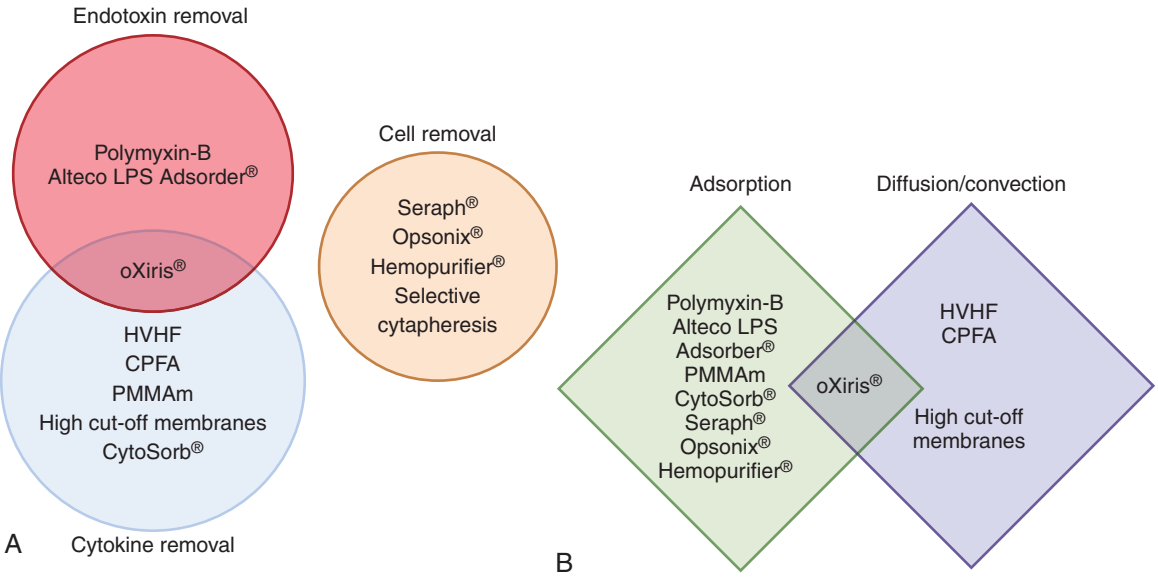

Fig. 98.2 Blood purification techniques. **A,** Targets. **B,** Mechanisms of epuration. *CPFA,* Coupled plasma filtration and adsorption; *HVHF,* high volume hemofiltration; *LPS,* lipopolysaccharide; *PMMAm,* modified PMMA.

mortality rates in the control group greatly differed in these two studies. Lately in 2018, the randomized blinded EUPHRATES trial included a selected population of patients presenting with high levels of circulating endotoxin activity (defined as an endotoxin activity assay [EAA, no unit] ≥0.60) rather than empirically suspected gram-negative sepsis (e.g., of abdominal origin)[19]. The results of this large-scale analysis ($n = 450$) failed to demonstrate a reduction in 28-day mortality. It was nevertheless later speculated that patients with EAA ≥0.90 could bear an endotoxin burden exceeding the adsorption capacities of Toraymyxin. A post hoc analysis was performed, focusing on the subpopulation of patients with EAA between 0.6 and 0.9.[20] In this particular subgroup, 28-day mortality was lower in the hemoperfusion group (OR, 0.52; 95 % CI 0.27–0.99; $P = 0.047$). Evidence was recently found that Toraymyxin hemoperfusion also showed immunomodulation properties, improving mHLA-DR expression in septic patients.[21] This latest input supports the need for further research focusing on a specific selected population and optimal timing for polymyxin-B hemoperfusion initiation.

Another technology aimed at removing circulating endotoxin is the Alteco LPS adsorber (Alteco Medical AB, Lund, Sweden). This cartridge contains a polyethylene matrix covered in a specially designed synthetic peptide engineered for endotoxin adsorption thanks to high affinity for the lipid A moiety of the endotoxin. In a nonrandomized fashion, Adamik and colleagues tested this device on a few selected patients ($n = 18$) and were able to demonstrate an improvement from baseline in terms of EAA levels and clinical outcomes but no difference in ICU mortality between groups.[22] The ASSET trial (NCT02335723) designed as a feasibility study of this device was unfortunately stopped because of patient recruitment issues in 2017.

Cytokine Removal

Using Renal Replacement Therapy

A significant proportion of patients with septic shock develop acute kidney injury (AKI) and require RRT during their ICU stay. Techniques combining RRT and blood purification for sepsis could be of interest for these patients.

High-volume hemofiltration (HVHF) is a continuous renal replacement therapy (CRRT) technique exhibiting a higher ultrafiltration rate than usual (more than 50 mL/kg/h) and targeting improved removal of middle-molecular-weight hydrophilic molecules (i.e., cytokines). Promising experimental and preclinical works were published from 1990 to 2010, but the multicenter RCT IVOIRE published in 2013 was disappointing.[23–26] It did not find any significant mortality reduction, a finding that was confirmed in two subsequent meta-analyses.[27,28]

Increasing membrane permeability or adsorptive properties could confer with standard hemofilters' additional blood purification properties. Used in continuous venovenous hemofiltration (CVVH), high cut-off membranes (i.e., sieving coefficient >40 kDa) are able to remove middle-molecular-weight inflammatory mediators such as IL-6 and IL-1, but with the inconvenience of an important albumin leakage.[29–31] However, the use of such membranes in a diffusive modality allows albumin loss to be minimized and to simultaneously remove middle-molecular-weight molecules.[32–34] In 2016 Chelazzi and colleagues retrospectively studied a small series of patients treated with CVVH using high cut-off membranes.[35] They reported a significantly decreased mortality rate (37.5 vs. 87.5%; $P = 0.03$) compared with the controls. RCTs exploring the outcomes of the use of high cut-off membranes in septic AKI are still needed to draw more robust conclusions regarding the effects of these membranes.

The polymethylmethacrylate (PMMA) membrane has adsorption properties because of its symmetric microporous structure. It removes cytokines and immunoglobulin light chains. Thus its use in septic patients has been studied successfully with respect to intermediate outcomes such as hemodynamics, blood lactate, and IL-6 levels.[36] However, the suitability of this membrane was questioned because of the very high rates of clotting and clogging observed. The PMMA component was modified to address this defect, allowing it to preserve its adsorbing abilities while limiting its high thrombogenicity.[37] CRRT with the modified PMMA membrane has not yet been studied in septic AKI.

Coupled plasma filtration and adsorption (CPFA) is a technique combining blood purification and RRT. First, plasma is separated from total blood and is run through a nonspecific charcoal sorbent cartridge, which adsorbs cytokines. The plasma then returns to the circuit, where conventional RRT with hemofiltration occurs through a standard hemofilter. Recently, the COMPACT2 trial (NCT01639664) assessed high doses of CPFA. This study was terminated early because of to a highly

suspected increased mortality rate in the treatment group. Consequently, CPFA is no longer proposed for septic shock management.

Hemoperfusion

The CytoSorb hemoperfusion cartridge (CytoSorbent, Monmouth Junction, NJ) contains polymer beads with adsorption properties (surface adsorption and pore capture). This adsorption process affects small- to middle-molecular-weight hydrophobic agents: inflammatory mediators (both pro- and anti-), myoglobin, bilirubin, PAMPs, and DAMPs, as shown in various studies.[38,39] This device can be used as a standalone treatment or can be coupled with an RRT circuit, and the same cartridge can be used for up to 24 hours. In both situations, it should be administered daily for 2–7 days (24-hour sessions). Early initiation (i.e., less than 24 hours from the moment when septic shock is uncontrolled despite usual care) seems to lead to better patient outcomes.[40,41] In the several RCTs available, CytoSorb was unable to decrease patient mortality, although blood lactate levels and hemodynamic parameters improved.[42–44] Interestingly, in the most recent of these RCTs, a significant IL-6 clearance was observed, whereas its circulating levels did not differ.[43] Hypotheses to explain this observation are the following: either IL-6 clearance might diminish the levels of cytokine inside organ tissues with an unchanged blood level, or adsorption, being a concentration-dependent mechanism, means that CytoSorb should be delivered to patients presenting with higher circulating IL-6 levels (i.e., IL-6 levels >1000 pg/mL, whereas median levels in that study reached only 565 pg/mL).

Endotoxin and Cytokine Removal

The oXiris membrane (Baxter, Meyzieu, France) is an RRT hemofilter with enhanced adsorption properties, targeting cytokine and endotoxin removal at the same time. oXiris represents an advanced version of the AN69 polyacrylonitrile membrane, coated with polyethyleneimine (PEI) and pregrafted with heparin. The whole bulk of the membrane is able to bind cytokines, like the previous versions of AN69 membranes. PEI ensures better biocompatibility and allows for endotoxin adsorption thanks to its positively charged amino groups. Standard oXiris treatment sessions are recommended to last 24 hours, although the filter life span may be longer (up to 72 hours).

Malard and colleagues recently showed that oXiris in vitro clearances of cytokines and endotoxins were comparable to that of CytoSorb and Toraymyxin, respectively.[38] Few good-quality studies regarding the outcomes associated with the use of oXiris in septic AKI are available. In a randomized cross-over study, Broman and colleagues showed significantly improved cytokine and endotoxin clearances compared with standard CRRT, lower blood lactate level, and a decreased need for vasopressors.[45]

Most of the available data on oXiris are observational. Schwindenhammer and colleagues studied 31 patients and reported a lower-than-expected in-hospital mortality rate in the most severe septic patients treated with oXiris[46]. In a propensity-matched cohort, a beneficial effect of oXiris treatment was found in terms of hemodynamics, urinary output, and PaO_2/FiO_2 ratio, as compared with standard RRT.[47] RCTs are now warranted to draw robust conclusions about the impact of oXiris on patient outcome in sepsis-induced AKI (ECRO NCT03426943, ENDOTOX NCT01948778).

Cell Removal

More recently, a variety of binding components have been developed aiming at removing pathogens and/or inflammatory cells.

Removing Pathogens

The Seraph 100 Microbind Affinity Blood Filter (ExThera Medical, Martinez, CA) is a hemoperfusion device composed of heparin-grafted polyethylene beads. It can be used in a series within an RRT circuit or as a standalone hemoperfusion treatment. Heparan-sulfate is a glycosaminoglycan that can bind pathogens; it shares its affinity with heparin, which is very similar. A large number of bacteria, parasites, and viruses were found to interact with the Seraph.[48–50] A safety study took place in Germany on patients with septic shock requiring RRT. No adverse events occurred (NCT02914132). However, the clinical impact of Seraph treatment has yet to be investigated.

Still in an early stage of development, a hemoperfusion device using the FcMBL protein has shown interesting results in animal models. The FcMBL protein (Opsonix, Wakefield, MA) is an engineered molecule containing the properties of opsonin mannose-binding lectin (MBL) that natively adheres with PAMPs to the Fc domain (i.e., the unchanging section) of human immunoglobulin. Hemadsorption using FcMBL could trap both pathogens as a whole or their debris once destroyed by antimicrobial therapy.[51] Such a device is currently in testing and has shown favorable outcomes in septic mouse models, displaying a certain level of synergy with antibiotics.[52]

The Hemopurifier (Aethlon Medical, San Diego, CA) is a technique using coupled plasmapheresis and adsorption to clear blood-circulating viruses. After separation, plasma is put in contact with a lectin protein found in the common snowdrop (*Galanthus nivalis* agglutinin), which has a powerful affinity for the glycoproteins found on the envelope of some viruses. This device is not yet available except for research. It was successfully applied to treat a patient with Ebola virus and showed significant clearance of circulating hepatitis C virus.[53,54]

Removing Inflammatory Cells

Cytapheresis targeting activated white blood cells is currently under study. Pino and colleagues developed a synthetic biomembrane able to catch activated leukocytes that can be plugged within a CRRT circuit.[55] A preliminary safety study on septic patients requiring RRT reported improved survival compared with case-matched controls, but this was not confirmed by the RCT conducted subsequently.[56,57] On a side note, some of the aforementioned hemoperfusion devices (e.g., CytoSorb) targeting inflammatory mediators could clear activated white blood cells, as shown by Rimmelé and colleagues.[58] That effect could participate in the overall immunomodulatory result.

BLOOD PURIFICATION FOR NONSEPTIC INDICATIONS

Nonseptic Inflammatory States

Acute pancreatitis usually has a mild course, with a global mortality rate below 1%. However, around 10% of patients will develop severe acute pancreatitis (SAP), involving extrapancreatic tissues and other organ systems, with a much higher mortality rate. The outcome and pathophysiology of SAP are closely related to early systemic inflammation and cytokine release. Treatments based on antioxidants, platelet-activating antagonists, antibodies against mediators of inflammation such as TNF-alpha, or nonsteroidal antiinflammatory drugs all failed to demonstrate improvement of morbidity and mortality in RCTs.[59,60]

In a meta-analysis, Hu and colleagues analyzed 12 trials (4 RCTs and 8 prospective studies) investigating blood purification techniques, mainly HVHF, in SAP. This meta-analysis demonstrated a significant lower incidence of mortality and ICU length of stay in the blood purification group (OR, 0.60; 95% CI 0.38–0.94). However, this improvement was no longer significant when only RCTs were taken into account (OR, 0.56; 95% CI 0.21–1.49).[61] The ongoing PACIFIC trial, a prospective multicenter case-control study, aims at investigating whether or not early administration of hemoperfusion with CytoSorb in patients with SAP can improve hemodynamic parameters.[62]

Extracorporeal blood purification techniques can also be proposed for severely burned patients. Indeed, these patients exhibit a prolonged and fulminant inflammatory state, with high levels of proinflammatory and antiinflammatory mediators.[63] Peng and colleagues evaluated hemoperfusion with polymyxin-B immobilized fibers in septic burned patients (total body surface area [TBSA] ≥50%). The use of polymyxin-B columns in these patients infected with gram-negative bacteria decreased levels of endotoxin, IL-1β, IL-6, IL-8, and TNF-alpha.[64] Less data are available regarding the use of PMMA membrane for burned patients. Nakae and colleagues reported three cases with severe burn injury (TBSA >30%) treated with CVVH and a PMMA membrane and observed a reduction in IL-6 levels in all three patients.[65] Another interesting point consists in the ability of CytoSorb to remove myoglobin in vitro,[66] which might be a promising therapy for rhabdomyolysis that occurs in conjunction with thermal injury, but no data are available for humans.

Blood purification techniques might also be used for severe trauma patients, although no data are available in humans. McKinley and colleagues showed in a rat model of hemorrhagic shock and traumatic brain injury a better survival (86% vs. 47%) in the group undergoing hemoperfusion with CytoSorb.[67]

Blood purification might also be interesting in other diseases in which the immunoinflammatory response is dysregulated. We can, for instance, mention cardiorenal syndromes or cancers like T-cell lymphoma causing cytokine release syndrome (CRS) with some chemotherapies. Recently, Stahl and colleagues published a case report of a 65-year-old male patient undergoing refractory shock on grade 4 CRS after chimeric antigen receptor (CAR) T-cell treatment for diffuse large B-cell lymphoma.[68] After failure of conventional treatment, including IL-6 blockers, they reported that a wide range of proinflammatory cytokines were lowered by more than 50% compared with their initial concentration after 24 hours of treatment with CytoSorb. Interestingly, the substantial decrease of IL-6, interferon (IFN)-gamma, TNF-alpha, and IL-1 was followed by significant hemodynamic improvement. An RCT investigating extracorporeal treatment with CytoSorb in patients with severe CRS is ongoing (NCT04048434).

Artificial Liver Support Systems

The liver is a complex organ responsible for vital functions such as protein synthesis, heat production, and detoxification. The European Association for the Study of the Liver distinguishes acute liver failure in healthy liver (ACL) from acute on chronic liver failure, in which cirrhosis is decompensated by an acute injury (ACLF). These two syndromes have different pathophysiologies, etiologies, and outcomes. Importantly, and since the end of the twentieth century, artificial livers have been developed to be used as supportive therapy until liver transplantation (bridge-to-transplant) or liver regeneration (bridge-to-recovery) has occurred.

The most described devices are the molecular adsorbent recirculating system (MARS, Gambro Hospal GmbH, Planegg-Martinsried, Germany), the single-pass albumin dialysis (SPAD), and the fractionated plasma separation and adsorption system (FPSA, Prometheus, Fresenius Medical Care, Bad Homburg, Allemagne).[69] These systems, based on albumin dialysis, are supposed to remove from the blood albumin-bound toxins that accumulate during liver failure. These toxins are potentially involved in the development of liver encephalopathy, hepatorenal syndrome (HRS), cardiovascular failure, and immunosuppression. In addition, these devices can theoretically remove plasmatic nitric oxide (NO) and cytokines such as TNF-alpha, IL-6, or IL-10, although the contribution of those to multiple organ failure in ALF or ACLF is still unknown.[70] Evidence has shown that artificial liver support systems may replace, at least partially, the liver detoxification function. However, clinical data on improved survival are very conflicting, and these devices are also very costly.

The MARS is a complex device in which treatment occurs in three steps (Fig. 98.3). First, the blood is dialyzed through the MARS membrane (a high-flux dialysis membrane) where albumin-bound toxins are released in a dialysate enriched with albumin, according to the diffusion principle. Second, the albumin in the dialysate is regenerated while toxins are cleared when passing through two adsorbing columns that contain activated charcoal and anion exchange resin. Third, the albumin circuit itself is dialyzed in the RRT circuit, cleaning the blood from water-soluble molecules and toxins (see Fig. 98.3).

To date, few meta-analyses have reported outcomes of MARS-treated patients. In 2015 Tsipotis and colleagues analyzed 10 RCTs including 620 patients with ACL or ACLF treated with MARS (7 RCTs) or Prometheus (3 RCTs). They showed an improvement in liver encephalopathy with albumin dialysis (relative risk [RR], 1.55; 95% CI 1.16–2.08); however, no benefit in mortality was observed (RR, 0.95; 95% CI 0.84–1.07).[71] He and colleagues conducted a separate

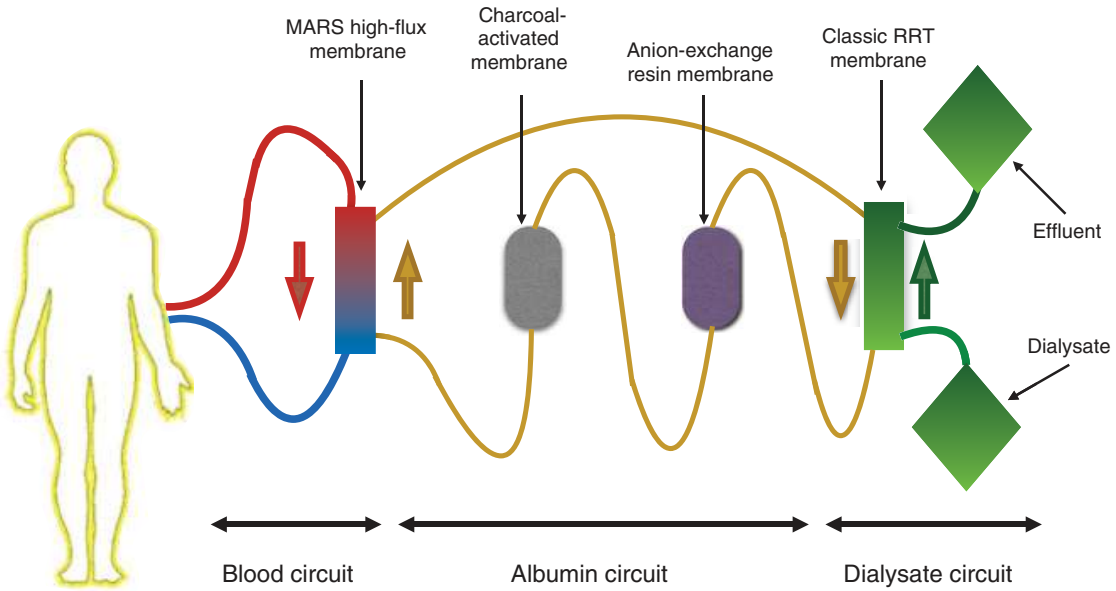

Fig. 98.3 The molecular adsorbent recirculating system (MARS).

meta-analysis of trials involving patients with ALF or ACLF exclusively treated with MARS. They found that MARS therapy significantly reduced mortality compared with standard care (RR, 0.61; 95% CI 0.38–0.97; $P = 0.04$). However, the authors also highlighted that many patients were finally not included because they went to transplantation first, resulting in the low number of patients (n = 49) finally analyzed. There was no significant survival benefit in ACLF patients treated with MARS (RR, 0.88; 95% CI 0.74–1.06; $P = 0.16$).[72]

The SPAD is an artificial liver device in which the blood is dialyzed with an albumin-containing dialysate. After diffusion through the membrane, albumin-bound toxins are removed with the dialysate. With SPAD, albumin is not regenerated (in contrast with the MARS and Prometheus systems); therefore high amounts of albumin are required. Sponholz and colleagues in a controlled crossover study compared the detoxification capacity and clinical outcomes of SPAD (4% albumin dialysate solution; 700 mL/h dialysis flow rate) with MARS (20% albumin flow rate equal to the blood flow rate, 2000 mL/h dialysis flow). They observed similar reductions in bilirubin levels between the two devices. Interestingly, in contrast with other studies, neither MARS nor SPAD reduced cytokine levels. The effects of MARS and SPAD on liver encephalopathy and hemodynamic parameters were small and similar.[73] Of note, another randomized crossover trial comparing MARS with SPAD is currently ongoing (NCT02310542).

The FPSA (i.e., Prometheus) system uses the patient's own albumin to first enter the circuit through the AlbuFlow membrane. Then, the albumin is purified from its bound toxins, using a neutral resin adsorber and an anion-exchange column and returns to the blood circuit. The blood is run through a second circuit for conventional high-flux hemodialysis before being returned to the patient. The efficacy of Prometheus has recently been confirmed by Grodzicki and colleagues, who found significant decreases in serum ammonia, bilirubin, aspartate aminotransferase, alanine aminotransferase, urea, and creatinine in patients with ALF.[74] Sentürk and colleagues found similar results in their study in which 27 patients with ALF or ACLF underwent several sessions of albumin dialysis with Prometheus. They observed a significant decrease in total bilirubin, ammonia, blood urea nitrogen, serum creatinine levels, and liver encephalopathy scores.[75] In 2012 Kribben and colleagues published the HELIOS study, a multicenter RCT comparing the use of Prometheus with standard medical care in patients with ACLF. They could not demonstrate any survival improvement at day 28 (66% vs. 63%, $P = 0.70$) and at day 90 (47% vs. 38%, $P = 0.35$), and the study was interrupted early because of futility. However, among the subgroup of patients with severe liver failure (Model for End-Stage Liver Disease [MELD] >30), probability of survival at day 90 was greater for patients treated with Prometheus (48% vs. 9%, $P < 0.05$).[76]

Among other devices, the Advanced Life Support System (ADVOS) showed promising results in animal studies.[77] This device is composed of three circuits: a standard RRT circuit, an albumin running circuit, and a third circuit for regeneration and detoxification of toxin-loaded albumin. In 2017 Huber and colleagues confirmed positive results in an observational trial of 14 patients treated with ADVOS, demonstrating significant hemodynamic and biochemical improvements.[78]

CONCLUSION

Extracorporeal blood purification techniques are designed to clear excessive inflammatory mediators from the blood. This removal is nonspecific, but most of the techniques target a group of molecules (such as cytokines or endotoxins), activated white blood cells, or pathogens. The rationale for use is that removing harmful intermediaries could avoid triggering the unwanted cytokine storm and the following immunoparalysis responsible for poor outcome in patients with sepsis. These properties of blood purification could also apply to nonseptic inflammatory shocks such as acute pancreatitis and severe burns. So far, improved outcomes have been shown regarding secondary criteria (e.g., hemodynamics, oxygenation), but none of the techniques has shown conclusive evidence regarding survival.

Nevertheless, as stated by the Surviving Sepsis Campaign, research on this topic should be continued, as septic shock remains deadly and immunomodulation could be a leading treatment option in this context. Treatment timing and patient selection need to be carefully addressed in future trials. Blood levels of cytokines and endotoxin should be monitored to decide on the best treatment to use. Techniques allowing for simultaneous RRT should be kept for patients requiring RRT, and standalone therapies should be preferred for those without AKI. Artificial liver support systems are proposed for the removal of albumin-bound toxins.

Lately, extracorporeal blood purification has been suggested for the treatment of severe SARS-CoV-2 infections. These patients experience hyperinflammation, and therefore blood purification has been proposed in various ways to prevent pulmonary and other organ damage. For now, only case reports or case series have been published, and additional data are warranted to draw robust conclusions on the effects of these therapies in patients with COVID-19.[79]

KEY POINTS

- Blood purification techniques aim at removing different components from the blood, targeting the dysregulated immunoinflammatory response.
- Mostly described in sepsis, blood purification techniques may also be proposed in acute pancreatitis, trauma, burns, and cancer.
- The lack of morbidity and mortality improvement in RCTs may possibly be explained by significant heterogeneity in these trials in terms of indications, timing of initiation, and patient populations.
- Most of the artificial liver support systems are based on albumin dialysis. These systems are supposed to remove albumin-bound toxins from the blood.
- These devices are not routinely implemented in ICUs because of the lack of conclusive RCTs.

References for this chapter can be found at expertconsult.com.

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Fluid and Volume Therapy in the ICU

Todd W. Robinson and Barry I. Freedman

The goals of fluid administration are to optimize tissue oxygenation by augmenting intravascular volume, improving left ventricular preload, and increasing cardiac output.[1] This chapter reviews the timing and considerations for choice of therapy in volume repletion and the effects of fluid volume overload in the postresuscitation period.

TIMING OF INITIAL VOLUME THERAPY

Studies from the early 2000s suggested that earlier recognition and treatment of septic shock correlated with improved outcomes. In a report by Rivers and colleagues, the Early Goal-Directed Therapy Collaborative Group randomized subjects to receive either intensive treatment for septic shock within the initial 6 hours of therapy or standard therapy provided in the emergency department.[2] Standard and early goal-directed therapy (EGDT) groups received antibiotics, vasoactive medications, and intravenous (IV) fluid for volume resuscitation. Goals for fluid administration included infusion of crystalloid in 500-mL boluses every 30 minutes with a target central venous pressure of 8–12 mm Hg as a marker of effective repletion of intravascular volume and response to fluids. Although the total volume of fluid administered by 72 hours was equivalent, the EGDT group received substantially more IV fluid in the first 6 hours of treatment. Compared with the standard therapy group, significant improvements related to in-hospital mortality were observed in the group assigned to earlier administration of volume-based resuscitation in conjunction with other therapies, including the optimization of central venous oxygen saturation with red blood cell transfusions and use of inotropes, if necessary. In-hospital mortality was 30.5% in the EGDT group, compared with 46.5% in the standard therapy group ($P = 0.009$). Replication of results in other studies prompted guidelines for the treatment of sepsis to include early volume repletion as part of protocol-based, quantitative resuscitation to reverse tissue hypoperfusion.[3,4] In the Surviving Sepsis Campaign, initial resuscitation recommendations for the first 6 hours included treatment aimed at maintaining a central venous pressure of 8–12 mm Hg, a mean arterial pressure more than or equal to 65 mm Hg, urine output more than or equal to 0.5 mL kg/hr, and mixed venous oxygen saturation greater than 65%.[5] In 2018 the Surviving Sepsis guidelines were further revised to accelerate this protocol-driven timeline and include recommendations for initiating fluid resuscitation within 1 hour for hypotension or lactatemia.[6]

Meeting hemodynamic stabilization endpoints in such a manner with goal-directed therapy and other supportive measures remains desirable in most cases, especially in patients who prove to be fluid responsive. However, other multicenter studies that have re-examined this topic have not replicated survival benefits, and the advantages of aggressive EGDT have been questioned. The Australasian Resuscitation in Sepsis Evaluation (ARISE) study examined EGDT resuscitation in patients with septic shock.[7] Sixteen hundred patients were randomized to EGDT or usual care. On average, patients in the EGDT group were treated with more IV fluid in the initial 6 hours of therapy compared with those randomized to usual care. Those in the EGDT group were also more likely to receive red blood cell transfusions. At 90 days, no significant differences were observed in patient survival. In-hospital mortality, the duration of organ support, and the length of hospital stay were also similar. The Protocol-based Care for Early Septic Shock (ProCESS) investigative group showed comparable results, with no benefits found with EGDT.[8] ProCESS was a prospective multicenter trial that randomized 1341 emergency department patients with septic shock to receive 6 hours of protocol-based EGDT, protocol-based standard therapy, or usual care. The investigators did not require placement of central venous catheters, administration of inotropes, or blood transfusions in the protocol-based standard therapy group, as compared with the use of these therapies in the EGDT group. Overall, the total volume of fluid administered during the 6-hour study period was reported as being significantly different between the groups. Again, no differences in survival were observed at 90 days. There was also no significant impact on 1-year mortality, the duration of time spent on mechanical ventilation, or the duration of time on renal replacement therapy. ProMISe was a pragmatic randomized trial that examined mortality and other critical illness outcomes in patients with septic shock across 56 hospitals in England.[9] Participants were randomized to either EGDT or usual care. A total of 1260 patients were enrolled, and there were no statistically significant between-group differences in mortality or the other secondary outcomes, including adverse events and quality of life. Additionally, EGDT increased the cost of care for these critically ill patients. Fig. 99.1 shows the relative risk of mortality in EGDT versus usual care in these four major randomized controlled trials.

TYPE OF VOLUME THERAPY

When deciding on IV fluid therapy, the choices can be broadly classified into three major categories. Crystalloid fluids have long been considered the mainstay of volume replacement in the hospital setting and include normal saline (NS), lactated Ringer's (LR) solution, Hartmann's solution, and other balanced salt solutions such as Plasma-Lyte. A second broad category includes colloid preparations such as albumin, hydroxyethyl starch (HES), dextran, and gelatin. Finally, blood products, including packed red blood cells, can be used for volume repletion in the treatment of hypoperfusion caused by inadequate circulating volumes. Table 99.1 compares the osmolality and composition of human plasma and common isotonic crystalloid fluid preparations.

CRYSTALLOIDS VERSUS COLLOIDS

The choice between crystalloids and colloids as therapeutic fluids in the intensive care unit (ICU) has long been a topic of debate and

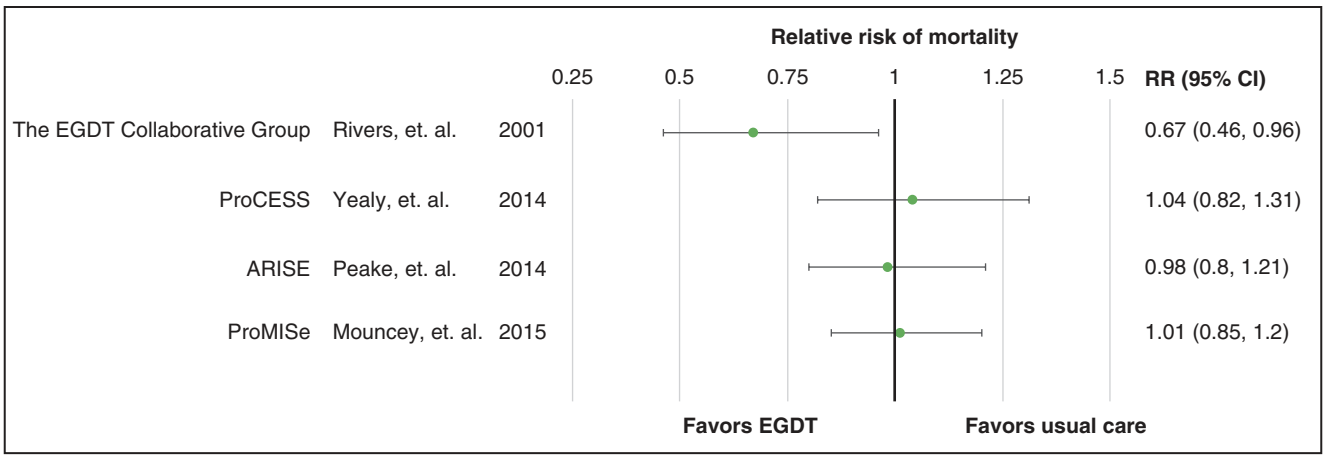

Fig. 99.1 Relative risk of mortality in early goal-directed therapy vs. usual care.

TABLE 99.1 Osmolality and Composition of Plasma Versus Common Isotonic Crystalloid Fluid Preparations

	Plasma	0.9% Normal Saline (NS)[a]	Lactated Ringer's (LR)[b]	Plasma-Lyte-LYTE A (PL)[c]	Sterile Water With 150 mEq/L Sodium Bicarbonate[d]
Osmolality (mOsmol/L)	280–310	308 (calc)	273 (calc)	294 (calc)	300 (calc)
Sodium (mEq/L)	135–145	154	130	140	150
Potassium (mEq/L)	4.0–5.0	–	4.0	5.0	–
Chloride (mEq/L)	95–110	154	109	98	–
Calcium (mEq/L)	2.2–2.6	–	2.7	–	–
Magnesium (mEq/L)	1.0–2.0	–	–	3.0	–
Lactate (mEq/L)	0.8–1.8	–	28	–	–
Acetate (mEq/L)	–	–	–	27	–
Gluconate (mEq/L)	–	–	–	23	–
Bicarbonate (mEq/L)	24–31	–	–	–	150

[a]Baxter Healthcare Corp. Sodium Chloride Injection, USP. Package Insert.
[b]Baxter Healthcare Corp. Lactated Ringer's Injection, USP. Package Insert.
[c]Baxter Healthcare Corp. Plasma-Lyte A Injection pH 7.4, USP. Package Insert.
[d]Hospira, Inc. Sodium Bicarbonate Injection, USP. Package Insert.

investigation. In an analysis of multiple population studies, Goldwasser and Feldman observed that mortality was inversely associated with serum albumin levels.[10] With each 2.5 g/L lower serum albumin concentration, a correlative 24%–56% increase in risk of death was detected. This relationship held true in healthy populations and in those who suffered from acute and chronic illnesses. Several mechanisms for the protective effects of the albumin molecule have been explored. Among these, infused albumin reportedly has free radical scavenging antioxidant properties that may have clinical importance.[11] Moreover, the proposed advantages for prescribing colloid over crystalloid fluid in resuscitation strategies for critically ill patients include concepts based on hemodynamic Starling's principles and the role of plasma oncotic pressure. Theoretically, large colloid molecules that persist in the circulation enhance water reabsorption from the interstitial space and maintain the volume within the vasculature for longer periods.[12] Ideally, this characteristic would reduce the large fluid volumes that are often required for resuscitation and improve clinical outcomes.[13]

Prospective randomized trials examining the potential benefits of albumin and colloids in lieu of crystalloid solutions for volume repletion have yielded variable results. For example, there are investigations that demonstrated benefit with albumin administration and support its clinical safety. In one such study, a group of 100 patients with hypoalbuminemia in the ICU were randomized to receive (versus not receive) albumin as part of their treatment regimen.[14] The groups were well matched and had similar baseline serum albumin concentrations and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores. Significant improvements in Sequential Organ Failure Assessment (SOFA) scores were observed in the albumin-treated group. Interestingly, significant decreases in fluid gains were also seen in the albumin-treated group. These results led the investigators to suggest that treatment with albumin may lead to better outcomes in critically ill patients with hypoalbuminemia. Similarly, the Saline versus Albumin Fluid Evaluation (SAFE) study was a large trial that included nearly 7000 ICU patients with trauma, acute respiratory distress syndrome (ARDS), and severe sepsis.[15] The participants were randomized to receive either 4%

albumin or NS for intravascular fluid resuscitation. In a subgroup analysis of patients with severe sepsis, those in the albumin-treated group had a significantly lower heart rate and a significantly higher central venous pressure on days 1–3.[16] No between-group differences were detected in the total SOFA score, and similar numbers of patients required renal replacement therapy in the saline- and albumin-treated groups. Multivariate logistic regression analysis revealed that the adjusted odds ratio (OR) for death in the albumin-treated versus saline-treated group was 0.71 (85% confidence interval [CI]: 0.52–0.97; $P = 0.03$), suggesting that albumin treatment may decrease the risk of death in severe sepsis. Furthermore, data from a meta-analysis suggested that albumin administration is safe. In 55 trials that evaluated many different types of patients, including those with trauma, burns, hypoalbuminemia, and ascites, albumin administration did not adversely affect mortality.[17]

In contrast to studies suggesting benefit with albumin therapy in sepsis, other large prospective randomized trials failed to support a clear benefit of infusing albumin over crystalloid solutions in patients in the ICU setting. In the larger and more diverse group of original SAFE study participants discussed earlier, investigators found no between-group differences in death or new episodes of single- or multiorgan system failure between those treated with albumin versus saline.[15] There was also no significant difference in the number of days spent in the ICU, length of hospital stay, or days of renal replacement therapy in the subgroup analyses. Similarly, the Colloids Versus Crystalloids for the Resuscitation of the Critically Ill (CRISTAL) trial examined outcomes for ICU patients with shock from sepsis, trauma, or hypovolemia who were randomized to treatment with colloid solutions compared with crystalloids.[18] In addition to 4% and 20% albumin, the colloid arm of CRISTAL included gelatins, dextrans, and HES. At 28 days after study enrollment, even though colloid resuscitation was associated with fewer days of mechanical ventilation and more days without vasopressor therapy, no significant differences in mortality were observed between the patients who received colloids and those who received crystalloids. Patients with severe sepsis have also been randomized to receive crystalloid plus albumin therapy compared with crystalloids alone. In the more than 1800 randomized patients in the Albumin Italian Outcome Sepsis (ALBIOS) study, significantly higher mean arterial pressures and lower net fluid gains were observed in the albumin plus crystalloid therapy group.[19] However, the investigators also noted that the total daily amount of fluids administered did not differ between the groups and, more importantly, there were no significant differences in patient survival at 28 or 90 days between the groups. The Cochrane analysis of pooled data on this topic also found no evidence that colloids reduced the risk of death compared with crystalloids in the treatment of critically ill patients.[20] Overall, there remains a paucity of data to suggest that clear benefits exist for administering albumin or other colloid solutions instead of crystalloids in critically ill patients requiring volume repletion. The lack of resounding benefit is compounded by the high cost of albumin, which also makes it less attractive for routine use.[20]

There is also evidence suggesting that colloid solutions such as albumin may be associated with harmful effects. Though they tended to have higher critical illness severity scores, patients in the Sepsis Occurrence in Acutely ill Patients (SOAP) study who received albumin at any time during their ICU stay had a higher risk of death.[21] A systematic review of 37 randomized trials comparing crystalloid with colloid administration also hinted at safety concerns. The investigators found that colloid resuscitation was associated with a 4% increase in the absolute risk of mortality (95% CI, 1.00–1.08) and concluded that the difference in the effect of the colloids was not related to the types of inciting injuries.[22]

The harm associated with colloid infusion may be more pronounced with respect to specific organ systems or types of colloids. In a post hoc analysis of the SAFE study, albumin administration in patients with traumatic brain injury was associated with higher mortality compared with those who received crystalloids.[23]

HYDROXYETHYL STARCH

Convincing evidence for harm was reported for critically ill patients treated with the synthetically derived HES. Of 7000 randomized patients in the Crystalloid versus Hydroxyethyl Starch Trial (CHEST), there was no significant mortality difference in those resuscitated with NS versus HES.[24] However, there was a significant difference in adverse outcomes. Of 3352 patients receiving HES, 235 (7.0%) experienced a kidney-related adverse outcome that ultimately required renal replacement therapy. In comparison, only 196 of 3375 (5.8%) required this intervention in the NS group (relative risk 1.21 [95% CI, 1.00–1.45]; $P = 0.04$). Additional studies also suggest harm. Among patients with sepsis who were randomized to receive IV fluid resuscitation with HES versus Ringer's acetate, the risk of death at 90 days was higher in those who received HES.[25] In that study, patients with sepsis who were treated with HES were also more likely to require renal replacement therapy. In major abdominal surgery, patients have also been randomized to either HES or saline in the postoperative period. There were no differences in mortality or adverse events within 14 days of the surgery.[26] The commonality between these findings have been confirmed in meta-analysis data from more than 35 trials in which HES was associated with a significantly increased risk of mortality and acute kidney injury (AKI).[27] Mechanistically, the total mass of the HES molecule has been proposed as directly toxic to renal proximal tubular cells, leading to the pathologic sequence of events that culminates in AKI.[28] This is contrary to other reports suggesting that it is the origin of the HES molecule (potato or corn), the carrier solution, or the effects of systemic inflammation that may be damaging to kidney cells.

ALBUMIN USE IN SELECT CLINICAL SETTINGS

Just as there are clinical situations in which the infusion of albumin and colloid solutions may be harmful, there are also specific circumstances where these fluids could have important and beneficial roles in the treatment of critically ill patients. In a randomized, nonblinded clinical trial that examined 126 patients with cirrhosis and spontaneous bacterial peritonitis, participants were randomized to treatment with either IV antibiotics alone or IV antibiotics with albumin.[29] The dose of albumin administered was 1.5 g/kg at diagnosis, with another 1 g/kg infused on day 3. In the patients who received albumin in addition to antibiotics, statistically significant reductions in renal impairment and death were observed. Additionally, a recent meta-analysis in 688 burn shock patients reported that treatments that included IV albumin were associated with statistically significant reductions in mortality and in the occurrence of compartment syndrome.[13] Although larger, prospective randomized trials are needed to guide management in burn shock resuscitation, these results suggest that albumin has the potential to improve outcomes.

In the majority of cases that require volume resuscitation in the ICU, there does not seem to be a robust signal favoring infusion of albumin or other colloid therapies over crystalloid fluids as first-line treatment for hypovolemia and septic shock. Crystalloids remain the treatment of choice in most settings.

CHLORIDE-RESTRICTIVE AND BALANCED CRYSTALLOID STRATEGIES

Increasing evidence indicates that isotonic crystalloid fluid preparations are not uniform or equivalent with respect to their side effect and

physiologic profiles. Despite isotonicity, NS is hyperchloremic relative to plasma (see Table 99.1). In animal studies, the effects of high chloride levels have been implicated in severe renal vasoconstriction, the suppression of plasma renin activity, and reduced glomerular filtration rate.[30–32] In healthy human volunteers, magnetic resonance imaging studies have demonstrated that infusions of NS can cause significant reductions in renal blood flow velocity and reductions in the perfusion of renal cortical tissue.[33]

Organ hypoperfusion is common in critically ill patients, but lactic acid production alone is not sufficient to explain all cases of metabolic acidosis in the ICU.[34–36] In addition to the aforementioned renal hemodynamic changes, IV fluids with superphysiologic concentrations of chloride, such as NS, have been associated with development of hyperchloremic metabolic acidosis. McFarlane and Lee observed this phenomenon while studying surgical patients randomly assigned to receive either 0.9% NS or Plasma-Lyte 148 during major abdominal surgery.[37] Patients receiving NS had significantly higher serum chloride concentrations, lower serum bicarbonate concentrations, and higher base deficit measurements compared with those who received Plasma-Lyte 148. Administration of NS has reproducibly been associated with decreases in serum bicarbonate levels or acidemic-range arterial pH values.[33,38–40] Extracellular dilution of buffer caused by the infusion of large volumes of fluid that lack bicarbonate may explain some of these changes.[41] Another hypothesis employs the strong ion difference (SID) theory of acid-base evaluation to describe these effects. In the SID theory, acidosis can occur if the apparent difference between strong cations and anions in solution is reduced.[42] As such, hyperchloremia caused by excessively larger gains in chloride (anion) concentration may contribute to the metabolic acidosis that has been observed with NS administration.[43–46]

In large-cohort observational studies, the deleterious physiologic effects of hyperchloremia and NS administration are reflected in clinical outcomes. In 22,851 surgical patients with normal preoperative kidney function and normal serum chloride concentrations, postoperative hyperchloremia was associated with higher 30-day mortality, longer hospital stay, and more frequent postoperative kidney dysfunction.[47] A similar study in more than 30,000 adult patients undergoing major abdominal surgery found that those who received NS had more postoperative complications, including infection, renal failure requiring dialysis, and blood transfusions.[48] Among patients in the ICU with sepsis, a retrospective analysis of more than 50,000 patients showed that balanced fluid administration (e.g., LR) was associated with a significantly lower in-hospital mortality (19.6% vs. 22.8%; relative risk, 0.86; 95% CI, 0.78–0.94).[49] Similarly, among patients with systemic inflammatory response syndrome, in-hospital mortality was lower when the total chloride load was reduced.[50] Yunos and colleagues detected adverse events associated with chloride-liberal IV fluid administration in critically ill ICU patients.[51] These investigators conducted a prospective, open-label pilot study that examined patients in an academic ICU. Patients were treated with standard IV fluids during a 6-month control period, after which NS and other chloride-rich fluids were restricted to specialty-attending approval. The primary outcomes included a rise in serum creatinine concentration from baseline and incident AKI as defined by RIFLE (Risk, Injury, Failure, Loss, and End-stage kidney disease) classification. During the intervention period, saline administration decreased significantly. When the study periods were compared, those who received chloride-restrictive therapy had a lower mean rise in serum creatinine concentration while in the ICU and the incidence of AKI was significantly diminished. After adjustment for covariates, an increased risk of requiring renal replacement therapy was observed in the chloride-liberal cohort.

Historically, prospective trials examining chloride-liberal versus balanced crystalloid solutions were predominately focused on perioperative and trauma patients. When comparing resuscitation with 0.9% NS versus Plasma-Lyte A in 65 trauma patients, administration of Plasma-Lyte resulted in a lower frequency of hyperchloremia and was associated with greater correction of acid-base abnormalities.[52] However, investigators found no significant differences in cumulative urine output, measures of resource use, or mortality between those resuscitated with saline versus Plasma-Lyte at 24 hours. Similarly, a report in 60 patients undergoing abdominal aortic aneurysm repair revealed that intraoperative randomization to LR or NS (double-blinded) resulted in a higher frequency of acidosis requiring bicarbonate therapy in those receiving NS, but did not significantly affect the duration of mechanical ventilation, length of ICU stay, length of hospital stay, or postoperative complications.[53] In patients undergoing kidney transplantation, the use of NS versus balanced crystalloids has been associated with a higher incidence of metabolic acidosis; however, fluid type did not negatively affect kidney allograft function as determined by serum creatinine concentration on postoperative day 3.[38,54]

Contemporary meta-analyses have also examined the question of balanced crystalloids versus isotonic saline in critically ill patients.[55] Results from data in six randomized controlled trials and a total cohort consisting of nearly 20,000 patients found no significant difference in in-hospital mortality (11.5% vs. 12.2%; OR 0.92; 95% CI 0.85–1.01; $P = 0.09$). Differences in AKI, overall ICU mortality, and need for renal replacement therapy were also similar between groups.

In 2018 a large, prospective, multicenter, cluster-randomized clinical trial with more than 15,000 critically ill adults provided strong support to the clinical trend of using more balanced physiologic crystalloid solutions relative to formulations such as NS.[56] The SMART investigators studied critically ill participants who were randomized to either NS versus LR or Plasma-Lyte. The cohorts were well matched for ICU admission diagnosis, vasopressor support, and baseline kidney function. The primary outcome included kidney outcomes and a composite of death from any cause. There were significantly fewer adverse kidney outcomes in the LR group compared with NS ($P = 0.04$). There was also a trend toward fewer new episodes of renal replacement therapy ($P = 0.06$) and development of persistent renal dysfunction ($P = 0.08$) in the LR group. A secondary analysis of these data was performed in patients with a specific sepsis diagnosis.[57] Of the original 15,802 SMART participants, 1641 had a diagnosis of sepsis. When this group was analyzed, there was a significant improvement for in-hospital 30-day mortality when patients received balanced fluids versus NS, and the results were also favorable in terms of 30-day mortality, adverse kidney events, and vasopressor use.

Although additional large clinical trials that continue to directly compare various crystalloid solutions in patients with sepsis and other common ICU conditions are needed, based on the aforementioned evidence, the role for chloride-restrictive alternatives to NS in patients who have developed (or are at risk for developing) metabolic acidosis and/or renal insufficiency will likely continue to grow and gain clinical favor in the ICU.

Concerns with administering physiologically balanced solutions more closely matched to serum, for example, LR, have included the perceived risk of hyperkalemia because of their higher potassium concentrations. Even in clinical situations potentially associated with a higher risk for hyperkalemia, evidence supports that these balanced solutions are generally safe with appropriate monitoring. For example, in a prospective randomized trial of patients with rhabdomyolysis, treatment with LR was not associated with significant differences in serum potassium concentration compared with treatment with NS.[58] In patients with diabetic ketoacidosis, in which serum potassium levels

can rise because of the combination of hyperosmolality, insulin deficiency, and AKI, patients who were resuscitated with balanced Plasma-Lyte instead of NS had faster resolution of acidosis and lower 6- and 12-hour serum potassium concentrations.[59] After kidney transplantation, patients who received NS had higher frequencies of hyperkalemia relative to those who received LR.[38]

BLOOD TRANSFUSIONS

In critically ill patients with severe blood loss and hemorrhagic shock, blood transfusions are a foundation of treatment. In patients suffering from sepsis and other acute illnesses, red blood cell transfusions have been used to enhance oxygen delivery to poorly perfused tissue as a supplement to other fluid resuscitation and vasopressor/inotropic support. Unfortunately, data sufficient to guide management and support the benefit of red blood cell transfusion in critically ill patients with sepsis have yet to emerge.

Observational studies have detected possible mortality benefits with red blood cell transfusions in critically ill patients with sepsis.[60,61] Among the European ICUs that participated in the SOAP study, multivariate analysis of more than 3000 patients revealed that blood transfusions were not associated with significantly higher mortality rates. In matched-pair propensity analysis, a higher 30-day survival rate was observed in the group that had a transfusion at any time while in the ICU ($P = 0.004$).[60] In contrast, other multicenter and randomized trials have not shown similar benefit. In 838 critically ill patients in the ICU that were randomized to receive either restrictive or liberal blood transfusion strategies when hemoglobin concentrations were less than 9.0 g/dL, the in-hospital mortality was significantly lower when patients were treated with a limited transfusion strategy (22.2% vs. 28.1%, $P = 0.05$).[62] In an examination of 45 observational cohort studies that combined data from 272,596 critically ill patients, red blood cell transfusions were linked with increased morbidity and mortality.[63] The pooled OR for death generated from the results of 12 studies was 1.7 (95% CI, 1.4–1.9). Transfusions were also associated with infectious complications, risk for developing multiorgan dysfunction syndrome, and ARDS.

The Surviving Sepsis guidelines include recommendations to provide blood transfusions in order to maintain hematocrits above 30% during the first 6 hours of resuscitation if there is evidence of tissue hypoperfusion after adequate repletion of the circulating volume. Guidelines for transfusion after the resolution of tissue hypoperfusion aim to keep the hemoglobin concentration between 7.0 g/dL and 9.0 g/dL in most patients.[5] To examine these target values, Holst and colleagues randomized approximately 1000 patients with septic shock and hemoglobin concentrations ≤9 g/dL to receive red blood cell transfusions to hemoglobin thresholds of 7 g/dL or 9 g/dL.[64] Those who were randomized to the higher hemoglobin target were transfused a median of four units of blood, whereas a median of one unit was given to those in the lower hemoglobin target group. At 90 days, there was no significant difference in mortality between the groups. These results held true after adjusting for baseline risk factors. In addition, there was no significant difference in the number of ischemic events, severe reactions, or use of life support between the two groups. As such, the optimal hemoglobin target in patients with sepsis in the ICU remains uncertain, and based on the available current evidence, administering blood transfusions when the hemoglobin is above 7 g/dL does not appear to provide a significant benefit to infusion of crystalloids alone.

EFFECTS OF VOLUME OVERLOAD

Volume therapy in critically ill patients aims to avoid and reverse the consequences of hypoperfusion and end-organ damage. Because of the large volumes of IV fluid that are often required, deleterious effects from volume overload can develop during the management of shock and in the postresuscitation period. These effects may be manifested systemically, for example, by hypertension and increased myocardial demand, pulmonary congestion with respiratory failure, and/or peripheral edema.[65]

Evidence supports that fluid resuscitation resulting in clinical volume overload is not beneficial to critically ill patients and negatively affects clinical outcomes. An early signal came from a retrospective study of patients with sepsis.[66] Achieving a net negative fluid balance greater than or equal to 500 mL within the first 3 hospital days correlated with improved survival independent of age, critical illness, and kidney function. The previously mentioned SOAP study evaluated more than 3000 ICU patients with sepsis. One of the most significant predictors of death was a net positive fluid balance, and multivariate regression analysis implicated positive fluid balance as an independent predictor of outcome despite disease severity.[67] Similarly, the Vasopressin and Septic Shock Trial (VASST) investigators determined that more positive fluid balance was significantly associated with an increase in mortality.[68] In these patients with sepsis, the cumulative mean fluid balance was 11 L fluid positive by postenrollment day 4. In patients who received conservative fluid management after the initial resuscitation, equating to net "even" or negative fluid balance on at least 2 consecutive days during the first week after the onset of septic shock, lower in-hospitality mortality was observed.[69] Volume overload is not only associated with increasing mortality but also with greater use of related medical interventions, including thoracentesis and the prescription of diuretic agents.[65] Higher cumulative fluid balance has been associated with both acute lung injury (ALI) and ARDS.[70] Both disorders portend poorer ICU outcomes. In contrast, more conservative fluid management strategies are associated with shorter durations of mechanical ventilation and improved outcomes in patients with ALI.[71,72] In patients admitted to the ICU with cancer, mean cumulative fluid balances exceeding 1.1 L in 24 hours were more frequently observed in the nonsurvivors.[73] Among patients admitted to the neurosurgical ICU for subarachnoid hemorrhage, positive net fluid balances after 3 days predicted the occurrence of vasospasm by transcranial Doppler and was associated with a longer length of hospital stay.[74]

Volume overload is common in critically ill patients who develop AKI, particularly with oliguria. In patients who require renal replacement therapy, fluid overload at the time of dialysis initiation has been associated with a higher 90-day mortality.[75] These differences in mortality persist after adjusting for disease severity, the timing of initiation of renal replacement therapy, dialytic modality, and sepsis. Additionally, patients enrolled in the Program to Improve Care in Acute Renal Disease (PICARD) study who had evidence of volume overload when the serum creatinine concentration was at its peak had significantly lower chances of recovering kidney function; their OR for death was 2.07 (95% CI, 1.27–3.37) when volume overload was present at dialysis initiation.[76]

However, there is no clear prescription for avoiding the unintended complications of volume overload. Management decisions that limit or restrict aggressive fluid resuscitation may lead to poorer outcomes. In 1490 patients who were randomized to restrictive fluid intake with a goal of net zero fluid balance around major abdominal surgery vs. traditional practices, those who had a restrictive regimen suffered a significantly higher rate of AKI without a difference in disability-free survivial.[77]

Complicating the issue is the fact that the assessment of volume overload and cumulative fluid balance is often subjective; results may be inconsistent because of errors in recording intakes and outputs and inaccurately measuring patient weights. A positive fluid balance might not correlate with clinical evidence of volume overload.[65] Furthermore, objective measurements of volume status, such as central venous

pressure readings, may not always correlate with fluid balance. Additional clinical trials are necessary to further guide clinical decision making in volume administration.

CONCLUSION

Replenishing and maintaining an adequate intravascular volume in critically ill patients remains somewhat of an art, without a universally applicable "recipe" to guide fluid replacement. Individualization of care is required, often balancing the administration of vasopressors with proper fluid repletion. Nonetheless, randomized trials support several guiding principles that appear to optimize patient outcomes (Table 99.2). In sepsis, early goal-directed fluid administration using IV crystalloids before colloids or blood products remains a mainstay of therapy in patients who lack active blood loss or symptomatic anemia. In the settings of cirrhosis with peritonitis and possibly severe burns, albumin infusion along with crystalloids may improve outcomes. Infusion of HES appears to be associated with higher complication

TABLE 99.2 Major RCTs Evaluating Type of Fluid With Mortality and Dialysis Outcomes in the ICU

First Author	Year	Journal	Type of Fluid	n	Mortality Outcome	*P*	Dialysis Outcome	*P*
Colloids								
Finfer (SAFE)[15]	2004	NEJM	Albumin vs. Saline	6997	No difference	0.87	No difference in RRT days	0.41
Myburgh (SAFE)[23]	2007	NEJM	Albumin vs. Saline in Traumatic Brain Injury	460	Higher with albumin	0.003	Not evaluated	–
Perner[25]	2012	NEJM	Hydroxyethyl Starch (HES) vs. Ringer's Acetate	804	Higher with HES	0.03	RRT higher with HES	0.04
Myburgh (CHEST)[24]	2012	NEJM	HES vs. Saline	3315	No difference	0.26	RRT higher with HES	0.04
Annane (CRISTAL)[18]	2013	JAMA	Colloids vs. Crystalloids	2857	No difference	0.26	No difference in RRT	0.19
Zarychanski[27]	2013	JAMA	HES vs. Crystalloid, Albumin, or Gelatin*	10,880	Higher with HES	–	RRT higher with HES	–
Caironi[19]	2014	NEJM	Albumin + Crystalloid vs. Crystalloid	1818	No difference	0.94	No difference in RRT	0.11
Futier (FLASH)[26]	2020	JAMA	HES vs. Saline in Major Abdominal Surgery	826	Death or major complication: no difference		No difference in RRT	0.2
Chloride-Restrictive Crystalloids								
Yunos[51]	2012	JAMA	Chloride Liberal vs. Chloride Restrictive	760	No difference	0.42	RRT higher with chloride liberal	0.005
Young (SPLIT)[78]	2015	JAMA	Buffered Crystalloid vs. Saline	1067	No difference	0.4	No difference in RRT	0.91
Semler (SMART)[56]	2018	NEJM	Balanced Crystalloid vs. Saline	7942	Tended higher with saline	0.06	Kidney events higher with chloride liberal	0.04
							RRT less with balanced	0.08
Blood								
Hebert[62]	1999	NEJM	Lower vs. Higher Hemoglobin Threshold	838	No difference	0.11	Not evaluated	–
Villaneuva[79]	2013	NEJM	Liberal vs. Restrictive Transfusion Acute in Acute GI Bleed	921	Higher in liberal strategy	0.02	No difference in AKI	0.13
Holst[64]	2014	NEJM	Lower vs. Higher Hemoglobin Threshold	998	No difference	0.44	No difference	0.49
Murphy[80]	2015	NEJM	Liberal vs. Restrictive Transfusion after Cardiac Surgery	2007	Higher in restrictive	0.045	Not evaluated	–
Restrictive vs. Liberal Administration								
Wiedemann[71]	2006	NEJM	Liberal vs. Restrictive Fluid Management in Acute Lung Injury	1000	No difference	0.3	RRT to day 60 higher with liberal	0.06
Myles (RELIEF)[77]	2018	NEJM	Liberal vs. Restrictive Fluid Therapy in Major Abdominal Surgery	3000	No difference	0.61	RRT higher in restrictive	0.048
EGDT vs. Usual Care								
Rivers[2]	2001	NEJM	Early Goal-Directed Therapy (EGDT) vs. Usual Care	263	Higher in usual care	0.009	Not evaluated	–
Yealy (ProCESS)[8]	2014	NEJM	Protocol-Based EGDT vs. Usual Care	1341	No difference	0.83	No difference in RRT days	0.92
Peake (ARISE)[7]	2014	NEJM	EGDT vs. Usual Care	1600	No difference	0.9	No difference in RRT	0.94
Mouncey (ProMISe)[9]	2015	NEJM	EGDT vs. Usual Care	1260	No difference	0.9	No difference in RRT	0.62

*Meta-analysis of 38 clinical trials.

rates, particularly AKI. Prescription of chloride-containing crystalloids has begun to lose favor based on the desire to avoid the adverse effects of hyperchloremia and metabolic acidosis. Finally, excessive transfusion of packed red blood cells for sepsis-induced hypoperfusion in lieu of crystalloids appears to provide little benefit. Hemoglobin levels above 7 g/dL do not seem to improve outcomes. It remains imperative to avoid volume overload, electrolyte abnormalities, and acid-base imbalance when replenishing intravascular volume in critically ill ICU patients.

KEY POINTS

- Before considering the administration of colloids or blood products in critically ill patients with an inadequate vascular volume, intravenous crystalloids remain the mainstay of volume repletion therapy (except in the settings of active bleeding or symptomatic anemia).
- In patients with cirrhosis and accompanying peritonitis, albumin infusion along with IV crystalloids may improve outcomes.
- Administration of HES appears to be associated with higher complication rates, particularly AKI.
- NS is losing favor for volume resuscitation based on its risk of inducing hyperchloremia and metabolic acidosis.
- Excessive transfusion of packed red blood cells in patients with sepsis and hypoperfusion appears to provide little added benefit to the infusion of crystalloids alone.

References for this chapter can be found at expertconsult.com.

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Acute Kidney Injury

Elwaleed A. Elhassan

Acute kidney injury (AKI) is recognized as one of the most serious complications in critically ill patients. It is strongly associated with higher short- and long-term mortality, increased resource utilization, and a higher risk for the development of chronic kidney disease (CKD) and end-stage kidney disease (ESKD).[1] AKI is defined as a sudden decrease in the glomerular filtration rate (GFR) occurring over a period of hours to days.[2] AKI is not a single disease, but rather a loose collection of various syndromes as heterogeneous as sepsis, cardiorenal syndrome, and urinary tract obstruction, which can often coexist.[3] Historically, AKI has been categorized according to the anatomic location of the presumed insult into prerenal, intrinsic renal, and postrenal AKI. However, the diverse nature of AKI, resulting from multiple etiologies with different pathophysiologies, has given way to specific descriptive syndromes, such as sepsis-associated AKI, nephrotoxic AKI, and cardiorenal syndrome.[3]

AKI can result from decreased renal perfusion not severe enough to cause cellular injury, such as in hypovolemia, systemic vasodilation, or acute worsening of cardiac function. If renal tubular and glomerular structure are presumably intact but solute clearance is limited, the injury is termed *prerenal azotemia*. If renal dysfunction is related to an obstruction of the urinary outflow tract, it is termed *postrenal azotemia*. AKI can also result from a renal insult, such as nephrotoxic exposure, glomerular or interstitial inflammatory process, or in the setting of a systemic syndrome like sepsis. Prerenal azotemia and renal injury caused by sepsis, ischemia, and nephrotoxins are responsible for most episodes of AKI.[4] The term *acute tubular necrosis (ATN)* was employed because of the demonstration of patchy necrosis of the tubular cells from autopsy studies late in the course of the disease. However, when performed, kidney biopsy findings in some conditions, such as sepsis and shock, show near absence of tubular necrosis despite profound kidney dysfunction. Furthermore, prerenal azotemia and intrinsic acute tubular necrosis can, and often do, coexist in the same patient. Because of the patchy nature of ATN, it is possible that some regions of the kidneys can have severe morphologic and functional ATN, whereas other parts may be structurally intact, awaiting only reperfusion to resume normal filtration. Therefore the use of the terms prerenal azotemia and ATN can be misleading and is becoming more questioned.[3,5]

Renal blood flow is approximately 1200 mL/min and constitutes 20% of cardiac output. Given this apparently generous perfusion, it may seem surprising that the kidneys are so susceptible to hemodynamic insults. The majority of perfusion (80%–90%), however, is to the renal cortex, where glomerular filtration occurs. The medulla is designed to concentrate and dilute urine. During urine concentration, the high osmotic gradient required for the reabsorption of water is associated with a low rate of blood flow. In fact, oxygen tension in the outer medulla in the region of the metabolically active thick ascending limb of Henle is only around 10 mm Hg.[6] This combination of low blood flow and diminished oxygen tension in a metabolically active environment makes the kidneys very susceptible to ischemic injury.

RENAL HYPOPERFUSION

Renal hypoperfusion is a consequence of the reduction in renal perfusion without cellular injury. As such, this is a reversible process if the underlying cause is corrected. It may be secondary to decreased blood volume (e.g., vomiting, hypovolemia, and hemorrhage), or it may be caused by a reduction in the effective arterial blood volume (e.g., congestive heart failure and cirrhosis). Further, the administration of medications that interfere with the normal autoregulatory ability of the kidney can contribute to prerenal azotemia. In settings of diminished renal perfusion, the administration of nonsteroidal antiinflammatory drugs (NSAIDs) or renin–angiotensin–aldosterone system (RAAS) inhibitors can precipitate overt prerenal azotemia. During prerenal azotemia, the RAAS becomes activated secondary to a decrease in renal blood flow, accompanied by increased activity of the adrenergic nervous system. Increased levels of angiotensin II and adrenergic activation increase proximal reabsorption of sodium, whereas aldosterone increases sodium reabsorption in the distal tubule. Together, these actions decrease the urine sodium concentration to less than 20 mmol/L and fractional excretion of sodium to less than 1%.[7] Therapy of prerenal AKI involves reversing the underlying cause, such as volume replacement or discontinuation of offending agents.

POSTRENAL CAUSES OF AKI

Postrenal AKI occurs when there is a bilateral (or unilateral in the case of a single kidney) obstruction of urine flow. In this setting, intratubular pressure increases and, in turn, decreases the net glomerular filtration pressure. Obstruction of urine flow is a relatively uncommon cause of AKI and is more frequent in the community than in the intensive care unit (ICU). Postrenal AKI can be divided into renal and extrarenal causes. Extrarenal causes include prostatic disease, pelvic malignancy, and retroperitoneal disorders. Intrarenal causes include crystal deposition, as occurs in ethylene glycol ingestion, or uric acid nephropathy in tumor lysis syndrome. Cast formation and tubular obstruction also occur in light-chain diseases, such as multiple myeloma. Possible postrenal causes of AKI should be evaluated with renal ultrasonography and the measurement of postvoid residual urine in the bladder (>50 mL is abnormal). It is important to rule out these causes rapidly because the potential for renal recovery is inversely related to the duration of obstruction.

INTRINSIC AND SYNDROMIC CAUSES OF AKI

Intrinsic causes of AKI can affect the glomerulus, vasculature, interstitium, or tubule. Suspicion of glomerulonephritis or vasculitis should be raised in a patient with renal failure who has an active urine sediment with red cells and red cell casts. In contrast, acute interstitial nephritis can present with pyuria and white cell casts in the urine; on occasion, hematuria is also present. Most cases of AKI from interstitial nephritis are drug related, commonly the result of antibiotics or NSAIDs. Recovery usually occurs with the removal of the offending agent and may be hastened by a short course of steroids: for example, 1 mg/kg per day of prednisone for approximately 1–1.5 months.[8] Intrinsic renal failure is often termed ATN, although, as explained earlier, this is a histologic diagnosis that is rarely confirmed by biopsy. ATN can be broadly classified into ischemic ATN, when it follows prolonged renal hypoperfusion, and toxic ATN, when it results from exposure to nephrotoxic drugs (such as antibiotics, contrast media, or chemotherapeutic agents) or endogenous toxins (such as myoglobin and uric acid). These toxins can have a direct cytotoxic effect on renal epithelial cells, affect intrarenal hemodynamics, or cause precipitation of metabolites or crystals, among others.[3] The most common cause of AKI in critically ill patients is sepsis. The pathophysiology of sepsis-associated acute kidney injury (S-AKI) remains incompletely understood. Previously, S-AKI was considered primarily a disease of the renal macrocirculation[9] resulting from global renal ischemia, cellular damage, and ATN. However, an increasing body of evidence suggests that S-AKI can occur in the absence of overt signs of hypoperfusion and clinical signs of hemodynamic instability.[10] A consistent finding in septic patients, independent of the severity of AKI, is the presence of microcirculatory dysfunction, inflammation, and adaptive bioenergetic response to injury.[11] The role of these mechanistic theories in the genesis of S-AKI and the potential therapeutic implications have been reviewed.[10]

Another form of AKI in the hospital is connected with the use of contrast media. Many studies have shown that contrast-related AKI, defined by small decrements in kidney function, is associated with increased mortality. However, a recent analysis using the Bradford Hill criteria points to significant uncertainty on a causal link between contrast and AKI.[12] Because other factors (e.g., medications, hypotension, or atheroemboli) can precipitate AKI after such exposure, the term *contrast-associated acute kidney injury (C-AKI)* has gained favor.[13] The pathogenesis of AKI in this setting involves both the hemodynamic and toxic effects of contrast. Contrast media cause renal vasoconstriction and medullary ischemia, in addition to direct tubular toxicity.[14] Preexisting renal disease, the use of contrast medium at a high volume (>350 mL or >4 mL per kilogram), and repeated administration within 72 hours after initial administration have been shown to be associated with an increased risk.

DEFINITION AND DIAGNOSIS

AKI is the abrupt decrease in GFR with resultant retention of urea and other nitrogenous waste products along with dysregulation of body fluids and electrolytes. The term *acute kidney injury* was proposed by the Acute Kidney Injury Network (AKIN) as an alternative to acute renal failure to encompass the entire range of insufficiency based on data showing that a small change in serum creatinine influences outcome. The Acute Dialysis Quality Initiative (ADQI) group proposed a consensus categorized definition, the RIFLE criteria.[15] Subsequently, AKIN proposed a revision of the RIFLE criteria[16–18] to better account for small changes in serum creatinine not captured by RIFLE criteria. Several large observational trials confirmed the validity of the RIFLE and AKIN revised criteria, as increasing severity of AKI was associated with increasing risk of death.[19,20] The Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for AKI included a revision to the definition of AKI while retaining the AKIN staging criteria, and these are now globally embraced (Table 100.1).[21] In an international cross-sectional study using these criteria, 57.3% of ICU patients met KDIGO criteria for AKI.[22] The adjusted odds ratio for in-hospital mortality was progressive with the stage of AKI. All criteria mentioned earlier have the greatest utility in epidemiologic studies and in designing clinical trials in AKI. Despite this progress, the sensitivity and accuracy of AKI criteria have been generally acknowledged to remain limited by a reliance on the imperfect assessment methods on which they are built: namely, urine output and serum creatinine. Multiple novel biomarkers are being extensively studied for early diagnosis and prognostication of AKI (Table 100.2).[23] AKI is a clinical diagnosis that requires making changes in kidney function in the clinical context of the patient. Although sepsis is well recognized as the leading cause of AKI in the critically ill, it has been shown that 40% of critically ill patients develop sepsis after AKI.[24] This suggests that AKI may increase the risk of sepsis. Furthermore, both sepsis and AKI are clinical diagnoses, and it is usually difficult to define the precise time either of these syndromes begin. Therefore the term S-AKI has been introduced to acknowledge the uncertainty around the attribution of etiology.[10] S-AKI is defined as AKI in the presence of sepsis (based on Sepsis-3, the current consensus definition of sepsis) without other significant contributing factors explaining AKI or characterized by the simultaneous presence of both Sepsis-3 and KDIGO criteria.

There are several limitations to the use of serum creatinine and urine output for the diagnosis of AKI. There is no consensus method to establish baseline serum creatinine in the absence of previous values. Moreover, creatinine rise is often delayed and could be blunted in sepsis because of decreased creatinine production in addition to aggressive fluid resuscitation. Urine output is insensitive to detect AKI compared with creatinine, is less reliable outside the ICU setting, and

TABLE 100.1 Criteria and Staging for Acute Kidney Injury

Stage	Serum Creatinine	Urine Output
1	1.5–1.9 times baseline OR ≥0.3 mg/dL (26.5 micromol/L) increase	<0.5 mL/kg/h for 6–12 h
2	2.0–2.9 times baseline	<0.5 mL/kg/h for ≥12 h
3	3.0 times baseline OR Increase in serum creatinine to ≥4.0 mg/dL (353.6 micromol/L) OR Initiation of renal replacement therapy OR In patients <18 years, decrease in eGFR to <35 mL/min per 1.73 m^2	<0.3 mL/kg/h for ≥24 h OR Anuria for ≥12 h

Data from KDIGO clinical practice guideline for acute kidney injury. *Kidney Int.* 2012;2(Suppl. 1):8.
eGFR, Estimated glomerular filtration rate.
Minimum criteria for acute kidney injury include an increase in serum creatinine (SCr) by ≥0.3 mg/dL (26.5 micromol/L) observed within 48 hours; or an increase in SCr to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or urine volume <0.5 mL/kg/h for 6 hours.

TABLE 100.2 Biomarkers Used for Detection of Acute Kidney Injury

Type of Biomarker	Subclass of Biomarker	Examples of Biomarkers	Comments
Functional biomarker of AKI	Biochemical markers of glomerular filtration/function	Serum creatinine, serum cystatin c, proenkephalin, visible fluorescent injectates	Serum creatinine remains the gold standard, but other novel markers of glomerular function have been shown to rise earlier and with the same accuracy as creatinine. Injectables may represent the future of GFR measurement, with the injection of small dextrans providing rapid determination of GFR at the bedside. May be elevated in the setting of CKD
	Global assessment of nephron function	Urine output	Urine output detects less severe AKI compared with creatinine and can be affected by diuretics and other drugs. Generally needs indwelling catheter for reliable measurement, with measurements being less frequent outside the ICU
	Global assessment of nephron capacity	Furosemide stress test, renal reserve testing	These tests interrogate the kidney's capacity for increased function via protein loading (hyperfiltration) or diuretic responsiveness
Damage/injury biomarkers	Global assessment of nephron injury	Urinalysis	Urinalysis can detect injury along the entire nephron (from glomerulus to tubules); although scoring systems exist, none has been widely validated in any setting of AKI
	Biochemical biomarkers of renal tubular injury	Urinary NGAL, urinary KIM-1, soluble FAS	These remain an area of intense AKI research but have yet to be widely validated in the setting of human AKI
AKI risk biomarkers	Biochemical biomarkers of AKI risk	TIMP2*IGFBP7, plasma NGAL	Increasingly available for clinical use, these markers quantify an individual patient's risk for impending AKI
	Biomarkers of AKI risk	Electronic alerts, electronic risk algorithms	Several alerts have shown their ability to predict the impending development of sepsis and AKI separately. Using these alerts in concert with biochemical biomarkers may help to enrich AKI detection and risk stratification

AKI, Acute kidney injury; *CKD,* chronic kidney disease; *GFR,* glomerular filtration rate; *ICU,* intensive care unit; *IGFBP7,* insulin-like growth factor binding protein-7; *KIM-1,* kidney injury molecule-1; *NGAL,* neutrophil gelatinase–associated lipocalin; *TIMP2,* tissue inhibitor of metalloproteinase-2. Adapted from Poston JT, Koyner JL. Sepsis associated acute kidney injury. *BMJ*. 2019;364:k4891.

can be affected by diuretics and other drugs. Urinalysis and urine microscopy may aid identification of S-AKI. Observational studies have shown that S-AKI shows more renal tubule epithelial cells and cast elements compared with nonseptic AKI.[25,26] Patients with S-AKI had higher urine microscopy scores when compared with those with AKI from other causes.[27] Thus urine sediment may help establish the cause of AKI, but its sensitivity is poor. Several biomarkers have been developed and may assist in the early detection of AKI in patients with sepsis (see Table 100.2). Further studies are required to establish any of these or other potential biomarkers as practical diagnostic tools in the early clinical diagnosis of AKI. Such tools may facilitate timely and aggressive therapeutic interventions. A specific one worth mentioning is the furosemide stress test (FST). This test was proposed as a tool for determining the risk of AKI progression.[28] It uses a protocolized dosage of furosemide (1.0 mg/kg of furosemide to diuretic-naive subjects and 1.5 mg/kg in subjects with prior furosemide exposure) in patients with AKI stages 1–2 to determine the risk of progression to stage 3 AKI or requirement for renal replacement therapy (RRT). The cutoff for predicting AKI progression during the first 2 hours after FST was a urine volume of less than 200 mL with high sensitivity and specificity. Since the original publication of the FST by Chawla and colleagues, this test has been prospectively validated to predict worsening AKI among critically ill patients and used to identify patients for randomization to different RRT initiation times.[29,30] Two other recently developed biomarkers of cell cycle arrest are tissue inhibitor of metalloproteinases 2 (TIMP2) and insulin-like growth factor binding protein-7 (IGFBP7).[3] Those markers have been incorporated into the first diagnostic test for AKI approved by the US Food and Drug Administration (FDA): Nephrocheck (Astute Medical, San Diego, CA). Unlike damage markers, TIMP2 and IGFBP7 can be released in response to noninjurious, noxious stimuli and thus serve as kidney stress markers.[31,32]

EPIDEMIOLOGY AND OUTCOMES

The incidence of AKI is now believed to be significantly higher than previously thought, with over 50% of patients in the ICU developing stage 1 AKI at some point during the course, whereas stages 2 and 3 AKI are considerably less.[33] Sepsis remains one of the most common sources of AKI, and S-AKI is strongly associated with poor clinical outcomes. Precise estimation of the incidence of S-AKI is difficult, given the many confounders common in critically ill patients.[23] Bagshaw and colleagues found sepsis considered responsible in 47.5% of an international cohort of 753 critically ill patients with AKI. Moreover, they demonstrated that S-AKI was associated with higher risk of in-hospital mortality and longer duration of hospitalization.[34] More recently, a larger international consortium showed similar findings.[1] The Sepsis Occurring in Acutely ill Patients (SOAP) cohort study recruited patients admitted to 198 ICUs across Europe.[35] About a third of this cohort had sepsis, whereas AKI occurred in half of the cases and was associated with an ICU mortality of 41%.

About two-thirds of AKI episodes resolve within 7 days.[36] When a case does not resolve or relapse occurs with subsequent lack of resolution, substantially worse clinical outcomes are expected. AKI is now increasingly recognized as having a bidirectional relationship with CKD in hospitalized patients. Although preexisting CKD increases the susceptibility toward the development of AKI, AKI has also been found to accelerate the development of CKD. After recovery from AKI, patients carry the risk of developing CKD, ESKD, and death.[37] The severity of

AKI, RRT requirement, and recovery status during hospitalization has been shown to determine the risk of progression to CKD.[38,39] Over 1 year, CKD developed in 21%, 30%, and 79% of 105 survivors with AKI reversal, recovery, and nonrecovery, respectively.

PREVENTION AND TREATMENT

In light of its dismal outcome, it is imperative that therapies to prevent or ameliorate AKI be developed. The fundamental principles of prevention of AKI are identifying patients at risk and timely instituting appropriate protective measures. Recently reviewed evidence has focused on clinical risk prediction, novel kidney damage biomarkers, automated electronic alerts embedded within electronic health records, and the concept of the renal angina index.[40] If prerenal factors contribute, they should be identified and intravascular volume maintained or rapidly restored. Patients deemed at increased risk should have appropriate drug adjustment, discontinuation, or avoidance of nephrotoxins, including unnecessary exposure to contrast media (Fig. 100.1). Beyond such seemingly obvious interventions, only a limited number of preventive treatments are potentially available.

Fluid resuscitation. Prompt resuscitation of the circulation with administration of intravenous fluids is a key component of sepsis management. High-quality resuscitation care of the patient with sepsis includes an initial modest bolus of resuscitation fluid (30 mL/kg within the first 3 hours) followed by a frequent assessment with dynamic measures of fluid responsiveness to determine whether additional fluids or

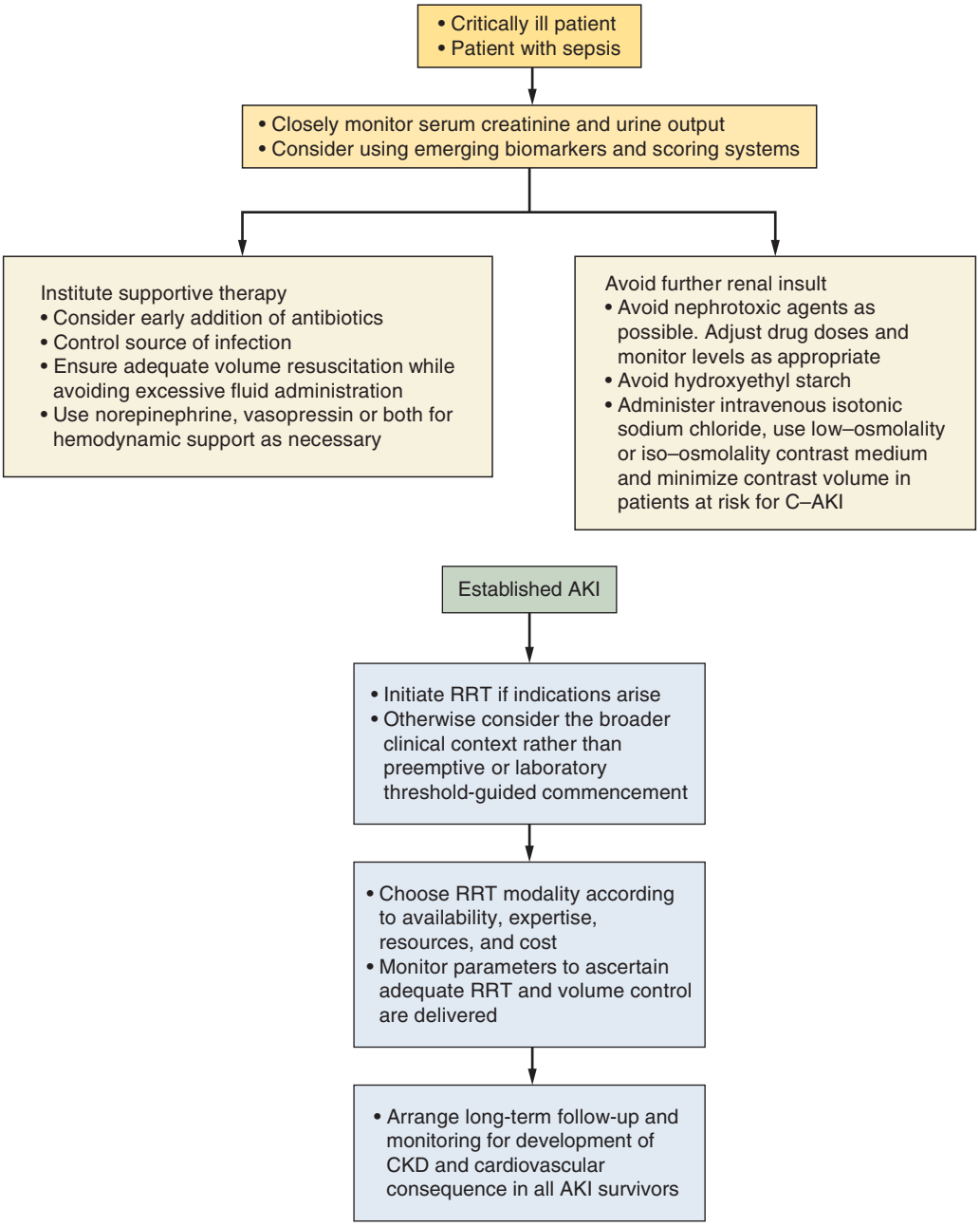

Fig. 100.1 Recommendations for the Evaluation and Treatment of Acute Kidney Injury. *AKI*, Acute kidney injury; *C-AKI*, contrast-associated acute kidney injury; *CKD*, chronic kidney disease; *RRT*, renal replacement therapy.

vasoactive drugs are indicated.[41] Recent studies have shown that protocolized resuscitation strategies did not improve outcomes, but a minimal degree of resuscitation is needed to mitigate the risk of adverse outcomes. When volume replacement is indicated, both crystalloids (e.g., isotonic saline and Ringer's lactate) and colloid-containing solutions (e.g., albumin solution and colloidal substances) have been used to replace the extracellular fluid deficit. Crystalloids are the most common form of volume replacement, but their effect on plasma volume is limited. Colloidal substances, such as albumin, dextran, and hydroxyethyl starches (HESs), because they are macromolecules, are better retained within the intravascular space and have a greater effect on plasma volume. Albumin has been used for decades, but it is expensive. In view of the absence of evidence of a mortality benefit from albumin and its increased cost compared with crystalloids, albumin may be avoided according to a Cochrane Group systematic review.[42] Dextran cannot be recommended for plasma volume expansion because of serious side effects, such as coagulation abnormalities and increased development of AKI. Hyperoncotic starch solutions should be avoided in sepsis and in all other patients at risk for AKI, as multiple studies have shown that HESs are associated with increased risk of AKI and need for RRT compared with a variety of crystalloid solutions.[43–46]

Although crystalloids remain the first choice for fluid therapy in critically ill patients, there may be differences in renal outcomes among them. Isotonic 0.9% saline is widely available and is inexpensive, but is hyperchloremic relative to plasma. A large-volume resuscitation using isotonic saline may be associated with the development of a hyperchloremic metabolic acidosis. A number of clinical trials tested the differential effects of the so-called balanced crystalloids (chloride concentrations <110 mmol/L) compared with isotonic saline on clinical outcomes. The recent Saline Against Lactated Ringer's or Plasma-Lyte in the Emergency Department (SALT-ED) and Isotonic Solutions and Major Adverse Renal Events (SMART) trials found fewer major adverse kidney events.[47,48] Both trials found about 1% absolute risk reduction for major adverse kidney events by 30 days in patients treated with balanced crystalloid. However, a subsequent meta-analysis of 21 randomized controlled trials found no convincing evidence of an effect of balanced crystalloids on in-hospital mortality or AKI when compared with isotonic saline.[49] Until further research is available, balanced crystalloids may be preferred in patients in whom large volumes of fluids are administered (e.g., >2 L) in addition to those with hyperchloremic acidosis.

Fluid overload. As previously pointed out, aggressive fluid therapy is crucial to the successful management of both sepsis and AKI. However, septic AKI may not be characterized by hypoperfusion. Clear evidence shows that in addition to the risks of underresuscitation, in the setting of AKI, volume overload from aggressive overresuscitation is also harmful, creating a J- or U-shaped curve for resuscitation and mortality.[23,50] The pathogenetic mechanism may involve renal edema, which, in an encapsulated organ, may induce congestion and ischemia.[51] Fluid bolus therapy, combined with the oliguria of AKI, is likely to lead to fluid accumulation in septic patients.[52] Fluid accumulation was associated with adverse outcomes and increased mortality in multiple studies,[53–55] with persistent and abundant data demonstrating harm in a variety of patient populations, including those with septic AKI. In contrast, in the setting of major abdominal surgery, a fluid-liberal strategy was associated with lower rates of AKI and no difference in disability-free survival. This was based on a recent large-scale international pragmatic trial that investigated the impact of fluid restriction on the development of organ dysfunction after major abdominal surgery.[56] Future investigations are still needed to determine the ideal fluid strategy for the prevention of septic and postoperative AKI.

Supportive care. Earlier and appropriate antimicrobial therapy, along with septic source control, has been associated with lower risk of AKI.[57,58] For each hour that appropriate antimicrobial therapy was delayed, the risk of AKI increased by approximately 40%. Moreover, earlier antimicrobial therapy was associated with a greater likelihood of kidney recovery within 24 hours. Nephrotoxic therapies, such as treatment with aminoglycosides, vancomycin particularly when combined with piperacillin-tazobactam[59] and amphotericin B, should be used with caution to prevent kidney injury. Systematic surveillance for nephrotoxic medication exposure and AKI risk can lead to sustained reductions in avoidable harm.[58] Strict therapeutic drug monitoring should be considered when applicable.

Diuretics are frequently used in patients with AKI, especially in an attempt to convert oliguric into nonoliguric AKI. Furosemide is not associated with any significant clinical benefits in the prevention or treatment of acute renal failure in adults.[60] Although the use of loop diuretics in early or established AKI facilitates management of fluid overload, hyperkalemia, and hypercalcemia, any active role in the prevention or amelioration of the AKI course remains unproven. Therefore if diuretics are employed, care must be taken to avoid delaying the initiation of dialysis if clinically necessary. Metabolic acidosis is one of the complications of AKI. The administration of bicarbonate in patients with metabolic acidosis (pH <7.2) and severe AKI may help to delay or avoid unnecessary RRT.[61] By increasing pH to levels >7.3, bicarbonate therapy reduced 28-day mortality and the need for dialysis. However, in patients with lactic acidosis, the primary aim of therapy is reversal of the underlying disease (e.g., shock, sepsis).

Vasopressor support. Although hemodynamic monitoring is of unproven benefit, it is the standard of care in order to guide vasopressor drug institution after fluid resuscitation. This typically includes physical examination or invasive monitoring (e.g., central venous catheter, arterial cannula, and even cardiac output monitoring in some cases) in severely ill patients. If patients remain hypotensive (e.g., mean arterial pressure [MAP] <65 mm Hg) after adequate intravascular volume expansion, restoration of MAP will require the addition of vasopressor drugs.[3] Because such agents cause vasoconstriction, there has been concern about their use in AKI. Norepinephrine is recommended as a mainstay of therapy for septic shock treatment, showing the ability to increase MAP and improve renal perfusion.[62] Compared with norepinephrine, vasopressin showed similar outcomes and no increased adverse events.[63,64] These data suggest that vasopressin is a viable first-line alternative to norepinephrine. Dopamine is not recommended for renal protection and is associated with more adverse events than norepinephrine.[65]Angiotensin II is a potent vasopressor without inotropic or chronotropic properties. Clinical trials have demonstrated this novel vasoconstrictor may improve patient outcomes in the setting of vasodilatory shock and outcomes in the setting of shock-associated severe AKI.[66,67] Fenoldopam, a selective dopamine receptor-1 agonist, resulted in less adverse renal outcomes but not decreased mortality.[68]

GLYCEMIC CONTROL AND NUTRITIONAL SUPPORT

It has been proposed that tight glycemic control can reduce the incidence and severity of AKI in critically ill patients. However, studies have highlighted significant concerns regarding the effectiveness and safety of using intensive insulin therapy with tight glycemic control to prevent or ameliorate morbidity and mortality of AKI or other forms of organ injury. The international Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study enrolled over 6000 patients and set out to determine the risk/benefit of tight glycemic control in critically ill patients.[69] It

showed that in contrast to conventional insulin therapy, intensive glucose control increased mortality among these patients. A blood glucose target of ≤180 mg/dL resulted in a lower mortality than a target of 81–108 mg/dL. Therefore it may be prudent to use conventional insulin therapy in ICU patients at risk of AKI to target plasma glucose of 140–180 mg/dL to avoid hypoglycemia. Nutritional support in patients with AKI does not differ significantly from that of critically ill patients. AKI affects water, electrolyte, and acid-base balance, but it also induces changes in protein, carbohydrate, and lipid metabolism. Although requirements vary based upon the underlying catabolic state, patients with AKI should be supplemented with 20–30 kcal/kg body weight per day. Even in hypermetabolic states such as sepsis, energy expenditure is rarely greater than 130% of the calculated basic energy expenditure. Protein requirement increases with the severity of the underlying illness and with initiation of RRT. Whereas nondialysis patients with only mild to moderate illness require only 0.8–1.2 g/kg per day, critically ill patients or patients who are on RRT generally require 1.2–1.5 g/kg per day or more.[70] Dietary restrictions on potassium, phosphorus, sodium, and fluid intake (1–1.5 L per day, except if volume depleted) are generally indicated.

SPECIAL TYPES OF AKI

Abdominal compartment syndrome. *(ACS)* is defined as intraabdominal hypertension (IAH) with intraabdominal pressure (IAP) greater than 20 mm Hg with or without an abdominal perfusion pressure less than 60 mm Hg accompanied by end-organ dysfunction.[71] Epidemiologic studies differ widely in their report of the incidence and prevalence of ACS in the ICU. However, there is agreement that the occurrence of IAH during the ICU stay is an independent predictor of patients' outcome.[72] This was reflected in studies conducted by Malbrain and colleagues and Vidal and colleagues showing significantly higher mortality rates and a higher incidence of organ failure or dysfunction—predominantly renal and pulmonary.[73,74] A large systematic review and meta-analysis of studies identified multiple risk factors for IAH and ACS in ICU patients; many were specific to the type of patient population under study. These risk factors include large-volume crystalloid resuscitation, the presence of shock/hypotension, obesity, sepsis, abdominal surgery, severe acute pancreatitis, and ileus development.[75] Several mechanisms have been reviewed as the etiology for IAH-induced renal dysfunction and failure.[72] The World Society of the Abdominal Compartment Syndrome proposed a management algorithm centered mostly on expert opinion that is based on the principles of serial IAP monitoring, optimization of systemic organ perfusion, IAP control, and reducing potential end-organ damage and surgical decompression for refractory ACS.[76]

Contrast-associated acute kidney injury. Multiple trials and meta-analyses have compared intravenous isotonic sodium bicarbonate with isotonic sodium chloride for the prevention of C-AKI, on the hypothesis that urinary alkalinization would reduce contrast-induced generation of injurious oxygen free radicals. The results of these analyses were inconclusive, and they collectively formed the basis for the recent Prevention of Serious Adverse Events Following Angiography (PRESERVE) study.[77] This was a double-blind trial that randomly assigned 5177 high-risk patients undergoing nonemergency angiography to receive intravenous isotonic sodium bicarbonate or intravenous isotonic saline, in addition to oral acetylcysteine or oral placebo, for the prevention of a primary composite endpoint of death, need for dialysis, or persistent impairment in kidney function. The trial showed no significant difference in the incidence of the primary outcome or in the incidence of C-AKI. Thus our recommendation for preventing contrast nephropathy in high-risk patients is to seek an alternative procedure not requiring contrast when possible. If that is not feasible, adequate hydration with isotonic sodium chloride should be performed.

Acute kidney injury in critically ill cancer patients. Cancer patients are particularly at risk for AKI secondary to infection and sepsis, tumor lysis syndrome, kidney damage induced by immunosuppression after hematopoietic stem cell transplantation, and direct effects from the primary malignancy.[78,79] The development of AKI can further jeopardize cancer treatment, increase the toxicity, and/or reduce the delivery of chemotherapy and exclude patients from clinical trials. AKI requiring RRT is more common in ICU patients with cancer compared with those without cancer, and hospital mortality rates are high in cancer patients with AKI, especially when RRT is required.[80]

ROLE OF THE NEPHROLOGIST IN THE ICU

There are wide variations in the probability and timing of nephrology consultation in patients with AKI. The role of the nephrologist in managing ICU AKI patients also depends on the ICU model: that is, "closed" where the intensivist treats patients with AKI without input from a nephrologist versus "open" where management would be combined. Although "closed" models are reported to result in fair patient outcomes,[81] integrating nephrologists into the care of critically ill patients from the early stages of AKI has been shown to be associated with a lower incidence of progression to severe AKI, lower mortality, and enhanced patient recovery.[82,83] Given their in-depth understanding of AKI and RRT technologies,[84] nephrologists are proficient at delivering dialytic and nondialytic treatment options for patients with AKI and in transitioning patients between these two treatment options based on each patient's changing clinical status. They can facilitate transition of AKI-RRT to outpatient dialysis, aid in proper follow-up and management of patients at risk of progressive CKD, and assist in avoiding or discontinuing RRT when treatment is futile or not consistent with the patient's goals of therapy.[85] Early follow-up by a nephrologist after an AKI episode in those requiring RRT was associated with improved survival.[86]

RENAL REPLACEMENT THERAPY

Indications and Timing

As mentioned previously, about half of patients in the ICU develop AKI. Of those, an estimated 8%–12% receive RRT for severe AKI.[22] The optimal timing of the initiation of dialysis is not defined. There is little disagreement in commencing dialysis in the presence of life-threatening conditions, such as diuretic-resistant volume overload, refractory hyperkalemia, acidosis, or overt symptoms and signs of uremia (e.g., encephalopathy and pericarditis). Medical treatment approaches for hyperkalemia result in intracellular shifts of potassium. When intermittent hemodialysis (IHD) is used to correct hyperkalemia after such measures have been used, dialytic potassium removal will be reduced, and higher serum levels of postdialysis potassium can occur.[87] Metabolic acidosis is common in severe AKI, but can be corrected with bicarbonate and rarely requires urgent dialysis if not accompanied by volume overload or uremia. Some poisons, drug overdoses, and toxic compounds can contribute to acid-base disturbances and AKI. In such cases, dialysis can be supportive and facilitate the removal of these substances and their metabolites. In acute salicylate poisoning, RRT is indicated when the patient exhibits altered mental status, pulmonary or cerebral edema, renal impairment, fluid overload that prevents the administration of sodium bicarbonate, or clinical deterioration despite aggressive and appropriate supportive care.[88]

Ethylene glycol and methanol poisoning are important causes of anion-gap metabolic acidosis and can be cleared by dialysis. Metformin-associated lactic acidosis may be an indication for dialysis, especially in critically ill patients at risk of death. In particular, such patients demonstrate a low pH (<6.9) and high serum lactate and metformin concentrations.[89]

The ideal time to consider RRT in AKI when "conventional" indications are absent has long been a perplexing challenge for clinicians. The lack of high-quality evidence has contributed to decisional uncertainty and practice variation.[90,91] Potential advantages of accelerated initiation of RRT include early control of electrolyte and acid-base derangements and uremia, avoidance of volume overload, and clearance of inflammatory mediators. However, evidence that such effects translate into clinical benefits is sparse. Randomized controlled clinical trials focused on the timing of RRT initiation in critically ill patients with AKI have recently been reported. The Early Versus Late Initiation of Renal Replacement Therapy in Critically Ill Patients With Acute Kidney Injury (ELAIN) trial was a single-center trial that enrolled 231 mostly surgical patients, comparing early RRT (starting within <8 hours of fulfilling KDIGO stage 2 AKI) with delayed RRT (starting within <12 hours of developing KDIGO stage 3 AKI or upon an absolute indication).[92] The trial demonstrated a mortality benefit of early RRT compared with delayed treatment. The Artificial Kidney Initiation in Kidney Injury (AKIKI) trial was a multicenter trial that compared two strategies for starting RRT in 620 mixed critically ill patients with AKI who were receiving mechanical ventilation and/or vasoactive agents. The early strategy started RRT within <6 hours of fulfilling KDIGO stage 3 AKI, and the delayed strategy started upon fulfilling clinical criteria related to worsening AKI or its complications.[93] There was no difference in mortality; however, the RRT utilization differed significantly, with only half of patients in the delayed strategy receiving RRT compared with almost all in the early strategy. The IDEAL-ICU study was a multicenter, randomized, controlled trial that compared patients with early-stage septic shock and AKI but without life-threatening complications to receive RRT within 12 hours after documentation of failure-stage AKI (early strategy) or after a delay of 48 hours if renal recovery had not occurred (delayed strategy).[94] Follow-up data at 90 days showed that mortality did not differ significantly between the two groups. Notably, 38% of patients in the delayed-initiation group did not receive RRT. The findings of these clinical trials leave the question of elective RRT initiation in the absence of compelling indications incompletely resolved. The Standard versus Accelerated Initiation of RRT in AKI (STARRT-AKI) study is ongoing. This multinational trial completed enrollment of its target of 2866 patients with KDIGO stage 2 or 3 AKI who do not have an emergent indication for RRT. Enrolled patients were randomly assigned to either early (within 12 hours) or delayed RRT initiation.[95] Pending further evidence, we agree with the KDIGO group that RRT should be initiated emergently when life-threatening changes exist. However, a clinical judgment considering the broader clinical context, the presence of conditions that can be modified with RRT, and trends of laboratory tests, rather than using any specific parameters, should be employed when making the decision to initiate RRT.[21] Finally, it is important to consider the volume status when deciding the time for initiating RRT because volume overload, as previously discussed, appears to be an important factor associated with mortality in AKI. Table 100.3 depicts acceptable indications for initiating RRT in the ICU.

TABLE 100.3 Potential Indications for Renal Replacement Therapy in the ICU

Nonobstructive oliguria (urine output <200 mL/12 h) or anuria
Refractory severe acidemia
Refractory hyperkalemia (K^+ >6.5 mmol/L)*
Uremia (encephalopathy, pericarditis, neuropathy, myopathy)
Severe dysnatremia (Na^+ >160 or <115 mmol/L)
Clinically significant organ edema (especially lung) unresponsive to diuretics
Drug overdose with dialyzable toxin
Coagulopathy requiring large amounts of blood products in a patient at risk for acute respiratory distress syndrome
NOTE: Any one of these indications is sufficient to consider initiating renal replacement therapy. Two of these indications make renal replacement therapy desirable.

*Intermittent hemodialysis removes K^+ more efficiently than continuous modalities.

Renal Replacement Therapy Modality

In the ICU, acute RRT includes standard IHD, prolonged intermittent renal replacement therapies (PIRRTs; e.g., sustained low-efficiency dialysis [SLED]), continuous renal replacement therapies (CRRTs), and peritoneal dialysis (Table 100.4). RRT is required in severe AKI to remove uremic toxins and maintain fluid, electrolyte, and acid-base balance. All modalities are effective therapies that may be used and exchanged according to the hemodynamic status or coagulation problems of the patient. A recent meta-analysis compared clinical outcomes among critically ill adults with AKI treated with CRRT, IHD, and SLED.[96] The RRT modality was not associated with in-hospital mortality or dialysis dependence. The authors concluded that they did not find a definitive advantage for any RRT modality on short-term patient or kidney survival.

PIRRTs have demonstrated comparable or better clinical outcomes to CRRT in small clinical trials.[97,98] SLED is performed by using dialysis machines to deliver a slow dialysate flow for periods ranging from 8 to 12 hours per day, depending on the needs of the patient and tolerance to ultrafiltration. Advantages of this technique include high hemodynamic tolerance, excellent solute-removal capability, and the capacity to be instituted using regular hemodialysis machines without acquiring new equipment. CRRT represents a spectrum of modalities that provides continuous support for severely ill patients with AKI. These include continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD), and continuous venovenous hemodiafiltration (CVVHDF), which involve both convective and diffusive therapies. CRRT has been advocated in patients with AKI because of its enhanced ability to remove inflammatory mediators, which may provide benefit in septic patients, particularly using convective modes of continuous therapy while maintaining hemodynamic stability. However, there are no studies clearly showing superior clinical outcomes with different CRRT modes. The main disadvantage of CRRT is the need for prolonged anticoagulation to prevent clotting of the filter. This can be done with low-dose systemic heparin; however, there remains the risk of bleeding or heparin-induced thrombocytopenia. Regional citrate anticoagulation (RCA) is increasingly used in some centers. A number of clinical studies have shown advantages of RCA compared with heparin resulting in prolonged circuit life, reduced incidence of hemorrhagic complications, and lower transfusion needs.[99] On the basis of these data, the KDIGO Clinical Practice Guidelines recommend the use of RCA as the preferred anticoagulation modality for CRRT in patients without contraindications for citrate, even in the absence of an increased bleeding risk or deranged coagulation. The guidelines also highlighted potential drawbacks to RCA, including the necessity of complex protocols and risk of metabolic complications.

TABLE 100.4 Comparison of Various RRT Modalities

	IHD	SLED	CRRT
Cost	+	++	++++
Duration	4 hours daily/alternate days	8–12 hours daily/alternate days	24 hours (though actually achieves less on average)
Hemodynamic instability	Least suitable	Good	Most compatible
Compatible with extracorporeal life support	No	No	Yes
In raised intracranial pressure	Increases	Can increase	Usually no change
Anticoagulation	Can be omitted	Can be omitted	Predilution can be used to maintain circuit
Serum concentration of renally cleared drugs	Major fluctuations	Some fluctuation	Least fluctuation
Vascular access	AV fistula or nontunneled or tunneled catheter	AV fistula or nontunneled or tunneled catheter	Nontunneled or tunneled catheter
Compatible with supporting large-volume infusions (antibiotics, nutrition, etc.)	No	Would need to be daily and longer sessions	Most compatible
Mobilization	Most compatible	Could be compatible if done at night/rest time	Not compatible—would need to be discontinued

AV, Arteriovenous; *CRRT*, continuous renal replacement therapy; *IHD*, intermittent hemodialysis; *SLED,* sustained low-efficiency dialysis.
Modified from Ahmed AR, Obilana A, Lappin D. Renal replacement therapy in the critical care setting. *Crit Care Res Pract.* 2019;16;2019:6948710.

In the absence of definitive data to support a particular modality, the modalities of RRT should be viewed as complementary, with the choice of RRT modality influenced by availability, expertise, resources, cost, and physician preference. The current KDIGO recommendations suggest that CRRT is preferable over intermittent therapies in patients who are hemodynamically unstable and/or have cerebral edema. Selection of RRT in special groups of patients has been reviewed.[100] In patients with acute brain injury or increased intracranial pressure, CRRT is generally preferred over IHD, which may worsen neurologic status. A decline in neurologic status may result from the compromise of cerebral perfusion pressure during intradialytic hypotension. Alternatively, cerebral edema and intracranial pressure may be enhanced by rapid intracellular solute-mediated volume shifts. Because the rates of volume and solute removal are slower during CRRT, this modality is seemingly better tolerated by patients with brain injury or increased intracranial pressure at risk for acute herniation. CRRT may also be preferred among those with fulminant hepatic failure and patients with severe chronic metabolic disturbances such as hyponatremia. In contrast, IHD is the preferred modality with intoxications because of its more rapid clearance of toxins.

Peritoneal dialysis is an alternative modality for AKI in which vascular access may be difficult, in conditions where anticoagulation may be problematic, in underresourced regions, or after large disasters with mass casualties. Single-center studies have shown similar or better outcomes for selected patients treated with high-volume or tidal peritoneal dialysis compared with IHD or CRRT.[101,102]

Adequate Therapy Dosing

IHD is most commonly provided on a thrice-weekly or every-other-day schedule. In chronic hemodialysis patients, adequacy of dialysis is primarily determined by the level of small-solute (urea) clearance. This is reflected by the *Kt*/*V* formula, where *K* is the dialysis membrane clearance of urea, *t* is the time on dialysis, and *V* is the volume of distribution of urea, which is equal to the total body water content. As seen from the formula, one can increase the time on dialysis or increase the dialyzer clearance to enhance urea clearance. Dialyzer clearance depends on blood flow and dialysate flow rates, in addition to the inherent properties of the membrane. Regarding IHD dosing, the VA/NIH Acute Renal Failure Trial Network Study (ATN study) did not find a benefit for a more intensive strategy for RRT.[103] This study compared IHD (hemodynamically stable patients) with sustained low-efficiency dialysis (hemodynamically unstable patients) performed three (less intensive) versus six (more intensive) times a week in 563 critically ill patients with AKI and failure of at least one nonrenal organ or sepsis. The prescribed *Kt*/*V* per session was 1.2–1.4, and the actual delivered mean dose was 1.3 in the less intensive arm. The 60-day mortality rate and percentage of patients recovering renal function were similar in both groups. The Hannover Dialysis Outcome study was a prospective randomized, parallel group study that used intensified extended dialysis (dosed to maintain plasma urea levels <90 mg/dL) versus standard dialysis (dosed to maintain plasma urea levels between 120 and 150 mg/dL) on 14- and 28-day mortality and renal function.[104] The mortality and frequency of renal function recovery were similar between the two groups. Based on these two well-designed and performed clinical trials, it appears that increasing urea target clearances does not improve mortality or rates of renal recovery. Therefore at least the smaller dose used in these trials should be pursued, with monitoring of the delivered dose of therapy to ascertain a minimum delivery of *Kt*/*V* of 1.2 per treatment when intermittent RRT in AKI patients is used. Nevertheless, applying the concept of *Kt*/*V* remains controversial in patients with AKI because urea generation and urea distribution volume are not constant or accurately measurable. Moreover, few AKI patients are in metabolic steady state, and many show a high protein catabolic rate or have a fluctuating volume status and renal function.[105] Based on these arguments, the European Renal Best Practice position statement does not recommend using *Kt*/*V* as a measure of dialysis dose when using IHD and suggests that its duration be adapted to allow maintenance of metabolic and volume status.[106] Currently there are no standards for dose prescription of PIRRT. Daily laboratory and clinical parameters can be used to assess for adequacy of dialysis. Regarding CRRT, much of the dosing guidelines stem from two large-scale, multicenter, randomized controlled trials. In the aforementioned VA/ATN study, 201 patients received CVVHDF in the less intensive arm (mean delivered effluent of 22 mL/kg/min) and 179 in the intensive therapy group (mean delivered effluent of 36 mL/kg/min). The higher dose of CRRT did not influence mortality or renal recovery. The Randomized Evaluation of Normal versus Augmented Level of RRT (RENAL) study was conducted at 35 centers throughout Australia

and New Zealand.[107] It compared the effects of postdilutional CVVHDF doses of 25 and 40 mL/kg/h on the 24-day and 90-day mortality rates of 1508 critically ill AKI patients. Treatment with a higher-intensity regimen did not reduce the mortality at 90 days. In conclusion, the results of the two well-designed and executed VA/ATN and RENAL clinical trials did not show any benefit of higher CRRT doses for critically ill AKI patients beyond a threshold necessary to optimize clinical outcome. Therefore when using CRRT for treating such patients, the dose to be targeted may be the minimal one used in these trials: 20–25 mL/kg/h. Notably, observational studies have suggested that the actual delivered effluent volume during CRRT is substantially less than the prescribed dose.[108] Therefore to ascertain that the target dose is delivered despite potential therapy interruptions, we recommend an effluent flow rate of approximately 25 mL/kg/h. Unfortunately, the clinical trials of RRT dose evaluated only a fixed-dose prescription; it remains uncertain whether a fixed dose is appropriate for all critically ill patients or whether RRT dose should be individualized, dynamic, and continuously adapted to changing clinical status.[109]

Medication Dosing

During AKI, drugs normally eliminated by the kidney exhibit a markedly decreased clearance. As the physiochemical characteristics of the drugs affect the removal by dialysis and hemofiltration, the amount of the drug removed during these procedures may be sufficient to require supplemental dosing. For patients on hemodialysis, a supplemental dose of the drug is most commonly administered at the completion of the dialysis session. Drug clearance with CVVH is through convective transport and approximates the unbound drug concentration in plasma multiplied by the ultrafiltration rate.[110] Drugs with molecular weights of less than 500 Da are readily removed by either conventional hemodialysis or CVVH, but those with higher weights of 1000–5000 Da are eliminated more efficiently by CVVH because of the use of high-flux membranes that allow the passage of larger molecules.

The volume of distribution greatly affects the clearance of a drug, in that drugs with large volumes of distribution are likely to be bound to a greater extent in the tissues. In this setting, only a small amount has access to the vasculature at any time. For such drugs, clearance with CVVH is greater than with intermittent therapies because of the continuous nature of the clearance. The extent of protein binding of a drug is important because the protein–drug complex has a molecular weight greater than 50,000 Da. At this size, neither intermittent nor continuous therapies will efficiently remove the drug. However, the extent of protein binding is dependent on pH, uremia, concentration of free fatty acids, heparin therapy, and relative concentrations of drug and protein. In critically ill patients, serum albumin is often decreased, thereby making more drug available for clearance during RRT. Because of the potential medication toxicities, in addition to the need to maintain therapeutic levels of multiple medications, it is important to consider and adjust dosing during AKI and with RRT. Dosages of medications must be adjusted for the type of RRT and for the specific characteristics of the drug. In septic patients, the altered volume of distribution increases drug half-life and affects the protein-binding capacity of many antimicrobials. The variability in body size and fluid composition often determines delayed achievement of antibiotic pharmacodynamic targets and results in potentially subtherapeutic antibiotic concentrations at the infection site.[111]

CONCLUSION

Despite extensive clinical experience and improvements in supportive care, the mortality rate of critically ill patients with AKI remains high. Sepsis is the most common cause of AKI in the ICU. Current tools to diagnose AKI are suboptimal; thus biomarkers are being developed to better detect and prognosticate AKI. Specific treatment for AKI is still lacking; therefore prevention is key. Optimal volume management, appropriate antimicrobial therapy, and avoidance of further renal insults are imperative once AKI is established. Timely and efficient RRT provisions are frequently necessary in critically ill patients with AKI.

KEY POINTS

- S-AKI is a common complication in hospitalized and critically ill patients. It is associated with extremely high mortality and increases the risk of developing chronic comorbidities.
- Blood urea nitrogen and creatinine are the most common parameters measured, but they are not sensitive indicators of renal dysfunction in an acute setting. Intense ongoing research is characterizing the diagnostic and prognostic roles of injury biomarkers to improve supportive care and clinical outcomes.
- The FST accurately predicts patients at increased risk for severe AKI and requirement for RRT.
- Balanced solutions appear to minimally decrease the risk of major adverse kidney events in critically ill patients.
- Pretreatment with isotonic saline is similar to isotonic bicarbonate, and treatment with acetylcysteine is similar to placebo in reducing the risk of kidney-related outcomes after contrast procedures.
- Early nephrology consultation may lead to improved outcomes and facilitate interventions and transitions of care for patients with AKI.
- Dialysis initiation should be based on the broad clinical context and patient needs rather than any specific threshold.
- RRT modalities for critically ill patients are comparable and complementary. CRRT is preferable over intermittent therapies in patients who are hemodynamically unstable and/or have cerebral edema.
- When using intermittent dialysis in AKI, monitoring the delivered dose of therapy is recommended to ascertain the minimum delivered Kt/V of 1.2 per treatment. With CRRT, effluent flow rates of at least 20 mL/kg/h should be attained.

References for this chapter can be found at expertconsult.com.

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These three trials have investigated early versus delayed initiation of RRT (in the absence of obvious indications) in critically ill patients with AKI. Although differing, their results do not imply a clear benefit of early initiation. Further evidence is awaited to optimally guide the timing of RRT initiation in critically ill AKI patients.

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Urinary Tract Obstruction

John Montford, Scott Liebman, and Isaac Teitelbaum

A patent urinary tract is necessary for optimal kidney function. Under normal circumstances, urine passes unimpeded from the renal pelvises to the tip of the urethra. Obstruction can occur anywhere along this pathway and may lead to both acute and progressive kidney parenchymal damage.

Several definitions may be encountered when considering urinary tract obstruction:

- *Obstructive uropathy* refers to any disorder that interferes with drainage of the urine. It may be acute or chronic and either partial or complete; the resulting symptom complex typically depends on both the acuity and severity.
- *Obstructive nephropathy* refers to cases in which obstructive uropathy causes a decline in kidney function.
- *Hydronephrosis* refers to dilatation of the urinary collecting system and is usually, but not exclusively, seen in obstructive disorders. Nonobstructive pathogenesis of hydronephrosis includes vesicoureteral reflux or excessive flow through the collection system, such as with habitual water drinking or diabetes insipidus. Common anatomic variants, including the presence of an extrarenal pelvis and duplicated collecting systems, are also associated with hydronephrosis on imaging.

EPIDEMIOLOGY

Urinary tract obstruction is a common disorder. On autopsy, 3.1% of adults have hydronephrosis.[1] Data from the Healthcare Cost and Utilization Project's Nationwide Inpatient Sample (based on ICD-9 codes) indicate that 1.75% of all hospital discharges are complicated by either hydronephrosis or obstruction.[2] When hydronephrosis is excluded, urinary tract obstruction occurs in approximately 1% of hospital discharges.[2] Urinary tract obstruction accounts for approximately 10% of community-acquired acute kidney injury[3–5] and is a factor in 2.6% of acute kidney injury cases in the intensive care setting.[6]

ETIOLOGY

Many disorders may lead to urinary tract obstruction. A useful classification is to first separate pathology arising from within the urinary tract itself (intrinsic obstruction) from those diseases that arise outside the urinary tract causing external compression of the system (extrinsic obstruction). This discussion will also consider upper (from the renal pelvis to the ureterovesicular junction [UVJ]) and lower (from the bladder to the urethra) urinary tract obstruction separately.

Intrinsic Obstruction

Intrinsic urinary tract obstruction may be the result of pathology within the lumen *(intraluminal)* or within the walls of the collecting system *(intramural)*.

Intraluminal Causes

Obstruction at the level of the renal tubules may be the result of crystal-induced disease, uric acid nephropathy (as in tumor lysis syndrome), or cast nephropathy caused by multiple myeloma. Crystal-induced nephropathy has been classically described with sulfadiazine, acyclovir, indinavir, triamterene, and methotrexate.[7] Published case reports also implicate orlistat[8] and ciprofloxacin.[9]

Nephrolithiasis is a common cause of upper urinary tract obstruction at the level of the ureter, with the size of the stone determining the likelihood of obstruction. Stones $\leq$2 mm, 3 mm, 4–6 mm, and $>$6 mm will pass spontaneously 97%, 86%, 50%, and 1% of the time, respectively.[10] Typically, the obstruction occurs at one of the three narrowest portions of the ureter: the ureteropelvic junction (UPJ), the UVJ, or the point where the ureter crosses over the pelvic brim. Neoplasms, blood clots, and sloughed renal papillae are rarer causes of intraluminal obstruction at the level of the ureter.

The causes of intraluminal obstruction at the level of the bladder are similar to those affecting the ureter, with urolithiasis, blood clots, and neoplasms being the most common. Worldwide, infection with *Schistosoma haematobium* with resulting fibrosis is a common cause of bladder obstruction.[11] Although schistosomiasis is rare in industrialized nations, it should be suspected in patients from endemic areas such as Africa and the Middle East presenting with urinary tract obstruction.

Intramural Causes

Congenital malformations of the genitourinary tract can cause intramural obstruction of the upper urinary tract. UPJ obstruction (UPJO) warrants specific mention, as it is the most common congenital genitourinary disorder likely to present in adulthood. Kinks, valves, or an adynamic segment of ureter results in failure of peristalsis at the UPJ.[12] The widespread use of maternal prenatal ultrasound (US) has led to increased antenatal diagnosis of UPJO. The diagnosis can be made by US, intravenous urography (IVU), or in equivocal cases, isotope renography (see later imaging section).

Another intramural cause of upper urinary tract obstruction is ureteral stricture caused by genitourinary tuberculosis (GU TB). Although rare in the developed world, GU TB complicates up to 40% of patients with extrapulmonary tuberculosis.[13] Hematogenous spread of mycobacteria can seed the renal cortex and ureters, causing inflammation with resultant fibrosis, obstruction, and secondary infections.[13] Seeding of the retroperitoneum and bladder can also lead to complications in patients with GU TB.

More common are disorders affecting the neuromuscular control of the lower urinary tract such as cerebrovascular accidents,[14] spinal cord injury,[15] multiple sclerosis,[16] and diabetic neuropathy,[17] which may lead to bladder outlet obstruction. Multiple medications, including anticholinergics, opioid analgesics, nonsteroidal antiinflammatory

agents, alpha-adrenoreceptor agonists, benzodiazepines, and calcium channel blockers, have also been associated with urinary retention.[18] Stricture of the urethra may also lead to obstruction.

Extrinsic Compression

Pregnancy is typically associated with right-sided dilation of the renal pelvis, calyx, and ureter. Hormonal mechanisms and mechanical compression from an enlarging uterus and ovarian vein plexus have been implicated in these changes.[19] Clinically meaningful obstruction from the gravid uterus is extremely rare.

Malignancies can cause obstruction by several different mechanisms. Local ureteric compression may be seen in metastatic cancers of the cervix, bladder, and prostate and with expanding retroperitoneal soft tissue masses. Alternatively, the ureters may be compressed or encased by metastatic retroperitoneal lymphadenopathy.[20]

Retroperitoneal fibrosis may lead to the obstruction of one or both ureters via inflammation. It is an uncommon disorder, with a reported incidence rate of 1.3 cases per million population and a male:female ratio of 3.3:1.[21] Although the majority of these cases are idiopathic (>75%),[22] numerous conditions are suspected to cause retroperitoneal fibrosis, including malignancies, medications, infection, trauma, radiation, and IgG4-related systemic disease.[23,24] Treatment of idiopathic retroperitoneal fibrosis is initially with steroids, but recurrences are common. Case reports have described the use of cyclophosphamide, azathioprine, colchicine, mycophenolate, or tamoxifen for treatment relapses or steroid-resistant disease, although conclusive data are absent.[22]

Abdominal aortic aneurysms (AAAs) may also cause obstruction caused by compression of the ureter or via inflammation. A published series of 999 cases of inflammatory AAA found preoperative hydronephrosis in 7.4% of these cases.[25] The clinician must always bear in mind that hydroureter and/or hydronephrosis may be absent in obstruction caused by retroperitoneal processes. Thus one must maintain a high degree of suspicion and use alternative imaging modalities when considering these disorders.

Extrinsic compression of the lower urinary tract is more common in males, and the cause is usually either benign prostatic hypertrophy (BPH) or prostate cancer. The etiology of urinary tract obstruction is summarized in Box 101.1.

BOX 101.1 Causes of Urinary Tract Obstruction

Intrinsic Causes

Intraluminal

Renal Tubules

Crystal-induced disease
Uric acid nephropathy
Cast nephropathy (in multiple myeloma)

Upper Urinary Tract

Nephrolithiasis
Neoplasms
Blood clots
Sloughed renal papillae

Lower Urinary Tract

Urolithiasis
Blood clots
Neoplasms
Schistosomiasis

Intramural

Upper Urinary Tract

Congenital ureteropelvic junction obstruction
Genitourinary tuberculosis

Lower Urinary Tract

Disorders affecting neuromuscular control
- Cerebrovascular accident
- Spinal cord injury
- Multiple sclerosis
- Diabetic neuropathy

Medications
- Anticholinergic agents
- Opiates
- Nonsteroidal antiinflammatory agents
- Alpha-adrenoreceptor antagonists
- Benzodiazepines
- Calcium channel blockers

Urethral structure

Extrinsic Causes

Upper Urinary Tract

Pregnancy
Malignancy
Retroperitoneal fibrosis
Abdominal aortic aneurysms

Lower Urinary Tract

Benign prostatic hypertrophy
Prostate cancer

CLINICAL PRESENTATION

The clinical presentation of urinary tract obstruction depends on the location, duration, and severity of obstruction and may therefore be quite variable.

Pain

Acute ureteral obstruction often presents with severe flank pain, otherwise known as *renal colic*. This is usually the result of urolithiasis but may be the result of other causes of ureteral obstruction (see earlier). Obstruction causes increased intraluminal pressure and spasm of the ureteral muscles, which are responsible for the colicky pain.[26] Partial ureteral obstruction may present with a chronic dull pain. Bladder outlet obstruction may lead to distention and subsequent abdominal discomfort.

Changes in Urine Output

One pitfall in the diagnosis of obstruction is the expectation that patients will be anuric. Although this is true of patients with the obstruction of all functioning renal mass—complete bilateral ureteral obstruction, complete obstruction of a solitary functioning kidney, or complete obstruction distal to the bladder neck—this is not the case in patients with less severe disease. The degree of urine output does not reliably predict the presence or absence of obstruction. Patients may present with normal urine output or even polyuria because of the effects of obstruction on renal salt and water handling (reviewed later).

Lower Urinary Tract Symptoms

Obstruction of the lower urinary tract often presents with some or all of a constellation of symptoms known collectively as *lower urinary tract symptoms* (LUTS). LUTS include voiding symptoms (difficulty

urinating, incomplete emptying), postmicturition symptoms (postvoid dribbling), and storage symptoms (urgency, frequency, hesitancy, incontinence).[27] Alternatively, patients with lower urinary tract obstruction may be asymptomatic.

Renal Dysfunction

If asymptomatic, the initial clue to the underlying obstruction may be elevated serum creatinine on blood drawn for an unrelated reason. As urinary tract obstruction may be asymptomatic, it should be considered in the differential diagnosis of unexplained kidney failure. If blood work is not obtained during the course of the obstruction, the kidney function may deteriorate such that patients present with uremic symptoms and the need for dialysis.

Infection

The urinary retention associated with lower urinary tract obstruction provides an excellent culture medium for bacteria. Patients may present with cystitis, pyelonephritis, or sepsis. An obstructing renal stone may also be a nidus for infection. Recurrent infection should raise suspicion for possible anatomic abnormalities, especially in men. In one study, 25 out of 83 men (30%) with a febrile urinary tract infection had anatomic lesions in the lower urinary tract, supporting imaging of the lower tract in men with this presentation,[28] although data in men younger than 45 years old refute this.[29]

Laboratory Values

There are no laboratory values specific to obstruction. Blood tests may show no abnormalities or may show values consistent with kidney failure (elevated blood urea nitrogen, creatinine, potassium, and phosphorus levels and decreased calcium, bicarbonate, and hemoglobin values). The blood tests may also be indicative of renal tubular acidosis (RTA; see later). The urinalysis may be bland or may include red blood cells (in the setting of a stone or malignancy) or white blood cells (in the setting of infection). Significant albuminuria is uncommon, although low-grade proteinuria can be observed, especially in the setting of infection. An experienced observer may also be able to discern crystals in freshly voided urine. The fractional excretion of sodium (FE_{Na}) may be less than 1% in acute obstruction, but it is generally greater than 1% when the obstruction is chronic, owing to renal tubular dysfunction.

IMAGING IN URINARY TRACT OBSTRUCTION

Various imaging modalities may be used to diagnose obstruction: plain abdominal radiography, US, computed tomography (CT), IVU, retrograde pyelography, and nuclear scanning. It is important to understand the indications and limitations of each modality.

Plain Abdominal Radiography

Abdominal radiography (kidney, ureter, and bladder [KUB]) is often the first imaging modality performed in patients with acute flank pain. Although most stones are composed of calcium and should in theory be visible, only 59% of stones are detected on plain film.[30] Compared with CT scanning, the sensitivity and specificity of abdominal films were 45%–59% and 77%, respectively.[30] Further, plain films may not always be able to differentiate phleboliths from calculi. This limits the utility of plain abdominal films to the diagnosis of recurrent disease in those with known radiopaque stones.

Ultrasound

US is inexpensive, does not expose the patient to radiation, and is typically readily available. Its accuracy in detecting hydronephrosis makes

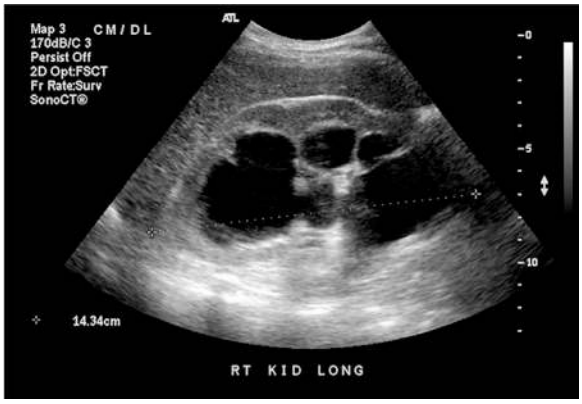

Fig. 101.1 Typical appearance of a hydronephrotic kidney showing renal pelvis and calyceal dilatation. Note the increase in the kidney length (14.34 cm) compared with normal (~10–11 cm).

US a good screening tool for obstruction in patients with unexplained kidney failure or patients with suspected lower urinary tract obstruction (Fig. 101.1). When CT is used as a reference, US has a traditionally reported sensitivity of 24% and a specificity of 90% for the detection of kidney stones and is likely to miss those less than 3 mm in size.[31] Another disadvantage of US compared with CT is that bowel gas may obscure visualization of the ureters.[32] Other conditions such as parapelvic cysts and renal artery aneurysms may mimic hydronephrosis on US.[32] These conditions are easily distinguished via CT scanning.

In a large multicenter randomized controlled trial of adults presenting to the emergency department with suspected nephrolithiasis, US was found to be noninferior when compared with CT in regard to the rates of repeat hospitalizations for missed high-risk diagnoses and adverse events.[33] Additionally, US is the imaging modality of choice when radiation is contraindicated, such as in pregnant women and children.

Computed Tomography

CT has a high sensitivity (96%) and specificity (98%) in the evaluation of acute flank pain and suspected nephrolithiasis (Fig. 101.2); although, as noted earlier, US may be a better first choice because of its lack of radiation. With CT, the retroperitoneum is also well visualized, making it ideal to detect retroperitoneal fibrosis or obstruction caused by retroperitoneal lymphadenopathy. In addition to defining the

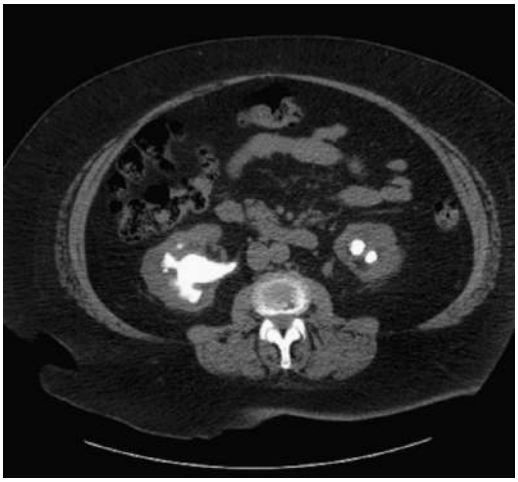

Fig. 101.2 Bilateral nephrolithiasis on an unenhanced computed tomography scan. Note the staghorn appearance in the right kidney.

anatomy of the collecting system, CT has the added benefit of visualizing other organ systems, thereby providing information regarding other conditions in the differential diagnosis of acute flank pain.

One concern raised with CT scanning is the high radiation dose administered. Each CT scan is equivalent to approximately 10 KUBs.[34] The reported dose of radiation, quantified in millisieverts (mSv), was significantly higher in patients initially undergoing CT (14.1 mSv) versus US (4.7–6.5 mSv) when presenting to the emergency department with acute flank pain and suspected nephrolithiasis.[33] Furthermore, this initial radiation exposure was cumulative and persisted at 6 months with CT (17.2 mSv) versus US (9.3–10.1 mSv) regardless of subsequent imaging.[33] Lower-dose-radiation CT protocols have previously been investigated. One study found that lower-dose-radiation CT scans (equivalent to that of plain film) have a sensitivity of 97% and a specificity of 96% for the diagnosis of acute renal colic when compared with the standard dose. The lower-dose CT was inferior at detecting stones less than 3 mm in size,[35] which may impair its ability to diagnose non–collecting system pathology. Because of these limitations, it is unclear whether spiral CT will remain the initial imaging procedure of choice for the evaluation of suspected nephrolithiasis.

Isotope Renography

In conventional renography, radiographic tracers, such as ^{99m}Tc-mercaptoacetyltriglycine (MAG3), are injected into the patient's bloodstream and renal uptake and excretion are measured with a scintillation counter (Fig. 101.3). This test provides functional information by demonstrating decreased excretion in an obstructed kidney. The sensitivity of the test may be enhanced by administering a loop diuretic during the scan, where the increased urine flow may unmask an occult obstruction. Isotope renography is often used to determine the degree to which anatomic obstruction (based on radiographic hydronephrosis) is causing functional obstruction.

For example, excretion can be normal despite the presence of hydronephrosis from a parapelvic cyst, duplicated ureter, or extrarenal pelvis. Alternatively, isotope renography can be useful to determine if functional obstruction is present despite little radiographic evidence of obstruction (such as in a patient with clinical suspicion of retroperitoneal fibrosis). One important limitation of isotope renography is that radiotracer uptake may be diminished and excretion prolonged with severely compromised glomerular filtration rate (GFR). This may lead to both false-negative and false-positive results, limiting its use in such situations.[36] Renography also does not provide detailed anatomic information.

Intravenous Urography

IVU, in which the collecting system is imaged after the administration of intravenous (IV) contrast, was historically the study of choice for patients with acute flank pain. The need to administer nephrotoxic IV contrast and the delay in obtaining information render IVU less attractive than a CT scan.[37]

Retrograde Pyelography

US and CT scanning have largely superseded retrograde pyelography for the diagnosis of obstruction. Retrograde pyelography may be indicated when obstruction is highly suspected on clinical grounds, the US is negative for hydronephrosis, and the patient is unable to receive IV contrast.[1]

PATHOPHYSIOLOGY OF OBSTRUCTION

Urinary tract obstruction may cause intrinsic kidney dysfunction. The most important effects are changes in renal blood flow, increased tubular hydrostatic pressure (as a result of increased ureteral pressure), and the development of fibrosis in long-standing obstruction. Specific tubular derangements in sodium, water, potassium, acid, and divalent cation handling occur as well.

Changes in Renal Blood Flow, Tubular Hydrostatic Pressure, and Glomerular Filtration Rate

Various animal models have provided a basis for understanding the renal hemodynamic changes with urinary obstruction. The initial renal response to obstruction follows a triphasic pattern.[38] During the first 2 hours of obstruction, there is an initial increase in both renal blood flow and ureteral pressure. This is followed by a brief (2–3 hours) period in which renal blood flow declines because of increased afferent arteriolar resistance, yet ureteral pressures continue to rise. Ultimately, the decrease in

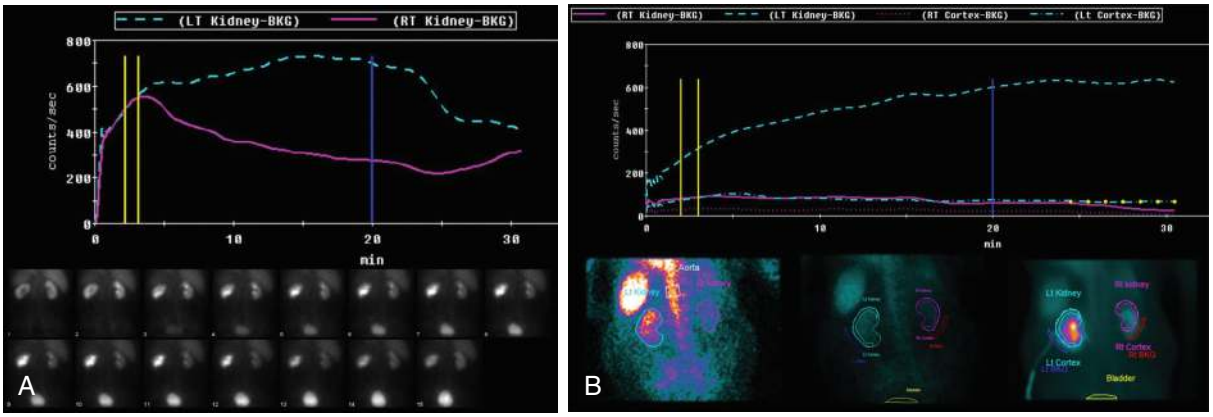

Fig. 101.3 Isotope renography. **A,** ^{99m}Tc-mercaptoacetyltriglycine-renogram performed on a 54-year-old male with large benign intraabdominal mass causing radiographic unilateral ureteral obstruction. Note that radiotracer peak uptake *(yellow vertical lines)* is normal in the right kidney, whereas tracer uptake is delayed in the obstructed left kidney. Furosemide administration *(blue vertical line)* resulted in reversal of the partial functional obstruction. Time-sequence images of radiotracer uptake are shown. **B,** Mag-3 renogram of a 78-year-old male with stage 4 metastatic bladder cancer with retroperitoneal metastases and bilateral, chronic ureteral obstruction. Images obtained after bilateral percutaneous nephrostomy tubes revealed a marginally functioning left kidney and completely nonfunctional right kidney. Perfusion *(lower left panel),* t = 0 tracer uptake *(lower middle panel),* and time-averaged tracer uptake *(lower right panel)* images are shown.

renal blood flow leads to a decrease in ureteral pressure, with the pressure returning to normal levels by 10–12 hours after obstruction.

The GFR, which is determined by Starling forces between the glomerular capillary and renal tubules, is initially diminished by transmitted tubular hydrostatic pressure but is maintained by the augmented renal blood flow. Unresolved obstruction leads to persistent afferent arteriolar constriction and a sustained decrease in both renal blood flow and GFR.

Structural Changes, Maladaptive Cell Signaling, and Renal Fibrosis

Early in ureteral obstruction, dilatation of the ureter and renal pelvis causes mechanical compression of the medulla and cortex, with tubular injury progressing in a retrograde manner.[39] Injured tubular epithelial cells lose polarity and de-differentiate, secreting chemokines that recruit circulating myeloid cells. A complex feed-forward loop of inflammatory cell signaling and oxidative stress ensues in the renal microenvironment.[40,41] If obstruction is not reversed, cellular apoptosis, senescence, capillary rarefaction, and the formation of atubular glomeruli are observed.[41] These changes ultimately result in the deposition of fibrillar collagen, with the contraction and loss of renal parenchymal volume typical of an end-stage kidney.

As with other progressive renal diseases, angiotensin-2 (AT-2) plays a central role in the perpetuation of renal parenchymal damage in chronic obstructive nephropathy. Independent of its vasoconstrictive properties, AT-2 has many other biologic functions, including the upregulation of several profibrotic mediators such as transforming growth factor beta-1, tumor necrosis factor alpha, and nuclear factor kappa B.[42]

Given the importance of the renin-angiotensin system in promoting renal injury after obstruction, antagonizing AT-2 would appear to be a viable strategy to attenuate injury. Although human data are lacking, animal data show benefits, provided the intervention is conducted after renal development is complete.[41]

Tubular Function

Tubular responses to unilateral or bilateral obstruction differ, with bilateral obstruction (or unilateral obstruction in a patient with a solitary kidney) being much more severe and having more important clinical implications. The following discussion will be limited to bilateral obstruction. Urinary tract obstruction impairs all aspects of renal tubular function, including the ability to transport sodium, potassium, and hydrogen and to regulate urine concentration.

Sodium Reabsorption

Upon release of a bilateral obstruction, sodium excretion increases five to nine times that of normal.[43] Because the GFR is also decreased because of the obstruction, the FE_{Na} may be 20 times higher than normal.[43] Clinically, this failure of sodium reabsorption may manifest as hypovolemia.

Sodium reabsorption in the kidney is accomplished by various apical membrane transporters, which are coupled to the basolateral sodium-potassium ATPase. Many of these transporters, including the sodium/proton exchanger, sodium-phosphate cotransporter, sodium-potassium-2/chloride cotransporter, and thiazide-sensitive cotransporter, are down-regulated during and after the release of the obstruction.[44] Recent studies suggest that the amiloride-sensitive epithelial sodium channel may be down-regulated as well.[45] In addition to the down-regulation of transporters, up-regulation of atrial natriuretic peptide, a potent stimulus for sodium excretion, has been demonstrated during and after the release of bilateral obstruction.[46]

Renal Water Handling

Several mechanisms render the kidneys unable to either concentrate or dilute urine after the release of an obstruction. In the case of urinary concentration, the sodium-potassium-2/chloride cotransporter is required to establish the medullary concentration gradient needed for osmotic water movement out of the collecting tubule. Dilution requires the removal of solute in both the loop of Henle and distal convoluted tubule via the sodium-potassium-2/chloride cotransporter and the thiazide-sensitive cotransporter, respectively. Osmotic diuresis caused by retained solutes may also lead to an inability to conserve water.

In addition to the effects of abnormal sodium reabsorption on water metabolism in the postobstructed kidney, animal data have demonstrated a direct role of antidiuretic hormone in the concentrating defect as well. Many studies have shown a down-regulation of aquaporins in the obstructed kidney,[47–49] which may persist for weeks, accompanied by a long-term defect in urinary concentration.[47] Clinically, this inability to conserve water may manifest as nephrogenic diabetes insipidus and hypernatremia.

Acid-Base and Potassium Balance

Clinically, obstructed or postobstructed patients often manifest a hyperkalemic, hyperchloremic metabolic acidosis. Although this may be solely the result of the decreased GFR, some patients have persistent metabolic abnormalities long after the release of obstruction and stabilization of GFR.[50] Human data have revealed several pathophysiologic mechanisms. The majority of patients studied have a distal RTA, characterized by a urinary pH above 5.5 despite the presence of a systemic acidosis.[50] Abnormalities in sodium transport in the distal nephron (see earlier) may render this tubular segment unable to generate the lumen negative transepithelial difference needed for proton excretion—a so-called voltage-dependent defect.[51] This voltage defect can also lead to potassium retention and hyperkalemia.

Other patients are able to acidify their urine to a pH below 5.5. These patients have low plasma levels of aldosterone with subsequent hyperkalemia, diagnostic of a type 4 RTA.[50] The underlying mechanism in this case is decreased ammoniagenesis, most likely because of the hyperkalemia, although the hypoaldosteronism may also contribute.[51] Patients with a type 4 RTA retain the ability to lower their urine pH and usually have a mild, self-limited acidosis, whereas those with a classic distal (type 1) RTA cannot excrete acid, and the resultant acidosis may be severe.

Animal studies have also demonstrated down-regulation of key renal acid-base transporters in urinary tract obstruction, including the cortical and medullary sodium hydrogen exchanger and several basolateral sodium-bicarbonate transporters.[52]

Postobstructive Diuresis

The release of bilateral obstruction (or unilateral obstruction of a solitary kidney) may lead to a profound diuresis. Several mechanisms have already been described. Defects in sodium and water handling predispose to large urinary losses of both. The osmotic load of retained solutes also contributes. Much of the diuresis is appropriate, however, in that previously retained solute and water must be excreted. Typically, postobstructive diuresis is mild and transient and requires no treatment. Often the degree and duration of this diuresis are worsened by overzealous fluid administration in the face of a large, but potentially appropriate, urine output.

The clinical manifestations of postobstructive diuresis that require treatment include volume depletion and hypernatremia (which may be managed by the administration of iso-osmotic and hypo-osmotic fluid, respectively). Careful attention to potassium, magnesium, phosphorus, and calcium levels is also warranted.

Other Tubular Functions

After the release of bilateral obstruction, phosphorus excretion rises proportionally to sodium excretion.[43] This may be mediated by a decrease in

the number of proximal sodium/phosphate cotransporters.[44] Magnesium excretion also rises, likely from decreased absorption in the thick ascending loop of Henle because of a decrease in the transepithelial voltage difference created by the decreased sodium-potassium-2/chloride cotransporter activity.[43] Calcium handling after obstruction is unclear and differs depending on the species of animal studied.[43]

TREATMENT

Management of obstructive uropathy depends on the location, severity, symptomatology, and etiology of the obstruction, in addition to the presence of concomitant factors such as infection or a decline in kidney function. The clinical scenario guides timing and whether initial management should be conservative or aimed at reestablishing the patency of the urinary tract. Chronic asymptomatic partial obstruction does not need emergent release, whereas acute, complete obstruction accompanied by infection, pain, or evidence of kidney dysfunction needs prompt intervention.

Lower urinary tract obstruction may be relieved simply by placing a urethral catheter. The combination of alpha-blockers and 5-alpha-reductase inhibitors has been shown to reduce symptoms of BPH and prevent urinary retention in men.[53] Additionally, alpha-blockers initiated at the time of urethral catheter placement may facilitate their subsequent removal once decompression has been achieved.[54] Upper urinary tract obstruction should be managed with either percutaneously inserted nephrostomy tubes or via retrograde (i.e., via cystoscope) ureteral stenting.

Factors that may cause or exacerbate obstruction, such as constipation or the use of medications associated with urinary retention, should be addressed. Other supportive measures such as antibiotics and IV hydration should be instituted if clinically warranted. The metabolic abnormalities of kidney failure, particularly hyperkalemia, should be addressed. If needed, dialysis should not be withheld while awaiting decompressive therapy.

Should the obstruction be chronic and the kidney deemed nonfunctional, it may be appropriate to proceed with nephrectomy if there is persistent pain or unresolved infection, such as in cases of xanthogranulomatous pyelonephritis. This decision requires an estimate of the likelihood of recovery of kidney function.

RECOVERY OF KIDNEY FUNCTION

Whether or not an obstructed kidney will regain function is of paramount importance to the clinician and may dictate whether aggressive interventions are indicated or if the affected kidney should be removed. Unfortunately, data addressing this question, particularly human data, are scant. Currently, there are no methods available that reliability predict kidney recovery after relief of an obstruction,[43] although one recent study found that a GFR of less than 10 mL/min in the obstructed kidney and abnormal renal perfusion (determined via isotope renography) predicted poor recovery in patients with unilateral ureteral occlusion.[54]

Animal studies demonstrate that the likelihood of renal recovery diminishes with longer duration of obstruction.[43] Even with the recovery of GFR, there may be ongoing injury and progressive long-term kidney damage after the release of the obstruction, likely the result of interstitial fibrosis associated with prolonged urinary tract obstruction.[54] In humans, the cutoff point at which renal function is unlikely to return has not been determined, and partial recovery has been seen even after months of obstruction,[55] suggesting that all obstructions should be relieved and followed by serial determinations of kidney function. If desired, a kidney biopsy may be performed to assess the degree of interstitial fibrosis and provide prognostic information.

KEY POINTS

- Urinary tract obstruction may be caused by pathology anywhere from the renal tubules to the tip of the urethra and should be considered in all cases of unexplained kidney injury.
- Upper urinary tract obstruction may present as renal colic with or without hematuria. Lower tract obstruction may present with frequency, urgency, nocturia, hesitancy, and incomplete emptying. Urinary tract obstruction may also be completely asymptomatic.
- The presence of urine output does not exclude urinary tract obstruction.
- Because of its sensitivity, CT is the most commonly used initial imaging modality for suspected nephrolithiasis; however, this practice has been challenged by recent data comparing US with CT.
- Renal tubular dysfunction may manifest as sodium wasting, abnormal water handling, and acidosis with or without hyperkalemia.
- Release of obstruction may result in postobstructive diuresis. The diuresis is usually an appropriate response to the retention of nitrogenous waste products.
- Recovery of renal function is dependent on the duration of obstruction, with reports of recovery in patients who were dependent on dialysis for months.

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Contrast-Induced Acute Kidney Injury

Edward G. Clark, Ayub Akbari, and Swapnil Hiremath

Iodinated contrast agents, which are administered intravascularly for medical imaging, are widely used pharmaceutical agents: more than 80 million doses were estimated to be administered annually over a decade ago.[1] Although vital for diagnostic and therapeutic purposes, their use can sometimes result in impairment of kidney function, resulting in a condition called *contrast-induced acute kidney injury* (CI-AKI) (previously known as *contrast-induced nephropathy*). In most cases, kidney dysfunction caused by contrast exposure is mild, transient, and only detected by sensitive tests. Clinically significant kidney injury is much less common, especially among individuals with previously normal kidney function.

CI-AKI has been traditionally defined as an absolute increase of 0.5 mg/dL (44 μmol/L) or a relative increase of 25% in serum creatinine within 72 hours of receiving an iodinated contrast agent, in the absence of another explanatory etiology.[2] However, the AKI Network and subsequently the Kidney Disease: Improving Global Outcomes (KDIGO) definitions (absolute increase in serum creatinine of 0.3 mg/dL [26.4 μmol/L] or a relative increase of 50% within 48 hours) have gained popularity in recent years.[2–4] These definitions, however, are mainly used for research purposes and are likely to evolve further as the use of biomarkers (such as tissue inhibitor of metalloproteinases 2 [TIMP-2] and insulin-like growth factor binding protein-7 [IGFBP-7]) further penetrates the clinical arena. For clinical purposes, severe AKI requiring renal replacement therapy (RRT, i.e., dialysis) is much more important. However, even milder forms of AKI, as defined earlier, are significant, because they not only result in longer hospital stays but also because they are associated with increased long-term morbidity and mortality.[5,6]

Awareness of the factors predisposing to contrast-associated nephrotoxicity has increased over time to the point that clinicians may now overestimate the risk associated with some specific medical conditions. However, the increasing use of radiographic contrast media, possibly combined with increasing age and comorbidities of the treated population, has contributed to the continuing importance of CI-AKI. In reality, given the mild and transient nature of the AKI in most cases, it is the association with subsequent clinical adverse events that drives the current interest in preventing CI-AKI.

EPIDEMIOLOGY

CI-AKI is often mentioned as the most common iatrogenic cause of AKI and overall the third most common cause of AKI in the hospital setting based on old and outdated literature.[7,8] The overall incidence of AKI requiring dialysis has been gradually increasing, but this appears largely driven by the increasing comorbidity in the population rather than more contrast use.[9] The actual incidence of AKI after contrast-enhanced imaging has been reported to vary from as low as 1% to as high as 30% and depends on the nature of the contrast administered and the underlying risk factors in the patient population.[10–15] In addition, these estimates are clouded by the fact that AKI after contrast administration can often be caused by other etiologies (e.g., acute tubular necrosis from cardiogenic shock in a patient with acute coronary syndrome undergoing coronary angiography or severe sepsis in a patient undergoing a contrast-enhanced computed tomography [CT] scan, or atheroembolic renal disease),[16,17] leading some researchers to use the term *contrast-associated AKI* or *postcontrast AKI*.[18]

The risk of CI-AKI varies with the route of administration. Typically, after elective coronary angiography, about 10%–15% of patients may develop AKI (as defined by the rise in creatinine), although the incidence of severe AKI requiring dialysis is much lower, at less than 1%. The incidence of AKI after intravenous administration of contrast (as with contrast-enhanced CT scans) is believed to be much lower. A prospective study reported this incidence at 2.5% overall, with the risk sequentially increasing as the underlying baseline kidney function decreases.[19] However, other studies have questioned whether the true incidence of contrast nephropathy after intravenous contrast is this high, given that there are underlying fluctuations in serum creatinine levels.[20] In the last decade, large epidemiologic studies that incorporated propensity-matched controls who did not receive contrast made a reasonable case that there is little additional increase in AKI after intravenous contrast administration when adjusted for the underlying baseline risk of AKI.[21–27] However, despite the fact that confounding can be accounted for in these analyses, selection bias, in addition to residual confounding cannot be excluded. As an example, patients perceived to be at high risk of AKI according to the treating clinician may not receive contrast and hence may be overrepresented in the controls in such studies. As an example, in one such analysis, contrast administration seemed to be associated with a lower risk of AKI, which is an implausible result merely reflecting underlying selection bias, as mentioned earlier.[27] Nevertheless, the totality of evidence suggests that the risk of true CI-AKI is low in most patients, especially after intravenous contrast and with preserved kidney function.

The most important underlying risk factor for the development of CI-AKI is compromised baseline kidney function. The incidence is less than 2% in the unselected general population but has been reported to be as high as 20%–30% with the addition of decreased kidney function and other risk factors.[28] The incidence of CI-AKI increases in a graded manner as the severity of the underlying kidney function worsens. Among patients undergoing percutaneous coronary intervention, the risk of CI-AKI has been reported[28] to be just under 20%, with a baseline glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m^2, compared with less than 1% in unselected populations.[29] These numbers mostly describe AKI, not necessarily CI-AKI. With IV contrast, there are mixed data on the difference in AKI with lower GFR.[22,26]

Among critically ill patients, one propensity score–matched study suggests that intravenous contrast (CT) was associated with higher AKI and need for dialysis among patients with GFR <45 mL/min/1.73 m^2 (odds ratio [OR] 2.72, 95% confidence interval [CI] 1.14–6.46), though with a very low absolute risk increase of 4.2%.[23] However, no such effect was seen in another study in critically ill patients with sepsis.[24]

Other risk factors for CI-AKI described in the literature include diabetes, older age, cirrhosis, proteinuria, and other comorbid conditions, including congestive heart failure, hypotension, volume depletion, and concomitant administration of other nephrotoxic agents (e.g., nonsteroidal antiinflammatory drugs). It is unclear if some of these risk factors constitute an additional risk after adjusting for the underlying GFR. In addition, some of these risk factors, such as hypotension and congestive heart failure, are risk factors for AKI, mostly from ischemic acute tubular necrosis (ATN), irrespective of contrast administration. Risk scores that include these factors identify patients at risk of AKI from ATN, not necessarily CI-AKI, and hence should be interpreted with caution.

Metformin is often considered to be a risk factor for CI-AKI (because the package insert advises withholding it for at least 48 hours before contrast imaging), but this is untrue. In patients who develop AKI, there is a higher incidence of metformin-associated lactic acidosis, which is associated with a high fatality rate. However, metformin-associated lactic acidosis only occurs in a fraction of those patients who are not only taking metformin but also either have unstable kidney function at baseline or do develop severe CI-AKI and in whom the recognition of kidney failure does not result in discontinuation of the metformin.[30,31]

Among patients who are already dialysis dependent, either on peritoneal dialysis (in which they often do have significant residual kidney function) or on hemodialysis, contrast imaging does not cause a decline in the residual kidney function.[32–34] There is no role for early or intensive dialysis to remove contrast material in these patients.

PATHOPHYSIOLOGY

Decreased renal blood flow, tubular cell damage, and tubular obstruction are the most commonly described pathways to AKI occurring after contrast administration.[35] Coronary angiography and left ventriculography have been shown to cause a decrease in renal blood flow measured directly using renal artery catheterization.[36] In addition, animal data suggest differential vasoconstriction of afferent more than efferent arterioles, causing a direct effect on decreasing GFR.[37] The vasoconstriction also occurs in the renal medulla via decreased blood flow in the vasa recta.[38] Tissue hypoxia then results in free radical release, leading to oxidant damage to the tubular cells from reactive oxygen species.[38] Contrast agent uptake in tubular cells has been reported to be via the brush border enzyme dipeptidase-1, and CI-AKI may be related to volume depletion and dependent on resident renal phagocytes, interleukin-1, and leucocyte recruitment.[39] Tubular filtration of relatively higher osmolar contrast media also results in osmotic diuresis, increasing medullary oxygen consumption and exacerbating the medullary hypoxia. Additionally, reabsorption of water leaves a high concentration of viscous contrast material in the tubules, which can result in intratubular physical obstruction.[35]

CLINICAL FEATURES AND DIAGNOSIS

Patients with CI-AKI are generally asymptomatic but have an acute rise in serum creatinine concentration 24–72 hours after the administration of the contrast agent.[40] Kidney failure is usually nonoliguric in mild cases, but it may be oliguric, especially if there is significant preexisting renal impairment.[41] Clinically significant deterioration is unlikely if the serum creatinine concentration does not increase by more than 0.5 mg/dL within 24 hours.[40] To make an unequivocal diagnosis of CI-AKI, other potential causes of AKI must be ruled out. Prerenal factors, atheroembolic disease, and other nephrotoxic insults should be excluded.[16,17] The relatively rapid onset and typical course may help differentiate CI-AKI from other causes of AKI. Urinalysis may be unremarkable or may show granular casts, tubular cells, or small amounts of proteinuria. Fractional excretion of sodium is usually low and is unhelpful in differentiating CI-AKI from prerenal, volume-responsive causes of AKI.[41] Because this is a clinical diagnosis, the criteria in Table 102.1 may be helpful to determine if an AKI episode should be attributed to contrast.[42]

PROGNOSIS

Usually, the natural course of CI-AKI is peak creatinine (i.e., reflecting the lowest point of kidney function) occurring between 24 and 72 hours after contrast administration followed by relatively rapid improvement over the next few days, back to baseline serum creatinine levels by 7–14 days.[40] Overall, less than 1% of patients with CI-AKI will develop kidney failure that requires dialysis, and a smaller proportion of such patients (estimated at 10%–50%) will remain dialysis-dependent. The minority that do remain dialysis-dependent consist of a mixture of patients who had true CI-AKI along with those who had

TABLE 102.1 Diagnostic Criteria for Contrast-Induced Acute Kidney Injury (CI-AKI)

Essential Criteria	Major Criteria	Minor Criteria
• Contrast exposure • Presence of AKI stage 2 (AKIN)	• Preexisting GFR <30 • Absence of sepsis or hypotension • Absence of other nephrotoxic exposure • Biopsy diagnosis of acute tubular injury not caused by pigment or other specified forms (myeloma, etc.) • Absence of embolic signs • Absence of RBC/WBC casts	• Preexisting GFR <45 • Arterial contrast • High-dose contrast • Nephrogram on subsequent noncontrast imaging • Oliguria

From Hiremath S, Velez JCQ. Preventing a nonexistent entity: The curious case of contrast and acute kidney injury. *Curr Opin Nephrol Hypertens.* 2020;29(1):152–160.

AKI, Acute kidney injury; *AKIN,* Acute Kidney Injury Network; *FENa,* fractional excretion of urine; *GFR,* glomerular filtration rate (in mL/min/1.73 m^2); *RBC,* red blood cell; *WBC,* white blood cell;

A diagnosis of CI-AKI could be confirmed on the basis of two essential with three major criteria, OR two essential with two major, two minor criteria.

atheroembolic disease or other causes of AKI that often occur in the population.[16,17] Nevertheless, despite the fact that most patients with CI-AKI recover, a large body of literature has emerged showing that an episode of AKI is associated with poor long-term outcomes, with a faster decline in kidney function and higher rates of subsequent RRT requirement, in addition to higher rates of hospitalization for heart failure and all-cause mortality.[5,43]

Although the association of CI-AKI with adverse clinical outcomes has been clearly and consistently shown, it is not yet known whether CI-AKI is on the causal pathway to these outcomes or if it is merely a marker of patients who are at high risk of these events.[44–46] If the latter is true, CI-AKI may indeed be a less important health issue. Future trials using a variety of interventions with different mechanisms of action showing parallel diminution in CI-AKI and adverse events are required to establish more robust evidence for causality.

PREVENTION

The most effective method of preventing CI-AKI is to not give iodinated contrast unless absolutely essential, especially in patients at high risk, such as those with advanced kidney disease. Unfortunately, the risks with contrast-enhanced magnetic resonance imaging in this patient population (i.e., the risk of nephrogenic systemic fibrosis from gadolinium)[47–50] also limit the imaging options, though these risks are much lower with the currently used group II gadolinium compounds.[51] Given the elective nature of the nephrotoxic insult that allows for attempting prophylaxis, many different interventions have been tested for CI-AKI prevention. Many of the studies are contradictory, and the numbers of systematic reviews and meta-analyses are also quite high, so the reader needs to look at the entire body of literature in order to interpret the data.[52]

FLUID ADMINISTRATION

Type of Fluid

Periprocedural volume administration has been the mainstay of preventive efforts and presumably works by reducing the concentration of the contrast medium in the tubules, improving medullary blood flow (via suppression of vasopressin), and increasing the urinary flow itself.[35] Isotonic saline has been shown to be superior to half-normal (0.45%) saline.[29] There has been significant research in the possible superiority of a bicarbonate-based strategy compared with normal saline, under the hypothesis that the resultant alkaline urine in the tubules will decrease free radical formation and the subsequent oxidant tubular damage. However, the initial promise from the first trial has been belied by the results of subsequent larger trials and meta-analyses.[53–56] In particular, the Prevention of Serious Adverse Events Following Angiography (PRESERVE) trial included 5177 patients undergoing angiography and did not report any difference in the incidence of AKI with bicarbonate compared with saline (OR, 0.93; 95% CI 0.72–1.22 for a composite endpoint of death, dialysis, or 50% rise in creatinine).[57,58] Another approach with very promising results relied on using left ventricular end-diastolic pressure (LVEDP) to guide fluid administration in patients undergoing cardiac catheterization, with a relative risk of 0.41 (95% CI 0.22–0.79; $P = 0.005$) for CI-AKI compared with the standard saline protocol.[59] This trial also showed a reduction in clinically meaningful outcomes (reduction in persistent renal impairment and all-cause mortality at 6 months), although the number of events was small. Another point to be noted is that the intervention group received significantly larger amounts of fluid (mean 1727 mL compared with 812 mL in the control group), thus questioning the role of LVEDP-guided therapy vis-á-vis more fluid alone. Further, LVEDP measurement is not practical in many settings, such as intravenous contrast administration with CT scans, especially in outpatient settings.

Route of Fluid

Small trials have tested oral hydration strategies compared with intravenous strategies, and although they may be as effective, the small numbers of events in these trials preclude any definitive recommendations at this stage.[60] Oral salt and water may be a reasonable option for the outpatient setting if hydration is warranted and the intravenous routine is not feasible.

Any Volume Expansion

The examination and the discussion earlier concluded that volume expansion is beneficial and decreases the risk of AKI after contrast administration. However, this presumption has been upended by two Dutch noninferiority trials. The A Maastricht Contrast-Induced Nephropathy Guideline (AMACING) trial enrolled 660 patients to intravenous hydration with normal saline compared with no prophylaxis.[61] Only two patients in both arms required dialysis, and there was no difference in any of the outcomes studied. The Kompas trial enrolled 523 patients to receive no prophylaxis or rehydration with 250 mL of sodium bicarbonate and also reported no difference in outcomes, with AKI in 11 versus 7 patients and no patients requiring dialysis.[62] Both of these trials included patients with a GFR >30 mL/min/1.73 m^2. Hence in patients with GFR >30 mL/min/1.73 m^2, no hydration is needed. Among those with a GFR <30 mL/min/1.73 m^2, especially with arterial contrast such as angiography, intravenous hydration may still be considered.

CHOICE AND VOLUME OF CONTRAST AGENT

Because the direct kidney damage occurs as a result of the contrast agent, significant research has been performed with respect to the physicochemical properties, specifically, the ionicity, osmolality, and viscosity, of the contrast agents and modifications to decrease CI-AKI (Table 102.2) for the classification of the different types). High-osmolality contrast agents, such as diatrizoate, have been shown to be worse with respect to low-osmolality agents and are thus no longer used in routine clinical practice.[63] When low-osmolality contrast agents were compared with iso-osmolar contrast agents (mainly iodixanol), the first

TABLE 102.2 Classification of Iodinated Contrast Media

Ionicity	Relative Osmolality	Osmolality (mOsm/kg H_2O)	Examples
Ionic monomers	High osmolality	1500–1900	Diatrizoate, iothalamate, metrizoate, iodamide, ioxithalamate
Ionic dimers	Low osmolality	600	Ioxaglate
Nonionic monomers	Low osmolality	500–700	Iopamidol, iohexol, iomeprol, iopentol, iopromide, ioversol, ioxitol, metrizamide
Nonionic dimers	Iso-osmolal	290–320	Iodixanol, iotrolan

trial showed a significantly lower risk of CI-AKI with iodixanol compared with iohexol[64]; however, subsequent larger trials have had different results.[15,65] Systematic reviews and meta-analyses have suggested the possibility of a small nonsignificant benefit with iodixanol but with significant heterogeneity. This heterogeneity has been resolved either by grouping trials based on the route of contrast (e.g., there is a lower risk of CI-AKI in intraarterial contrast imaging with iodixanol use)[66] or by specific contrast agents (e.g., iodixanol resulted in less CI-AKI compared with iohexol but not with other low-osmolar agents).[67] The volume of contrast agent administration also matters, suggesting a lower risk of CI-AKI with lower doses. A ratio of the volume (of contrast dose in mL) to creatinine clearance (variously from >2.6 to >4) has also been reported to be associated with a higher risk of CI-AKI, suggesting that the higher the creatinine clearance, the lower the necessary volume of contrast agent.[68,69]

PROPHYLACTIC RRT

Hemodialysis and hemofiltration, which are performed soon after contrast administration, have been studied for CI-AKI prevention with mixed results.[70] The rationale for doing this is to help remove the offending iodinated contrast material, especially in patients with reduced kidney function who may not be able to clear it quickly. However, biologically, the iodinated contrast material injected into, say, the coronary circulation or the left ventricle for ventriculography reaches and causes damage to the nephrons within a few cardiac cycles, so the efficacy of removing the contrast agent after the length of time it takes to set up RRT is not very plausible. Indeed, the results of the largest trial studying this were emphatically negative.[71,72] Other trials have reported a decrease in the proportion of patients with a decrease in creatinine clearance on the fourth day post contrast administration[73] or even in in-hospital mortality.[74] These trials are very challenging to interpret, given that the hemofiltration or hemodialysis itself would change creatinine clearance directly, and it is not possible to tease the effect of RRT on creatinine clearance from the effect of the CI-AKI attenuation. In addition, these procedures have inherent risks, such as those associated with central line placement and hemodynamic issues with the RRT procedure itself.[70,75]

PHARMACOLOGIC STRATEGIES

N-Acetylcysteine

N-acetylcysteine (NAC) replenishes endogenous glutathione, acts as a biologic antioxidant, and may also possess antiinflammatory effects. It has been reported to reduce the risk of CI-AKI in a small trial[76]; however, subsequent trials have provided conflicting results. Heterogeneity with respect to the dose and route of administration, and the possible effect of NAC on creatinine levels rather than kidney function, have made it difficult to determine the true efficacy of NAC.[77,78] Two large trials resolve this dilemma. The Acetylcysteine for Contrast-induced nephropathy Trial (ACT) included 2308 patients and measured not just CI-AKI on the basis of the change in creatinine but also clinical events, such as the need for RRT and mortality, and did not show any benefit of NAC.[79] The PRESERVE trial, with 5177 patients, also showed little benefit with NAC, with an OR of 1.02 (955 CI 0.78–1.33) for the primary outcome and no difference in dialysis, death, or hospitalization.[58] Arguments regarding the benign nature of NAC should take into account that the intravenous route can cause anaphylactoid reactions.[80] In addition, although NAC is not expensive, oftentimes, it has been used in place of—rather than in addition to—truly effective prophylactic strategies such as volume expansion.[81] Thus NAC has no role in CI-AKI prevention strategies.

DIURETICS

Diuretics, by their inherent effect, can increase urine flow and have been investigated for CI-AKI prevention because they may have a diluting effect on the iodinated contrast agent being filtered in the tubules. By themselves, the use of furosemide and mannitol has actually been shown to be detrimental[82] and increases the incidence of CI-AKI, which is not entirely unsurprising, given the protective effect of volume expansion. More recently, however, the use of furosemide in addition to intravenous fluids (in the "RenalGuard" system), dosed to achieve a urine output of >300 mL/hr, at which point contrast administration is permitted, with subsequent titration of intravenous fluids (and furosemide as required) to match urine output, has been shown to be more effective than hydration alone.[83,84] Of note, both the RenalGuard system and the LVEDP-guided hydration strategies result in a higher volume administered to the intervention group than to the controls, and the nature of both designs allows this to be performed in a safe manner.

STATINS

Statins have been found to be protective compared with placebo, in addition to when high-dose statins (e.g., atorvastatin 80 mg) are compared with low-dose statins in the prevention of CI-AKI.[85,86] However, these trials have been conducted in patients undergoing coronary angiography and/or interventions and not patients receiving intravenous contrast, and typically enrolled limited numbers of patients with chronic kidney disease; therefore these results cannot be easily translated into such populations. Last, under most current guidelines, the typical patient profile undergoing coronary angiography should be on a statin in the long term and not just for CI-AKI prevention.[87]

OTHERS

Small trials with ascorbic acid, calcium channel blockers, dopamine, fenoldopam, atrial natriuretic peptides, prostaglandin E1, theophylline, and nonselective endothelin antagonists have all either failed to show any benefit in CI-AKI prevention or have shown benefit in small trials that need replication.[88–92]

MANAGEMENT

In most instances, CI-AKI never becomes clinically evident, and kidney function returns to baseline within 2 weeks. In more severe cases, management is no different from that for AKI of any other cause.[4] Careful control of fluid and electrolyte balance, avoidance of further nephrotoxic insults, attention to nutrition, and surveillance for complications are generally all that is required, although dialysis may be necessary in the occasional patient. Indications for dialysis are no different from those in other patients with AKI, taking into account clinical and biochemical factors such as hyperkalemia and volume overload. Prophylactic hemodialysis soon after the administration of a contrast agent in patients with high serum creatinine concentrations has had inconsistent effects, as previously noted. Moreover, dialysis should not be performed for routine removal of contrast medium after imaging in previously dialysis-dependent patients.[34]

CONCLUSION

CI-AKI remains a concern, especially with interventions involving intraarterial contrast or in patients with advanced kidney disease. However, especially in the critical care setting when a prompt diagnosis can be lifesaving, the concern of kidney injury should not overrule the

need for contrast-based imaging. CI-AKI is not common in the absence of risk factors, and these are generally detectable with a history and physical examination and the determination of the serum creatinine concentration. Because CI-AKI can be associated with other adverse clinical outcomes, preventive measures are advisable, especially with advanced preexisting kidney disease when there is a risk that the patient may require dialysis. Although CI-AKI is associated with later adverse events, causality has not been proven, and the efficacy of preventive measures directed at CI-AKI in preventing these associated events has not been established. At this time, the optimal approach to preventing CI-AKI, which is summarized in the "Key Points" section, includes minimizing the contrast dose, using either iodixanol or a low-osmolar contrast agent other than iohexol, and using isotonic sodium bicarbonate or saline in high-risk patients. Whether volume expansion is beneficial at all in high-risk patients is worthy of study.[93] Finally, supportive care is indicated if severe CI-AKI does occur.

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KEY POINTS

- Assess the risk of CI-AKI in patients requiring a contrast imaging test.
  - Use the National Cardiovascular Data Registry (NCDR) risk score if the patient is undergoing percutaneous coronary intervention.[94]
  - For patients undergoing intravenous contrast administration, consider an estimated glomerular filtration rate <30 mL/min/1.73 m^2 as the principal risk factor.
  - Additional risk factors include diabetes mellitus and unstable kidney function.
- Assess the risk/benefit of the proposed contrast imaging, and consider alternative imaging in high-risk patients. In the context of critical illness, the risk of CI-AKI and its consequences may often be outweighed by the potential risks associated with a delayed or missed diagnosis as a result of inadequate imaging.
- Use the lowest possible dose of contrast media; consider using iodixanol or a low-osmolar contrast agent (other than iohexol).
- In high-risk patients, correct dehydration, hold diuretics, and consider intravenous fluids if there are no contraindications. Either normal (0.9%) saline or isotonic sodium bicarbonate, started at an initial rate of 3 mL/kg/hr at least 1 hour before and continued at 1 mL/kg/hr for 6 hours later, is commonly recommended.
- In high-risk patients, monitor creatinine within 24–72 hours post contrast administration.

References for this chapter can be found at expertconsult.com.

ANNOTATED REFERENCES

Hiremath S, Velez JCQ. Preventing a nonexistent entity: The curious case of contrast and acute kidney injury. *Curr Opin Nephrol Hypertens.* 2020;29(1):152-160.
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Glomerulonephritis

Dhruti P. Chen, Ronald J. Falk, and Gerald A. Hladik

Over half of all critically ill patients develop some degree of acute kidney injury (AKI), and nearly 5% require renal replacement therapy (RRT). For those patients with severe AKI requiring RRT, mortality can be as high as 70%, and up to 30% of surviving patients remain dialysis dependent.[1–6] AKI may be a consequence of prerenal causes resulting in hypoperfusion of the kidneys, intrinsic kidney disease, and postrenal or obstructive causes. In critically ill patients, most cases of AKI are related to ischemic or toxic acute tubular injury, which are treated with supportive measures and are often reversible. Acute glomerulonephritis (GN) accounts for about 4% of all cases of AKI.[7] In addition to supportive care, initiation of correct treatment is paramount for patient and renal survival. The focus in this chapter is on GN, a cause of AKI for which there is often disease-specific therapy.

GLOMERULONEPHRITIS

In GN, patients present with nephritic syndrome characterized by hematuria, proteinuria, AKI, edema, and hypertension.[8] Hematuria may be microscopic or macroscopic. The urine sediment demonstrates dysmorphic red blood cells (RBCs) and RBC casts. Urinary protein excretion typically exceeds 1 gram per day, and the degree of proteinuria can be rapidly assessed using simultaneous measurement of the urine protein-to-creatinine ratio (urine PCR) and the urine albumin-to-creatinine ratio (urine ACR). In general, the urine albumin-to-protein ratio (urine ACR/urine PCR) exceeds 0.5 in patients with glomerular disease. In contrast, an albumin-to-protein ratio of <0.4 is most consistent with tubular proteinuria when the urine PCR is <3. In some instances, patients may have nephrotic-range proteinuria (>3 g/d) with associated clinical manifestations, including edema, hypoalbuminemia, and hyperlipidemia. Leukocyturia with or without white blood cell casts may be observed with GN of inflammatory origin.

In renal biopsy series of patients with unexplained AKI, the most common diagnoses included various forms of GN (pauci-immune GN, immunoglobulin [Ig]A nephropathy, postinfectious GN, lupus nephritis, anti–glomerular basement membrane [anti-GBM] disease) and acute interstitial nephritis (AIN).[7,9–11] Indeed, the third most common cause of end-stage renal disease (ESRD) in the United States and Europe is GN.[8] Distinguishing the type of GN with kidney biopsy is critical for diagnosis and for assessing the degree of acute versus chronic disease, which helps guide treatment and informs prognosis.

The most aggressive form of GN is described clinically as rapidly progressive glomerulonephritis (RPGN). Rather than a single disease entity, RPGN is the most severe clinical presentation of many glomerular diseases that are divided into renal-limited etiologies and systemic diseases that involve the kidneys (Table 103.1). RPGN is defined as rapidly declining renal function, progressive oliguria, hematuria, proteinuria, and hypertension.[8] Although many critically ill patients may have hematuria associated with infection or trauma, hematuria and AKI should always prompt consideration of acute GN. Kidney ultrasound characteristically shows normal to slightly enlarged kidneys, although reduced kidney size may be present when the diagnosis is delayed. Kidney biopsy reveals a high degree of glomerular injury with extensive crescent formation (Fig. 103.1). Importantly, the transition from acute cellular crescentic disease to chronic, irreversible injury may occur rapidly over days. The rapid progression of such cases constitutes a need for prompt diagnosis with early intervention and therapy to interrupt a natural progression to chronic kidney disease. In adults, the most common cause of RPGN is pauci-immune GN associated with antineutrophil cytoplasmic antibodies (ANCAs), followed by immune-complex diseases such as lupus nephritis or mixed cryoglobulinemia. Anti-GBM disease (formerly called *Goodpasture disease*) is less common.[8,12] Immunofluorescence microscopy shows pauci-immune staining in ANCA-associated GN; linear IgG staining of the GBM in anti-GBM disease; and immune complex deposition in lupus nephritis, IgA nephropathy, and infection-related GN.

Pulmonary-renal syndrome, characterized by RPGN and diffuse alveolar hemorrhage (DAH), is a medical emergency requiring early aggressive treatment.[13–15] Untreated, it is associated with high mortality and rapid progression to ESRD. Admission to the intensive care unit (ICU) and mortality are related to both the disease itself and infectious complications. The clinical presentation is typically characterized by dyspnea, cough, hemoptysis, and in some cases fever, with chest radiography documenting pulmonary infiltrates. It may be difficult to distinguish from pneumonia, especially in patients without hemoptysis. Roughly 30% of patients with DAH do not have hemoptysis. The presence of renal dysfunction and hematuria in patients presenting with pulmonary symptoms should raise suspicion for a pulmonary-renal syndrome. Although Goodpasture syndrome was first used in 1958 to describe patients presenting with pulmonary hemorrhage and GN,[16] the most common cause of pulmonary-renal syndrome is ANCA-associated vasculitis.[8] Anti-GBM disease (formerly Goodpasture disease) now refers to the triad of DAH, RPGN, and the presence of anti-GBM antibodies. It is the second most common cause of pulmonary-renal syndrome. Much less common causes of pulmonary-renal syndromes are systemic lupus erythematosus (SLE), thrombotic microangiopathies, and other forms of systemic vasculitis.

A thorough history and physical examination may provide evidence for a systemic vasculitis (e.g., scleritis, purpuric rash, oral or sinus lesions). Bronchoscopy is critical to confirm DAH and evaluate for infection. The gold standard for diagnosis is renal or pulmonary biopsy, but critically ill patients are often at high risk for these procedures. The majority of patients have either ANCA-associated

TABLE 103.1 Diseases Associated With Rapidly Progressive Glomerulonephritis and Pertinent Laboratory Studies

RENAL LIMITED	
IgA nephropathy	
Infection-related glomerulonephritis	Low complement, streptococcal serologies, bacterial cultures
ANCA-associated glomerulonephritis (pauci-immune glomerulonephritis)	ANCA titers
Anti-GBM disease (Goodpasture syndrome)	Anti-GBM antibodies
SYSTEMIC DISORDERS	
Lupus nephritis	Low complement, ANA, dsDNA antibodies
ANCA-associated small vessel vasculitis	ANCA titers
Anti-GBM disease	Anti-GBM antibodies
Henoch-Schönlein purpura	None
Cryoglobulinemic vasculitis	Low complement, cryoglobulins, hepatitis C serologies, positive rheumatoid factor

ANCA, Antineutrophil cytoplasmic antibodies; *ANA,* antinuclear antibodies; *dsDNA,* double-stranded DNA; *GBM,* glomerular basement membrane; *IgA,* immunoglobulin A.

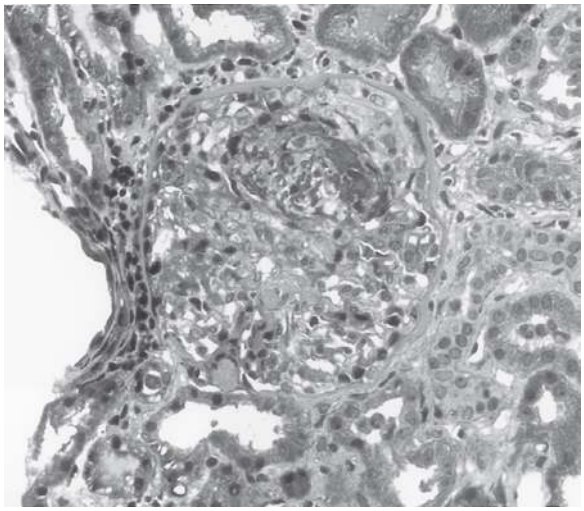

Fig. 103.1 Rapidly Progressive Glomerulonephritis. Cellular crescent is present in glomerulus (4- to 8-o'clock position), with fibrinoid necrosis of the glomerular capillary tuft (×200, trichrome).

vasculitis or anti-GBM disease. Because both diseases are treated similarly in the acute setting of RPGN and DAH, treatment with plasma exchange, corticosteroids, and cyclophosphamide may be initiated rapidly before the availability of serologic results.

PAUCI-IMMUNE NECROTIZING GLOMERULONEPHRITIS

Pauci-immune necrotizing GN or ANCA-associated GN may present as a systemic vasculitis, pulmonary-renal syndrome, or renal-limited disease. The spectrum of disease includes microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA or Churg-Strauss disease).[17,18] Kidney biopsy shows focal and segmental crescentic GN, fibrinoid necrosis, and an absence of Ig or complement within the glomeruli by immunofluorescence microscopy. Either anti-myeloperoxidase (MPO) or anti–proteinase 3 (PR3) antibodies are detectable in most patients. However, a minority of patients with characteristic clinical manifestations of these diseases and pauci-immune GN do not have detectable antibodies.

The mortality of untreated disease is roughly 90% at 2 years after disease onset.[19] However, advances in treatment have led to improved patient outcomes, with 80%–85% of patients achieving remission with effective immunosuppressive strategies.[20] Treatment consists of pulse intravenous (IV) methylprednisolone followed by oral corticosteroids and IV cyclophosphamide, rituximab, or both.[14,21–26] Even patients who are dialysis dependent on presentation often recover kidney function with appropriate treatment. Poor prognostic indicators for patient and renal survival are the presence of DAH, severe kidney dysfunction at the time of diagnosis, a high degree of glomerular injury and tubulointerstitial fibrosis on biopsy, and older age.[27–32] Patients with DAH have a high mortality rate, and plasma exchange may improve patient survival. Coagulation factors should be replaced in patients with active hemorrhage.[19,33–36] For severe pulmonary disease, a few patients have been successfully treated with extracorporeal membrane oxygenation (ECMO).[37,38] Patients with severe renal disease have a greater likelihood of renal recovery when treated with plasma exchange.[28,30,35,39,40]

With appropriate treatment, roughly 80%–90% of patients achieve remission.[19,27,33,41,42] Treatment resistance is more common in females, African Americans, and patients with severe renal disease. Relapse is more common in patients with anti-PR3 antibodies and in those with pulmonary and upper respiratory tract involvement. MPO ANCA is more commonly associated with MPA or renal-limited vasculitis. The ANCA-associated vasculitides (AAVs) follow a remitting and relapsing course, with the exception of drug-induced AAV (e.g., levamisole-adulterated cocaine, hydralazine),[43] making long-term monitoring a key component to patient and kidney survival.

ANTI–GLOMERULAR BASEMENT MEMBRANE GLOMERULONEPHRITIS

Anti-GBM disease (formerly Goodpasture disease) presents as DAH and RPGN with evidence of anti-GBM antibodies on serologic testing that target the noncollagenous domain of the α3 chain of type IV collagen. Kidney biopsy shows linear deposition of antibodies, most commonly IgG and C3, along the GBM with glomerular crescent formation. It is the most aggressive form of RPGN,[12] and roughly 30%–40% of patients present with renal-limited disease without pulmonary involvement. It commonly affects Caucasians in a bimodal age distribution with peaks during the third and seventh decades.[14,44–46]

Untreated disease is highly fatal, and death is usually caused by pulmonary hemorrhage or renal failure. Treatment with therapeutic plasma exchange, cytotoxic agents, and corticosteroids was introduced in the 1970s, resulting in improved patient and renal survival.[47] In patients with pulmonary and renal involvement, plasma exchange is crucial for rapid clearance of anti-GBM antibodies[48] and should be continued daily until antibodies are undetectable.[46] Long-term outcomes are related to the degree of pulmonary compromise and renal dysfunction at presentation. With appropriate treatment, survival rates may exceed 90% for acute disease, but patients requiring RRT on initial presentation have lower survival rates.[45,46,49] In fact, in patients with renal-limited anti-GBM disease requiring RRT

at presentation, less than 10% recover renal function at 1 year despite treatment with plasma exchange, corticosteroids, and cyclophosphamide.[45,49]

In contrast, patients with serum creatinine (SCr) levels below 5.7 mg/dL on presentation in one study had 100% 1-year patient and 95% renal survival.[50] In addition to dialysis dependence and elevated SCr, predictors of poor renal outcome include oligoanuria, high anti-GBM antibody titers, and a high percentage of glomeruli with crescent formation and extensive tubulointerstitial disease on kidney biopsy.[44,48,50,51] Although patient and renal survival is generally worse with anti-GBM disease than with ANCA-associated disease, late recurrence of anti-GBM disease almost never occurs, whereas recurrence of ANCA-associated disease is common.[12,46]

Both ANCA-associated vasculitis and anti-GBM disease are rare. Interestingly, a subset of patients have both types of antibodies detected on serologic studies. Approximately 15%–30% of patients with ANCA-associated disease also have anti-GBM antibodies, whereas only 5%–10% of patients with anti-GBM antibodies also have detectable ANCA titers.[12,45,46,52–54] Although outcome data are limited in this small group of patients, the outcomes of these patients may be better than patients with only anti-GBM antibodies.

LUPUS NEPHRITIS

Lupus nephritis occurs in 50%–60% of patients with SLE during the first 10 years of disease and is present in 35% of patients at initial diagnosis of SLE.[55] Less than 5% of patients present with RPGN or pulmonary renal syndrome. The incidence of ESRD attributed to lupus nephritis is higher among blacks and Hispanics.[56] In one study, up to 62% of blacks with lupus nephritis progressed to ESRD, compared with 19% of Caucasians.[57] In addition to history and physical examination, evaluation includes analysis of the urine sediment, because lupus nephritis may present as nephritic or nephrotic syndrome despite normal serum chemistries, quantitation of proteinuria, complement levels, and serologies for ANA and anti-dsDNA antibodies. Though the presence of cellular casts and/or proteinuria >0.5 g/d is consistent with the diagnosis of lupus nephritis, renal biopsy is critical for diagnosis, prognosis, and guiding treatment.

Kidney biopsy is used to classify lupus nephritis into six categories: class I (minimal mesangial lupus GN), class II (mesangial proliferative lupus GN), class III (focal proliferative lupus GN), class IV (diffuse proliferative lupus GN), class V (membranous lupus GN), and class VI (advanced sclerosing lupus GN).[58–60] Proliferative lesions in class III/IV lupus nephritis have poor renal survival without aggressive treatment. These classes often present with hematuria, proteinuria, hypertension, and AKI. Sclerosing lupus nephritis is a chronic, irreversible lesion that carries a poor prognosis.

Treatment of the more severe forms of lupus nephritis includes pulse methylprednisolone followed by oral corticosteroids and IV cyclophosphamide.[61–64] Similar to treatment of pauci-immune GN, pulse IV cyclophosphamide is preferred over oral cyclophosphamide to decrease the risk of hemorrhagic cystitis. Over 80% of patients respond to treatment.[61,65] Importantly, about 5%–10% of patients who require RRT initially recover enough kidney function to become dialysis independent after treatment.[66] Plasma exchange did not show additional benefit in a clinical trial using standard glucocorticoid plus cyclophosphamide for proliferative lupus nephritis induction therapy.[67] Plasma exchange may have a role in select patients with lupus nephritis and concomitant microangiopathy caused by antiphospholipid antibodies or ADAMSTS13 antibodies.[68] Studies comparing mycophenolate mofetil (MMF) to cyclophosphamide show equivalence, but not superiority, of one agent over the other. However, relapse appears more common in patients treated with MMF.[69–72] Induction should be followed by maintenance therapy—the preferred agent being MMF with low-dose prednisone. Depending on response and side effects, additional cyclophosphamide or azathioprine may be considered.[61,73–75] Other therapies under investigation include abatacept and belimumab, but they are not accepted as lupus nephritis induction or maintenance therapies at this time.

Poor prognostic indicators at the beginning of treatment include male gender, African American race, severe hypertension, antiphospholipid syndrome (APS), and delayed initiation of immunosuppressive therapy. After induction treatment, poor prognostic indicators are failure to achieve remission at 6 months and uncontrolled hypertension.[61,76] About one-third to half of patients will have relapse of disease. In some patients, recurrence of disease may be preceded by falling complement levels and rising anti-dsDNA titers. However, some patients with severe lupus nephritis have negative serologic studies.[61,77] Patients with only partial remission often recur sooner than patients with complete remission, and they are more likely to progress to ESRD.[78] All patients with a history of lupus nephritis should be carefully monitored for recurrence of disease, and repeat renal biopsy is often needed to guide treatment decisions.

INFECTION-RELATED GLOMERULONEPHRITIS

Bacterial, viral, fungal, protozoal, and helminth infections may all result in infection-associated GN. Poststreptococcal glomerulonephritis (PSGN) presents as a classic nephritic syndrome occurring about 1–6 weeks after bacterial infection. It most commonly occurs in children after a skin or pharyngeal infection with a nephritogenic strain of group A beta-hemolytic *Streptococcus* (GAS).[79,80] Although PSGN remains the most common cause of acute nephritic syndrome in the pediatric population in developing countries, the incidence of this disease has declined dramatically in the industrialized world. Recently, cases of infection-related GN (IRGN) caused by *Staphylococcus* and gram-negative bacteria have become more prevalent, especially in the setting of bacterial endocarditis and ventriculovascular shunt infections. In contrast to cases associated with GAS, renal insufficiency associated with *Staphylococcus* and other infections occurs while the patient is actively infected.

Children present with a classic nephritic syndrome with hematuria, proteinuria, hypertension, edema, and mild renal impairment. Severe hypertension with encephalopathy and seizures is uncommon and may require admission to the ICU.[81,82] Laboratory findings demonstrate depressed complement levels (CH50 and C3), consistent with activation of the alternative complement cascade; levels return to normal by 8–10 weeks.[17] Serologic studies may be used to confirm recent streptococcal infection, particularly with recent pharyngitis.[83,84] Renal biopsy demonstrates endocapillary proliferation and granular deposition of immune complexes by immunohistology.[79,83,85,86]

The acute nephritic syndrome usually resolves in 7–14 days, and the prognosis of children with PSGN is excellent. However, roughly 10%–20% of children have persistent urinary abnormalities, including proteinuria and hematuria.[6,8,84,87–89] Treatment is generally supportive, with antihypertensives and diuretics as needed in the acute phase. Active infections should be treated, and prophylactic antibiotics are often indicated in endemic situations and for household contacts in regions with high prevalence of disease.

In contrast to children, outcomes for IRGN in adults in the industrialized world are much worse, particularly for patients with underlying chronic disease or risk factors, including diabetes, cancer, alcoholism, liver disease, or IV drug use.[17,79,80,90–93] Elderly patients often present with AKI, congestive heart failure, and nephrotic-range proteinuria. Treatment

consists of supportive care, including diuretics, antihypertensives, or RRT and eradication of the infection. Although evidence is lacking from randomized controlled trials, pulse IV methylprednisolone can be considered in patients with extensive glomerular crescents and RPGN based on management of other glomerulonephridities.[17] One-quarter to one-half of patients have persistent renal dysfunction, and as many as 15% may progress to ESRD.[90–92,94] Long-term prognosis is worse in patients with persistent proteinuria >1 g/d after 6 months, and these patients should receive angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy.[17]

Other important causes of infection-related GN include cryoglobulinemic GN caused by hepatitis C virus (HCV), hepatitis B virus (HBV) or human immunodeficiency virus (HIV) infection. Signs and symptoms of systemic disease may include palpable purpura (dermal-renal syndrome), arthralgias or arthritis, and peripheral neuropathy.[95] Laboratory findings may include hypocomplementemia (especially undetectable C4), elevated rheumatoid factor (RF), circulating cryoglobulins, and positive viral serologies and nucleic acid testing. Kidney biopsy demonstrates intraluminal thrombi on light microscopy with immunoglobulin and C3 deposition on immunohistology. In addition to appropriate antiviral therapy, management of cases of rapidly progressive kidney disease may include plasma exchange, rituximab or cyclophosphamide, and antiviral therapy.[95–97]

IgA NEPHROPATHY

IgA nephropathy (IgAN) is an extremely common form of GN worldwide defined by dominant or codominant staining with glomerular IgA on kidney biopsy.[98] It commonly presents in the second or third decade of life—in North America it affects males twice as commonly as females.[99] The majority of patients present with macroscopic hematuria coinciding with an upper respiratory tract or gastrointestinal infection. Patients may develop hypertension and varying degrees of proteinuria and hematuria. Crescentic IgAN is associated with nephrotic-range proteinuria, severe hypertension, and rapidly declining renal function in less than 10% of cases.[100,101] Severe acute renal failure at initial presentation may also be the result of acute tubular necrosis caused by macroscopic hematuria. No specific laboratory study to date can establish the diagnosis; renal biopsy is required. The extent of changes by light microscopy is variable but is predictive of clinical outcome, and immunohistology demonstrates mesangial IgA deposits.

The long-term prognosis of patients with IgAN is highly variable, but many patients develop progressive renal failure. Progression to ESRD is approximately 15%–25% at 10 years and 25%–30% at 20 years after diagnosis.[102]

In all patients, hypertension should be aggressively treated with renin-angiotensin blockade and other agents if necessary.[17,103] In patients with significant proteinuria (>1 g/d) and declining renal function despite blood pressure control and antiproteinuric therapy, corticosteroids or immunosuppressive agents may be considered. Corticosteroids appear to reduce the risk of progression to ESRD and decrease proteinuria in selected patients.[104–108] Immunosuppressive medications such as cyclophosphamide or azathioprine should be reserved in rare cases of RPGN and crescentic GN.[17,100,102] Predictors of disease progression include degree of renal dysfunction at diagnosis, significant proteinuria, hypertension, and evidence of chronic disease by renal biopsy.[99,109,110]

IgA VASCULITIS

IgA vasculitis (IgAV, formerly named *Henoch-Schönlein purpura* [HSP]) is a systemic disease characterized by a distinct nonthrombocytopenic palpable purpuric rash, arthritis or arthralgias, gastrointestinal involvement, and IgAN. It occurs in children much more commonly than in adults. The classic presentation is sudden onset of rash, progressing from nonblanching erythematous macules, to urticarial papules, to purpura, with a symmetric distribution on the extensor surfaces of the distal extremities and buttocks.[111,112] Children present more frequently with gastrointestinal manifestations and fevers, whereas adults often have more severe renal involvement along with joint symptoms.[113,114] Renal involvement occurs in roughly one-third of children and two-thirds of adults.[115] The most common manifestation is microscopic hematuria with or without RBC casts and no or mild proteinuria.[116]

Renal involvement in IgAV is usually more severe at presentation than IgAN, but most children completely recover.[113,117,118] Estimates of recovery and chronic kidney disease vary widely, but the prognosis for renal recovery is worse in adults. Poor prognostic indicators include renal dysfunction and significant proteinuria at presentation, hypertension, and extensive glomerular disease by renal biopsy.[114,115,118,119] Treatment is primarily supportive care, and trials to date do not support any specific treatment regimen.[120] Corticosteroids may be useful in the short term, especially in the management of arthralgias and abdominal pain, but there is no clear evidence that prednisone prevents serious long-term renal disease.[121,122] Kidney Disease Improving Global Outcomes (KDIGO) recommendations suggest persistent IgAV be treated as isolated IgAN with corticosteroid therapy.[17] There are limited reports on the use of plasmapheresis for management of severe disease.[123,124] Two adults with severe systemic manifestations refractory to corticosteroids and immunosuppressive agents were treated with plasmapheresis, with subsequent improvement.[125]

THROMBOTIC MICROANGIOPATHIES

Thrombotic microangiopathy (TMA) is characterized by organ injury caused by widespread thrombosis of arterioles and capillaries, with intraluminal platelet aggregation and vessel wall thickening in the setting of thrombocytopenia and microangiopathic hemolytic anemia (MAHA).[126–128] The underlying pathophysiologic cause of TMA is endothelial damage caused by a variety of insults. Primary TMA syndromes include thrombotic thrombocytopenic purpura (TTP), Shiga toxin–mediated hemolytic uremic syndrome (HUS), drug-induced syndromes, complement-mediated syndromes, and metabolism-mediated disorders. Systemic disorders, including severe hypertension; pregnancy-associated syndromes, including severe preeclampsia/HELLP syndrome; and autoimmune disorders, including SLE,[129] catastrophic antiphospholipid syndrome, and scleroderma (systemic sclerosis), may present with microangiopathic anemia and thrombocytopenia not unlike primary TMA. However, in these cases management is focused on the primary disease process.

The classic pentad of findings in TTP includes MAHA, thrombocytopenia, neurologic symptoms and signs, impaired renal function, and fever.[126–128] Neurologic symptoms may dominate, presenting as confusion, headache, seizures, and coma. Renal manifestations are usually more prominent in HUS, and the typical presentation in children includes MAHA, thrombocytopenia, and AKI. Laboratory hallmarks include MAHA with schistocytes on peripheral smear, elevated lactate dehydrogenase levels, and thrombocytopenia, with platelets usually less than 60,000/μL.

Remarkable progress has been made in elucidating the molecular basis for TTP and HUS. TTP occurs as both hereditary (Upshaw-Shulman syndrome) and acquired forms related to either the deficiency or presence of antibodies that disrupt the function of a zinc metalloprotease, ADAMTS 13 (a disintegrin and metalloprotease with thrombospondin type 1 motif 13).[127,128,130] This protein is involved in

the cleavage of von Willebrand factor (vWF), and deficiency of ADAMTS 13 leads to the accumulation of large multimers of vWF, which bind platelets, leading to microvascular thrombosis. Historically, untreated TTP had a mortality rate of over 90%. However, mortality has fallen to 10%–20% with the advent of treatment using plasma exchange.[131,132] Other therapies include glucocorticoids and rituximab in the case of refractory or relapsing disease.[133,134] Hereditary forms require treatment with fresh frozen plasma or cryosupernatant that contains ADAMSTS 13. Because hereditary TTP is rare, acquired TTP is the presumed diagnosis in new cases.

HUS is the most common cause of AKI in children and presents with hemolytic anemia, thrombocytopenia, and AKI.[126,135–137] The classic or diarrheal form of HUS (D + HUS) occurs most commonly after diarrheal infection with Shiga toxin–producing *Escherichia coli* (*E. coli* O157:H7), which accounts for 90% of cases. The peak incidence occurs in children younger than 5 years of age. The illness begins with abdominal cramps and nonbloody diarrhea, followed by hemorrhagic diarrhea in 70% of patients. As the diarrheal illness is improving, patients develop severe renal failure, anemia, and thrombocytopenia. These children are often critically ill, and roughly one-half to two-thirds of patients require RRT. About 70% of patients will require RBC transfusions, and 25% will have neurologic involvement. Over the last few decades, mortality rates have fallen from roughly 40%–50% to 3%–5%, primarily as a result of aggressive supportive care with RBC transfusions and RRT as needed. Numerous therapies for HUS have been investigated without clear benefit, and treatment remains largely supportive. Treatment of the diarrheal illness associated with *E. coli* O157:H7 with antibiotics is associated with increased risk of developing HUS. Spontaneous resolution occurs 1–3 weeks after disease onset, and the majority of patients demonstrate renal recovery. Unfortunately, some children develop ESRD, and up to 40% have long-term sequelae, including chronic kidney disease, persistent proteinuria, and hypertension. Nondiarrheal-associated HUS occurs in a minority of patients and may be associated with other infections such as *Streptococcus pneumoniae*.

A small percentage of patients with HUS have sporadic or familial forms, known as *complement-mediated HUS* (previously called *atypical HUS*). These patients have defects in the regulation of the alternative complement pathway, and mutations have been described in complement factor H, complement factor I, and membrane cofactor protein.[127,128,132] Mortality rates are highest in patients with complement factor H mutations, and most survivors progress to ESRD. Patients with severe complement-mediated HUS, such as those with complement factor H and complement factor I mutations who are at increased risk for ESRD, should receive treatment with eculizumab.[138] Other supportive measures may include RBC and platelet transfusions and provision of dialysis and nutritional support as indicated.

An extensive variety of drugs have been associated with TMA. Although the mechanism of action as to why certain drugs cause this phenomenon is not completely understood, it is hypothesized to be either an immune-mediated effect or direct drug toxicity.[139] The immune-mediated effect occurs when a drug induces formation of antibodies that ultimately react with endothelial cells, platelets, and neutrophils. This results in platelet microthrombi with platelet consumption and thrombocytopenia in addition to microvascular damage. The formation of these antibodies is triggered by the presence of the drug itself or an active metabolite of the drug. Thus once the drug is cleared from the system, no new organ damage occurs.[140] Drugs that cause TMA include quinine, gemcitabine, quetiapine, and oxaliplatin.[141,142]

A small percentage of patients with APS present with "catastrophic" APS characterized by acute TMA involving the small vessels of multiple organs.[143] The disease progresses over days to weeks and commonly affects the kidneys, lungs, central nervous system, heart, and skin. The kidney is the most common organ affected, with renal involvement in over 70% of patients. Renal disease manifests as malignant hypertension and AKI, with 25% of patients requiring RRT. Mortality is estimated at 50% of patients, and treatment based on case reports includes management of cause (e.g., infection), systemic anticoagulation, corticosteroids, and plasma exchange to remove anticardiolipin antibodies with or without IV Ig.[144]

Scleroderma renal crisis presents as AKI with abrupt onset of moderate to severe hypertension and may be accompanied by encephalopathy, seizures, or flash pulmonary edema.[145] A subset of patients may not be hypertensive, but have blood pressures higher than baseline values, portending a worse prognosis.[146] Roughly 10% of patients develop scleroderma renal crisis, usually occurring within 4 years of disease onset. The risk is greatest with diffuse cutaneous disease. Antecedent treatment with high-dose corticosteroids increases the risk of scleroderma renal crisis.[147,148] Patients demonstrate MAHA, thrombocytopenia, proteinuria, microscopic hematuria, and marked increases in plasma renin. In the past, untreated disease had a dismal prognosis, with less than 10% survival. The use of angiotensin-converting enzyme (ACE) inhibitors has revolutionized treatment; acute mortality rates are now below 25% with appropriate treatment.[145,149,150] About half to two-thirds of patients will require RRT, but half of those patients recover sufficient renal function to become dialysis independent. Poor outcomes are associated with SCr level >3 mg/dL at the initiation of ACE inhibitor therapy, dialysis dependence, poor blood pressure control, male gender, older age, and congestive heart failure. Patients with scleroderma renal crisis who do not require RRT have 90% survival rates at 5 years. In contrast, patients who become dialysis dependent have only 40% survival at 5 years. Early recognition and treatment are critical for both patient and renal outcomes. ACE inhibitors should be initiated rapidly and continued even if patients develop progressive renal failure or require RRT.

KEY POINTS

- Many underlying causes for AKI resulting from intrinsic renal disease are reversible. Because the transition of active glomerular lesions to irreversible scar occurs rapidly, prompt diagnosis and early intervention are crucial.
- Pulmonary-renal syndrome constitutes a medical emergency. Studies demonstrate that early aggressive treatment improves patient and renal survival.
- Detailed history and physical examination is important for distinguishing renal-limited disease from systemic diseases.
- Initial evaluation should include basic chemistries, evaluation of urine sediment, complete blood counts with peripheral blood smear review, assessment for proteinuria, and renal ultrasound.
- Serum complement levels are important tools in distinguishing causes of GN: (1) normal serum complement (IgAN, IgAV, pauci-immune necrotizing GN, and anti-GBM) and (2) depressed serum complement (immune complex GN, including infection-related GN and lupus nephritis).
- Depending on the clinical scenario, additional evaluations may include ANCAs, anti-GBM antibodies, antinuclear antibodies (ANAs), anti–double-stranded DNA (dsDNA) antibodies, serologies for streptococcal infection, viral serologies, and bacterial cultures.
- The diagnosis of most glomerular syndromes requires kidney biopsy. However, critically ill patients are often at increased risk for complications, and it may be necessary to proceed with treatment in the absence of kidney biopsy in certain situations.

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104

Interstitial Nephritis

Elizabeth S. Kotzen, Evan M. Zeitler, and Gerald A. Hladik

Acute interstitial nephritis (AIN) is an important cause of acute kidney injury (AKI) characterized by inflammation of the renal interstitium and tubules, sparing the glomeruli and vasculature.[1] It is more properly called *acute tubulointerstitial nephritis* (Fig. 104.1). The disorder results from an inflammatory reaction, often of the hypersensitivity type.[2] Biopsy series show that AIN is present in 6.5%–27% of kidney biopsies performed for unexplained AKI; it is probably the third most common cause of AKI in hospitalized patients, following prerenal AKI and acute tubular necrosis (ATN).[3,4]

Medication-associated AIN is the most frequent etiology (50%–85% of cases) (Table 104.1); other etiologies include autoimmune disorders (0%–41% of cases) and infections (2%–16% of cases) (Table 104.2).[5–8] Systemic disorders associated with biopsy-proven AIN include systemic lupus erythematosus (SLE), sarcoidosis, Sjogren syndrome, and IgG4-related disease (Table 104.3).[3,5,9] A subset of patients with AIN have tubulointerstitial nephritis and uveitis (TINU) syndrome, which is characterized by AIN and bilateral uveitis. TINU comprises 5%–22% of biopsy-proven AIN.[6–8,10] Furthermore, AIN may be present in the context of a drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. Allopurinol is one of the more common culprit drugs associated with DRESS.[11] Critically ill patients are routinely treated with medications associated with AIN, including antibiotics, NSAIDs, proton pump inhibitors, and diuretics (see Table 104.1).[2,7,12] Immune checkpoint inhibitors are recent additions to available therapy that cause AIN.[13]

Prompt recognition of AIN is important in order to identify inciting drugs that should be discontinued to minimize ongoing kidney injury. The prototypical example of AIN is methicillin-associated AIN. The first case series described a classic triad of fevers, eosinophilia, and pyuria within 8–36 days after exposure.[14] Unfortunately, this classic triad occurs in only 5%–10% of patients with AIN and does not provide a useful diagnostic strategy to identify patients with the condition.[2,3,15] Measurement of urinary eosinophils has previously been touted as a diagnostic test for AIN. This test is no longer recommended because of poor sensitivity and specificity.[3,16] The fractional excretion of sodium (FeNa) is commonly calculated in the evaluation of AKI to distinguish between prerenal AKI and ATN; however, there is no characteristic FeNa value that distinguishes AIN from other causes of AKI.[3]

The most typical presentation of AIN is nonoliguric AKI, although a minority of patients may develop oliguria and dialysis dependence.[12] Clinical signs and symptoms that are suggestive (but not diagnostic) of AIN in the context of unexplained AKI include recent exposure to a drug implicated in AIN (see Table 113.1), morbilliform rash, elevated serum eosinophils, pyuria, and the presence of white blood cell casts on urine microscopy. Hematuria and low-level proteinuria may be present. Biomarkers are under investigation, and further study may bring about a noninvasive diagnostic approach to AIN in the future.[17] For now, kidney biopsy remains the only validated way to diagnose AIN.[3]

Typically, kidney manifestations develop, on average, 10 days after initiation of the inciting medication, with 80% of patients developing kidney manifestations within 21 days of the drug exposure.[2] It is important to note that the classic description of drug-induced AIN as an acute process occurring within a few weeks after exposure to the offending medication is too narrow. Renal manifestations may occur as soon as a few days after exposure (especially in the setting of prior exposure) or many months after the exposure (nonsteroidal antiinflammatory drugs [NSAIDs] are often associated with a 6- to 18-month period of exposure before development of renal dysfunction).[8,12] Additionally, the kidney injury may be acute, subacute, or chronic.[8,12] Risk factors for

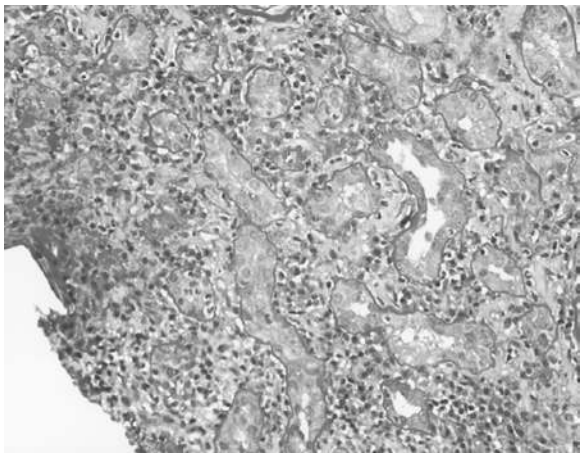

Fig. 104.1 Acute Interstitial Nephritis. Diffuse, predominantly mononuclear cell infiltrate is present within an expanded and mildly edematous interstitium, and periodic acid–Schiff (PAS)-positive tubular basement membranes have wrinkling. Foci of tubulitis are also present (×200, PAS).

TABLE 104.1 Medications Most Frequently Associated With Acute Interstitial Nephritis

Antibiotics: beta-lactams, rifampin, fluoroquinolones
Antiinflammatories: NSAIDs, 5-aminosalicylates
Proton pump inhibitors
Immune checkpoint inhibitors
Allopurinol
Anticonvulsants: phenytoin, carbamazepine, phenobarbital
Diuretics: thiazides, loop diuretics, triamterene
Herbal medications

NSAID, Nonsteroidal antiinflammatory drug.

TABLE 104.2 Pathogens Associated With Infection-Related Acute Interstitial Nephritis

BACTERIAL INFECTIONS
Brucella
Chlamydia
Corynebacterium
Enterococcus
Escherichia coli
Francisella
Legionella
Leptospirosis
Streptococcus
Treponema
Yersinia

FUNGAL INFECTIONS
Candida
Coccidioidomycosis
Histoplasmosis

MYCOBACTERIAL INFECTIONS
Mycobacterium tuberculosis
Mycobacterium kansasii
Mycobacterium haemophilum

PARASITIC INFECTIONS
Leishmania
Toxoplasma

VIRAL INFECTIONS
Adenovirus (kidney transplant recipients)
Cytomegalovirus
Epstein-Barr virus
Polyomavirus (kidney transplant recipients)

TABLE 104.3 Systemic Diseases Associated With Interstitial Nephritis

Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis
Antitubular basement membrane antibody–associated interstitial nephritis
Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome
Hypocomplementemic tubulointerstitial nephritis
Immunoglobulin G4–related disease
Sjögren syndrome
Systemic lupus erythematosus
Tubulointerstitial nephritis and uveitis (TINU) syndrome

adverse renal outcomes include older age, delay of diagnosis, and recurrent AIN episodes, which often happen either because of TINU syndrome or because of re-exposure to the offending drug.[8]

The cornerstone of treatment for AIN is removal of the suspected offending agent. In the case of drug-induced AIN, any potentially causative medication should be stopped whenever possible. When present, underlying infections should be identified and treated. If indicated, dialysis should be provided.

Corticosteroids are commonly used in the treatment of AIN. However, high-quality evidence is lacking and is derived from retrospective trials. The three largest retrospective studies reached discordant conclusions.[2,15,18] Of note, in the two studies that did not find a benefit of steroids, patients who received steroids had higher pretreatment serum creatinine levels. In contrast, a benefit was observed in steroid-treated patients in the study in which the treatment and control groups had similar baseline serum creatinine levels. Prospective randomized controlled trials regarding the use of corticosteroids in AIN are required.

A recent retrospective study of 182 patients with biopsy-proven AIN treated with corticosteroids revealed 41% complete recovery of kidney function, 45% partial recovery, and 13% with no improvement in kidney function. Five percent of patients were dialysis-dependent at 6 months follow-up.[19]

In the absence of evidence from prospective randomized trials to guide treatment, we recommend the following approach to management, which is generally in line with other expert recommendations:[2,12,20]

1. In the event of unexplained AKI, after excluding obstructive AKI with imaging and evaluating for ATN and acute glomerulonephritis with urine microscopy, consider removal of medications frequently associated with AIN when possible.
2. For unexplained AKI requiring dialysis, kidney biopsy should be performed as soon as feasible. For unexplained AKI not requiring dialysis, we perform kidney biopsy if there is no improvement in kidney function within 5–7 days of withdrawal of the potentially offending medication.
3. If the biopsy confirms AIN, with minimal fibrosis present on the biopsy, we pursue a trial of corticosteroids as follows: prednisone 1 mg/kg per day (max 80 mg per day) for 1–3 weeks. In severe or dialysis-dependent AIN, we would consider an initial 3-day pulse of 500 mg intravenous methylprednisolone before initiation of oral corticosteroids. The severity of inflammatory morphologic changes on biopsy also helps to guide our decisions about the duration of therapy and whether to employ pulse methylprednisolone. If no response is observed within 3 weeks, the prednisone can be rapidly tapered. Prednisone is generally tapered more slowly in responsive patients, with up to 8 weeks of total steroid exposure. There is evidence that there is no benefit in continuing steroid treatment for >8 weeks.[19]

Some authors have maintained that AIN resulting from NSAID exposure is less likely to respond to corticosteroid therapy. However, Gonzalez and colleagues found benefit of corticosteroids in NSAID-induced AIN. Therefore it is reasonable to consider corticosteroid therapy in patients with NSAID-induced AIN.

Mycophenolate mofetil (MMF) was found to provide possible benefit in a case series of eight patients with steroid-resistant AIN. MMF has also been used in 14 patients who experienced recurrent AIN upon steroid discontinuation.[8,21]

KEY POINTS

- The diagnosis of AIN should be considered in patients with AKI and sterile pyuria or systemic manifestations of hypersensitivity, especially when temporally associated with medication initiation or infection.
- Medications, particularly antibiotics, are responsible for over two-thirds of cases of AIN.
- A definitive diagnosis of AIN can only be made with kidney biopsy.
- Treatment of drug-induced AIN begins with discontinuation of the causative agent. Treatment with corticosteroids is an important adjuvant when discontinuation of the causative agent alone is not sufficient to produce improvement in kidney function.

References for this chapter can be found at expertconsult.com.

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Antimicrobial Stewardship

*Marin H. Kollef** and *Scott T. Micek*

Antimicrobial stewardship is an important concept that is pertinent to virtually every clinician. Its goals are to combat the emergence of resistance, improve clinical outcomes, and decrease healthcare costs (Fig. 105.1).[1–7] In this chapter, we will focus on the advances in and obstacles to antimicrobial stewardship as outlined in Table 105.1 by breaking this discussion into two major areas: optimization of antimicrobial therapy and avoidance of unnecessary antibiotic administration.

OPTIMIZATION OF ANTIMICROBIAL THERAPY

Appropriate Antimicrobial Selection

Appropriate antibiotic therapy is the cornerstone of management in septic shock and in any serious infection requiring intensive care unit (ICU) care and has a great influence on hospital mortality. Appropriate antibiotic therapy is defined as an initial antimicrobial regimen that demonstrates in vitro activity against the isolated organisms responsible for the infection, whereas inappropriate antibiotic therapy is defined as an initial regimen demonstrating a lack of in vitro activity against the causative pathogens.[8] The administration of inappropriate initial antibiotic therapy can lead to treatment failures and adverse outcomes.[9–15] Similar associations between the administration of inappropriate initial antimicrobial therapy and greater mortality have been shown for bloodstream infections by *Candida*.[16–18] Moreover, the importance of treating all pathogens associated with serious infection is further emphasized by a retrospective analysis of patients with severe sepsis and septic shock.[19] For the entire cohort, the number needed to treat with appropriate antimicrobial therapy to prevent one patient death was 4.0 (95% confidence interval [CI], 3.7–4.3). The importance of early appropriate antibiotic selection was also demonstrated in a recent randomized trial among patients with *Escherichia coli* or *Klebsiella pneumonia* bloodstream infection and ceftriaxone resistance demonstrating that definitive treatment with piperacillin-tazobactam compared with meropenem resulted in greater 30-day mortality.[20] This study also highlights the importance of early identification of antibiotic resistance to optimize antimicrobial prescription in order to improve patient outcomes.

*Conflicts of Interest: Dr. Kollef's effort was supported by the Barnes-Jewish Hospital Foundation.

The importance of selecting appropriate initial antimicrobial therapy has been emphasized in the most recent Surviving Sepsis Guidelines.[21] The guidelines recommend that initial empiric antiinfective therapy include one or more drugs that have activity against all likely pathogens (bacterial and/or fungal or viral) and that the antibiotics penetrate, in adequate concentrations, into the tissues presumed to be the source of sepsis (grade 1B).[21] This guideline urges clinicians to use the patient's history (including drug intolerances), recent receipt of antibiotics, underlying disease, clinical syndrome, and susceptibility patterns of pathogens in the community and hospital and that have been previously documented to colonize or infect the patient when making decisions regarding initial antimicrobial regimen selection.

Timing of Antibiotic Administration

In addition to selecting an appropriate antimicrobial regimen, the timing of antibiotic delivery is an essential element in determining the outcome of critically ill patients with infection. Several studies have found strong relationships between delays in effective antimicrobial initiation and in-hospital mortality for serious infections, including ventilator-associated pneumonia (VAP) and septic shock.[22,23] A meta-analysis of randomized and observational studies evaluating the impact of goal-directed bundles on the outcomes of patients with septic shock found that timely antibiotic administration was statistically more common among patients receiving protocolized management of septic shock.[24] Members of the Surviving Sepsis Campaign subsequently performed a retrospective analysis of a large data set collected prospectively from 165 ICUs in Europe, the United States, and South America.[25] In-hospital mortality was 29.7% for the cohort as a whole, and there was a statistically significant increase in the probability of death associated with the number of hours of delay for the first antibiotic administration.

Timely administration of effective antibiotics seems to be an important element in determining the outcome of critically ill patients. As discussed later, prediction tools for the presence of antibiotic resistance and rapid diagnostics may allow for a more rapid administration of appropriate therapy. However, emergency departments and ICUs should also ensure that they have processes in place to obtain and deliver antibiotic therapy expeditiously once the order for such therapy is received from the treating physicians.

The use of treatment bundles for the management of patients with sepsis and septic shock has been associated with lower hospital mortality

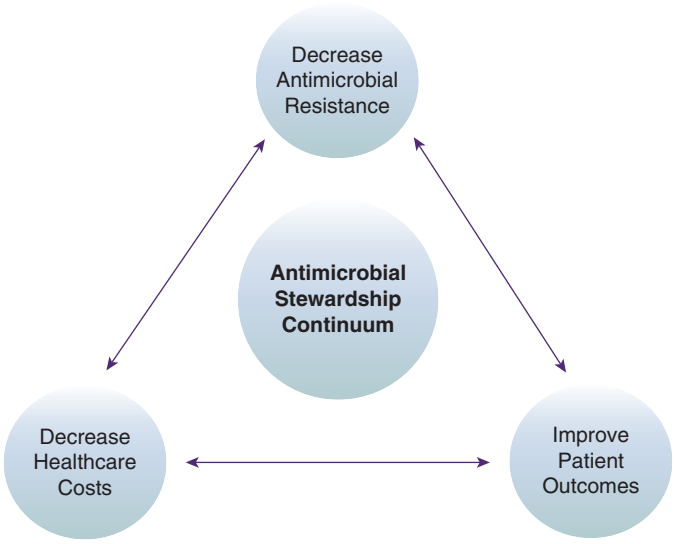

Fig. 105.1 The goals of antimicrobial stewardship programs.

TABLE 105.1 Antimicrobial Stewardship Program for the ICU Setting

1. Optimization of antimicrobial therapy
   a. Appropriate antimicrobial selection
   b. Timing of antibiotic administration
   c. Adequate dosing of antimicrobials and PK/PD considerations
   d. Duration of antibiotic treatment
   e. Augmented renal clearance
   f. Therapeutic drug monitoring
2. Avoidance of unnecessary antibiotic administration
   a. Deescalation of empiric antibiotic regimen
   b. Use of antibiotic resistance prediction tools
   c. Biomarker guidance of antimicrobial therapy
   d. Formalized antimicrobial stewardship programs
   e. Rapid microbiologic diagnostics
   f. Telemedicine driven stewardship
   g. Closed multidisciplinary ICU management
   h. Optimized infection control program

ICU, Intensive care unit; *PK/PD,* pharmacokinetic/pharmacodynamic.

thought to be caused primarily by the earlier administration of antibiotics.[26,27] However, these treatment bundles fail to examine important clinical issues, including whether antibiotic therapy is necessary in all patients with presumed sepsis, the dosing strategies and duration of antibiotics, and whether the administered antibiotic regimen is active against the offending pathogens. The success of sepsis treatment bundles has now been used, in part, by the authors of the Surviving Sepsis Campaign Guidelines to recommend the use of broad-spectrum antibiotics within 1 hour of presentation in all patients with clinically suspected sepsis.[28] However, a recent editorial has attempted to focus attention on the problems associated with the overuse of antibiotics in patients with possible sepsis.[29] This editorial highlights the difficulties in establishing an accurate diagnosis of sepsis attributed to underlying infection, the adverse consequences associated with routine administration of antibiotics in critically ill patients, and the problem of equating sepsis with the more severe condition of septic shock.[29] Recent pleas have emerged from the Infectious Diseases Society of America, emergency medicine thought leaders, and critical care thought leaders urging for more rational approaches for directing antibiotic therapy in complex patients and eliminating the 1-hour sepsis bundle.[30–33]

Adequate Dosing of Antimicrobials and Pharmacokinetic/Pharmacodynamic Considerations

In addition to delivering timely appropriate antibiotic regimens, adequate drug concentrations at the site of infection are needed to optimize clinical outcomes. Beta-lactam and carbapenem antibiotics are time-dependent antimicrobials whose activities are primarily related to the duration the free drug concentration exceeds the pathogen minimum inhibitory concentration (T_{FREE}/MIC).[34–36] Many factors influence the pharmacokinetics of antimicrobials in critically ill patients. Hypoalbuminemia, large-volume crystalloid administration, large pleural effusions or abdominal ascites, catecholamines, augmented renal clearance (ARC), and renal replacement therapies can all significantly alter infection site concentrations of administered antibiotics.[37]

In VAP treatment, particularly for gram-negative bacteria (GNB), dose and duration of treatment might need to be augmented despite having selected an appropriate initial regimen. For instance, meta-analyses of tigecycline showed an increased mortality in nosocomial pneumonia, particularly VAP driven by GNB infections.[38–40] A randomized trial of patients with hospital-acquired pneumonia (HAP) found that tigecycline with or without ceftazidime had inferior cure rates to imipenem-cilastatin with or without vancomycin across all pathogens.[41] The hypothesis that the tigecycline dose (75 mg every 12 hours) was too low to achieve high enough concentrations above the MICs of pathogens prompted a higher-dose study (100 mg every 12 hours) compared with imipenem-cilastatin.[42] Similarly, ceftobiprole, a cephalosporin with activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and an extended GNB spectrum equivalent to ceftazidime or cefepime, was compared with linezolid and ceftazidime in patients with HAP/VAP.[43] Even though it achieved similar cure rates in patients with HAP, ceftobiprole was inferior to linezolid and ceftazidime in patients with VAP, in large part thought to be a result of the underdosing of ceftobiprole in critically ill patients. This concern has led to a doubling of the dose of ceftolozane/tazobactam for the treatment of HAP/VAP.[44]

Critically ill patients display different pharmacokinetics; therefore newer drug administration strategies for beta-lactams and carbapenems have been investigated to include the use of prolonged infusions in order to optimize antibiotic delivery to infection sites. Several recent meta-analyses suggest that prolonged infusions of beta-lactam and carbapenem antibiotics may be associated with improved outcomes in critically ill patients.[45–47] However, the results from the largest multicenter trial performed to date of prolonged antibiotic infusion in critically ill patients failed to demonstrate any mortality benefit.[48]

One of the best examples of the need for proper antibiotic dosing and drug exposure at the site of infection was recently demonstrated in a multicenter trial.[49] These investigators aimed to determine whether beta-lactam antibiotic dosing in critically ill patients achieves concentrations associated with maximal activity and whether antibiotic concentrations affect patient outcome. Of the 248 patients treated for infection, 16% did not achieve a T_{FREE}/MIC ratio greater than 1 at 50% of the dosing interval, and these patients were 32% less likely to have a positive clinical outcome. Positive clinical outcome was associated with a T_{FREE}/MIC ratio greater than 1 at both 50% and 100% of the dosing intervals. These data suggest that many critically ill patients experience adverse outcomes as a result of inadequate antibiotic exposure.

Duration of Antibiotic Therapy

For most critically ill patients, empiric antibiotic courses of 7–8 days of treatment should suffice, unless specific infections are identified, such as bacteremia, fungemia, endocarditis, osteomyelitis, or meningitis, which would require longer treatment durations. The data supporting the use of shorter courses of antibiotic therapy are probably strongest for VAP, depending on clinical severity, rapidity of clinical improvement, and most important, the underlying microbiology.[50–53] The exceptions to shorter courses of antibiotic therapy in VAP are the difficult-to-treat pathogens such as *Pseudomonas aeruginosa* and other nonfermenters that experience higher recurrence rates with shorter treatment regimens.[50] At least one randomized trial has found a greater mortality among patients with *P. aeruginosa* VAP receiving only 7 days of treatment.[54] Longer durations of treatment for nonfermenting GNB may be most important in situations where antibiotic exposure in the lung is limited by host factors such as increased volume of drug distribution and ARC.

The inflammatory biomarker procalcitonin has been shown to aid in limiting the duration of antibiotic exposure for patients with VAP and other types of infections.[55–57] However, other clinical trials have failed to replicate these findings. A study performed in nine ICUs in Denmark enrolled 1200 critically ill patients to receive either the "standard-of-care-only," receiving treatment according to the current international guidelines and blinded to procalcitonin levels, or the "procalcitonin arm," in which current guidelines were supplemented with a drug-escalation algorithm and intensified diagnostics based on daily procalcitonin measurements.[58] Although there was no mortality difference, length of stay in the ICU was increased by 1 day in the procalcitonin arm. A recent multicenter trial from Australia that enrolled 400 patients with suspected bacterial infection/sepsis also failed to demonstrate reductions in the overall median number of antibiotic treatment days with the use of procalcitonin.[59] Similarly, a large U.S. study failed to show a reduction in antibiotic duration among patients with suspected lower respiratory tract infections.[60]

In summary, clinicians should be aware that 7–8 days of therapy should suffice for empiric antibiotic therapy in most ICU patients. However, even shorter courses of empiric therapy should be used when the presence of infection is excluded, and longer treatment regimens may be required when dealing with specific host- and pathogen-related factors such as ARC, increased volume of distribution, and presence of infection with *P. aeruginosa* or other nonfermenters. It is probably most important to critically review all antibiotics on a daily basis to ensure that they are indeed necessary and, if so, that they are delivered in adequate concentrations.[61]

Augmented Renal Clearance

ARC is defined as an 8-hour creatinine clearance more than or equal to 130 mL/min/1.73 m^2. One recent study has suggested that over 65% of ICU patients have ARC on at least one occasion during the first 7 days of their critical illness.[62] ARC has been linked with subtherapeutic beta-lactam[63] and glycopeptide concentrations[64] and increased therapeutic failures in patients receiving antimicrobial therapy, resulting in adverse patient outcomes.[54,65,66] However, several recent studies have cast doubt on whether ARC is associated with excess mortality, especially when antibiotic dosing is optimized.[67,68] One group of investigators has developed a scoring system to identify patients at high risk for ARC based on the following factors: age of 50 years or younger (6 points), trauma (3 points), and Sequential Organ Failure Assessment (SOFA) score of 4 or less (1 point).[69] A subsequent study found that the ARC score was 100% sensitive and 71.4% specific for detecting ARC.[70] Monte Carlo pharmacokinetic simulations demonstrated increased time at therapeutic antibiotic levels with the use of extended infusion dosing in the setting of ARC at drug cost savings of up to 66.7% over multiple intermittent dosing regimens. In addition to ARC, the use of renal replacement therapies can result in underexposure of antibiotics at the site of infection, requiring careful dosing adjustments.[71] Further research is required to determine the influence of ARC on the outcomes of critically ill patients and how to optimize antimicrobial therapy when ARC is present.

Therapeutic Drug Monitoring

Therapeutic drug monitoring (TDM) for beta-lactams and carbapenems can be accomplished by several methodologies, allowing serum concentrations of antibiotics to be assessed in order to optimize delivery and minimize the occurrence of toxicity.[72,73] However, the use of TDM for antibiotics other than vancomycin, aminoglycosides, and voriconazole has not become a routine or standard practice in most ICUs. Recent studies have demonstrated the ability of TDM to identify the need for antibiotic dosing adjustments in the setting of continuous renal replacement therapy resulting from excess serum antibiotic concentrations[74] and during treatment of multidrug-resistant (MDR) *P. aeruginosa* with fluctuating renal function.[75] Unfortunately, at the present time, large variations exist in the types of beta-lactams tested, the patients selected for TDM, drug assay methodologies, pharmacokinetic/pharmacodynamic targets, and dose adjustment strategies employed among critically ill patients.[76] An ongoing trial assessing continuous infusion of piperacillin-tazobactam guided by TDM in patients with sepsis should provide needed clarity to this issue.[77]

AVOIDANCE OF UNNECESSARY ANTIBIOTIC ADMINISTRATION

Deescalation of Empiric Antibiotic RegimensAntimicrobial deescalation is a clinical approach to empiric antibiotic therapy of serious infections that attempts to balance the need for appropriate initial therapy with the need to limit unnecessary antimicrobial exposure in order to curtail the emergence of resistance.[78] A deescalation approach usually requires initial combination antimicrobial treatment targeting nonfermenting GNB and MRSA.[79] However, depending on the clinical presentation, patient risk factors, and local epidemiology, other pathogens such as *Candida* species and *Clostridium difficile,* especially when diarrhea is present, may also need to be covered. Once the microbiologic results are available and the patient's clinical response is observed, the antibiotic regimen can be narrowed based on the susceptibilities of the identified pathogens. Our local experience, and that of other groups, bears this out in demonstrating that the administration of appropriate initial antibiotic therapy with subsequent antimicrobial deescalation is associated with improved survival and shorter hospital stays.[80–82] Moreover, local antibiotic deescalation guidelines have been able to successfully limit the use of broad-spectrum antibiotics targeting GNB in patients with skin and skin structure infections, representing an example of antimicrobial stewardship.[83,84]

Computer decision support systems have also been employed to facilitate antimicrobial deescalation practices in the ICU setting. Thursky and colleagues employed a real-time microbiology browser and computerized decision support system for pathogen isolate–directed antibiotic prescription and found significant reductions in the proportion of patients prescribed carbapenems, third-generation

cephalosporins, and vancomycin.[85] Similarly, our hospital has developed an automated decision support system with real-time access to patients' prior antibiotic exposures and microbiologic results.[86] Our experience with this system has shown that the use of inappropriate therapy can be reduced by almost 50% and that access to these data assist in the performance of timely deescalation.[86] Similar outcomes have been achieved using pharmacist-driven diagnostic testing for antimicrobial deescalation in community-acquired pneumonia (CAP).[87] However, the impact of antimicrobial de-escalation as a casual contributor to survival and not simply representing a marker of disease severity is still controversial.[88]

Use of Antibiotic Resistance Prediction Tools

Knowledge of patient risk factors for the presence of infection with antibiotic-resistant pathogens should be a routine part of antibiotic decision making. For example, antibiotic-resistant pathogens are more commonly found in patients with CAP who have healthcare–associated risk factors (recent hospitalization, admission from a nursing home, or recent antibiotic treatment).[89,90] However, a recent meta-analysis found that the current definition employed for healthcare–associated pneumonia (HCAP) did not accurately identify infections attributed to antibiotic-resistant pathogens, providing further support for the use of more specific criteria to make this clinically important determination.[91]

Shindo and colleagues demonstrated that independent risk factors for antibiotic-resistant bacteria occur in patients diagnosed with both CAP and HCAP, including prior hospitalization, immunosuppression, previous antibiotic use, gastric acid–suppressive therapy, tube feeding, and nonambulatory status.[92] Another Japanese study prospectively applied a therapeutic algorithm based on the presence of risk factors for MDR pathogens in a multicenter cohort study of patients with CAP and HCAP.[93] These investigators found that MDR pathogens were more common in patients with HCAP than in those with CAP. Moreover, these same investigators found that using these risks in a unified algorithm allowed antibiotic therapy to be simplified in the majority of patients with CAP.[93]

Potential benefits derived from the use of computerized systems include improvements in the efficiency and costs of existing stewardship programs, improvements in clinicians' knowledge regarding the treatment of infectious diseases, and improvements in pathogen prediction.[94,95] Thiel and colleagues demonstrated that the implementation of a standardized order set for patients with sepsis—that is currently automated and includes orders for antimicrobial therapy—resulted in more appropriate initial antimicrobial therapy and improved clinical outcomes in patients with severe sepsis and bacteremia.[96]

Unfortunately, antibiotic prediction tools can also lead to overuse of broad-spectrum agents. The 2016 Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) updated guidelines for hospital- and ventilator-acquired pneumonia recommend MRSA coverage if the local resistance patterns are unknown or greater than 10%–20% and, similarly, double antimicrobial coverage for *P. aeruginosa* if the local resistance patterns for monotherapy are unknown or greater than 10%.[97] They also incorporated patient-specific risk factors, such as recent intravenous antibiotic administration; need for mechanical ventilation or renal replacement therapy; and even the presence of shock, acute respiratory distress syndrome, or structural lung disease. However, a recent study of 3562 patients with HAP found that the IDSA/ATS guidelines would result in 56% of HAP cases being empirically treated for MRSA, whereas 23% would be treated with antipseudomonal agents even though cultures for MRSA and antibiotic-resistant gram-negative rods were positive in only 5.17% and 2.30% of patients, respectively.[98] Looking forward, new artificial intelligence/machine learning techniques will be iteratively developed so we may move beyond labeling an infection by where it is diagnosed and instead focus on a patient-specific cumulative risk for MDR pathogens, leading to highly tailored empiric therapy and less overuse of broad-spectrum antibiotics.[99]

Biomarker Guidance of Antibiotic Therapy

Procalcitonin has demonstrated utility, especially in the ambulatory setting, in guiding decisions regarding antimicrobial therapy.[55–57] However, not all experiences with procalcitonin-guided decision making have shown reductions in duration of antibiotic exposure.[58,59] A recent comprehensive literature review of procalcitonin-guided antibiotic management in critically ill patients found that the diagnostic value of serum procalcitonin concentrations to discriminate among systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock was unestablished.[100] On the other hand, at least two meta-analyses suggest that procalcitonin guidance can be used to shorten the duration of antimicrobial therapy in the ICU setting.[101,102] The routine use of procalcitonin as an aid in antibiotic decision making should depend on whether a particular ICU has an already established culture of successful antimicrobial deescalation and stewardship.[100]

The serum markers (1,3)-β-D-glucan and galactomannan have been used in identifying pathogens associated with invasive fungal infections to assist clinicians in guiding antifungal therapy. Based on their high negative predictive value in the appropriate clinical setting, the most suitable use of these markers seems to be in excluding the presence of invasive fungal infections.[103,104] However, one study suggests that the use of (1,3)-β-D-glucan is the most rapid method for the identification of intraabdominal candidiasis in order to provide timely therapy in such patients.[105] In addition, an investigation that measured galactomannan levels in bronchoalveolar lavage (BAL) fluid obtained from ICU patients lends support to its use in pathogen identification and early treatment of pulmonary infection.[106] Nonetheless, a more recent study only showed modest agreement between galactomannan in BAL fluid and validated clinical diagnostic criteria for invasive fungal disease.[107] These markers of infection certainly have the potential to enhance stewardship—primarily through deescalation once a fungal infection has been excluded—and future clinical experience with these markers will determine if this potential can be fully realized.[108]

Formalized Antimicrobial Stewardship Programs and Telemedicine

Formally implemented antimicrobial stewardship programs (ASPs) have been associated not only with reduced infection rates but also with significant cost saving associated with reductions in the defined daily doses of antimicrobials targeted by the ASP.[84,109,110] ASPs have been shown to increase the appropriateness of therapy for serious infections such as CAP and to increase the number of infectious disease consultations, which might also dramatically improve patient outcomes, including mortality, hospital length of stay, and rates of readmission by providing a more precise antibiotic prescription.[84,111–113] These attributes of ASPs account for why they are now recognized as mandatory components of hospital quality improvement efforts.

A recently updated meta-analysis of ASPs has solidified the benefits of these quality improvement initiatives.[114] This meta-analysis found that ASPs could significantly result in less antimicrobial usage and reductions in *C. difficile* infections and colonization or infection with

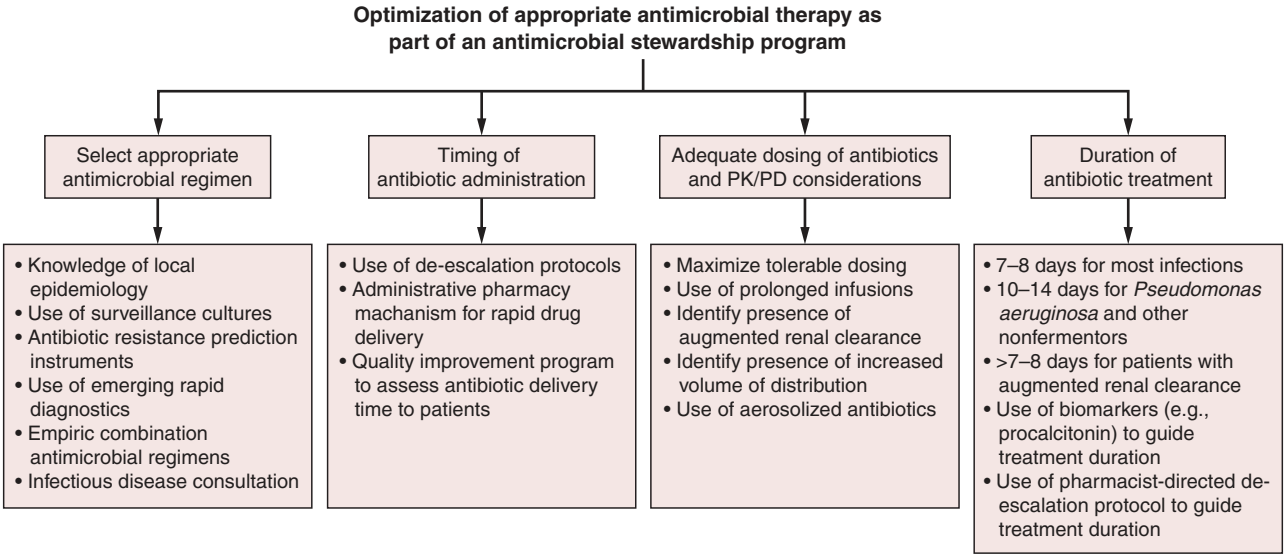

Fig. 105.2 Optimization of appropriate antimicrobial therapy as part of an antimicrobial stewardship program.

antibiotic-resistant bacteria.[114] Additionally, more effective antibiotic prescribing practices for pneumonia because of the presence of an ASP were associated with a significant reduction in mortality, whereas practices aimed at decreasing excessive antibiotic prescribing were not associated with any significant increase in mortality.

Telemedicine is emerging as a feasible strategy for implementing antibiotic stewardship, especially in hospitals lacking infectious disease consultants and preexisting robust stewardship programs.[115–117] Given the increasing complexity of decision making in infectious diseases, advancements in telemedicine will likely drive future use of this strategy for stewardship.[118]

Rapid Microbiologic Diagnostics

Conventional microbiologic procedures typically require several days for isolation, identification, and antimicrobial susceptibility testing of isolated bacteria from clinical samples, including blood, respiratory tract, urine, and sterile site specimens. A number of molecular platforms currently exist for the rapid identification of pathogens and antibiotic susceptibility. These include polymerase chain reaction (PCR), multiplex PCR, matrix-assisted laser desorption-ionization time-of-flight (MALDI-TOF) mass spectrometry (MS), fluorescent in situ hybridization, immunochromatography, nuclear magnetic resonance, and volatile organic compound analysis, with each having specific advantages and disadvantages.[119] Additionally, automated microscopy methods such as the Identification/Antimicrobial Susceptibility Testing (ID/AST) system (Accelerate Diagnostics, Tucson, AZ) have been developed using both genomic and phenotypic technologies to provide pathogen identification and antimicrobial susceptibilities in a rapid manner.[120]

The potential benefit of rapid microbiologic diagnostics (RMDs) on patient outcomes with serious infections is illustrated by several recent studies. Clinical samples from patients with monomicrobial gram-negative bacteremia were tested and compared between the Accelerate Pheno System and standard-of-care methods, including Verigene and Bruker MALDI Biotyper systems for ID and the Vitek 2 system for AST.[121] ID mean time was 21 hours for MALDI-TOF MS, 4.4 hours for Verigene, and 3.7 hours for the Accelerate Pheno System. AST mean time was 35 hours for Vitek 2 and 9.0 hours for the Accelerate Pheno System. If the Accelerate Pheno System results had been available to inform patient care, 25% of patients could have been put on active therapy sooner, whereas 78% of patients who had therapy optimized during hospitalization could have had therapy optimized sooner. These findings are similar to those found at our institution employing similar diagnostic approaches.[122]

CONCLUSION

Although antimicrobial therapy is frequently prescribed, clinicians should realize that these important therapeutic agents should be used wisely. Judicious use of antibiotics serves to combat the emergence of resistance, improve clinical outcomes, and decrease costs. Clinicians should realize the advances that have been made with regard to antimicrobial stewardship and use these tools, and any future advances, to promote improved antimicrobial use. We are currently at a crossroads where antimicrobial stewardship offers us an opportunity to move forward in terms of enhancing the treatment of antibiotic-resistant infections for years to come (Figs. 105.2 and 105.3). ICU clinicians must be leaders in ensuring that their institutions have robust and effective ASPs.[123]

KEY POINTS

- All ICUs should participate in active ASPs directed at optimizing the use of antimicrobials in critically ill patients.
- The ASPs should focus on both optimizing the delivery of antimicrobial agents to infected patients and avoiding the unnecessary use of these agents.
- Optimal antibiotic administration can be achieved by ensuring appropriate selection of drugs, timely administration of antibiotics, adequate dosing of these agents, avoidance of prolonged durations of therapy, and adjustments in delivery of drugs based on the physiology of critically ill patients (e.g., potential use of higher drug doses and/or prolonged infusions in the setting of augmented renal clearance and increased volume of distribution).
- Minimizing the unnecessary use of antibiotics can be achieved with the use of deescalation strategies, use of antibiotic resistance prediction tools or biomarkers, and in the future, rapid diagnostics for pathogen detection and antimicrobial susceptibility.

References for this chapter can be found at expertconsult.com.

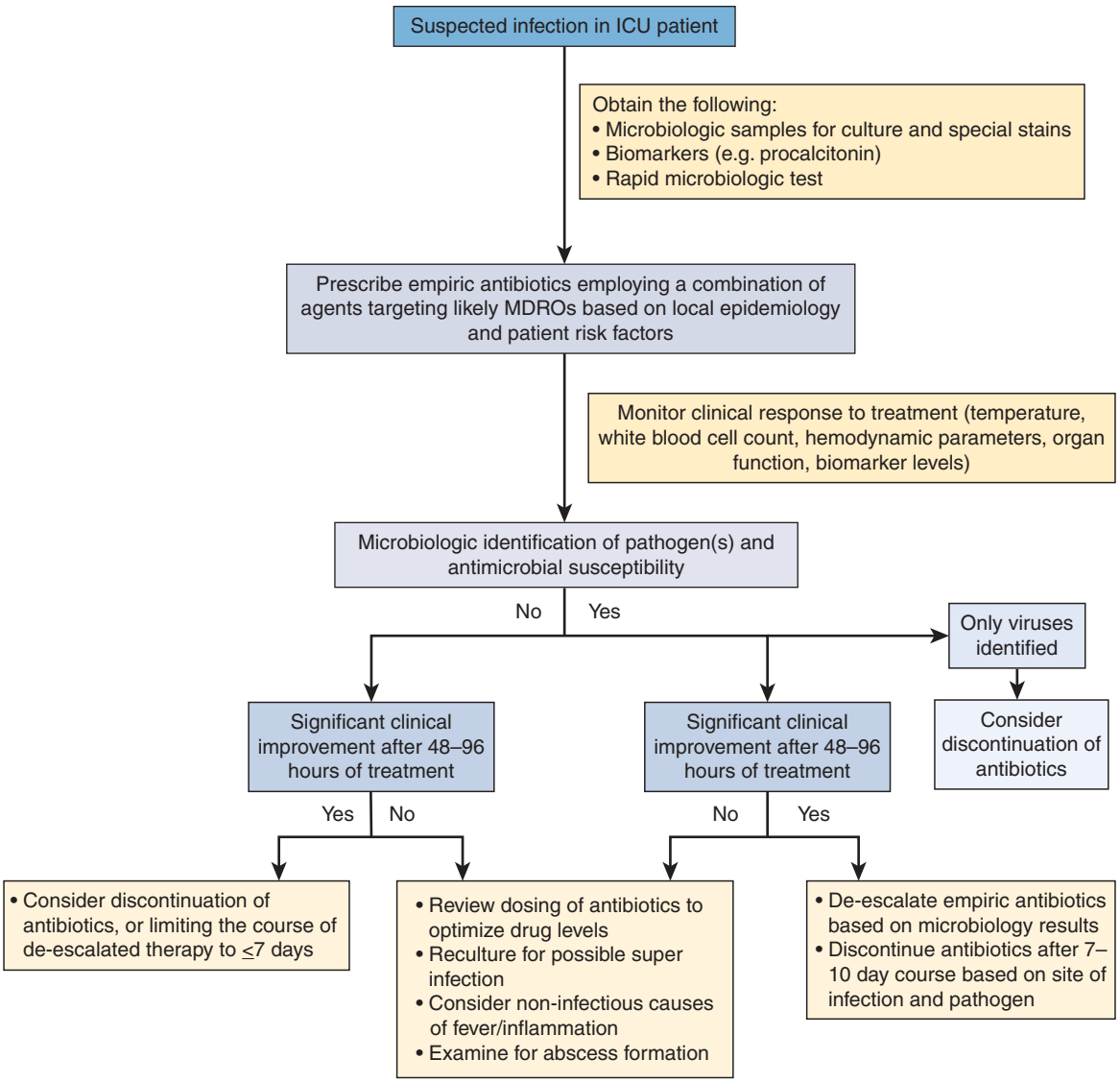

Fig. 105.3 An algorithm for the use of antimicrobial therapy in critically ill patients attempting to balance the need for early appropriate therapy in infected patients with the need to avoid the unnecessary use of broad-spectrum antibiotics.

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Prevention and Control of Nosocomial Pneumonia

Richard G. Wunderink

Pneumonia causes 79% of all infectious deaths in the United States and is a leading cause of death around the world.[1] Although community-acquired pneumonia (CAP) causes most of these deaths, nosocomial pneumonia, both hospital-acquired pneumonia (HAP) in general and the ventilator-associated pneumonia (VAP) subset, remains an important cause of mortality and morbidity in the critically ill.[2] Preventing pneumonia in the critically ill is a daunting task, and even controlling the incidence is difficult. Although complete prevention of nosocomial pneumonia is unlikely,[3] substantial progress has been made.

With a prevalence of 21.8%, pneumonia remains the most common nosocomial infection,[4] including in the intensive care unit (ICU).[5] The incidence varies significantly among different types of ICU patients. Postoperative patients, especially those undergoing cardiothoracic, neurosurgical, and trauma-related surgery, appear to have the highest rates.[6] Coronary care unit patients appear to have the lowest rates; medical, respiratory, and other surgical patients demonstrate intermediate rates.

Despite significant improvements in other important nosocomial infections, the prevalence of nosocomial pneumonia has not decreased.[4] However, prevention strategies discussed in this chapter have substantially changed the clinical presentations of HAP/VAP. VAP rates have decreased as prevention strategies effectively decrease the incidence of early-onset (within 7 days of intubation) VAPs.[7] Conversely, VAP now occurs in a subset of patients who enter a vicious cycle of prolonged ventilation, which increases the risk of pneumonia, leading to further prolongation of ventilation and high risk of recurrent pneumonia. One major factor characterizing these patients is the dramatic increase (from 18.7% to 29.9% over 13 years) in the proportion of pneumonia patients with any immunocompromising condition.[8]

A distinction should be made between prevention of all nosocomial pneumonia and prevention of life-threatening nosocomial pneumonia. Differential effects of prevention strategies have resulted in a shift in the etiology of VAP. For example, methicillin-resistant *Staphylococcus aureus* (MRSA) caused up to 30% of VAPs in the past,[9,10] whereas more recent studies find rates as low as 7%.[10,11] Conversely, the frequency of pneumonia multidrug-resistant (MDR) strains of Enterobacterales has progressively increased for both HAP and VAP. Prevention of HAP/VAP due to *Pseudomonas aeruginosa, Acinetobacter* species, and MDR Enterobacterales, especially carbapenem-resistant Enterobacterales (CRE), is more likely to affect mortality. Unfortunately, the most effective strategies to prevent pneumonia work predominantly or exclusively in early-onset VAP and therefore have not resulted in a significant improvement in mortality. Conversely, one of the most consistent adverse effects of VAP (including early-onset) is a prolonged duration of mechanical ventilation. Because duration of ICU stay is the principal determinant of cost of care, prevention measures may be cost-effective even if they do not result in improved mortality.

The other major shift in nosocomial pneumonia epidemiology in the ICU is that HAP precipitating the need for mechanical ventilation is now more common than VAP.[12] The influence of endotracheal intubation is so dominant that ICU-acquired pneumonia was once considered almost synonymous with VAP. Endotracheal intubation increases the rate of nosocomial pneumonia between 3-fold and 21-fold.[9] HAP associated with mechanical ventilation appears to have an equal risk of MDR pathogens and higher crude mortality rates than VAP.[12,13] Even in the ICU, increased use of noninvasive ventilation and high-flow oxygen delivery results in more HAP patients who are not intubated. Therefore prevention strategies need to be extended outside the ICU and to non-intubated patients to make further progress in preventing overall pneumonia rates and associated morbidity and mortality.

Lack of diagnostic accuracy severely compromises efforts to prevent HAP/VAP.[14,15] Etiologic diagnosis is particularly difficult in patients who are not intubated. Radiographic interpretation is also problematic. The National Nosocomial Infections Surveillance (NNIS) definition of infectious ventilator-associated complication (IVAC), which does not require a chest radiograph in the definition,[15] is neither sensitive nor specific, and VAP prevention strategies to alter the frequency of this entity have been disappointing.[16] Others ignore the need for abnormal chest radiographs and instead combine VAP with a newly defined ventilator-associated tracheobronchitis (VAT).[17–19] Whether VAT is an early stage of VAP and progresses to VAP is still debatable.

PATHOGENESIS

Two keys to prevention and control strategies are a clear understanding of the underlying pathogenesis of nosocomial pneumonia and a comprehensive approach to prevention. The benefit of both is best demonstrated by a study deploying seven interventions to prevent HAP in high-risk patients with an automatically triggered order set in a large integrated healthcare system.[14] These interventions (Table 106.1) were based on the pathogenesis of HAP. Over a 6-year period, HAP rates decreased from 5.9 to 1.79/1000 admissions ($P = 0.003$), with mortality decreasing from 1.05 to 0.34/1000 admissions and highly significant decreases in broad-spectrum antibiotics.

The essence of nosocomial pneumonia pathogenesis involves three basic steps:

1. Colonization of the oropharynx with pathogenic microorganisms
2. Aspiration of oropharyngeal contents into the lower respiratory tract
3. Overwhelming of the lower respiratory tract's host defense mechanisms.

Effective prevention and control measures can be analyzed by their effect on one or more of these steps.

TABLE 106.1 Interventions for High-Risk Patients to Prevent Hospital-Acquired Pneumonia

Aggressive mobilization
Upright posture for meals
Careful swallow evaluation before any feeding
Attention to sedation levels
Elevated head of bed for sleep
Rigorous oral care
Feeding tube care

From Lacerna CC, Patey D, Block L, et al. A successful program preventing nonventilator hospital-acquired pneumonia in a large hospital system. *Infect Control Hosp Epidemiol.* 2020;41(5):547–552.

Despite the simplicity of this paradigm, assumption that the pathogenesis of all types of HAP/VAP is the same would be naive and incorrect. An example is the role of gastric colonization preceding oropharyngeal colonization, the basis for attention to enteral feedings and stress ulcer prophylaxis in VAP prevention. Although possibly important for pneumonia caused by Enterobacterales, gastric and enteric colonization has no role in the pathogenesis of *S. aureus* or *P. aeruginosa* pneumonia, the two common causes of VAP. Conversely, daily chlorhexidine baths did not prevent VAP in a trauma population but did significantly decrease VAP from MRSA.[20] Therefore prevention strategies should be individualized to the patients, pathogens, and mechanisms prevalent in a specific ICU.

COLONIZATION WITH PATHOGENIC MICROORGANISMS

The major antecedent event to most nosocomial pneumonias is colonization of the oropharynx with pathogenic bacteria. The oropharynx is not sterile, but the character of the normal flora is remarkably constant. A variety of factors alter the normal flora, allowing replacement by more pathogenic microorganisms. The importance of the normal flora is illustrated by the adverse effects of iseganan, an antimicrobial peptide active against almost all bacteria.[21] Oropharyngeal application of iseganan did not significantly decrease VAP rates but was associated with a trend for increased mortality.

Time of exposure to these selective forces within the hospital is critical. Early-onset pneumonia, even early-onset VAP, tends to be caused by less pathogenic microorganisms characteristic of CAP such as streptococci, *Hemophilus influenzae,* or methicillin-sensitive *S. aureus*. Most selective forces are introduced in the hospital environment itself, rather than specifically in the ICU. Therefore patients who develop pneumonia during the first few days of ICU admission or mechanical ventilation are at risk for MDR pathogens if preceded by a 3- to 5-day hospital stay. Many of the same factors also operate in skilled-care nursing facilities and lead to the designation of healthcare–associated pneumonia (HCAP). Although this term has been abandoned,[22] the risk factors remain.

Previously, colonization of the oropharynx by gram-negative enteric bacilli, generally from the Enterobacterales order, was emphasized. As part of the normal bowel flora, oropharyngeal colonization occurred by one of two main routes. The first is reflux of bacteria into the stomach from the duodenum, with subsequent gastroesophageal reflux into the esophagus and oropharynx. Colonization and proliferation in the stomach are critical intermediate steps in this pathway. Therefore many prevention strategies logically target the stomach. The other route is self-inoculation by the fecal-oral route, through contamination of equipment or the hands of healthcare providers or the patient.

The pattern with Enterobacterales does not apply to all HAP/VAP pathogens. None of *S. aureus*, *P. aeruginosa*, and *Acinetobacter* species, common causes of VAP, have a typical colonization pattern like that of Enterobacterales. *S. aureus* is a normal colonizer of the skin and the nasopharynx. Antegrade colonization of the oropharynx from the nose, especially with the use of nasogastric tubes in many critically ill patients, can occur quite easily. Lack of nasal colonization, detected on admission screening, effectively excludes MRSA as a cause of HAP/VAP. *Acinetobacter* is found on moist body surfaces and in the gingival crevices of patients with poor oral hygiene. *P. aeruginosa* is usually not part of normal bowel flora but is ubiquitous in the environment. One of the unique aspects of *Pseudomonas* VAP is the appearance of tracheal colonization before oropharyngeal colonization.[23] Because colonization of the stomach is not an important intermediary step for these pathogens, prevention measures directed at the stomach are not likely to affect pneumonia caused by them. Conversely, both MRSA and *Acinetobacter* colonization can be decreased with the use of chlorhexidine whole-body bathing.[20]

Recent data from the lung microbiome have suggested that gram-negative pathogens may potentially cause pneumonia without antecedent oropharyngeal colonization. A gut-specific *Bacteroides* strain was found to be increased in patients with acute respiratory distress syndrome (ARDS) and/or sepsis.[24] This finding may represent hematogenous spread of enteral pathogens to the lung via gut translocation, independent of oropharyngeal colonization, and may explain the association of septic shock and ARDS with the risk of MDR pathogens.[25] Protection of the gastrointestinal (GI) brush border with enteral nutrition or selective decontamination of the digestive tract (SDD) may be more important in some of these patients in addition to those with chemotherapy-induced mucositis.

AVOIDANCE OF ANTIBIOTICS

The single most important factor that leads to colonization of the oropharynx with pathogenic microorganisms is use of systemic antibiotics, especially broad-spectrum, that include coverage of gram-positive pathogens.[26] Antibiotic killing of the usual oropharyngeal flora gives pathogens a selection advantage; at the same time, some pathogens are also eliminated. For this reason, antibiotics function more as amplifying agents rather than as true causes of colonization. The pathogenic microorganisms must still reside in the area normally, such as nasopharyngeal carriage of *S. aureus,* or be transferred from other sites, including the environment to colonize. Thus pneumonia can still occur despite avoidance of antibiotics. However, the causative microorganisms are more likely to be less virulent pathogens or even normal flora, such as alpha-hemolytic streptococci, and less likely to lead to life-threatening pneumonia.

Diagnostic strategies for fever in the ICU that result in the use of fewer antibiotics have been associated with lower mortality.[27] Shorter courses and fewer antibiotics for documented infections in critically ill patients have also been associated with a decreased risk of superinfection.[28–30] Although avoiding antibiotics may have only a small effect on the risk of developing the first episode of pneumonia, limiting their usage has a major effect on secondary pneumonia and infection-related death in the ICU.

Topical Antibacterial Agents

In contrast to systemic antibiotics, the use of topical antibiotics for the prevention of colonization may be beneficial. In general, strategies rely on controlling pathogenic microorganisms at specific sites, despite the

effect on normal flora. Topical agents generally do not have the toxicity of systemic agents, and although the use of topical antibiotics can lead to MDR isolates, the risk may not be as great as with systemic antibiotics.

Selective Digestive Decontamination of the Digestive Tract

By far the most extensively studied and most aggressive form of topical antibiotic strategy to prevent colonization is SDD. Although the specific agents used in different studies vary, the major focus is on controlling oropharyngeal colonization by sterilizing almost the entire GI tract, including the large bowel. SDD is discussed more extensively in Chapter 110.

Topical Oropharyngeal Agents

Controlling colonization of the oropharynx alone has also generated interest because little disruption of the normal bowel flora is expected by treating only the primary area of concern. Oropharyngeal decontamination alone appears to be equivalent to SDD for the prevention of VAP.[31] Chlorhexidine oral rinse has been the most extensively studied.[32] Unfortunately, different concentrations of chlorhexidine have been used and different populations have been compared. The strongest support for efficacy is for the 2% concentration. Chlorhexidine may not be able to prevent infection with MDR pathogens such as *Pseudomonas* and *Acinetobacter*.[33] Oral decontamination with other agents, such as povidone/iodine and antimicrobial peptides,[21] has not demonstrated benefit. Universal decolonization of patients with daily chlorhexidine for 5 days and nasopharyngeal mupirocin demonstrated lower MRSA bacteremia and surgical site infection rates but no effect on pneumonia.[34]

Aerosolized Antibiotics

The earliest studied form of topical colonization prevention was aerosolized antibiotics. In the early era of mechanical ventilation, daily aerosolized polymyxin B resulted in a dramatic decrease in the rate of gram-negative VAP.[35] Not surprisingly, routine use was soon complicated by the emergence of antibiotic-resistant microorganisms. This feature, combined with a lack of mortality benefit, led to abandonment of this strategy. Aerosolized ceftazidime did not decrease VAP rates in trauma patients but did not increase MDR pathogen colonization either.[36] A recent variation of this practice is to use aerosolized antibiotics for purulent tracheobronchitis, thought to be a precursor to VAP.[37]

AVOIDANCE OF INCREASED GASTRIC pH

The normally acidic environment of the gastric lumen is extremely effective in preventing colonization with either swallowed oropharyngeal flora or refluxed enteric flora. Several prevention strategies focus on this aspect of prevention.

Stress Ulcer Prophylaxis

Because GI bleeding from stress ulceration was at one time a substantial problem in ventilated patients and a major cause of death, prophylaxis against stress ulceration was considered critical for ventilated patients. This generated a debate regarding the optimal GI bleeding prophylaxis, which has evolved over the last few decades. Initially, antacids were found to be inferior to histamine-2 blockers (H2 blockers). In addition to increasing gastric pH, antacids increase gastric volume, probably an independent risk factor for VAP. Subsequently sucralfate was hypothesized to be superior to H2 blockers because it did not affect gastric pH and might have intrinsic antibacterial properties. No clear-cut benefit of sucralfate over H2 blockers in reducing VAP was found, whereas a slight but consistent increase in GI bleeding has been documented.[38] Proton pump inhibitors (PPIs) appear equivalent to H2 blockers.[39]

However, the incidence of stress mucosal ulceration has decreased markedly as a result of better hemodynamic resuscitation, improved ventilatory strategies, and earlier use of enteral nutrition. Several multivariate analyses found PPIs associated with increased pneumonia rates, including HAP/VAP,[40,41] HCAP, and even CAP.[42] Based on this concern, the need for stress ulcer prophylaxis at all in most mechanically ventilated patients has been questioned. Multicenter placebo-controlled trials have not found a benefit in either mortality or even GI bleeding, with inconsistent increases in VAP rates.[38,43] Ironically, GI prophylaxis had been encouraged as part of a ventilator/VAP bundle in many institutions. A subgroup of patients at increased risk for GI hemorrhage can be identified, and patients without these high-risk factors may not need prophylaxis.[43,44]

Enteral Nutrition Strategies

Malnutrition is clearly associated with an increased risk of pneumonia and increased mortality in the critically ill. In addition to classic effects on cell-mediated immunity, an effect specific to pneumonia is increased binding of gram-negative bacilli, including *Pseudomonas,* to epithelial cells.[23]

Enteral administration of nutrition is the preferred route for treating and preventing malnutrition in the critically ill, although parenteral nutrition in high-risk patients is preferable to no nutrition.[45] Meta-analysis has suggested that patients can even be fed soon after GI surgery.[46,47] However, continuous enteral nutrition infusions may increase both gastric pH and gastric volume, increasing VAP risk.[48,49] A randomized trial found that the risk of VAP was increased with early aggressive feedings compared with low-level enteral nutrition (approximately 20% of goal feeding rate).[50] The lower rate was chosen to avoid atrophy of the microvilli of the enteric mucosa, potentially avoiding gut translocation. The increased risk of VAP was attributed to an increased risk of aspiration, also seen in a surgical series.[47] However, meta-analysis of early vs. delayed enteral nutrition suggests a mortality benefit and probable decreased risk of VAP with early feedings.[51] A balance between potential risks would be early initiation of enteral feeding but avoidance of high gastric residuals and gastric distention. Neither bolus feedings[52] nor acidification of enteral feedings[53] improved VAP rates but were associated with increased adverse consequences.

MODIFIED ENDOTRACHEAL TUBES

Bacteria can adhere to the polyvinyl chloride surface of endotracheal tubes through secretion of a glycocalyx. Protected from systemic antibiotics and host defense mechanisms, microorganisms in this glycocalyx can become a source of reinoculation of the lower respiratory tract. This mechanism may explain the high recurrent VAP rates, particularly for *Pseudomonas*. A silver-impregnated endotracheal tube demonstrated a lower incidence of VAP and a delay in onset in those that do develop VAP,[54] although cost remains a barrier to routine use.

CROSS-INFECTION

The role of cross-contamination in the ICU should never be underestimated. Cross-contamination can cause colonization with specific pathogenic bacteria in a patient who has no other risk factors for that microorganism. In particular, *P. aeruginosa* and MRSA appear to have the greatest potential to cause cross-contamination and subsequent infection.

By far the most important factor in cross-infection is handwashing among caregivers. Multiple studies document poor infection control

practices of medical personnel, including physicians and bedside nurses. The risk of inadequate handwashing increases with the intensity of care needed for an individual patient and with the number of patients per nurse.[55] Use of an alcohol-based, self-drying hand wash appears to be effective and to increase compliance with handwashing.[56,57] Routine decolonizing also appears to decrease rates of cross-infection.[34]

Avoiding cross-contamination via medical equipment is also important. Contaminated equipment remains a major cause of epidemic outbreaks of nosocomial pneumonia. Any clustering of VAP, especially when caused by an unusual microorganism, should raise this possibility. Respiratory therapy equipment is particularly suspect, and adherence to standards for the sterilization of ventilators, bronchoscopes, and other reusable equipment should be rigorous.

ASPIRATION

The role of aspiration in nosocomial pneumonia is probably the least controversial, although the possibility of hematogenous spread from GI tract to lung has been raised.[24] Aerosolization, the third major mechanism for microbes to gain access to the lung, is rare outside of contaminated respiratory therapy equipment. Evidence from a variety of sources documents the importance of aspiration, although the definition of aspiration may vary.

LARGE-VOLUME ASPIRATION

Large-volume aspiration is clearly a risk factor in nonintubated ICU patients. Although the aspirated material itself may not be infectious, such as enteral feedings, aspiration of a large bolus clearly predisposes to pneumonia. Large-volume aspiration may result in ARDS, which by itself is associated with an increased risk of VAP.[25] Predisposing factors for this type of aspiration are GI, such as protracted vomiting from bowel obstruction or GI bleeding, and neurologic, including seizures, induction of anesthesia, and alcohol intoxication. Two components of the successful HAP prevention program (see Table 106.1) are specifically directed at preventing aspiration.[14]

Appropriate endotracheal intubation is actually a protective factor for this type of aspiration acutely, and tracheostomy may be useful for chronic issues with aspiration. Once large-volume aspiration has occurred, selective use of bronchoscopy to extract solid material that might occlude a bronchus and cause a postobstructive pneumonia is one of the few preventive measures of benefit. Empirical antibiotics, especially prolonged courses, do not clearly prevent pneumonia but do select for more virulent microorganisms.

SMALL-VOLUME ASPIRATION

Aspiration of a smaller volume of secretions is also associated with pneumonia in both intubated and nonintubated patients. Neurologic disease with inability to protect the upper airway is consistently documented as a risk factor for pneumonia. In this situation, aspiration occurs before or in conjunction with endotracheal intubation. The bolus can be either oropharyngeal secretions or gastric secretions. In the former situation, a large inoculum of oropharyngeal flora can reach the lower respiratory tract, and clinical pneumonia usually occurs within 48–72 hours. High levels of amylase in bronchoalveolar lavage (BAL) fluid is a marker of this risk.[58]

Prevention of pneumonia from acute small-volume aspiration is probably best achieved by prophylactic antibiotics. Prospective observational studies have suggested that antibiotics early in the course of mechanical ventilation are associated with a lower incidence of pneumonia.[48,59] However, two prospective, randomized trials of short-course (2 days or less) beta-lactam prophylaxis in patients intubated for nontraumatic coma provide the best evidence.[60,61] In both studies, the incidence of subsequent VAP in the prophylaxis group was decreased by at least 40% compared with the control group that did not receive any antibiotic. These findings have also been independently corroborated by a before/after quality improvement study[62] and the many SDD studies that find decreased pneumonia incidence only if a short course of systemic antibiotics was included with the topical antibiotics. Prophylactic antibiotics are of benefit only in the initial intubation of patients not previously hospitalized for a significant period. Efficacy of the short course is dependent on the fact that the aspirated bolus contains mainly normal oral flora rather than a high concentration of MDR pathogens. Continuing antibiotics for longer courses has no additional benefit.[63]

This prevention strategy seems to contradict the importance of avoiding unnecessary antibiotics discussed earlier. Two aspects of this strategy outweigh the potential downside of increased risk of oropharyngeal colonization with more pathogenic bacteria. First, the antibiotics are continued for 48 hours or less. Second, the 40% lower risk of pneumonia in patients given prophylaxis avoids a subsequent longer course of antibiotics, often with a broader-spectrum agent.

MICROASPIRATION

Microaspiration is by far the most important form of aspiration in endotracheally intubated patients. Oropharyngeal secretions pool above the cuff of the endotracheal tube in most intubated patients. Extremely small volumes of secretions can pass below the cuff during small movements of the endotracheal tube associated with head repositioning, high airway pressures, coughing, and other activities. Up to 45% of patients have abundant aspiration (as documented by measurable pepsin in ≥65% of tracheal aspirates) in the first 48 hours post intubation.[64] Because oropharyngeal secretions contain 10^6–10^{10} bacteria/mL, even 0.1 mL of secretions can present a significant challenge to the host defenses of the lower respiratory tract.

Shorter Duration of Endotracheal Intubation

The risk of VAP is not linear; the greatest risk occurs early, with a 3%/day risk in the first week, 2%/day in the second week, and 1%/day subsequently.[59] In addition, early-onset VAP (within 5–7 days of intubation) has the lowest attributable mortality.[9,65] Therefore the sooner the patient is extubated, the lower the cumulative risk of pneumonia and the lower the risk of lethal nosocomial pneumonia.

The best strategy is avoiding intubation completely. Management of many patients with noninvasive ventilation (NIV) is now standard practice in most ICUs. However, patients who fail NIV appear to have an increased duration of subsequent endotracheal intubation and thus an increased risk of VAP. Careful selection of candidates for NIV and early abandonment in unsuccessful cases are critical to decreasing the pneumonia risk. The use of high-flow nasal cannulas as an alternative to NIV may also decrease the risk of pneumonia and days of ventilation.[66]

Even when patients are intubated, variations in the duration of mechanical ventilation for the same type and severity of critical illness suggest that efforts to shorten this duration are the most viable approach to preventing VAP. Several protocolized strategies have demonstrated a significant benefit,[67] including daily interruption of sedation and daily assessment of ability to wean.[68–71] The overall benefit is partially attributable in part to lower VAP rates, which in turn decrease the duration of ventilation.

The downside of an aggressive extubation strategy is the association between reintubation and a threefold increase in risk of VAP.[72,73] Need for reintubation re-exposes the patient to the risk of small-volume aspiration. In addition, colonization of the oropharyngeal secretions by

more pathogenic bacteria is more likely because of the prior episode of intubation, and short-course antibiotics will not have the same beneficial effect. Therefore although avoiding or shortening the duration of mechanical ventilation is clearly a laudable goal, an increase in the risk of VAP may occur with an overly aggressive approach.

Avoidance of Ventilator Tubing Manipulation

Condensation of exhaled gas in the expiratory limb of the tubing or from humidifiers in the inspiratory limb can become heavily colonized with bacteria. Instillation of this liquid bolus into the patient's airway during manipulation of the tubing or movement of the patient can present a significant bacterial challenge to the lower respiratory tract defenses. The most consistent evidence that ventilator tube manipulation may increase the risk of VAP is that increasing the interval between changes of the ventilator tubing decreases the incidence of VAP. Most institutions no longer change ventilator tubing unless gross contamination is present.

Meta-analysis of randomized controlled trials of heat and moisture exchangers (HMEs) rather than heater-humidifiers suggested a 30% reduction in VAP rates, especially if the patient was ventilated for more than 7 days.[74] Increased rates of endotracheal tube occlusion secondary to inspissated secretions with the use of HMEs and other considerations, especially cost, determine the frequency of their use.

Transporting patients outside the ICU, usually for diagnostic procedures, is also associated with an increased risk of VAP.[73] In a prospective study, 24% of patients requiring transport outside of the ICU developed VAP, compared with only 4% of patients who did not. The need for ventilation by bagging, changing ventilators, moving the patient out of bed, and other aspects of the process all increase the possibility of inadvertent introduction of condensate from the ventilator tubing into the patient. In addition, unintentional extubation is greater when transferring ventilated patients.

Maintenance of Artificial Airway Cuff Pressure

Adequate pressure (generally $\geq$25 cm H_2O) to maintain a seal around the cuff of artificial airways is critical to prevent microaspiration. Maintaining continuous control of tracheal cuff pressure resulted in a decrease in VAP incidence from 22 to 9.7 confirmed cases/1000 ventilator days.[64] Maintenance of cuff pressures may also decrease proximal airway secretions, the hallmark for the diagnosis of VAT.[37] The addition of low levels of positive end-expiratory pressure (PEEP) has been associated with decreased aspiration[75] and risk of VAP,[76] possibly partially because of the greater attention to tracheal cuff pressures required in patients on PEEP. Inattention to tracheal cuff pressure may cancel the benefit of other airway interventions, such as specially designed tubes and continuous aspiration of subglottic secretions.[77]

Modified Endotracheal Tubes

A variety of modifications of the endotracheal tube itself have been designed to decrease microaspiration. Most attempt to minimize the longitudinal folds seen in standard tracheal cuffs by changing either the type of material or the shape of the cuff.[78] No significant difference in VAP rates has been found in tapered versus cylindrical or polyurethane versus polyvinyl chloride cuffs.[79]

An endotracheal tube that allows continuous aspiration of subglottic secretions (CASS) pooled above the endotracheal tube cuff has been the most extensively studied modification. This tube has an extra channel with the lumen on the dorsal surface, just above the level of the inflatable cuff. One clinical practice guideline found the greatest level of evidence for VAP prevention was demonstrated with CASS.[80] Studies of CASS have variably demonstrated lower VAP rates[81,82] but mainly in early-onset VAP. No decrease in VAP caused by MDR microorganisms and no mortality differences have been demonstrated. Consistent with this pattern, the benefit is obviated if the patient receives antibiotics early in the course of mechanical ventilation,[77] similar to the benefit of prophylactic antibiotics in early-onset VAP.[60] Pneumonia can also occur if the system malfunctions, usually a result of plugging of the lumen or low cuff pressures, allowing secretions to drain into the distal trachea rather than collecting above the cuff. These factors and the high cost have limited the use of this modality.

Early Tracheostomy

Tracheostomy has several potential benefits for the prevention of VAP. The glottis is not held open by the endotracheal tube and the vocal cords can be opposed, decreasing the risk of aspiration significantly. The security of a tracheostomy may allow greater mobilization and a greater amount of time spent in the upright position, also decreasing aspiration. Routine tracheostomy may be one explanation for the leveling off of VAP incidence after several weeks of mechanical ventilation. Early reports of an increased risk of pneumonia with tracheostomy were compromised by lack of adjustment for prior duration of mechanical ventilation, inaccurate diagnosis (with some tracheostomy site infections classified as pneumonia), and variable surgical techniques. The benefit of early tracheostomy remains unsettled but likely of greater benefit in patients with brain injury or other serious neurologic insults.[83–85] Technique may also matter, with early tracheostomy performed by the percutaneous dilatational technique more beneficial.[84]

SEMIRECUMBENT POSITIONING

The degree of gastroesophageal reflux is significantly greater in supine patients than in semirecumbent patients.[86] Not only is reflux greater, but bowel flora colonized the oropharynx and bronchial tree in 68% of patients ventilated in the supine position, compared with only 32% in the semirecumbent position. A prospective, randomized trial clearly demonstrated that both clinically suspected and microbiologically confirmed cases of VAP were more common in patients ventilated in the supine position (8% of clinically suspected VAPs versus 34% for semirecumbent).[49] Supine body position (odds ratio 6.8) and enteral nutrition (odds ratio 5.7) were both independent risk factors for VAP, with the highest frequency in patients receiving enteral nutrition in the supine position (14 of 28; 50%).

Avoiding the supine position as much as possible is a simple and effective preventive measure that should be practiced in all ICUs.[80] However, compliance with elevation of the head of the bed to 45 degrees is difficult, and achieving lower degrees of elevation are not associated with decreased VAP rates.[87] Lateral Trendelenburg positioning did not substantially decrease VAP rates,[88] and prone positioning may actually increase rates.[89] Early mobilization of ventilated patients to both sitting upright at the bedside and actual ambulation not only decreases pooling of secretions and microaspiration but also appears to shorten the duration of ventilation.[90]

Avoidance of Gastric Overdistention

Even in a semirecumbent position, many patients still have gastroesophageal reflux and microaspiration when given enteral feedings. The major issue is overdistention of the stomach. The first is use of nasoenteric tubes rather than nasogastric tubes. Although attractive theoretically, meta-analysis of randomized, controlled trials did not show a benefit for VAP prevention by postpyloric feeding compared with gastric feeding.[91] The major limitation is the difficulty in placing postpyloric tubes.

The second strategy is the use of gastric prokinetic agents, such as metoclopramide. An additional benefit of these agents is increased

tone of the lower esophageal sphincter, potentially decreasing the risk of reflux while increasing gastric emptying. Once again, a randomized, controlled trial failed to confirm the benefit of using this agent to decrease the risk of VAP.[39]

OVERWHELMING LOWER RESPIRATORY TRACT HOST DEFENSES

An underappreciated fact regarding nosocomial pneumonia is that despite aspiration of oropharyngeal secretions documented to contain pathogenic bacteria, only a minority of colonized patients actually develop pneumonia. In the classic study of Johanson and colleagues, only 23% of patients with gram-negative colonization of the oropharynx subsequently developed pneumonia.[92] Others have shown that quantitative culture levels of microorganisms equivalent to those found in pneumonia can transiently appear in routine nonbronchoscopic BAL samples without causing clinical VAP.[93] Thus the two steps described earlier—colonization by pathogens and aspiration—are necessary, but not sufficient, causes of nosocomial pneumonia.

The third step in the pathogenesis of nosocomial pneumonia—overwhelming lower respiratory tract defenses—is the least studied or understood. One major reason for this lack of emphasis may be that the causes are heterogeneous and patient dependent, rather than the stereotypical steps of colonization and aspiration. As infection control and patient safety efforts have become more effective, the remaining patients who do develop VAP are likely to have significant defects in host immunity. Patients who develop VAP should generally be considered to have a form of acquired immunosuppression.[94] The more frequent occurrence of other nosocomial infections in patients with VAP supports this concept. In addition, some VAP patients develop multiple separate episodes of VAP,[95] suggesting disproportionate compromise of lower respiratory tract defenses.

Many of the causes of compromised lower respiratory tract defenses are caused by the underlying disease or critical illness precipitating ICU admission and need for mechanical ventilation. However, several risks generic to most ICU patients may be targets for prevention.

MINIMIZING ANTIBIOTIC USE

Rather than being sterile, lung alveoli harbor a normal bacterial flora. This recognition raises important issues in understanding the development of HAP/VAP. The normal lung microbiome is similar to that of the normal oropharynx, predominantly streptococci, but also anaerobes, *Hemophilus,* and *Mycoplasma,* but at significantly lower concentrations.[96,97] These normal flora therefore represent an important component of host defense adversely affected by systemic antibiotics, similar to the oropharynx and the GI tract. *Pseudomonas* pneumonia is virtually never seen without prior antibiotic exposure and develops with progressive monolithic replacement of the normal heterogeneous lung microbiome in response to antibiotic pressure.[98] Minimizing the effect of antibiotics on VAP may occur with enteral probiotics,[99] but lung-specific therapy is not available. Consistently, diagnostic strategies for VAP that result in less antibiotic treatment[27,30] and earlier discontinuation in culture-negative patients[100] have resulted in improved mortality and less superinfection.

CORTICOSTEROIDS

Systemic corticosteroids have well-documented antiinflammatory effects that can influence immune function. The difficulty in determining the effect of corticosteroids on the risk of VAP is the competing beneficial effect on other risk factors for VAP. An example is the use of corticosteroids may allow earlier extubation of a patient intubated for an exacerbation of asthma, thereby lowering the risk of VAP. This dual effect probably holds true for most cases in which corticosteroids are used acutely for critically ill patients. The potential benefits begin to be outweighed by adverse consequences after more prolonged courses.

TRANSFUSIONS

A common cause of immunosuppression is red blood cell transfusions. This effect of transfusions has been known for decades and was used therapeutically in the past for pre-transplantation management of patients with end-stage renal disease. The trigger for red blood cell transfusion varies widely among institutions and even among individual practitioners. A more restrictive transfusion policy may avoid compromising host immunity. A conservative transfusion policy was associated with equivalent mortality to more liberal transfusions in most ICU patients[101] and decreased VAP rates in trauma patients.[102]

KEY POINTS

- Two keys to prevention and control strategies are a clear understanding of the underlying pathogenesis of nosocomial pneumonia and a comprehensive approach to prevention.
- A distinction should be made between the prevention of all nosocomial pneumonia and the prevention of life-threatening nosocomial pneumonia, usually caused by MDR pathogens.
- Pathogenesis of nosocomial pneumonia can be broken down into three basic steps: colonization of the oropharynx with pathogenic microorganisms, aspiration, and overwhelming of the lower respiratory tract's host defense processes.
- The most important factor in colonization of the oropharynx with pathogenic microorganisms and compromise of distal lung defenses is the suppression of normal flora at these sites by systemic antibiotics, especially broad-spectrum antibiotics.
- The risk of VAP is time dependent, so any maneuver that decreases the duration of mechanical ventilation will decrease pneumonia rates.
- Avoiding the supine position as much as possible in ventilated patients and maintaining adequate tracheal cuff pressure are simple and effective measures to prevent microaspiration and should be practiced in all ICUs.
- Causes of the relative immunocompromise that allows bacteria to overwhelm local host defenses in the lung are heterogeneous and patient dependent, unlike the stereotypical steps of colonization and aspiration.

References for this chapter can be found at expertconsult.com.

ANNOTATED REFERENCES

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Antimicrobial Agents With Primary Activity Against Gram-Negative Bacteria

Michael S. Niederman, Despoina Koulenti, and Jeffrey Lipman

Gram-negative bacteria are ubiquitous microorganisms of particular concern, especially the gram-negative bacilli (GNB), because of the fast spread of multidrug resistance (MDR). GNBs have intrinsic abilities to find new pathways of resistance and to transmit genetic material that allows other bacteria to become resistant as well (i.e., resistance acquisition via horizontal gene transfer). Mutations lead to new phenotypes with modified antibiotic targets, such as ribosomal mutation, whereas genes encoding drug efflux permeases and genes encoding antibiotic-modifying enzymes, such as beta-lactamases, are most often acquired via horizontal transfer.[1,2] Specifically, the development of extended-spectrum beta-lactamases that confer resistance to penicillins and cephalosporins and of carbapenemases that confer resistance to carbapenems, as well, is considered of critical importance. It is noteworthy that in the World Health Organization (WHO) priority list, all the critical priority (Priority 1) microorganisms are gram-negative—carbapenem-resistant *Acinetobacter baumanni* (CRAB), carbapenem-resistant *Pseudomonas aeruginosa*, third-generation cephalosporin-resistant and carbapenem-resistant *Enterobacteriaceae* (CRE); the vast majority of the high-priority ones (Priority 2).[3]

In the intensive care setting GNBs are responsible for multiple infections, such as bloodstream infections, ventilator-associated pneumonia (VAP), device-associated infections, intraabdominal infections (IAIs), urinary tract infections (UTIs), and soft tissue infections. MDR GNBs represent a healthcare burden and are associated with poor outcomes (i.e., increased morbidity and mortality).[4] The antimicrobial agents most commonly used in the intensive care unit (ICU) to combat MDR GNBs include beta-lactams, fluoroquinolones, aminoglycosides, polymyxins, and newly introduced tetracyclines.

It should be highlighted that several reports have demonstrated suboptimal concentrations of antimicrobial agents in critically ill patients when conventional dosing schemes were used.[5] Therefore during the last decade, apart from the efforts to develop new antimicrobial agents, research has focused on optimization of the use of the currently available antimicrobial agents in the critical care setting, aiming for both improvement of clinical outcomes and limiting resistance emergence.[6,7] For dose optimization, alternative dosing schemes have been recommended, based on the pharmacokinetic and pharmacodynamic (PK/PD) characteristics of the antimicrobial agents and dosing individualization. For dosing individualization, nomograms validated in critically ill patients and dosing software can be used; however, therapeutic drug monitoring (TDM)–guided dosing is recommended as the safer and more effective means to achieve optimal antimicrobial exposures.[7–11]

In this chapter we summarize the characteristics of the classes of antimicrobial agents used in the critical care setting for GNBs, including "older" antimicrobial agents that have been "reintroduced" as salvage treatments, and introduce novel approved antimicrobial agents.

BETA-LACTAMS

Beta-lactams include penicillins, cephalosporins, carbapenems, and monobactams. They share a four-membered beta-lactam ring. Aztreonam is a monobactam that contains only the beta-lactam ring. In penicillins, the beta-lactam ring is connected to a five-membered thiazolidine ring and a side chain that distinguishes the different penicillins; in cephalosporins, it is connected to a six-membered sulfur-containing dihydrothiazine ring and two side chains that distinguish the different cephalosporins, whereas in carbapenems, the beta-lactam ring is connected to a five-membered thiazolidine ring that contains a carbon double bond instead of sulfur, and a side chain differentiates the different members of the class.[12]

Mode of Action of Beta-Lactams

Beta-lactams exert bactericidal action by inhibition of the synthesis of the peptidoglycan layer of the cell wall: via acylation of penicillin-binding protein transpeptidase enzymes (PBPs), they inhibit the cross-linkage of the peptidoglycan chains with subsequent bacteriolysis and cell death.[13–15] The efficacy of a beta-lactam antimicrobial agent is determined, at least in part, by its ability to reach the target PBPs and its binding affinity to various PBPs.[13–16]

Resistance to Beta-Lactams

Resistance to beta-lactams occurs via (1) PBP modifications that decrease their binding affinity (mainly in gram-positive bacteria), (2) loss or deficiency of outer membrane proteins that decrease permeability (in gram-negative bacteria), (3) presence of efflux pumps that force out the beta-lactams, and (4) hydrolysis by beta-lactamases (chromosomally encoded or via plasmids or transposons).[17–20] Beta-lactamase production is the most common mechanism of beta-lactam resistance in clinically important gram-negative bacteria and is largely responsible for GNB resistance in hospitals and, particularly, in the critical care setting.[20] Beta-lactamases are mainly classified either based on their molecular structure (i.e., their amino acid sequence) or based on their function.[21–23] Molecular classification is the simplest and least controversial approach, whereby beta-lactamases are divided into four classes, A, B, C, and D (Ambler classification).[21] The hydrolysis of the classes A, C, and D is done though an active-site serine, whereas class B includes metalloenzymes that hydrolyze beta-lactam through at least one active-site zinc.[21] The functional classification, on the other hand, relates the varied beta-lactamases to their clinical role and classifies

them in three groups with several subgroups.[22,23] Group 1 are cephalosporinases belonging to class C of molecular classification (including the AmpC beta-lactamases) that inactivate most cephalosporins and aztreonam and are not inhibited by clavulanate or tazobactam, and, moreover, in the case of large production, particularly in hosts with decreased beta-lactam accumulation, can inactivate carbapenems, especially ertapenem.[22,24–26] Group 2 are serine beta-lactamases belonging to molecular classes A and D and represent the largest group, as they include the extended-spectrum beta-lactamases (ESBLs) that hydrolyze third-generation cephalosporins and aztreonam (subgroup 2be), found in GNBs, particularly *Enterobacteriaceae.*[22,23] ESBLs are another beta-lactamase of particular concern, as the number of nosocomial infection outbreaks caused by ESBL-producing GNBs is high and ever increasing, and in many parts of the world ESBL-producing strains are endemic.[22,27–33] Group 3 are metallo-beta-lactamases (MBLs), a unique group both structurally and functionally, with the ability to hydrolyze carbapenems (although some serine beta-lactamases have also acquired this ability); the imipenemase (IMP) and Verona integron metallo beta-lactamase (VIM) that have appeared globally, mainly in lactose nonfermenting GNBs but also in *Enterobacteriaceae*, belong to this group.[22,23,34] Contrary to the serine beta-lactamases, MBLs have poor hydrolytic capability for monobactams and are not inhibited by clavulanic acid or tazobactam.[22,23] Functional classification is more subjective than the molecular one; nevertheless, it correlates the properties of a specific beta-lactamase with the microbiologic resistance profile for an isolate that is more useful in the medical setting.[22,23] Finally, regarding resistance to beta-lactams, it should be emphasized that although ESBL- and AmpC- producing GNBs are susceptible to carbapenems, carbapenemase-producing strains have been rapidly increasing worldwide (and are already endemic in several countries) and represent a serious public health threat, as these strains generally display MDR, including all beta-lactams and aminoglycosides and fluoroquinolones.[35–37]

Spectrum of Activity of Beta-Lactams

Beta-lactam antimicrobial agents have a wide spectrum of activity against gram-positive and gram-negative aerobic and anaerobic bacteria. However, each individual class of beta-lactams has a unique microbiologic spectrum. Natural penicillins are seldom used in critical care settings because they lack activity against beta-lactamase–producing bacteria. The class of cephalosporins is categorized into five generations depending on their temporal discovery and their spectrum of activity.[38] The first- and second-generation cephalosporins generally have only limited use in the critical care setting. Third-generation cephalosporins include the parenterally administered cefotaxime, ceftazidime, cefoperazone, ceftizoxime, and ceftriaxone.[39] They provide a broad coverage of gram-negative bacteria, with expanded activity against the *Enterobacteriaceae* and *Streptococcus pneumoniae* but lack activity against enterococci, methicillin-resistant *Staphylococcus aureus* (MRSA), *Listeria monocytogenes, Stenotrophomonas maltophilia*, and many *Acinetobacter* spp. Based on their antipseudomonal activity, cefoperazone and ceftazidime have clinically useful potency against *P. aeruginosa.* Third-generation cephalosporins can be hydrolyzed by ESBL-producing GNBs. The fourth-generation cephalosporins, cefpirome (not available in the United States) and cefepime, have improved penetration to the outer membrane of gram-negative bacteria because of an additional quaternary ammonium group.[15] Their spectrum is the widest of all cephalosporins: against gram-negative bacteria, their activity is similar to ceftazidime, but they are less susceptible to inactivation by AmpC beta-lactamases, whereas against gram-positives, they have activity similar to cefotaxime and ceftriaxone.[15,38,40] Resistance to fourth-generation cephalosporins is increasing, and they can be inactivated by many new ESBLs and carbapenemases.[15] Moreover, therapy for infections by ESBL-producing strains with maintained susceptible minimum inhibitory concentrations (MICs) is controversial.[15,41] Both third-generation (especially ceftriaxone and cefotaxime) and fourth-generation cephalosporins penetrate the blood-brain barrier.[15,38]

Ceftaroline and ceftobiprole are considered fifth-generation cephalosporins and are the first ones with anti-MRSA activity. Their activity against gram-negative bacteria corresponds to that of the third-generation cephalosporins (i.e., they are hydrolyzed by ESBL and AmpC beta-lactamases).[42,43] Ceftaroline was approved by the Food and Drug Administration (FDA) in 2010 and by the European Medicines Agency (EMA) in 2012 for the indication of community-acquired pneumonia (CAP) and complicated skin and soft tissue infections (cSSSIs).[44–46] Ceftobiprole has been approved in several European countries and in Canada for the treatment of CAP and hospital-acquired pneumonia (HAP), excluding VAP, but is not approved in the United States.[43,44] For further details on the anti-MRSA cephalosporins, ceftaroline and ceftobiprole, we refer the reader to the relevant chapter (i.e., antimicrobial agents against gram-positive bacteria).

The carbapenems are the broadest-spectrum beta-lactams and are typically reserved for severe nosocomial infections. Imipenem is degraded by the enzyme dehydropeptidase-1 (DHP-1) of the renal tubules and is combined with cilastatin, a DHP-1 inhibitor, whereas meropenem, doripenem, and ertapenem have increased stability towards the action of DHP-1.[47] Carbapenems have a broad spectrum of in vitro activity, covering gram-positive bacteria, excluding MRSA and *Enterococcus faecium,* and gram-negative bacteria, excluding *S. maltophilia*, and anaerobes. Imipenem/cilastatin and meropenem are typically reserved for severe nosocomial infections, having established efficacy in the treatment of a variety of infections, including complicated UTIs (cUTIs; including pyelonephritis), complicated IAIs (cIAIs), SSSIs, CAP, nosocomial pneumonia (including VAP), meningitis (meropenem only), and febrile neutropenia.[47] In general, doripenem has been demonstrated to have better in vitro activity than imipenem and similar or slightly better activity than meropenem against *P. aeruginosa.*[48] However, its clinical use is more limited compared with meropenem and imipenem, as its approved indications include cIAIs and cUTIs (including pyelonephritis) only, whereas there is a labeling warning for increased risk of death for VAP patients.[49,50] Ertapenem's spectrum of activity is less wide compared with imipenem, meropenem, and doripenem, as it is inactive against important lactose nonfermenting GNBs, including *P. aeruginosa* and *A. baumannii*, in addition to against Enterococci, and it is more suited for community-acquired than for nosocomial infections. Because of its favorable pharmacokinetic properties, it is also suitable for outpatient intravenous (IV) antimicrobial treatment.[47] Carbapenems are stable against ESBL and AmpC beta-lactamase–producing GNBs but are susceptible to carbapenemases and MBLs.[51,52]

Aztreonam is a monobactam with broad aerobic gram-negative activity, but it lacks efficacy against gram-positive bacteria and anaerobes.[14]

Combination of Beta-Lactams with Beta-Lactamase Inhibitors

One strategy for achieving beta-lactamase stability is combining beta-lactams with beta-lactamase inhibitors, such as clavulanate, sulbactam, and tazobactam and, more recently, with novel inhibitors such as avibactam, vaborbactam, relebactam, zidebactam, nacubactam, and taniborbactam.[53] Although beta-lactamase inhibitors lack antibacterial activity at clinically relevant concentrations, they preserve and enhance the antibacterial activity of the partner beta-lactam against beta-lactamase–producing pathogens. For the co-formulation of a

beta-lactam/beta-lactamase inhibitor, two main factors are taken into consideration, namely the activity of the inhibitor against the beta-lactamases that the partner beta-lactam is susceptible to and the similarities in the PK properties between the partners to warrant structural integrity protection of the beta-lactam throughout a given dosing interval.[53] Ampicillin/sulbactam is active against gram-positive bacteria, including *Enterococcus* spp., gram-negative cocci, and certain strains of *Enterobacteriaceae* (not ESBL-producing ones).[54–56] Ticarcillin/clavulanate and piperacillin/tazobactam have a broader spectrum of activity, including *P. aeruginosa, Enterobacteriaceae,* and several anaerobes. Piperacillin has better antipseudomonal activity than ticarcillin.[57,58] However, the resistance rates of *P. aeruginosa* to piperacillin/tazobactam in the ICU are significantly increasing worldwide, necessitating optimization of drug exposure or combination therapy to ensure the efficacy against it.[59–62]

PK/PD of Beta-Lactams

Beta-lactam antibacterial agents are generally hydrophilic, with a low volume of distribution (V_d) similar to the extracellular fluid, and the main route of elimination is the kidneys (although in piperacillin/tazobactam, biliary excretion may be important, and ceftriaxone has significant biliary excretion as well).[63] Frequent physiologic alterations in critically ill patients, such as increased V_d because of sepsis and/or fluid resuscitation and augmented renal clearance (increased glomerular filtration rates [GFR], lead to inadequate (subtherapeutic) concentrations of beta-lactams.[64,65] On the other hand, acute renal injury may lead to higher plasma concentrations and increased toxicity. The protein binding of beta-lactams is moderate (30%–50%) to low (<30%); however, they are members of a class with high protein binding, which includes ertapenem (~95%), ceftriaxone, flucloxacillin, and oxacillin. For these agents, the hypoalbuminemia that is common in critical illness may lead to low unbound concentrations towards the end of the dosing interval, because of the higher clearance of the (increased) free fraction.[8,66] The in vivo half-lives of beta-lactams vary.[38,47]

Beta-lactams are time-dependent killing antibiotics; the PK/PD index associated with optimal beta-lactam activity is the percentage of time that the free serum concentration is above the pathogen MIC (% *f*T>MIC).[8] Data from critically ill patients suggest that longer beta-lactam exposures (e.g., 100% fT>MIC) and higher concentrations (e.g., 2–5 × MIC) than previously described may be beneficial with maximal killing effect and suppressed bacterial resistance.[8,67–70] Finally, a recent analysis of pooled data of critically ill patients with monomicrobial gram-negative bloodstream infections reported that beta-lactam fCmin/MIC >1.3 was a significant predictor of a positive clinical outcome and recommended it as an antibiotic dosing target.[71]

Dosing and Monitoring of Beta-Lactams

As mentioned earlier, because of the physiologic alterations of critically ill patients, conventional antibiotic dosing of beta-lactams antimicrobial agents may lead to subtherapeutic concentrations.[72,73] A recent position paper on TDM of antimicrobial agents in critical care recommended an initial loading dose of beta-lactams followed by prolonged infusion, continuous or extended (3–4 hours), in order to maximize PK/PD target attainment and possibly improve clinical outcomes.[8] The panel recommended routine TDM of beta-lactams to optimize dosing of critically ill patients, achieving therapeutic targets in the critically ill populations, and at the same time, minimizing toxicity. For continuous administration, samples can be taken any time point during the infusion (with target Css>MIC).[8] For intermittent administration, minimum concentration (*Cmin*) should be monitored (with target 100% fT>MIC); sampling should occur 24–48 hours after treatment initiations, with one sample taken 30 minutes before or just before the administration of the following dose.[8]

Prolonged dosing of beta-lactams. Some evidence exists that suggests better outcomes are achieved with prolonged administration of beta-lactams (i.e., continuous or extended 3-hour IV infusions) compared with the standard intermittent administration, especially for critically ill patients with infections by resistant GNBs.[74–78] Although results from randomized controlled trials (RCTs) are controversial, a meta-analysis of three RCTs comparing continuous with standard intermittent bolus administration of beta-lactam antibiotics in septic critically ill patients found decreased hospital mortality with continuous beta-lactam administration, but no difference in clinical cure rates.[79] BLING III is an ongoing, prospective, international phase III RCT with a recruitment target of 7000 critically ill patients with sepsis, which compares continuous with intermittent administration of beta-lactams (piperacillin-tazobactam or meropenem), aiming to provide evidence to support one method of administration over the other.[80]

Synergy of Beta-Lactams in Combination with other Antimicrobials

Synergy (i.e., effect of a combination greater than expected based on individual antimicrobial agents) is frequently reported with the combination of a cell wall–active antimicrobial, such as a beta-lactam, with other agents, most commonly, an aminoglycoside or a fluoroquinolone, even against pathogens with higher MICs. Several studies have demonstrated survival benefit from early administration of such a combination therapy in patients with sepsis and septic shock.[81–83] Other studies have not shown benefit from a combination, such as an RCT in patients with septic shock in a country with a quite low level of MDRs, which failed to demonstrate a decrease in organ failure when fluoroquinolones were added to carbapenems.[84] Nevertheless, it should be noted that for the empiric management of septic shock, the Surviving Sepsis Campaign guidelines suggest the empiric combination of at least two antibiotics of different antimicrobial classes, targeting the most likely potential pathogens, noting that the recommendation is weak and the quality of evidence low.[85,86]

Adverse Events of Beta-Lactams

Beta-lactams are the most commonly reported antibiotic classes to cause allergic drug reactions, especially penicillins (~10%) and cephalosporins (less than penicillins; 1%–7%), whereas the incidence of allergic reactions caused by carbapenems is lower (<3% in the general population).[12,14,87,88] Immediate hypersensitivity reactions are immunoglobulin E (IgE)–mediated and usually occur within 6 hours (typically within 1 hour) from last drug administration, whereas the nonimmediate hypersensitivity reactions are mediated by the T cells and may occur any time after the first drug administration, typically after several days of treatment.[89] Immediate reactions usually present with symptoms and signs from the skin (e.g., itching, rash, angioedema), the upper and lower respiratory system (e.g., sneezing, nasal congestion, hoarseness, wheezing), the gastrointestinal system (e.g., mild abdominal pain, nausea, diarrhea), and the cardiovascular system (e.g., tachycardia, hypotension); they can appear isolated or in combination as severe anaphylaxis. Nonimmediate hypersensitivity reactions are most commonly manifested with maculopapular exanthema and urticaria.[12]

Penicillins can cause gastrointestinal disturbances, particularly diarrhea, but hematologic toxicity is rare.[13,90] Also, high doses of penicillins cause abnormalities of platelet aggregation, while Coombs-positive hemolytic anemia is a rare adverse event.[13,91,92] Renal toxicity of penicillins varies and can range from allergic angiitis to interstitial nephritis.[93]

Cephalosporins have low toxicity and are generally safe and well tolerated.[38] The most frequent adverse reactions of cephalosporins include nausea, vomiting, lack of appetite, and abdominal pain.[38] Less common reactions include hypersensitivity reactions, drug-induced immune hemolytic anemia, pseudomembranous colitis, disulfiram-like reactions, vitamin K deficiency, and enhancement of the nephrotoxicity of aminoglycosides.[38]

Carbapenems are generally well-tolerated. The most common adverse events include gastrointestinal disturbances, such as nausea, vomiting and diarrhea, headache, dermatologic reactions such as rash, and injection site effects such as phlebitis.[14] As carbapenems have minimal hepatic metabolism, clinically significant hepatotoxicity is rare, although mild-to-moderate asymptomatic increases in serum aminotransferases may occur, but rapidly resolve after drug discontinuation.[94] Also, carbapenems are considered to have low propensity for nephrotoxicity, coagulation disorders, and *Clostridium difficile* diarrhea.[14] Seizures are the most serious adverse event, particularly for imipenem (1%–2% compared with 0.1%–0.3% for the other carbapenems), especially when higher doses are used (≥4 g/day).[95,96] Although seizures are overall rare, the incidence increases in cases with renal impairment, lower body weight, and history of seizures or other central nervous system (CNS) comorbidities.[96–98] Carbapenems do not have significant drug interactions, although concomitant administration with valproic acid may lead to subtherapeutic levels of valproic acid.[99]

Aztreonam is generally well tolerated, with more common adverse events including infusion site reactions such as phlebitis, gastrointestinal disturbances (nausea, vomiting, and diarrhea), and rash.[14]

It should be noted that the more aggressive beta-lactam dosing to account for altered drug PK in critically ill patients might have led to excessive drug exposure being increasingly reported over the last decade.[8] TDM of beta-lactams, apart from helping to optimize exposures, can help in decreasing related toxicities.[8] C_{min} samples at steady state, or even earlier when dosing software is used, can help avoid overexposure to beta-lactams.[10,100]

Cross-reactivity of beta-lactams. Although subjects can be sensitized by any of the beta-lactam's components, the side chains are those structures that have the main contribution to immunologic recognition and therefore cause cross-reactivity among beta-lactam antibiotics.[12] The immunologic cross-reactivity related to the common β-lactam ring (i.e., cross-reactivity between all beta-lactams) is very rare, especially in subjects with T-cell–mediated allergy.[12] If a complete allergy workup cannot be performed and there is an urgent need to use a beta-lactam, the evaluation can be done with skin tests with beta-lactam agents that do not share identical/similar side chains with the culprit agent; in case of negative results, the alternative beta-lactam can be administered with graded challenges. In case of patients with history of mild, nonimmediate beta-lactam hypersensitivity reaction and no time available for delayed pretreatment skin test reading, the administration of a full dose of a beta-lactam structurally unrelated to the culprit is an option.[12]

Novel Approved Beta-Lactamase/Beta-Lactamase Inhibitor Combinations

Ceftolozane/Tazobactam

Ceftolozane/tazobactam is a combination of the novel oxyimino-aminothiazolyl cephalosporin ceftolozane with the irreversible beta-lactamase inhibitor tazobactam.[101,102] It was approved in 2014 by the FDA for the indication of cUTIs and for cIAIs in combination with metronidazole, whereas EMA approval was granted in 2015 for cIAIs, acute pyelonephritis, and cUTIs.[43,103] In 2019 the EMA approved ceftolozane/tazobactam for the indication of HAP/VAP as well.[43,103]

Mode of Action, Spectrum of Activity, and Resistance Mechanisms. Ceftolozane/tazobactam is active mostly against gram-negative pathogens, including *Enterobacteriaceae* and *P. aeruginosa,* whereas its activity against gram-positive pathogens and anaerobes is very limited.[104,105] Ceftolozane's MIC against *P. aeruginosa* is 9–16 times lower than the MICs of ceftazidime, imipenem, and ciprofloxacin, having also an earlier in vitro and a faster in vivo killing than ceftazidime.[101] Nevertheless, it is still vulnerable to the action of Ambler class A (e.g., ESBLs) and class C beta-lactamases (although the stability to AmpC enzymes varies).[101] Although tazobactam seems to add little to the antipseudomonal activity of ceftolozane, this addition does provide ceftolozane stability against several class A and C enzymes produced by other GNBs and thus increases ceftolozane's coverage, including several ESBL-producing strains, particularly of the CTX-M family, and in part strains producing AmpC.[15,106] Ceftolozane/tazobactam does not have appreciable activity against GNBs producing *Klebsiella pneumoniae* carbapenemases (KPCs) or MBLs or class D beta-lactamases (e.g., OXA-carbapenemases).[107,108] Resistance mechanisms to the action of ceftolozane/tazobactam include production of class A beta-lactamases (some of ESBLs and most of KPCs), class B MBLs, class D carbapenemases (OXA-48-like), and hyperproduction of AmpC (not in *P. aeruginosa*).[43,53]

PK/PD. Ceftolozane/tazobactam has dose-independent linear PKs and has a relatively short half-life of 2.7 hours in healthy, uninfected adults, without significant accumulation after multiple doses.[109] The protein binding of ceftolozane/tazobactam is low (16%–21% for ceftolozane and 30% for tazobactam).[110] It is renally cleared with minimal metabolism, and the clearance of tazobactam is not affected by the combination with ceftolozane. Both ceftolozane and tazobactam penetrated well into the lung parenchyma, with the epithelial lining fluid (ELF) to plasma area under the inhibitory curve (AUC) ratio of 48% and 44%, respectively.[111,112]

Clinical efficacy. In a phase II RCT (NCT01147640) that compared ceftolozane/tazobactam in combination with metronidazole with meropenem in cIAIs, the microbiologic success was 100% against *P. aeruginosa* (100%), and *K. pneumoniae* and 89.5% against *Escherichia coli* (89.5%).[113] In a phase III RCT (NCT01345929) in patients with cUTIs, superiority was demonstrated for ceftolozane/tazobactam compared with levofloxacin, with microbiologic eradication at test-of-cure (TOC) 88.9% and 74.4%, respectively.[43,114] ASPECT-NP, a double-blind phase III RCT (NCT02070757) that compared ceftolozane/tazobactam with meropenem (3 g ceftolozane/tazobactam versus 1 g meropenem IV every 8 hours for 8–14 days) in patients with gram-negative nosocomial pneumonia (VAP or ventilated HAP) demonstrated noninferiority of ceftolozane/tazobactam on both clinical cure at TOC and mortality at day 28.[115] It is noteworthy that based on the ELF/plasma ratio, the dose used in the ASPECT-NP trial is double the dose used for cIAIs and cUTIs.[115,116] Regarding resistance development, in the ceftolozane/tazobactam arm of a phase III RCT, no emergence of nonsusceptibility was reported for any participant with susceptible *P. aeruginosa* at baseline.[115,117]

Dosage. See Table 107.1 for dosages.[118–121] The recommended duration of treatment is 7 days for cUTIs, including acute pyelonephritis; 4–14 days for cIAIs; and 8–14 days for HAP/VAP.[121]

Adverse events. Mild to moderate nausea, headache, constipation, diarrhea, and pyrexia were the most common (≥3%) adverse reactions in pooled phase III RCTs of cUTIs and cIAIs.[122] There are warnings related to decreased efficacy in a subgroup of patients with baseline CrCl of 30–50 mL/min, serious anaphylactic reactions in patients with hypersensitivity to beta-lactams, and *C. difficille*–associated diarrhea.[121]

TABLE 107.1 Recommended Adult Dosing Regimens and Dosing Alterations*

Antimicrobial Agents	Adult Dose§§	Dosing Alteration (Renal or Hepatic Impairment)
B-Lactams ±		
Ampicillin/ sulbactam	1.5–3 g q6h *Note: Off-label doses of 24 g have been suggested for CRAB (18 g ampicillin + 6 g sulbactam)*	CrCl 15–29 mL/min: 1.5–3 g q12h CrCl 5–14 mL/min: 1.5–3 g q24h CRRT: 1.5–3 g q8–12h
Ticarcillin/ clavulanate	3.1 g q4–6h	CrCl 30–60 mL/min: 3.1 g LD, then 2 g q4h CrCl 10–30 mL/min: 3.1 g LD, then 2 g q8h CrCl <10 mL/min: 3.1 g LD, then 2 g q12h CRRT: 2–3.1 g q6–8h
Piperacillin/ tazobactam	2.25–4.5 g q6h	CrCl 40–60 mL/min: 3.75–4.5 g q6h CrCl 20–40 mL/min: 2.25–3.375 g q6h CrCl: <20 mL/min: 2.25 g q6–8h CRRT: 4.5 g q6–8h
Cefazolin	1–1.5 g q6–8h	CrCl: 11–34 mL/min: 500 mg q12h CrCl: ≤10 mL/min: 500 mg q18–24h CRRT: 1–2 g q12h
Cefotetan	2–3 g q12h	*Renal impairment:* CrCl: >30 mL/min: 2–3 g q12h CrCl: 10–30 mL/min: 2–3 g q24h CrCl: <10 mL/min: 2–3 g q48h CRRT: 1–2 g q12h
Cefoxitin	2 g q4–6h	CrCl: 30–50 mL/min: 1–2 g q8–12h CrCl: 10–29 mL/min: 1–2 g q12–24h CrCl: <10 mL/min: 0.5–1 g q12–48h CRRT: 1–2 g q8–12h
Cefuroxime	1.5 g q8h	CrCl: 10–20 mL/min: 750 mg q12h CrCl: <10 mL/min: 750 mg q24h CRRT: 1 g q12h
Ceftazidime	1–2 g q8h	CrCl: 31–50 mL/min: 1 g q12h CrCl: 16–30 mL/min: 1 g q24h CrCl: 6–15 mL/min: 0.5 g q24h CrCl: <5 mL/min: 0.5 g q48h CRRT: 2 g q8–12h
Ceftriaxone	1–2 g q24h	No adjustment CRRT: 1–2 g q12h
Cefepime	1–2 g q8–12h	CrCl: 11–29 mL/min: 1–2 g q24h CrCl: ≤10 mL/min: 1 g q24h CRRT: 2 g q8–12h
[1]Ceftobiprole	500 mg q8h	CrCl 30–<50: 500 mg q12h CrCl <30: 250 mg q12h CrCl <15: 200 mg q12h *(In severe renal impairment, it should be used with caution because of a risk of accumulation)* ESRD on HD: 25 mg q24h *(hemodialyzable)*
Ceftaroline	[2]Standard dose: 600 mg q12h [3]High dose: 600 mg q8h	CrCl 31–50: 400 mg q12h CrCl 15–30: 300 mg q12h CrCl <15: 200 mg q12h CRRT: 400–600 mg q12h
Ceftazidime/ avibactam	2.5 (2 + 0.5) g q8h (2-h IV infusion)	CrCl 31–50: 1.25 (1 + 0.25) g q8h CrCl 16–30: 927.5 (750 + 187.5) mg q12h CrCl 6–15: 927.5 (750 + 187.5) mg q24h #ESRD: 927.5 (750 + 187.5) mg q48h
Ceftolozane/ tazobactam	1.5 (1 + 0.5) g q8h IV (1-h IV infusion) ^For HAP/VAP: 3 (2 + 1) g q8h	CrCl 30–50: 750 (500 + 250) mg q8h and for HAP/VAP 1.5 (1 + 0.5) g q8h CrCl 15–29: 375 (250 + 125) mg q8h and for HAP/VAP 750 (500 + 250) mg q8h #ESRD on HD: Single LD of 750 (500 + 250) mg followed by 150 (100 + 50) mg q8h for the remainder of the treatment duration and for HAP/VAP: single LD of 2.25 gr followed by 450 (300 + 150) mg q8h
Imipenem	500 mg–1 g q6–8h	CrCl 41–70 mL/min: 500–750 mg q8h CrCl 21–40 mL/min: 250–500 mg q6h CrCl <20 mL/min: 250–500 mg q12h CRRT: 500 mg q6h
Imipenem/ cilastatin/ relebactam	1.25 g (0.5 + 0.5 + 0.25) q6h (30 min IV infusion)	CrCl 60–89 mL/min: 1 g (0.4 + 0.4 + 0.2) q6h CrCl 30–59 mL/min: 0.75 (0.3 + 0.3 + 0.15) g q6h CrCl 15–29 mL/min: 0.5 (0.2 + 0.2 + 0.1) g q6h CrCl <15 mL/min: should not be administered unless HD is instituted within 48 h ESRD on HD: 0.5 mL/min: 0.5 (0.2 + 0.2 + 0.1) g q6h
Meropenem	1 g q8h (3-hour IV infusion) High dose: 2 g q8h (3-h IV infusion)	CrCl 25–50 mL/min: 1 g q12h CrCl 10–25 mL/min: 500 mg q12h CrCl <10 mL/min: 500 mg q24h CRRT: 1 g q12h
Meropenem/ vaborbactam	4 (2 + 2) g q8h (3-hr IV infusion)	CrCl 30–49: 2 (1+1) g q8h CrCl 15–29: 2 (1 + 1) g q12h CrCl <15: 1 (0.5 + 0.5) g q12h

Continued

TABLE 107.1 Recommended Adult Dosing Regimens and Dosing Alterations—cont'd

Antimicrobial Agents	Adult Dose§§	Dosing Alteration (Renal or Hepatic Impairment)
Ertapenem	1 g q24h	CrCl <30 mL/min: 500 mg q24h CRRT: 500 mg–1 g q24h
Doripenem	500 mg q8h	CrCl 30–50 mL/min: 250 mg q8h CrCl 10–29 mL/min: 250 mg q12h CRRT: 500 mg q8h
Aztreonam	1–2 g q8h	CrCl 10–29 mL/min: 500 mg–1 g q8h CrCl <10 mL/min: 500 mg–1 g q12h CRRT: 2 g q12h
Cefiderocol	Cr Cl 90–<120: 2 g q8h (3-hr IV infusion) Augmented CrCl ≥120: 2 g q8h	CrCl 60–<90: 2 g q8h CrCl 30–<60: 1.5 g q8h CrCl 15–< 30: 1 g q8h ESRD (CrCl <15) with/without IHD: 0.75 g q12h CRRT: Base the dosage on the effluent flow rate: • ≤2 L/hr: 1.5 g q12h • 2.1–3 L/hr: 2 g q12h • 3.1–4 L/hr 1.5 g q8h • ≥4.1 L/hr: 2 g q8h
Aminoglycosides†		
Gentamicin and tobramycin	1.5–2.5 mg/kg q8h or 5 mg/kg q24h once-daily dose recommended	CrCl 40–59 mL/min: 1.5–2.5 mg/kg q12h CrCl 20–39 mL/min: 1.5–2.5 mg/kg q24h CrCl <20 mL/min: Redose when trough levels <1 μg/mL CRRT: Redose when trough levels <1 μg/mL
Amikacin	7.5 mg/kg q8h or 15 mg/kg q24h once-daily dose recommended	CrCl 40–59 mL/min: 5–7.5 mg/kg q12h CrCl 20–39 mL/min: 5–7.5 mg/kg q24h CrCl <20 mL/min: Redose when trough levels <5 μg/mL CRRT: Redose based on trough levels <5 μg/mL
Plazomicin≠	15 mg/kg q24h	CrCl ≥60 and <90: 15 mg q24h CrCl ≥30 and <60: 10 mg q24h CrCl ≥ 15 and <30: 10 mg q48h CrCl <15 and CRRT: insufficient information to recommend a dosage regimen
Fluoroquinolones		
Ciprofloxacin	400 mg q8–12h	CrCl 5–29 mL/min: 200–400 mg q18–24 h CRRT: 400 mg q12h
Levofloxacin	750 mg q24h	CrCl 20–49 mL/min: 750 mg q48h CrCl 10–19 mL/min: 750 mg initially, then 500 mg q48h CRRT: 750 mg initially, then 500–750 mg q24h
Omadacycline^	LD on D1: 200 mg once (60-min IV infusion) or 100 mg twice (30-min IV infusion) Maintenance dose: 100 mg q24h (30-min IV infusion)	*No dosage adjustment is warranted in patients with renal or hepatic impairment*
Polymyxins		
Colistin (polymyxin E)‡	LD of CMS: 300 mg CBA (~9 million IU) Daily maintenance dose of CMS (CrCl ≥90): 360 mg CBA daily dose (10.9 million IU)	CrCl / mg CBA daily dose[4] / million IU daily dose[4] CrCl 80–<90: 340 / 10.30 CrCl 70–<80: 300 / 9.00 CrCl 60–<70: 275 / 8.35 CrCl 50–<60: 245 / 7.40 CrCl 40–<50: 220 / 6.65 CrCl 30–<40: 195 / 5.90 CrCl 20–<30: 175 / 5.30 CrCl 10–<20: 160 / 4.85 CrCl 5–<10: 145 / 4.40 CrCl : 0 130 / 3.95 Intermittent HD: On a nondialysis day, CMS dose of 130 mg CBA/day (~3.95 million IU/day); on a dialysis day, administration of a supplemental dose of CMS 40 mg CBA (~1.2 million IU) or 50 mg CBA (~1.6 million IU) for a 3- or 4-hour IHD session, respectively; SLED: 10% of the CMS dose should be added to the baseline daily dose per SLED-hour CRRT: CBA 440 mg/day (~13.3 million IU/day)
Polymyxin B‡	LD: 2.0–2.5 mg/kg for polymyxin B (equivalent to 20,000–25,000 IU/kg) Maintenance dose: 1.25–1.5 mg/kg (equivalent to 12,500–15,000 IU/kg) q12h	Unnecessary renal dose adjustments may lead to underexposure and clinical failure

Tetracyclines		
Tigecycline	Initial dose 100 mg, then 50 mg q12h (30–60 min IV infusion) *Off-label high dose:* Initial dose 200 mg, then 100 mg q12h	*Severe hepatic impairment (Child-Pugh C):* Initial dose 100 mg followed by 25 mg q12h
Eravacycline	1 mg/kg q12h (1-hr IV infusion)	*Severe hepatic impairment (Child-Pugh C):* On D1: 1 mg/kg q12h From D2: 1 mg/kg q24h *Concomitant use of a strong cytochrome P450 isoenzymes (CYP)3A inducer:* 1.5 mg/kg q12h
Miscellaneous		
Fosfomycin	[5]Dose for CrCl >80: 12–24 g in 2–3 divided doses	*% of the considered appropriate dose if the renal function was normal* CrCl 40–<30: 70% (in 1–2 divided doses) CrCl 30–<20: 60% (in 1–2 divided doses) CrCl 20–<10: 40% (in 1–2 divided doses) CrCl 10: 20% (in 1–2 divided doses) IHD q48h: 2 g at the end of each HD session Postdilution CVVHF: no dose adjustment Predilution CVVHF or other types of CRRT: no available data

CBA, Colistin base activity; *CMS,* colistimethate (also known as colistin methanesulfonate); *CRAB:* carbapenem-resistant *A. baumannii; CrCl,* creatinine clearance; *CRRT,* continuous renal replacement therapy; *CVVHF,* continuous venovenous hemofiltration; *ESRD,* end-stage renal disease; *h,* hours; *HD,* hemodialysis; *IHD,* intermittent hemodialysis; *LD,* loading dose; *min,* minutes; q, every; *SLED:* sustained low-efficiency dialysis,

*Data compiled from package insert information and references included in the relevant sections of the chapter.

CrCl in mL/min, calculated using the Cockcroft-Gault formula.

±Renal replacement therapy can efficiently eliminate most beta-lactam antimicrobial agents.

†For aminoglycoside dosing, adjusted body weight should be used: (0.45 × [total body weight − ideal body weight] + ideal body weight). For plazomicin, however, the dosage should be calculated using TBW; for patients with TBW greater than IBW by ≥25%, adjusted body weight should be used.

‡For colistin, dosing should be based on adjusted body weight. For polymyxin B, the dose should be based on total body weight; PK data do not support capping an upper absolute loading dose in milligrams in obese patients, but there are limited data with administration of >200 mg per infusion.

§§All administration is intravenous; dosing is for serious, life-threatening infections.

∞In critically ill patients with augmented renal clearance, dose of 3 g/8 h achieved respective PD targets.

#On hemodialysis days, administer the dose at the earliest possible time after completion of dialysis; for critically ill patients undergoing CVVHF, a population PK model-guided evaluation of ceftolozane/tazobactam dosing suggested a front-loaded regimen: a single loading dose of 3 g followed by 0.75 g/8 h.

≠Assessment of creatinine clearance before initiation and daily afterwards is recommended; for TDM, the plasma collection time is approximately 30 minutes before the second dose, targeting to maintain plasma trough concentrations <3 μg/mL.

^Omadacycline must not be administered with any solution containing multivalent cations (e.g., calcium and magnesium) through the same intravenous line.

[1]IV infusion of 2 hours; in patients with a supranormal CrCl (>150 mL/min), prolongation of the infusion duration to 4 hours is recommended.

[2]IV infusion of 5–60 minutes in patients with supranormal CrCl and standard dose, an infusion time of 60 minutes may be preferable.

[3]High doses for cSSTI confirmed or suspected to be caused by *S. aureus* with an MIC to ceftaroline of 2 mg/L or 4 mg/L to ceftaroline; high dose to be administered as 120-minute IV infusion.

[4]To achieve a desired target plasma colistin $C_{ss,avg}$ of 2 mg/L for patients with narrow windows of creatinine clearance; daily dose administered in two divided doses 12 hours apart; in cases of renal impairment, the loading dose and the maintenance dose should be adapted to renal function that should be monitored daily.

[5]The high-dose regimen in three divided doses should be used in severe infections known or expected to be caused by less susceptible bacteria. Acute osteomyelitis and nosocomial lower respiratory tract infections: 12–24 g in two to three divided doses; cUTI: 12–16 g in two to three divided doses; Bacterial meningitis: 16–24 g in three to four divided doses. Safety data for doses >16 g/day are limited; special caution advised. Individual doses must not exceed 8 g.

Ceftazidime/Avibactam

Ceftazidime/avibactam is a combination of the cephalosporin ceftazidime and the novel beta-lactamase inhibitor avibactam.[102] It was approved by the FDA in 2015 for the indications of cUTIs, including acute pyelonephritis, and, in combination with metronidazole, cIAIs, and in 2018 it was approved for hospital-acquired bacterial pneumonia (HABP)/ventilator-associated bacterial pneumonia (VABP).[123,124]

Mode of Action, Spectrum of Activity, and Resistance Mechanisms. Although ceftazidime is resistant to hydrolysis by several older narrow-spectrum beta-lactamases (such as TEM-1 or SHV-1) or by most of the class D carbapenemases, it is hydrolyzed by class A ESBLs and class C beta-lactamases (AmpC type) and carbapenemases, such as KPCs and MBLs.[43,53] Avibactam is a diazabicyclooctane, a first-in-class non-beta-lactam beta-lactamase reversible inhibitor without intrinsic antimicrobial activity, which binds covalently to beta-lactamases by a process that, contrary to beta-lactam beta-lactamase inhibitors, does not involve hydrolysis.[43,101,125,126] When avibactam is combined with ceftazidime, it protects ceftazidime from hydrolysis by class A and C beta-lactamases and increases its antimicrobial activity.[43,125,127] In in vitro studies, it is active against >99.9% of meropenem-, ceftazidime- and piperacillin/tazobactam-resistant isolates of *Enterobacteriaceae* and *P. aeruginosa,* including KPC and OXA-48 producers.[127,128] Although ceftazidime/avibactam covers ESBL-producing and most KPC-producing isolates, it is inactive against MBL-producing ones.[129–131] The addition of avibactam does not provide any additional activity towards the limited antimicrobial spectrum of ceftazidime against gram-positive microorganisms and anaerobes.[43] Combinations of ceftazidime/avibactam with aztreonam, meropenem, amikacin, and fosfomycin have been reported to be synergistic in vitro against MDR *K. pneumoniae* and *P. aeruginosa.*[132] Regarding resistance development, the main mechanism to ceftazidime/avibactam includes production of class B MBLs, hyperexpression of efflux pumps, porin alteration, increased expression of the *eblaKPC* gene or mutations on-loop of KPC enzymes, whereas mutations in PBPs occur rarely.[53]

PK/PD. Ceftazidime/avibactam has linear PKs.[43] The V_d after multiple doses is 17 L and 22.2 L for ceftazidime and avibactam, respectively.[123] The protein binding of ceftazidime/avibactam is low (<10% for ceftazidime and 5.7%–8.2% for avibactam).[123] It is primarily renally excreted as unchanged drug (>80% of ceftazidime and >95% of avibactam).[133] It has modest lung penetration, and in a phase I study of healthy subjects, the mean ELF/plasma ratio was 35% and 31% for avibactam and ceftazidime, respectively, and the concentration increased in a dose-dependent way.[134]

Clinical efficacy. Ceftazidime/avibactam demonstrated noninferiority in several phase III RCTs: versus doripenem in a phase III RCT (RECAPTURE; NCT01595438) in hospitalized adult patients with cUTIs; versus the best available treatment (BAT) in patients with cUTIs or cIAIs caused by ceftazidime-resistant strains (REPRISE; NCT01644643); combined with metronidazole versus meropenem in patients with cIAIs (NCT01726023); and versus meropenem in patients with HAP, including VAP (REPROVE; NCT01808092).[135–138]

Dosage. See Table 107.1 for dosages.[123,139] The recommended duration of treatment is 5–14 days for IAIs and 7–14 days for cUTIs and HABP/VABP.[123,139]

Adverse events. Ceftazidime/avibactam is generally well tolerated, usually with mild adverse events. The most frequent events were gastrointestinal disturbances, such as diarrhea and/or nausea and/or vomiting (≥5% in patients with cIAIs (combined with metronidazole) and in patients with HABP/VABP and 3% in patients with cUTIs).[123] Other adverse events include hypokalemia, liver function test alteration, headache, and fever.[43] Less common (<1%) adverse events include blood count alterations such as eosinophilia, thrombocytosis or thrombocytopenia, candidiasis, and seizures.[123] There is a warning about decreased efficacy in patients with cIAIs with baseline CrCl of 30–50 mL/ min and a recommendation of at least daily monitoring of CrCl and dose adjustment accordingly.[123]. In the phase III trial in patients with cIAIs, mortality in the subgroup with baseline CrCl 30–50 mL/min was 19.5% and 7% for the ceftazidime/avibactam plus metronidazole arm and the meropenem arm, respectively, but patients in the ceftazidime/avibactam arm received 33% lower daily doses than suggested.[123] There are also warnings related to hypersensitivity reactions, *C. difficile* diarrhea, and CNS reactions, especially in patients with renal impairment.[123]

Meropenem/Vaborbactam

Meropenem/vaborbactam is a combination of the broad-spectrum carbapenem meropenem and the novel cyclic boronic acid–based beta-lactamase inhibitor vaborbactam.[101] Approval was granted by the FDA in 2017 for the indication of cUTIs.[140] In 2018 the EMA granted marketing authorization for meropenem/vaborbactam for the indications of cUTIs, including pyelonephritis, cIAIs, HAP (including VAP), bacteremia associated or suspected to be associated with any of the previously mentioned indications, and infections caused by aerobic GNBs with limited treatment options.[141,142]

Mode of Action, Spectrum of Activity, and Mechanisms of Resistance. Meropenem covers a wide range of gram-positive, gram-negative, and anaerobic bacteria and is stable to hydrolysis by penicillinases and cephalosporinases.[43] Nevertheless, it is vulnerable to hydrolysis by other beta-lactamases, such as serine beta-lactamases and MBLs.[101] Vaborbactam exerts potent inhibition of serine beta-lactamases of class A (including ESBLs and KPCs) and class C (including AmpC) by forming reversible covalent bonds with them, and although it does not have intrinsic antimicrobial activity, when combined with meropenem, it provides protection to meropenem against degradation by these enzymes.[101,143,144] Vaborbactam does not inhibit class B (MBL)– and class D (OXA)-beta-lactamase–producing strains.[43,101,106,145] Therefore the spectrum of activity of meropenem/vaborbactam is that of meropenem, supplemented with activity against several serine beta-lactamase–producing strains.[43,101,143] Combined with vaborbactam, a decrease of meropenem's MIC against most *Enterobacteriaceae* ranging from 2- to >1024-fold, in addition to activity close to 100% against KPC-positive *Enterobacteriaceae* isolates, have been reported.[146,147] Vaborbactam does not increase the activity of meropenem against strains of *P. aeruginosa* with MDR phenotypes mediated by porin changes and/or efflux mechanism changes or against *A. baumannii* strains producing primarily class D (OXA-type) beta-lactamases.[43,147] Also, resistance to meropenem/vaborbactam has been reported in *S. maltophilia, Elizabethkingia,* and *Aeromonas.*[43,148] It should be noted that vaborbactam does not enhance meropenem's activity against gram-positive bacteria and anaerobes.[43,147]

The main mechanisms of resistance to meropenem/vaborbactam include class B MBLs, class D carbapenemases (OXA-48-like), porin alterations (e.g., loss of outer membrane porins OmpK36 and 35 used by vaborbactam to penetrate the bacterial cell, decreased expression of other porins), and hyperexpression of efflux pumps.[43,53] In summary, meropenem/vaborbactam is active against most *Enterobacteriaceae,* particularly KPC-producing strains, in addition to ESBL- and AmpC-producing ones, but is inactive against MBL- and class D–producing strains, whereas for *P. aeruginosa* it has similar activity as meropenem.[53]

PK/PD. The V_d of meropenem/vaborbactam at steady state is 20.2. L and 18.6 L, the protein binding is 2% and 33%, and the half-life is 1.22 and 1.68 hours for meropenem and vaborbactam, respectively.[43,140] Meropenem/vaborbactam is primarily renally excreted.[140,141] Meropenem has a minor pathway of metabolism by hydrolysis (22%),

whereas vaborbactam is not metabolized, but excreted unchanged in the urine.[140,141] The lung disposition profile is favorable, with ELF-to-plasma unbound concentration ratios of 65% for meropenem and 79% for vaborbactam in healthy subjects.[43,149]

Clinical efficacy. Meropenem had similar efficacy to piperacillin/tazobactam (clinical success and microbiologic eradication) in a phase III RCT (TANGO I study; NCT02166476) in patients with cUTIs.[150] In another open-label, phase III RCT (TANGO II study; NCT02168946) in patients with cUTIs, IAIs, HABP/VABP, or bacteremia caused by CRE, meropenem/vaborbactam achieved increased clinical cure rate and decreased 28-day all-cause mortality versus BAT, along with decreased nephrotoxicity.[151]

Dosage. See Table 107.1 for dosages.[140,141] The recommended duration of treatment is up to 14 days: 5–10 days for cUTIs and IAIs, 7–14 days for HAP/VAP, and duration according to the site of infection for bacteremia and MDR GNB infections with limited treatment options.[140,141]

Adverse events. Meropenem/vaborbactam has a favorable safety profile, similar to comparators. In the phase III TANGO II clinical trial, the most common (≥3%) adverse events reported for meropenem/vaborbactam included headache, phlebitis, and diarrhea, and other adverse events occurring ≥1% included hypersensitivity, nausea, increases of alanine and aspartate aminotransferases, pyrexia, and hypokalemia.[140,151,152] There are warnings related to hypersensitivity reactions, seizures, and other CNS reactions; *C. difficile*–associated diarrhea; and decreased levels of valproic acid when coadministered with meropenem.[140]

Imipenem/Cilastatin/Relebactam

Imipenem/cilastatin/relebactam is a novel triple antimicrobial agent that combines the carbapenem imipenem, the dehydropeptidase inhibitor cilastatin, and the novel beta-lactamase inhibitor relebactam.[106] It was approved by the FDA in 2019 for the cUTIs, including pyelonephritis, and cIAIs caused by susceptible GNBs when there are limited or no alternative options; in 2020 it was approved for HABP/VABP as well.[153,154] EMA approval was granted in 2020 for the indications of HAP (including VAP), bacteremia with to (or suspected to be associated with) HAP/VAP, and infections caused by gram-negative microorganisms with limited treatment options.[155,156]

Mode of Action, Spectrum of Activity, and Resistance Mechanisms. Imipenem/cilastatin/relebactam covers *Enterobacteriaceae* and lactose nonfermenting GNBs.[101] Relebactam, which is structurally related to avibactam, inhibits class A and C beta-lactamases and enhances the antimicrobial spectrum of imipenem/cilastatin, increasing the activity of imipenem against most *Enterobacteriaceae* and *P. aeruginosa,* as shown by a 2- to 128-fold and 8-fold decrease of MIC, respectively.[157–159] Imipenem/cilastatin/relebactam is active against *E. coli* (including ESBL- and KPC-producing isolates), *K. pneumoniae* (including ESBL, KPC, AmpC, and imipenem-resistant *K. pneumoniae* expressing AmpC beta-lactamases or KPC carbapenemases), and *P. aeruginosa* isolates with AmpC expression or outer membrane protein D (OprD) deficiency.[101,160,161] Nevertheless, it is inactive against *A. baumannii;* imipenem-resistant isolates of *Enterobacteriaceae* producing IMPs, VIMs, or NDM MBLs; and *P. aeruginosa* producing IMP or VIM MBLs.[101] Moreover, although there is a theoretical background for activity against OXA-producing isolates, the reported data are variable, and a quite recent surveillance study failed to demonstrate such activity.[162] It has similar gram-positive activity as imipenem/cilastatin. The main mechanisms of resistance to imipenem/cilastatin/relebactam include production of class B MBLs, class D carbapenemases (OXA-48-like), specific class A carbapenemases (such as GES), hyperexpression of KPC, and porin alterations.[53] In summary, imipenem/cilastatin/relebactam can be used for various resistant *Enterobacteriaceae* (such as ESBL-, KPC-, and AmpC-producing ones), excluding MBL- and class D–producing strains, and for carbapenem-resistant *P. aeruginosa,* as relebactam reinstates imipenem's activity in 80% of imipenem-resistant *P. aeruginosa* strains.[53]

PK/PD. The best PD predictor of activity of relebactam in animal and in vitro models is $fAUC_{0-24hr}$/MIC.[154] The half-life of relebactam is approximately 1.2 hours.[154] The steady-state V_d of imipenem/cilastatin/relebactam is 24.3 L, 13.8 L, and 19 L, respectively, and the protein binding is 20%, 40%, and 22%, respectively, and independent of concentration.[154] Imipenem/cilastatin/relebactam is mainly renally excreted by glomerular filtration and active tubular secretion.[155] Relebactam has minimal metabolism, and >90% is excreted unchanged in the urine, whereas the percentage of imipenem and cilastatin that is excreted unchanged is 63% and 77%, respectively.[154] Relebactam and imipenem have similar penetration to ELF, with exposure relative to plasma 55%.[163]

Clinical efficacy. The FDA granted approval to imipenem/cilastatin/relebactam based on the results of two phase II RCTs that compared it with imipenem/cilastatin in patients with cIAIs (NCT01506271) and cUTIs (NCT01505634).[164–165] Imipenem/cilastatin/relebactam also demonstrated noninferiority compared with piperacillin/tazobactam in a phase III RCT (RESTORE IMI-2; NCT02493764) conducted in bacterial HAP and VAP.[166] In another phase III RCT (RESTORE IMI-1 study; NCT02452047) that included only infections by imipenem-nonsusceptible but colistin- and imipenem/cilastatin/relebactam-susceptible pathogens (HAP/VAP, cUTIs, cIAIs), imipenem/cilastatin/relebactam monotherapy had similar efficacy to an imipenem/cilastatin and colistin combination.[167]

Dosage. For dosages, see Table 107.1.[154] The FDA recommends a duration of treatment ranging from 4 to 14 days depending on the severity and location of the infection and clinical response, whereas the EMA recommends 7–14 days for HAP/VAP.[154,155]

Adverse events. Treatment-related adverse events in the RESTORE IMI-2 trial were 11.7% and 9.7% for imipenem/cilastatin/relebactam and piperacillin/tazobactam, respectively.[166] In RESTORE IMI-1, the serious adverse events of the imipenem/cilastatin/relebactam arm were 16% compared with 31% of the imipenem/cilastatin plus colistin arm, and the nephrotoxicity was 10% and 56%, respectively.[167] The most common (≥2%) adverse events of imipenem/cilastatin/relebactam include gastrointestinal disturbances (diarrhea, nausea, vomiting), increases of alanine and aspartate aminotransferases, infusion site reactions/phlebitis, pyrexia, and hypertension.[154] Other adverse events include blood and lymphatic system disorders (agranulocytosis, increased eosinophils, hemolytic anemia, seizures, hepatobiliary disorders including jaundice and liver failure, rash, increased lactate dehydrogenase, and positive Coombs test).[154] There are warnings regarding hypersensitivity, seizures, and CNS adverse reactions; avoidance of concomitant use with valproic acid because of the risk of decreased serum concentrations of valproic acid and breakthrough seizures; and *C. difficile* diarrhea.[154] Concomitant use of imipenem/cilastatin/relebactam with ganciclovir should be avoided (unless the expected benefit outweighs the risk), as there are reports of cases of generalized seizures when used with imipenem/cilastatin.[154]

Novel Siderophore Cephalosporins

Cefiderocol is the first siderophore cephalosporin, and in 2019, was granted approval by the FDA for the treatment of adults with cUTIs, and in 2020 it was approved also for the treatment of bacterial HAP and VAP caused by susceptible GNBs: *A. baumannii* complex, *E. coli*, *Enterobacter cloacae* complex, *K. pneumoniae*, *P. aeruginosa,* and *Serratia marcescens.*[168,169] The EMA approved cefiderocol in 2020.[170,171]

Mode of Action, Spectrum of Activity, and Resistance Mechanisms. Cefiderocol has a unique structure, that is, combination of a catechol-type siderophore with a cephalosporin core that has similar side chains to cefepime and ceftazidime, which enhances its stability against many beta-lactamases, such as ESBLs and carbapenemases. Cefiderocol chelates with ferric ion and, apart from entering the gram-negative bacteria by passive diffusion via membrane porins like the other beta-lactams, it uses their iron uptake system to penetrate the siderophore-iron complex pathway, bypassing their outer membrane barriers. Its unique mode of action enables cefiderocol to overcome resistance by decreased porin expression. Moreover, the chelation with iron provides cefiderocol resistance to hydrolysis by all beta-lactamases (Ambler class B included).[1,101] As soon as it is within the periplasmic space, cefiderocol dissociates from iron and binds to PBPs, particularly PBP3, inhibiting peptidoglycan synthesis like the other beta-lactams.[172]

Cefiderocol is active against a wide range of gram-negative bacteria, including both lactose-fermenting, such as *E. coli*, *Klebsiella* spp., *Enterobacter* spp., *Proteus* spp., *Providencia* spp., *Salmonella* spp., *Yersinia* spp., and *Vibrio* spp., and nonfermenting GNBs, such as *Acinetobacter* spp., *Pseudomonas* spp., *Burkholderia* spp., and *S. maltophilia*. Cefiderocol is stable against many beta-lactamases, such as ESBLs (e.g., CTX-M) and carbapenemases (e.g., Ambler class B metallo-beta-lactamases [NDM, VIM, IMP] and serine-type beta-lactamases [OXA-23, OXA-48-like, OXA-51-like, OXA-58]).[173] However, cefiderocol has weak in vitro activity against aerobic gram-positive bacteria and anaerobic bacteria, demonstrating high MICs.[173,174] Reduced susceptibility to cefiderocol may occur via the mutation or differential expression of specific iron-transporters.[175]

PK/PD. The PD target best associated with the efficacy of cefiderocol is similar to the other cephalosporins. Cefiderocol appears to display linear pharmacokinetics, its V_d is 18 L, it has an elimination half-life of 2.72 hours, the protein binding (mainly albumin) is 40%–60%, and it is primarily renally excreted unchanged.[174] Cefiderocol appears to distribute fast and in parallel from plasma to ELF, with lung penetration of approximately 24%, whereas the penetration to alveolar macrophage seems to be much lower; further studies in critically ill patients are needed.[174,176]

Clinical efficacy. In an open-label phase III RCT (CREDIBLE-CR study; NCT02714595) conducted in critically ill patients with infections caused by carbapenem-resistant GNBs (sepsis/bloodstream infection, cUTI, healthcare–associated pneumonia [HCAP]/HAP/VAP), cefiderocol was compared with BAT.[177] Patients in the cefiderocol arm received monotherapy, whereas the BAT arm mostly received combination therapy (more frequently, colistin-based regimens).[172] In the CR-mITT population, clinical cure rates at TOC were comparable between arms overall and for each individual disease state, but all-cause mortality at day 14, day 28, and day 49 was numerically higher in the cefiderocol arm, particularly in patients with HCAP/HAP/VAP and bloodstream infections/sepsis.[172] The greater mortality imbalance was at day 49 in patients with *A. baumannii*.[172] In another phase III RCT (APEKS-NP study; NCT03032380) cefiderocol was compared with meropenem (both combined with linezolid for at least 5 days) in patients with HAP, VAP, or HCAP and demonstrated noninferiority with respect to mortality.[178,179] A phase II RCT that compared cefiderocol with BAT in patients with bloodstream infections is still ongoing.[180]

Dosage. For dosages, see Table 107.1.[170] The recommended duration is 7–14 days.[170]

Adverse events. Based on data of the clinical trials, cefiderocol appears to be well tolerated and with a similar safety profile as other cephalosporins. In the CREDIBLE-CR trial the reported treatment-related adverse events were 14.9% in the cefiderocol arm versus 22.4% in the BAT arm; the most common adverse events for cefiderocol, with incidence ≥10%, were diarrhea, increased transaminases, pleural effusion, and chest pain. It should be noted that cefiderocol has a labeled warning for an increase in all-cause mortality that was observed in patients treated with cefiderocol compared with BAT in the CREDIBLE-CR trial; the increased mortality occurred in patients with nosocomial pneumonia, bloodstream infections, or sepsis.[170,177]

FLUOROQUINOLONES

Fluoroquinolones were discovered in the early 1960s and are antimicrobial agents with a broad spectrum of activity. The most commonly used members of the class are ciprofloxacin, levofloxacin, and moxifloxacin, and recently the use of a new fluoroquinolone, delafloxacin, was approved.

Mode of Action of Fluoroquinolones

The action of fluoroquinolones is exerted by bacterial DNA synthesis inhibition; bacterial cell death follows this action.[181] Fluoroquinolones target two members of the topoisomerase enzymatic class, namely DNA gyrase and topoisomerase IV, that are essential for DNA replication: it appears that they trap the enzyme-DNA complexes after strand breakage and before resealing, generating a DNA break that the cell is unable to repair.[182] In gram-negative bacteria, the DNA gyrase is considered the most susceptible to fluoroquinolone inhibition, whereas in gram-positive bacteria, topoisomerase IV is considered the most susceptible one.[181]

Spectrum of Activity of Fluoroquinolones

Fluoroquinolones have activity against a wide range of both gram-positive and gram-negative organisms.[181] Levofloxacin and moxifloxacin are potent against penicillin-sensitive or -resistant *S. pneumoniae* but inactive against MRSA. Over the years, increasing resistance has reduced the usefulness of fluoroquinolones against gram-negative bacteria, especially in the critical care setting. Ciprofloxacin is considered the most potent fluoroquinolone against gram-negative bacteria, with the lowest MIC values, but a higher levofloxacin dose can be used to achieve similar efficacy. For common resistant ICU GNBs, fluoroquinolones are used in combination with beta-lactams.

Resistance to Fluoroquinolones

Mutations in target enzymes (DNA gyrase and topoisomerase IV) and in efflux pumps are the main mediators of resistance to fluoroquinolones.[183] Specifically, amino acid substitutions in genes encoding subunits of the target enzymes lead to structure alterations and, consequently, decreased fluoroquinolone-binding affinity, whereas in gram-negative bacteria, mutations that alter the outer membrane porin proteins can decrease the passive diffusion of fluoroquinolones into the cells.[183] It should be noted that mutations are selected first in the more susceptible target (i.e., A gyrase in gram-negative bacteria and topoisomerase IV in the gram-positive ones).[183] Additional mutations increase the resistance further, with the most resistant strains having mutations in several genes. Fluoroquinolone resistance can be also mediated by plasmids that protect cells from the lethal effects of quinolones.[183]

PK/PD of Fluoroquinolones

Fluoroquinolones have excellent oral bioavailability that approaches 100%.[184] The large V_d after rapid oral absorption suggests adequate

tissue concentrations. Fluoroquinolones are moderately lipophilic antibiotics and, apart from levofloxacin, their V_d generally is not affected by critical illness. It should be noted that in order to avoid chelation, oral fluoroquinolones should be administered at least 2 hours before or 6 hours after medications containing polyvalent cations (e.g., magnesium- or aluminum-containing antacids, sucralfate, iron supplements, or multivitamins containing zinc or iron).[184] Steady-state concentrations are achieved in 24, 48, and 72 hours for ciprofloxacin, levofloxacin, and moxifloxacin, respectively.[8] Protein binding for most of the members of the class is moderate to low. Fluoroquinolones have good penetration into multiple sites of the human body.[181] Ciprofloxacin and levofloxacin are excreted renally as unmetabolized drug, necessitating dosing adjustments in renal insufficiency.[181] Moxifloxacin does not require dose adjustments in renal impairment and, although is mainly metabolized in the liver, does not need adjustment in hepatic impairment either.[181]

Fluoroquinolones exhibit "concentration-dependent" bactericidal activity, with a steady-state AUC (AUC 0–24)/MIC ratio representing the best predictor of clinical efficacy.[8] Nevertheless, it should be noted that for optimal bactericidal activity, higher *C*max/MIC ratios (> 8–20 xMIC) might also be necessary. Higher AUC 0–24/MIC (≥125) are needed against gram-negative organisms compared with gram-positive ones (25–30).[185] On the other hand, for resistance emergence suppression in infections by GNBs, even higher AUC 0–24/MIC ratios (>100–200) are needed.[8]

Dosing and Monitoring of Fluoroquinolones

In critically ill patients a fluoroquinolone dosing regimen that maximizes the AUC 0–24/MIC (i.e., use of a loading dose and higher maintenance doses) might be required. A recent position paper on TDM use in critical care neither recommends nor discourages the use of TDM.[8] Taking into consideration the high PK variability in critically ill patients and the high propensity of resistance emergence, the expert panel notes that TDM might be useful, especially when MICs are close to breakpoint.[8] Fluoroquinolone TDM monitoring should be AUC/MIC based, with two samples taken 2 hours and 6 hours after dosing, with a target of *f*AUC0–24/MIC ≥80. In the case of *C*max/MIC monitoring, one sample should be taken 30 minutes after the end of infusion, targeting for *C*max/MIC ≥8–12. Regarding toxicity, the clinical PK/PD thresholds are unclear.[8]

Adverse Events of Fluoroquinolones

The most common adverse events are gastrointestinal and CNS stimulation.[181] Although less common, fluoroquinolones have also been related to a range of possible severe adverse events.[181] Disabling and potentially irreversible serious adverse reactions that have occurred together have been associated with fluoroquinolone use, including tendinitis and tendon rupture (such as Achilles tendon, rotator cuff, biceps, thumb), peripheral neuropathy, and CNS effects (such as insomnia, seizures, hallucinations, insomnia, depression, and severe headaches).[181,184] Fluoroquinolones should be avoided in patients with myasthenia gravis, as they can cause exacerbation.[181,184] Hypersensitivity reactions and *C. difficile* diarrhea may occur with administration of fluroquinolones.[181,184] Fluoroquinolones may alter the serum glucose concentration (hypoglycemia or hyperglycemia), especially in patients with a history of diabetes on hypoglycemic agents.[181] QTc interval prolongation and arrhythmias, including potentially fatal torsades de pointes arrhythmias, have been associated with the use of ciprofloxacin, levofloxacin, and moxifloxacin, particularly in patients with uncorrected hypokalemia or receiving class IA or III antiarrythmics.[184,186,187] There are reports of fluoroquinolone-associated seizures; however, certain causality is still under debate.[188–191] A warning was issued by the FDA in 2016 noting that in certain infections risks may outweigh the benefits of fluoroquinolone use.[192] Fluoroquinolones are a frequent target of antimicrobial stewardship programs aiming to optimize prescribing and decrease related adverse events.[193]

Novel Approved Fluoroquinolones

Delafloxacin

Delafloxacin, an anionic fluoroquinolone, was approved by the FDA in 2017 for the treatment of acute bacterial skin and skin structure infections (ABSSSIs) caused by designated susceptible bacteria, and in 2019 it was approved for the indication of bacterial CAP as well.[184,194,195]

Mode of Action, Spectrum of Activity, and Resistance Mechanisms. Delafloxacin exerts its action similarly as the other members of the class; however, unlike the other fluoroquinolones, it is regarded as a dual target agent (i.e., a fluoroquinolone with nearly equivalent affinity for both DNA gyrase and topoisomerase IV).[193] This property might explain its broad in vitro activity against both gram-negative and gram-positive bacteria, including MRSA (also MRSA with mutations in the quinolone resistance–determining region that confer resistance to both ciprofloxacin and levofloxacin), atypical bacteria, and mycobacteria.[193,196] Delafloxacin has the ability to penetrate *S. aureus* biofilms.[193] Moreover, the unique anionic property of delafloxacin provides increased potency in acidic environments, with a reported 2-fold to 32-fold decrease in MICs.[197] In vitro, delafloxacin had similar activity against *Enterobacteriaceae* as ciprofloxacin and levofloxacin, whereas for *P. aeruginosa* delafloxacin had similar activity as ciprofloxacin.[198] Against high-resistant-ciprofloxacin *Enterobacteriaceae* strains from UTIs, delafloxacin was inactive against all ESBL- and KPC-producing strains.[197]

PK/PD. Delafloxacin is fast absorbed after oral administration, but unlike other fluoroquinolones, its mean bioavailability is only 58.8% and compared with IV delafloxacin, the *C*max of oral administration was lower.[184,199,200] The V_d of delafloxacin nears the total body water, and the protein binding, mainly albumin, is approximately 84%.[199,200] A bioexponential decrease in plasma concentrations is demonstrated, with a half-life of 6–8 hours and steady state reached in 3 days for both IV and oral formulations.[199] Glucuronidation is the main metabolic pathway of delafloxacin; however, 50% or more of a single oral or IV dose of delafloxacin can be found unchanged in the urine.[184] As with the other fluoroquinolones, delafloxacin has concentration-dependent bactericidal activity and similar PD predictors for optimal efficacy.[184] An fCmax/MIC ratio of 12 or an AUC/MIC ratio of 100–125 correlates best with efficacy against gram-negative bacteria.[193] Delafloxacin's exposure increases with decreased renal clearance, whereas hepatic impairment seems to have no significant impact.[184]

Clinical efficacy. Delafloxacin demonstrated similar efficacy versus vancomycin plus aztreonam in two phase III RCTs in patients with ABSSIs (PROCEED studies: NCT01811732 and NCT01984684), and in obese patients, cure rate as assessed by the investigators was higher.[201–203] In a phase III RCT (DEFINE-CABP study; NCT02679573) in patients with community-acquired bacterial pneumonia (CABP) delafloxacin monotherapy (IV with potential switch to oral) was noninferior to moxifloxacin (IV with potential switch to oral and potential blinded switch to IV linezolid in case of MRSA confirmation).[204]

Dosage. Delafloxacin is administered at a dose of 300 mg by IV in a 60-minute infusion every 12 hours or a 450-mg tablet orally every 12 hours (see Table 107.1).[184] The recommended duration of treatment is 5–14 days and 5–10 days for ABSSSI and bacterial CAP, respectively.[184]

Adverse events. Delafloxacin was generally well-tolerated in clinical trials.[193] The most common adverse events reported in phase I and II trials were gastrointestinal (i.e., low- to moderate-intensity diarrhea, nausea, and vomiting), and in phase III trials the three most common ones (>5%) were diarrhea, nausea, and infusion site extravasation. In contrast to other fluoroquinolones, delafloxacin has not been associated with significant effects on the QTc interval.[205] Delafloxacin has several warnings and precautions (i.e., boxed warning about serious adverse reactions, including tendinitis and tendon rupture, peripheral neuropathy, CNS effects, and exacerbation of myasthenia gravis).[184] The majority are those in common with the other fluoroquinolones; however, delafloxacin has an additional warning related to its IV vehicle, the sulfobutylether-B-cyclodextrin (SBECD), which may accumulate in the case of moderate or severe renal impairment, and close monitoring of serum creatinine is advised.[206]

AMINOGLYCOSIDES

Aminoglycosides are commonly used in many ICUs, especially if resistant gram-negative infections are suspected, usually in combination with other antimicrobial agents, particularly beta-lactams. The most frequently used aminoglycosides in the ICU are amikacin, gentamicin, and tobramycin, and recently, a new aminoglycoside, plazomicin, was granted approval.[207,208]

Mode of Action of Aminoglycosides

Aminoglycosides, discovered in the 1940s, are an important element of the antimicrobial arsenal.[209] They are cationic antibiotics binding passively to negatively charged portions of the outer membranes of gram-negative bacilli and competitively displacing cell wall Mg^{2+} and Ca^{2+} that link lipopolysaccharides, interfering with transportation across the cell membranes.[209] Inside the cell they exert their antimicrobial activity by binding with high avidity and irreversibly to the 16S ribosomal RNA (rRNA) of the 30S subunit of prokaryotic ribosomes in a region that decodes the messenger RNA (mRNA), resulting in disruption of protein synthesis.[210] The avidity of binding presents variability between the different aminoglycosides, depending on the number of amino groups of each one.[209] In gram-positive bacteria, aminoglycoside uptake is reduced by the thicker outer cell wall membranes.[209] Aminoglycosides are generally bactericidal, and their efficacy can be enhanced in several cases by the combination with cell wall inhibiting antimicrobial agents such as beta-lactams and glycopeptides.[210]

Spectrum of Activity of Aminoglycosides

The primary action of aminoglycosides is directed against gram-negative bacteria and mycobacteria.[210] They are especially potent against *Enterobacteriaceae,* but they are also active against *Yersinia pestis, Francisella tularensis,* and lactose nonfermenting GNBs such as *P. aeruginosa* and *A. baumannii.*[210] There are some differences, however, between the different members of the group regarding their in vitro efficacy against different microorganisms.[209] Gentamicin is a potent agent against *Enterobacteriaceae*. Tobramycin has slightly higher activity than gentamicin against *P. aeruginosa* and *Acinetobacter* spp. Amikacin, despite generally having higher MICs than gentamicin against *Enterobacteriaceae,* usually (>80%) remains active against isolates that have acquired resistance to both gentamicin and tobramycin.[209] Against gram-positive bacteria, aminoglycosides are active against methicillin-sensitive *S. aureus* (MSSA). Although MRSA, streptococci, and enterococci are resistant, aminoglycosides are successfully used in combination with other drugs to provide synergistic effect.[209]

Resistance to Aminoglycosides

Bacterial resistance to aminoglycosides can be intrinsic or acquired. Intrinsic resistance may be nonenzymatic (i.e., mutations in the 16S rRNA that confer resistance) or enzymatic (i.e., methylating enzymes modifying 16S rRNA).[211] It should be noted that anaerobic bacteria have intrinsic resistance to aminoglycosides.[209] The main mechanisms of acquired resistance include reduced entry, the presence of efflux pumps (or a combination of both), and enzymatic modification of the drug.[209] Aminoglycoside-modifying enzyme genes are mostly transferred by plasmids and transposons and can result in rapid spread of resistance.[212,213]

PK/PD of Aminoglycosides

The members of the aminoglycoside class share similar PK properties: they are hydrophilic, rapidly distributed from the vascular to extravascular space, have low protein binding (10%–20%), have low V_d,(in healthy adults 0.2–0.3 L/kg), and are primarily excreted unchanged (>90%) by the kidneys with clearance proportional to the glomerular filtration rate (there is a need for dose adjustment in renal impairment).[8,209] The pathophysiologic changes that occur in critically ill patients significantly affect both V_d (significantly increased) and clearance, with a risk for subtherapeutic levels when clearance is augmented or toxic levels in the case of development of renal impairment.[8] In obese individuals, the V_d increases less than expected or even possibly decreases.[214]

The activity of aminoglycosides in vitro is reduced in anaerobic environments and/or environments with acidic PH, which may be particularly relevant in cases of empyema or abscess.[215] Because of their structural and chemical characteristics, aminoglycosides cross biologic membranes poorly, apart from the renal tubular cells and, possibly, the inner ear cells that might possess an inherent transport mechanism.[209] Aminoglycosides cross the blood-brain and cerebrospinal fluid (CSF) barriers poorly, achieving low concentrations in the CSF. They can be instilled in the lumbar sac or intraventricularly for meningitis caused by susceptible aerobic GNB in rare cases that such treatment is necessary.[216] Systematic administration of aminoglycosides achieves low concentrations in the respiratory secretions, and the penetration into the ELF ranges from 32% to 54% compared with serum.[217] Adjunctive inhaled (nebulized) amikacin has been used along with IV standard-of-care treatment for patients with VAP and ventilator-associated tracheobronchitis (VAT) caused by GNBs, but results of clinical trials have not supported its use yet. The results of a recent study suggested that ELF components might inhibit amikacin-mediated bacterial killing, even when amikacin's ELF concentrations are high.[218] Results from infection models regarding optimal dose/dosing interval for inhaled amikacin should be considered in future clinical trials.[218]

Aminoglycosides demonstrate "concentration-dependent" bactericidal activity, have a postantibiotic effect (PAE) (i.e., persistent suppression of bacterial growth after a short antibiotic exposure that is longer with higher concentrations), and show synergism with other antimicrobial agents with cell-wall activity.[8,219] The optimal Cmax is considered to be ≥8–10 × MIC, but recent data have claimed that the AUC 0–24/MIC ratio might better predict their activity and judge target attainment as well in extended-interval dosing of aminoglycosides.[8,220,221]

Dosing and Monitoring of Aminoglycosides

For systematic use, aminoglycosides can be administered IV or intramuscularly. IV, they are usually administered over a period of 15–30 minutes; however, in case of larger doses, it is reasonable to increase the infusion time up to 60 minutes to avoid the rapid rise in serum levels and decrease the potential risk of neuromuscular blockade.[209] It should be noted that aminoglycosides should not be administered at

the same time and same IV line as beta-lactams, because this would lead to inactivation of the aminoglycosides.[222,223] The optimal dosing strategy of aminoglycosides has been debated. Traditionally, the total daily dose of aminoglycoside based on the patient's renal function was administered divided into multiple times per day or, less frequently, the total once-daily dosing. However, once-daily dosing appears to have similar or even better clinical efficacy and may delay the nephrotoxicity onset if used in short durations.[224] Therefore a single high dose with extended intervals is currently recommended in patients with gram-negative infections.[8] Moreover, administration of a higher-than-standard aminoglycoside dosing regimen might be required for critically ill patients.[225–227] Results of PD evaluation of plasma and ELF exposures of amikacin against susceptible *P. aeruginosa* using a dynamic in vitro hollow-fiber infection model suggested that the use of high-dose amikacin may improve its efficacy because of rapid elimination of susceptible bacteria, whereas the efficacy of the subsequent doses may be reduced given the fast amplification of less susceptible bacteria.[228]

Therapeutic monitoring of serum concentrations of aminoglycosides to reguide dosing is essential for both efficacy and toxicity.[8] It has been reported that TDM-guided dosing with Bayesian dose adaptation of gentamicin administered for gram-negative infections led to a decrease of both hospital stay and nephrotoxicity.[229] For critically ill patients specifically, important alterations of V_d and CL have been widely described, and TDM should be routinely performed.

For *C*max/MIC monitoring, one sample should be taken 30 minutes after the end of infusion targeting *C*max/MIC ≥8–10 × MIC.[8,220,221] *C*min monitoring is recommended for treatment of more than 3 days, with one sample taken 30 minutes or just before the next dosing, targeting *C*min for amikacin <2.5 mg/L and for gentamicin/tobramycin <0.5 mg/L; the clinical *C*min threshold for ototoxicity and nephrotoxicity is >5 mg/L and >1 mg/L for amikacin and gentamicin/tobramycin, respectively. However, a recent position paper recommended AUC-based monitoring, with the first sample taken 30 minutes after the end of infusion and the second taken between 6 and 22 hours postinfusion, with target AUC 80–120 mg h/L.[8]

An international survey on aminoglycoside use in ICUs reported that short courses of high doses were mainly used in patients with septic shock, but wide variability existed between different units.[207] The most commonly used aminoglycoside was amikacin (66%), followed by gentamicin (33%) and, in the vast majority (98%), were prescribed in combination with other antimicrobial agents, mostly beta-lactams (96%).[207] TDM was performed in approximately half of the cases (C_{max} in 47% and C_{min} in 57%).[207]

Adverse Events of Aminoglycosides

Nephrotoxicity represents the most common adverse effect of aminoglycosides. Reported rates vary widely from 0% to 50%, with most reports in the range of 5%–25%; this variability may be attributed to different definitions used, different tests, or different clinical settings.[209] The typical presentation of aminoglycoside-related nephrotoxicity is nonoliguric acute kidney injury (AKI) occurring 7–10 days after the onset of treatment.[209] Factors that increase the risk of nephrotoxicity include patient-related factors (older age, preexisting renal disease, volume depletion and hypotension/shock, liver dysfunction), recent aminoglycoside use, larger doses, frequent dosing intervals, longer duration of therapy (≥3 days), concomitant use of other nephrotoxic drugs (e.g., vancomycin, amphotericin B, diuretics, foscarnet, nonsteroidal antiinflammatory drugs [NSAIDs], cyclosporin, tacrolimus, angiotensin-converting enzyme/angiotensin receptor blocker [ACE/ARB]), and use of IV radiocontrast agents.[209] Another serious adverse event of aminoglycosides is ototoxicity that can manifest as auditory (cochlear) or vestibular toxicity.[209] The reported frequency of ototoxicity also varies widely: 2%–10% and 3%–14% for cochlear and vestibular toxicity, respectively.[209] Cochlear and vestibular toxicity may be unilateral or bilateral.[209] Cochlear toxicity may appear days to weeks after discontinuation of aminoglycosides, and high-frequency hearing loss can occur with no symptoms.[209] The true frequency of vestibular toxicity is very difficult to determine, as patients may have suffered severe injury long before the initiation of symptoms.[209] Reported risk factors for ototoxicity include older age, longer treatment duration, impaired renal function, concomitant use of loop diuretics, concomitant use of vancomycin, associated bacteremia, liver dysfunction, hypovolemia, and degree of temperature elevation.[209,230,231] Ototoxicity and nephrotoxicity have been associated with high Cmin and AUC exposures over days.[8]

A rare but severe and potentially lethal adverse event after aminoglycoside administration is the neuromuscular blockade that may lead to flaccid paralysis and respiratory depression.[232] The mechanism of neuromuscular blockade is both presynaptic (inhibition of acetylcholine release) and postsynaptic (blockage of acetylcholine receptor).[209] Risk factors include rapid rise of aminoglycosides in the serum, concomitant use of drugs that interfere with the neuromuscular transmission (e.g., D-tubocurarine, succinylcholine, or similar), hypomagnesemia, hypocalcemia, and may be use of calcium channel blockers, and the role of myasthenia gravis as a risk factor is controversial.[209]

Novel Approved Aminoglycosides

Plazomicin. Plazomicin is a new semisynthetic aminoglycoside for IV use. It was approved by the FDA in 2018 for adult cUTIs, including acute pyelonephritis, in patients with limited or no alternative treatment options.[233]

Mode of Action, Spectrum of Activity, and Resistance Mechanisms. Plazomicin is derived by the addition of an N1 2(S)-hydroxy aminobutyryl and a hydroxyethyl substituent at the 6 position of sisomicin; these structure modifications protect plazomicin from most aminoglycoside-modifying enzymes (AMEs), which typically inactivate previous aminoglycosides, but not against 16S ribosomal methyltransferases that reduce aminoglycoside affinity for the ribosomal target.[101,233,234]

The antibacterial spectrum of plazomicin covers GNBs, including CREs.[101] It is more active against *Enterobacteriaceae* than against lactose-nonfermenting GNBs; it is inactive in vitro against *A. baumannii and S. maltofilia,* and its activity against *P. aeruginosa* is variable.[101,233] The activity of plazomicin against gram-positive bacteria is similar to that of other aminoglycosides; although it demonstrated in vitro activity against *S. aureus* and *Staphylococcus epidermidis,* it is inactive against streptococci (including *Streptococcus pneumoniae*) and enterococci.[208,233] As with the other members of the class, it is inactive against anaerobes.[233] Although plazomicin is active in vitro against CRE and aminoglycoside-resistant *Enterobacteriaceae* containing AMEs, such as acetyltransferases, phosphotransferases, and nucleotidyl-transferases, it is not active against ribosomal (16S mRNA) methyltransferase-containing strains found in most NDM-1-producing *Enterobacteriaceae* that are also resistant to other aminoglycosides, and may have reduced activity against *Enterobacteriaceae* with efflux pump or porin underexpression.[101,233,235,236] Synergy studies have evaluated in vitro the combination of plazomicin with older antimicrobial agents, such as piperacillin/tazobactam and ceftazidime, against MDR *Enterobacteriaceae,* including isolates with aminoglycoside and beta-lactam-resistance, with promising results.[237,238] Also, plazomicin combined with colistin, meropenem, or fosfomycin had synergistic activity against VIM-1– and KPC-2–producing *K. pneumoniae* isolates, whereas combination with meropenem or imipenem showed in vitro synergy against *A. baumannii.*[239,240]

PK/PD. Plazomicin, similar to the other aminoglycosides, is poorly absorbed orally and should be administered parenterally.[208] The V_d of plazomicin is 18–31 L, protein binding is 20% (concentration-independent), it has a half-life of approximately 3.5 hours when renal function is normal, and it is mainly renally eliminated like the other aminoglycosides, without metabolism to an appreciable extent.[101,208,233,241] The lung penetration of plazomicin is quite poor, with ELF to plasma ratio of AUC approximately 13% (similar to the 14% of amikacin).[233,241]

Clinical efficacy. Plazomicin has demonstrated noninferiority in phase III RCTs, in cUTIs, and in acute pyelonephritis compared with meropenem (EPIC study; NCT02486627).[242] In another phase III open-label RCT (CARE study; NCT01970371), plazomicin was compared with colistin (both combined with meropenem or tigecycline) in patients with bloodstream infections or cUTIs (including acute pyelonephritis) or HAP/VAP caused by CRE, and plazomicin showed favorable microbiologic response and decreased all-cause mortality at day 28.[237,243]

Dosage. For dosages, see Table 107.1.[233] The recommended duration for the treatment of cUTI, including pyelonephritis, is 4–7 days.[233]

Adverse events. In the phase III trials plazomicin was generally well-tolerated, and adverse effects were comparable between plazomicin and meropenem arms, with diarrhea, hypertension, headache, nausea, vomiting, and hypotension the most commonly reported ones (>1%).[233] There were no clinically significant events potentially related to ototoxicity.[241] Regarding renal function, increases of ≥0.5 mg/dL in serum creatinine occurred in 7.0% and 4% in the plazomicin and meropenem arms, respectively; after the last follow-up visit, it was assessed that plazomicin conferred an additional 2.3% in serum creatinine rise over the background rate of the patients at any time during the study. The incidence of nephrotoxicity was higher when plasma trough levels were ≥3 μg/mL (36% versus 5%, respectively).[208,233] Neuromuscular blockade has not been reported in the clinical trials of plazomicin to date; however, it is reasonable to be administered with caution in patients with neuromuscular diseases such as myasthenia gravis or when a neuromuscular blocking agent, such as succinylcholine, is administered. There are boxed warnings in the prescribing information of plazomicin regarding nephrotoxicity, ototoxicity, neuromuscular blockade, and fetal harm if administered in pregnancy.[233]

TETRACYCLINES

Tetracyclines are a class of bacteriostatic antibacterial agents that were discovered in the late 1940s. They exert their action by inhibiting bacterial protein synthesis, primarily by reversibly binding to the 30S ribosomal unit, while they also suppress bacterial adhesion to human cells, and thus reduce their pathogenicity.[244] They have a broad spectrum of antibacterial activity, including gram-positive and gram-negative bacteria, atypical bacteria, mycobacteria, and protozoan parasites.[244] The PD parameter that correlates best with activity of tetracyclines is the $fAUC_{0–24}$/MIC ratios. Tetracyclines inhibit bone growth and cause tooth discoloration/enamel hypoplasia and should not be used during tooth development (last half of pregnancy, infancy, and childhood to 8 years).[244]The first-generation tetracyclines include chlorotetracycline, oxytetracycline, tetracycline, and demeclocycline; the second generation includes doxycycline and minocycline; and the glycylcycline tigecycline belongs to the third generation. Very recently novel semisynthetic tetracyclines were branded: the fluorocycline eravacycline and the aminomethylcycline omadacycline.[101,244] In this chapter we only present the members of the class that are more relevant to the critical care setting (i.e., tigecycline, eravacycline, and omadacycline).

Tigecycline

Tigecycline is the first glycylcycline, a class of semisynthetic tetracyclines. It has been approved based on noninferiority studies by both the FDA (2005) and EMA (2006) for the treatment of adults with CSSSIs and cIAIs, and the FDA also granted approval to tigecycline for bacterial CAP in 2009.[245] During the last decade it has been used as salvage treatment for CRE and CRAB infections.[245]

Mode of Action, Spectrum of Activity, and Resistance Mechanisms. Tigecycline has the same mode of action as other tetracyclines, but it is specifically designed to overcome the common mechanisms of resistance against tetracyclines. Specifically, it has been developed by attaching an *N*-alkyl-glycylamido moiety to the 9-position of minocycline, and this addition confers unique microbiologic properties (i.e., tigecycline demonstrates fivefold higher binding affinity to ribosomes compared with older tetracyclines) and is able to overcome resistance mediated by acquired efflux pumps and/or ribosomal protection mechanisms.[246] Although tigecycline is generally considered bacteriostatic, it exerts bactericidal activity against isolates of *S. pneumoniae* and *Legionella pneumophila.*[247] Tigecycline is active against a wide variety of gram-positive and gram-negative aerobic and anaerobic bacteria and atypical bacteria.[245] It covers *Staphylococcus* spp. (methicillin-sensitive and methicillin-resistant strains), *Streptococcus* spp., and *Enterococcus* spp.; it is highly active against community-acquired MRSA and against vancomycin-resistant enterococci strains.[245] Against gram-negative bacteria, tigecycline has good activity against most *Enterobacteriaceae,* excluding *Proteus* spp., *Morganella* spp., and *Providencia* spp. and against lactose-nonfermenting GNBs, including *A. baumannii* and *S. maltophilia*, whereas *P. aeruginosa* and *Burkholderia cepacia* represent notable exceptions.[245] It should be noted that although tigecycline used to be considered one of the most active agents against *A. baumannii,* susceptibility has been reduced over recent years.[245,248] Moreover, high resistance of *Enterobacteriaceae* to tigecycline has been reported in several countries around the world.[245] In Europe, 11.4% of carbapenem-resistant *Enterobacteriaceae* in the SENTRY surveillance program were nonsusceptible to tigecycline, and in the United States resistance rates from 9.2% to 38.5% have been reported.[245,249,250]

The mechanisms of resistance against tigecycline are not fully unraveled. Overexpression of efflux pumps is the most common reported mechanism in gram-negative bacteria, whereas ribosomal alterations have been described in both gram-negative and gram-positive tigecycline-resistant bacteria.[251–253]

PK/PD. The steady-state V_d of tigecycline is high, 500–700 L, and the protein binding is 71%–89% (nonlinear plasma protein binding, with a decrease in unbound fraction as concentration increases).[247,254] It penetrates rapidly to the tissues with resulting low serum concentration that may confuse the assessment of the relationship between serum concentrations and outcomes.[254] It has a long half-life (37–64 hours), as it is released slowly from the tissues.[255] Tigecycline does not undergo extensive metabolism (<10%).[247] The predominant elimination route is biliary excretion of unchanged tigecycline and its metabolites (biliary/fecal excretion 59%), and glucuronidation and renal excretion of unchanged tigecycline represent secondary routes.[247] In healthy volunteers, $AUC_{0–12h}$ in alveolar cells and in the ELF was 78-fold and 32% higher than $AUC_{0–12h}$ in alveolar cells and ELF, respectively.[247] CSF penetration of tigecycline is low.[256,257] A PK study reported that after a single 100-mg IV dose of tigecycline, the concentrations in tissue/fluid were significantly higher compared with serum (expressed as $AUC_{0–4h}$ ratio): in bile (×537), gallbladder (×23), colon (×2.6), and lungs (×2), whereas they were lower in bone (×0.41), synovial fluid (×0.31), and CSF (×0.11).[257] Tigecycline has in vitro time-dependent activity with extended PAE, and the best PD predictor is $AUC_{0–24h}$/MIC.[258]

Clinical efficacy. The efficacy of tigecycline for the indications of cIAIs, cSSSIs, and CAP has been demonstrated in several phase III and IV RCTs.[259–265]. Nevertheless, efficacy for nosocomial pneumonia and

diabetic foot infections has not been established.[266–268] Moreover, in a pooled analysis of 13 clinical trials, an increase in all-cause mortality in tigecycline arms versus the comparators was found (mortality 4.0% versus 3.0%), without the cause of this increase having been clearly established.[247,269] Particularly, in patients with VAP, the arm that received tigecycline had lower cure rates (47.9% versus 70.1% for tigecycline and comparator, respectively) and higher mortality (19.1% versus 12.3% for tigecycline and comparator, respectively), whereas VAP with baseline bacteremia had the highest risk of clinical failure and mortality.[270] Another meta-analysis of 10 clinical trials (including trials after tigecycline's approval) conducted for FDA-approved uses only, also demonstrated increased mortality compared with other drugs (2.5% versus 1.8%, respectively).[247,269] Based on these data, a combination of tigecycline with other antimicrobial agents has been suggested, especially for critically ill patients, such as combinations with colistin, polymyxin B, rifampicin, or meropenem.[271] Also, higher doses (200 mg followed by 100 mg/12 hours instead of the approved dose of 100 mg followed by 50 mg/12 hours) have been used off-label for the treatment of MDR infections and in HAP/VAP.[245] A recent meta-analysis of 10 studies that assessed the effectiveness and safety of high-dose tigecycline compared with the standard dose or other non-tigecycline-containing regimens, reported that the high-dose regimen had lower all-cause mortality, a higher cure rate, and a higher microbiologic eradication rate for the treatment of severe infections. Nonetheless, it was emphasized that the included studies were mostly observational, with a high risk of bias, a fact that represents an important limitation for the generalization of the results, and further studies are needed.[272]

Dosage. For dosages, see Table 107.1. It should be highlighted that an off-label higher dose has been suggested, especially for the treatment of HAP/VAP, *A. baumannii,* CRE, and bacteremic infections (i.e., 100 mg every 12 hours after 200-mg loading dose).[272] The recommended duration of treatment is 5–14 days for SSSIs and cUTIs and 7–14 days for CAP guided by the severity, infection site, and bacteriologic progress.[247]

Adverse events. Nausea, vomiting, diarrhea, abdominal pain, headache, and serum glutamate pyruvate transaminase (SGPT) increase are the most common adverse events with an incidence >5%.[245,247] A higher dose of tigecycline has been related to an augmented risk of gastrointestinal tract adverse events and coagulopathy, usually reversible with tigecycline discontinuation, manifested by a decrease in fibrinogen levels and prolongation of prothrombin time and activated partial thromboplastin time.[245,273–275] Anaphylaxis/anaphylactoid reactions (including life threatening), hepatic dysfunction/liver failure, and pancreatitis, including fatalities, and *C. difficile*–associated diarrhea have been reported.[247] As with the other tetracyclines, tigecycline may cause fetal harm if administered during pregnancy and permanent discoloration of teeth if administered during tooth development.[247]

Eravacycline

Eravacycline is a novel fluorocycline of the tetracycline class of antimicrobial agents, with broad-spectrum antibacterial activity.[101] In 2018 eravacycline was approved by both the FDA and the EMA for the indication of adult cIAIs.[276,277]

Mode of Action, Spectrum of Activity, and Resistance Mechanisms. Eravacycline is a bacterial protein synthesis inhibitor, like the other tetracyclines. It is a synthetic tigecycline analogue with a pair of modifications to the D-ring core at C-7 and C-8; these modifications widen the activity of eravacycline against gram-positive and gram-negative bacteria that have acquired certain mechanisms of resistance against tetracyclines, such as efflux pumps and ribosomal protection mechanisms.[101,278,279] The in vitro ribosomal-binding affinity of eravacycline is 10 times higher than other tetracyclines and inhibits bacterial protein translation at concentrations four times lower.[278,280,281]

The antimicrobial spectrum of eravacycline, as demonstrated by vitro studies, is broad, covering a wide range of microorganisms, including MDR GNBs and MDR gram-positive microorganisms, such as MRSA and VRE.[106,282] Generally, eravacycline is bacteriostatic like the other tetracyclines; however, it is bactericidal against strains of *A. baumannii, E. coli,* and *K. pneumoniae*. Moreover, it should be noted that its activity includes CRAB strains, ESBL-*Enterobacteriaceae,* and some CRE strains, and it is also active against biofilms formed by uropathogenic *E. coli.* [281,283] It should be highlighted, though, that it is not active against *P. aeruginosa* and *Burkholderia cenocepacia.*[281]

PK/PD. The V_d of eravacycline at steady state is approximately 321 L, protein binding is 79%–100% and it increases with increasing plasma concentration, and it has a long half-life of approximately 20 hours. It is mainly metabolized via oxidation by CYP3A4 and FMO; concomitant administration with strong CYP3A4 inducers, such as rifampicin, phenobarbital, carbamazepine, and phenytoin, leads to a clinically significant increase of eravacycline's metabolism.[276,280] After a single IV dose, 34% and 47% of the dose is excreted in the urine and feces, respectively, as unchanged eravacycline and metabolites.[276] Regarding eravacycline's PD, the best predictors of activity are $fAUC_{0–24}$/MIC ratios.[276]

Clinical efficacy. Eravacycline showed noninferiority in phase III RCTs in patients with cIAIs compared with ertapenem (NCT01844856; IGNITE1) and compared with meropenem (NCT02784704; IGNITE4).[284] However, because of poor PK in the urinary tract, eravacycline failed to show noninferiority in two phase III RCTs in patients with cUTIs compared with levofloxacin (NCT01978938; IGNITE 2) and compared with ertapenem (NCT03032510; IGNITE3).[285,286] It is noteworthy that eravacycline is not indicated for cUTIs.[276]

Dosage. For dosages, see Table 107.1.[276] The recommended treatment duration is 4–14 days.[276]

Adverse events. Eravacycline's most common adverse reactions observed in clinical trials (incidence ≥3%) include infusion site reactions (7.7%), nausea (6.5%), and vomiting (3.7%).[276] As it has a similar structure to the tetracycline class of antimicrobial agents, it might have similar adverse reactions, and there are warnings about life-threatening hypersensitivity (anaphylactic) reactions; inhibition of bone growth and tooth discoloration (yellow-gray-brown)/enamel hypoplasia if used during tooth development (last half of pregnancy, infancy, and childhood to 8 years); reversible inhibition of bone growth (if administered from the second trimester of pregnancy to 8 years); and *C. difficile*–associated diarrhea.[276]

Omadacycline

Omadacycline is a novel antibacterial agent from the class of tetracyclines.[1,287,288] In 2018 the FDA approved omadacycline for the treatment of ABSSSIs and CABP.[288]

Mode of Action, Spectrum of Activity, and Resistance Mechanisms. Omadacycline is the first-in-class aminomethylcycline. Similar to the other members of the class, it blocks protein synthesis by binding to the 30S ribosomal subunit.[289] It is active against a broad spectrum of gram-positive microorganisms, including VRE and MRSA, and gram-negative microorganisms, some ESBL-producing *Enterobacteriaceae,* some strains of CRE (KPCs, NDM, OXA-48), *S. maltophilia, A. baumannii* (including some CRAB strains), atypicals, and anaerobes. Notably, it is not active against *P. aeruginosa, Proteus mirabilis, Providencia* spp., and *Morganella morganii.*[1,290] Although it is generally considered bacteriostatic, it showed bactericidal activity against strains of *S. pneumoniae* and *Haemophilus influenzae.*[288]

Similar to eravacycline, the unique structure enables omadacycline to overcome several resistance mechanisms that inactivate tetracyclines, such as efflux pumps and target site protection, and does not seem to have cross-resistance with other antibiotic classes.[288,291]

PK/PD. Omadacycline is the first 9-aminomethylcycline with IV and oral formulations. The V_d of omadacycline at steady state in healthy individuals is 168–288 L, and protein binding was 21%.[287,292] Omadacycline is excreted unchanged in the feces (81.1%) and urine (14.4%), and its potential for drug-drug interactions is low. As with older tetracyclines and eravacycline, the PD parameter that best correlates with activity is the $fAUC_{0-24}$/MIC ratios.[287,292] Omadacycline has PAE that is in general similar to tigecycline.[287,292]

Clinical efficacy. The noninferiority of omadacycline as effective monotherapy for ABSSSI and CABP in inpatient (not ICU patients) and outpatient settings has been established by three phase III RCTs: OASIS-1 (NCT02378480) and OASIS 2 (NCT02877927) studies in patients with ABSSI with linezolid as a comparator and OPTIC (NCT02531438) in patients with CABP with moxifloxacin as a comparator.[291,293,294] The role of omadacycline in the treatment of infections caused by MDR GNBs is still unclear, and clinical trials are needed to evaluate its role against pathogens such as CRE and *A. baumannii.*[1,287]

Dosage. There are formulations of omadacycline for both oral and IV use. For dosages, see Table 107.1.[288] The suggested duration of treatment is 7–14 days.[288]

Adverse events. The most common adverse reactions, with incidence ≥2%, include nausea, vomiting, infusion site reactions, alanine aminotransferase increase, aspartate aminotransferase increase, gamma-glutamyl transferase increase, hypertension, headache, diarrhea, insomnia, and constipation.[288,295] There is a warning for mortality imbalance in bacterial CAP (2% versus 1% for the moxifloxacin arm) but without a clearly established cause for the increased mortality, and caution is advised, especially for CAP patients with higher severity.[288] Moreover, as it belongs to the tetracycline class, there are warnings regarding administration during tooth development (it may cause discoloration and enamel hypoplasia), during bone development (it may cause reversible hypoplasia), and about the possibility of *C. difficile*–associated diarrhea.[288]

POLYMYXINS

Polymyxins are an "old" class of cationic antimicrobial agents that became available in the 1950s, including five different chemical compounds (polymyxin A–E); in clinical practice, polymyxin E (colistin) and polymyxin B have been mainly used. With the exponential increase of MDR GNB worldwide, polymyxins have been "rediscovered" and have become a last-line defense against infections by MDR/XDR (extensively drug resistant) GNBs that are otherwise untreatable.[296] Colistin and polymyxin E, although having almost identical in vitro microbiologic activity, differ in the form administered parenterally to patients, with clinical implications; when both are available, the choice should be carefully considered in each case based on the relative merits.[297]

Mode of Action, Spectrum of Activity, and Resistance Mechanisms

Polymyxins are bactericidal agents that exert their action by disrupting the bacterial membranes.[298] They interact with the lipid A component of lipopolysaccharide (LPS) through anionic displacement of LPS stabilizing magnesium and calcium, resulting in loss of integrity and increased permeability of outer membranes, leakage of cell contents, and eventually, cellular death.[298] This unique mechanism of action, apart from providing rapid bactericidal activity, may also increase the activity of other antibiotic classes.[298]

Polymyxins are active against a wide spectrum of GNBs, including *A. baumanni, P. aeruginosa,* and *K. pneumoniae.* It should be noted, however, that they have poor activity against *Proteus* spp. (most species present high resistance to polymyxins) and against *Providencia* spp., *Serratia* spp., *Moraxella* spp., *Morganella* spp., *Burkholderia* spp., *Aeromonas* spp., *Vibrio* spp., *Helicobacter* spp., *Vibrio* spp., and *Edwardsiella* spp. Polymyxins are not active against gram-positive microorganisms, gram-negative cocci, and anaerobes.[299]

Resistance of gram-negative bacteria to colistin seems to be related to an LPS modification that stops the initial interaction between the positively charged peptides of polymyxins and LPS.[300] A plasmid-mediated resistance mechanism (MCR-1) and resistance conferred by bacterial capsule polysaccharide mutations have been also described.[301,302] It should be highlighted that cross-resistance between polymyxins is complete.[297] Although resistance to polymyxins is still relatively rare, it has been increasingly reported in several countries worldwide, especially for *A. baumanni, P. aeruginosa,* and *K. pneumoniae,* and is in parallel with its increased use in human and animals.[303–305] Regrowth after polymyxin administration, rapid for *A. baumannii* and delayed for *P. aeruginosa,* has been described, attributed in part to the presence of heteroresistance, and therefore the combined use of polymyxins with another active agent has been suggested (with the dose of the other agent to be administered without a long interval from the dose of polymyxin).

PK/PD–Synergy

Polymyxins are rapidly bactericidal antimicrobial agents in a "concentration-dependent" manner, with a PAE for *P. aeruginosa* but not for *A. baumannii.*[8,296]

PK/PD of colistin (*polymyxin E*). Colistin is administered as an inactive prodrug, colistimethate (CMS), also known as colistin methanesulfonate, that is slowly hydrolyzed to active colistin; two forms of colistin are commercially available: for parenteral (IV, intrathecal, intraventricular) or aerosol use and for topical or oral use (not absorbed when given orally).[296,306] Colistin is mainly distributed within the extracellular space, so its V_d is low and can be altered in critically ill patients, as can its clearance.[306] The half-life of CMS is 2 hours, and the half-life of colistin hydrolyzed by CMS is 4 hours. Protein binding is concentration-dependent, reportedly 59%–74%.[307] Two-thirds of CMS is renally cleared within 24 hours, although the active colistin is not renally eliminated. The $fAUC_{0-24}$/MIC ratio is the best predictor of the activity of colistin; $fAUC_{0-24}$/MIC ratios of 10.9–13.7 and 3.5–9.0 are reported as optimal for bactericidal activity against *P. aeruginosa* and *A. baumannii,* respectively.[8,308] Colistin achieves adequate concentration in the liver, kidney, heart, and muscle, but the distribution in the bones, joint fluid, CSF, biliary tract, lung parenchyma, and pleural fluid is poor.[309] After inhalation, serum levels of colistin are very low.[310]

PK/PD of polymyxin B. Polymyxin B is administered in its active form. The profile of polymyxin B is similar to that of colistin, with the AUC_{0-24}/MIC ($fAUC_{0-24}$/MIC) ratio best predicting its activity.[8] The serum half-life of polymyxin B is 9–11.5 hours.[311] Protein binding is high, but presents great variability (58%–98.4%).[8] Contrary to colistin, polymyxin B is eliminated mainly by nonrenal pathways, with <1% recovered unchanged in the urine, and its clearance seems to be relatively unaffected by renal function.[8,312]

Combination of polymyxins with other antimicrobial agents. Colistin and polymyxin B have assumed an important role as salvage therapy for otherwise untreatable gram-negative infections, most notably MDR and XDR strains of *P. aeruginosa, A. baumannii,* and *Enterobacteriaceae.*[313] The increasing reports related to the emergence of polymyxin

resistance with monotherapy lend theoretical support to a possible benefit of a combination with other active antimicrobial agents to achieve enhanced bacterial killing and a suppression of resistant subpopulations.[314] However, the role of such combinations has been debated, and the evidence is quite controversial.[314] Polymyxins have been combined with other antimicrobial agents in vitro for synergy against MDR GNBs, such as imipenem, meropenem, piperacillin, ciprofloxacin, moxifloxacin, amikacin, gentamycin, minocycline aztreonam, cefotaxime, levofloxacin, fosfomycin, ceftolozane/tazobactam, and rifampicin, with maximum synergy having been observed with rifampicin.[314,315] A meta-analysis of RCT and observational studies comparing polymyxin monotherapy and polymyxin-based combination therapy for infections caused by carbapenem-resistant or carbapenemase-producing GNBs reported an increased mortality in cases of monotherapy; however, because of the low quality of evidence, it cannot be taken as proof of positive impact of the combination.[316] Moreover, regarding *A. baumannii* infections, three RCTs did not demonstrate any decrease in mortality with the use of rifampicin/colistin or fosfomycin/colistin.[316] The international guidelines on polymyxin use, although acknowledging and emphasizing the lack of strong evidence, recommend the use of combination therapy for infections caused by CRE, CRPA, and CRA.[296] Specifically, for CRE, CRPA, and CRA, colistin or polymyxin B is recommended to be used combined with one or more antimicrobial agents to which the pathogen displays a susceptible MIC.[296] In case of unavailability of another agent with susceptible MIC for the infecting CRE or CRPA, the combination with a second and/or third nonsusceptible agent (such as carbapenem) is recommended, with priority given to nonsusceptible agents with the lowest MIC relative to the respective susceptibility breakpoint.[296] For infections caused by CRAB, if no additional antimicrobial agent with a susceptible MIC is available, monotherapy with polymyxin B or colistin is recommended.[296]

Dosing and Monitoring

Because of different conventions used to describe dosing of the polymyxins, especially colistin, with several CMS commercial preparations, outdated product information, and other uncertainties regarding polymyxin's use that could lead to dose confusion, international guidelines were published for the optimal use of polymyxins.[296,317–319]

Colistin (polymyxin E) dosing. The international guidelines recommended, for clarity and harmonization, doses to be prescribed as milligrams of the chemical CMA; 1 million internal units (IU) corresponds to ~33 mg colistin base activity (CBA) and also corresponds to ~80 mg of the chemical CMS. For critically ill patients a loading dosing of colistin is recommended because of the expected increased V_d: initiation of IV therapy with a CMS loading dose of 300 mg CBA (~9 million IU) infused over 0.5–1 hours and after 12–24 hours, administration of the first maintenance dose.[8,296,306,307,319,320] The recommended maintenance daily dose is 300–360 mg CBA (~9–10.9 million IU), divided into 12-hour intervals (0.5- to 1-hour infusions). [8,296,319] In cases of renal impairment, the loading dose and the maintenance dose should be adapted to renal function that should be monitored daily (see Table 107.1). Colistin's TDM has an inherent difficulty because of ex vivo conversion of CMS to colistin.[296] The international guidelines recommend that TDM and adaptive feedback control (AFC) be used for colistin whenever available, although they emphasize that the optimal approach for TDM implementation needs to be researched further.[296,321] An $AUC_{ss,24\ hr}$ of ~50 mg·hour/L that is equivalent to a target average steady state plasma concentration ($C_{ss,avg}$) of ~2 mg/L for total drug is required, and this is considered the maximum tolerable target, as higher concentrations have been associated with increased incidence and severity of nephrotoxicity.[296] The *C*ss avg 2 mg/L target is expected to achieve an $fAUC_{0–24}$/MIC ratio of ~12 for pathogens with an MIC of ≤2 mg/L, which is the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoint for susceptibility to colistin for *P. aeruginosa, A. baumannii,* and *Enterobacteriaciae*.[8] The recent position paper on TDM neither recommends nor discourages routine TDM for colistin.[8] It suggests, however, that if TDM is used, as colistin's therapeutic index is remarkably narrow, the sampling and handling should be appropriate, that is, sampling should be done in a way that minimizes ex vivo conversion of CMS to colistin (sampling just before the next dose when both CSM concentrations and conversion are at the lowest), and the samples should be processed immediately.[8] It should be pointed out that colistin concentrations fluctuate only a little at steady state; thus the *C*ss average target can be applied for Cmin monitoring as well.[8]

Polymyxin B dosing. A loading dose of 2.0–2.5 mg/kg for polymyxin B, based on total body weight (equivalent to 20,000–25,000 IU/kg) administered IV over 1 hour, is recommended for patients with severe infections, and the maintenance dose is 1.25–1.5 mg/kg (equivalent to 12,500–15,000 IU/kg) every 12 hours as a 1-hour IV infusion. Adjustment of the loading or the maintenance dose of colistin B is not recommended for renal impairment; nonetheless, additional research is warranted for the definition of the optimal maintenance doses in terms of efficacy and safety.[296,321] Unnecessary renal dose adjustments may lead to underexposure and clinical failure.[296] The international guidelines on polymyxins recommend TDM and AFC to be used if there is availability, with the dosing guidance for polymyxin B having a similar target as for colistin (i.e., $C_{ss,avg}$ of 2 mg/L, seems appropriate). Nevertheless, emerging data suggest that polymyxin B might have a different toxicodynamic profile than colistin, and a $C_{ss,avg}$ of 2–4 mg/L ($AUC_{ss,24\ hr}$50–100 mg·hour/L) may be acceptable in terms of toxicity.[296] The recent position paper on TDM, on the other hand, neither recommends nor encourages monitoring for polymyxin B.[8]

Adverse Events

Dose-related, usually reversible, nephrotoxicity risk and neurotoxicity risk are the major dose-limiting adverse events of polymyxin use.[322,323] Neurotoxicity may manifest as paresthesias and peripheral neuropathy, but the most severe form is neuromuscular blockade resulting in muscle weakness and even apnea with need for ventilatory support until the effect of polymyxin wears off. Curariform drugs potentiate neurotoxicity, whereas IV administration of calcium may contribute to apnea reversal. Overdose of polymyxins, presence of renal impairment, and concurrent use of aminoglycoside increase the risk of nephrotoxicity.[323–326]

FOSFONIC ACID DERIVATIVES: FOSFOMYCIN

Fosfomycin is another "old" antibiotic, discovered in the 1960s, with its use almost abandoned until the mid-2000s, when it again attracted the interest of clinicians and was reintroduced into clinical practice as alternative/salvage treatment for infections by XDR and pandrug-resistant (PDR) GNBs, especially in the critical care setting.[327–338] IV fosfomycin has been approved in several countries, including European ones, encouraging salvage use in the labeling information.[327] In the United States, only the oral formulation is approved, whereas the IV formulation has been granted Qualified Infectious Disease Product and Fast Track designation by the FDA.[327,339]

Mode of Action

Fosfomycin represents an antimicrobial class of its own, without any structural relevance with other currently clinically approved class.[336] It is a bactericidal antibiotic and exerts its action by a unique mechanism of irreversible inhibition of peptidoglycan synthesis, one of the initial

steps of prokaryote wall synthesis, acting in an earlier step than beta-lactams and glycopeptides.[327,328,336] This inhibition eventually leads to cell lysis and death.[327,328,336] This unique mechanism of action makes cross-resistance with other antimicrobial agents most unlikely, and in addition, it allows for synergistic action with other antibiotics, such as beta-lactams, aminoglycosides, and fluoroquinolones.[327,331–333,336]

Spectrum of Activity

Fosfomycin is active against both gram-negative and gram-positive microorganisms, such as *Enterobacteriaceae*, including ESBL- and carbapenemase-producing ones; *S. aureus,* including MRSA, enterococci, including vancomycin-resistant strains; *L. monocytogenes*, and *Neisseria gonorrhoeae.*[327] The sensitivity of streptococcal species is variable, whereas *Staphylococcus capitis* and *Staphylococcus saprophyticus* are intrinsically resistant to fosfomycin.[327,336] The activity against *P. aeruginosa* is moderate with variable MICs, whereas *A. baumannii, B. cepacia,* and *M. morganii* are resistant to fosfomycin, and its use should only be considered as part of a combination regimen.[333,336] It should be noted that the susceptibility testing of fosfomycin is problematic.[327] Regarding resistance to fosfomycin, it can be inherent or acquired, chromosomal or plasmid-mediated, and the main mechanisms include reduced permeability, binding site modification, and enzymatic inactivation; more than one mechanism may coexist.[331,332] Whereas in vitro resistance development is fast, in vivo development is slower.[331,332]

PK/PD

Fosfomycin is a hydrophilic antimicrobial agent with V_d comparable to that of beta-lactams and aminoglycosides, and it has negligible protein binding.[328,336] It is not metabolized, it is almost entirely renally excreted by glomerular filtration unchanged to the urine, and its half-life is 2.3–7.4 hours.[328,333,336] It has good penetration into many tissue types, lungs, CSF, and abscess fluid.[327,336] However, the PK/PD of fosfomycin may be altered in critically ill patients and is not well-studied in the critical care setting.[327,328] A significant PK variability of fosfomycin that could only partially be explained by difference in renal function was reported in a population PK study in critically ill patients.[329] To date, the most appropriate parameter for the PK/PD profile of the drug has not been established, and no well-defined parameters exist to safely predict drug efficacy or resistance development.[327]

Clinical Efficacy

A meta-analysis of RCTs and comparative observational trials about IV fosfomycin reported that it was mostly used for sepsis/bacteremia and infections of the respiratory tract, bone/joint, and CNS and that there were no differences in clinical or microbiologic efficacy.[337] The main use of fosfomycin currently is for MDR, XDR, and PDR pathogens. Studies have shown good efficacy for MRSA infections (even as monotherapy) and against ESBL-producing *E. coli,* carbapenem-resistant *K. pneumoniae* (in combination regimens), and MDR *P. aeruginosa* (in combination regimens).[327,336]

Because of reports of fast resistance development during monotherapy, especially for GNBs, fosfomycin should be used in combination with other active antimicrobial agents, but no specific agent can be recommended, as the available data regarding possible synergies are inconsistent.[327] Some in vitro data suggest a benefit when fosfomycin is coadministered with carbapenems, aminoglycosides, fluoroquinolones, and colistin.[327,336] Also, time-kill experiments have reported promising results against MBL-producing *K. pneumoniae* with triple combinations of fosfomycin with antimicrobials such as colistin, meropenem, rifampin, vancomycin, telavancin, and daptomycin.[336]

Further studies are warranted to establish the correct dose/dosing intervals of IV fosfomycin and the most appropriate companion antimicrobial agents in order to optimize efficacy against difficult-to-treat GNBs.[327]

Dosage

Oral and IV formulations of fosfomycin are available.[327,333] IV doses of fosfomycin up to 24 g daily have been used for severe infections by MDR pathogens (see Table 107.1).[327,335] However, the individual minimum and maximum doses, the infusion duration, and the optimal dosing intervals for fosfomycin administration need to be further established.[327] The limited PK data in critically ill patients prevent accurate dosing guidance, and further studies are needed.[327]

Adverse events. Fosfomycin has a favorable safety profile with unremarkable toxicity and mild adverse events, with diarrhea being the most frequent.[327,336–338] The most significant adverse events are reversible hypokalemia and sodium overload (0.32 g [14 mEq] of sodium in 1 g of disodium fosfomycin), but both are closely monitored and can be corrected in the intensive care setting.[327] Nonetheless, it should be noted, however, that for high doses of fosfomycin (exceeding 16 g/day), further data on safety are needed.

KEY POINTS

- Concerns regarding the rapid spread of antimicrobial resistance against clinically important gram-negative bacteria are ever increasing at a worldwide level, with treatment choices for MDR strains being limited, especially for strains that produce extended-spectrum beta-lactamases and carbapenemases. Carbapenemases particularly inactivate the potent class of carbapenems along with all beta-lactams.
- During the last decade new antimicrobial agents or combinations of beta-lactam with beta-lactamase inhibitors have been approved, reinforcing our armamentarium against gram-negative bacteria, namely ceftolozane/tazobactam, ceftazidime/avibactam, meropenem/vaborbactam, imipenem/cilastatin/relebactam, plazomicin, eravacycline, omadacycline, and delafloxacin. However, the options against carbapenem-resistant *A. baumannii* and MBL-producing strains are still limited. Moreover, resistance against novel anti–gram-negative agents has already started to emerge; implementation of antimicrobial stewardship is essential for the preservation of their activity and the extension of their self-life.
- Older antibiotics, such as polymyxins and fosfomycin, have been "rediscovered" and used as "salvage" treatment for infections caused by MDR gram-negative bacteria.
- The potential for synergy of antibiotic combinations and the impact on outcome improvement are still controversial. However, although there is no definitive evidence yet about the impact of combination therapy on clinical outcomes, it is recommended in patients with difficult-to-treat MDR gram-negative bacteria in order to increase efficacy and limit resistance development. The potential of combinations of the novel antibiotics with the older ones needs to be explored.
- Apart from discovering novel antimicrobial agents, dosing optimization of the current antimicrobial agents, taking into consideration their PK/PD characteristics along with the physiologic changes of critically ill patients, is of utmost importance. TDM allows dosage individualization at the bedside and is expected to significantly contribute to outcome improvement, decrease potential toxicity, and curb resistance development.

References for this chapter can be found at expertconsult.com.

ANNOTATED REFERENCES

Abdul-Aziz MH, Alffenaar JWC, Bassetti M, et al. Antimicrobial therapeutic drug monitoring in critically ill adult patients: A position paper. *Intensive Care Med.* 2020;46(6):1127–1153.

A position paper endorsed by the European Society of Intensive Care Medicine (ESICM), Pharmacokinetic/Pharmacodynamic and Critically Ill Patient Study Groups of European Society of Clinical Microbiology and Infectious Diseases (ESCMID), International Association for Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT), and International Society of Antimicrobial Chemotherapy (ISAC). Available data on TDM of antibacterials, antifungals, and antivirals in critically ill adult patients in the ICU were reviewed and discussed, and a practical guide on how TDM can be applied in routine clinical practice in order to improve outcomes was provided. For critically ill patients, routine TDM was recommended for aminoglycosides, beta-lactam antibiotics, linezolid, teicoplanin, vancomycin, and voriconazole.

Koulenti D, Song A, Ellingboe A, et al. Infections by multidrug-resistant Gram-negative Bacteria: What's new in our arsenal and what's in the pipeline? *Int J Antimicrob Agents*. 2019;53(3):211–224.

A comprehensive review that critically summarizes the novel approved antibiotics for gram-negative bacterial infections, presents promising agents in the pipeline currently in clinical trials (phase III, II, or I), and introduces new alternative avenues with potential to combat multidrug-resistant gram-negative bacteria in the future.

Leone M, Roberts JA, Bassetti M, et al. Update in antibiotic therapy in intensive care unit report from the 2019 Nimes International Symposium. *Anaesth Crit Care Pain Med.* 2019;38(6):647–656.

The 2019 Nîmes International Symposium in Antibiotic Therapy Optimisation aimed at determining the best approaches of a number of the antibiotic management strategies for critically ill patients. A panel of experts, aiming to determine the best antibiotic management strategies in the critical care setting, reviewed the relevant latest literature and presented the available evidence and key messages for the following topics: requirements of optimal antibiotic stewardship program, risks of subtherapeutic dosing of antibiotics in critically ill patients, persisting issues about efficiency of combination therapy and the value of de-escalation, new perspectives of pharmacokinetics, drug toxicities including collateral damages associated with antibiotics, the place of nebulization of antibiotics, management of patients receiving extracorporeal therapies, and the place of new antibiotics.

Roger C, Louart B, Elotmani L, et al. An international survey on aminoglycoside practices in critically ill patients: The AMINO III study. *Ann Intensive Care.* 2021;11(1):49.

A prospective, multicenter, observational cohort study conducted in 59 ICUs in five countries that enrolled 931 consecutive patients receiving aminoglycosides (AG) for septic shock. The 84% of the patients received AG empirically; amikacin was the most frequently used AG, followed by gentamicin (33%), the median (IQR) duration of therapy was 2 (1–3) days, the median dose was 25 ± 6, 6 ± 2, and 6 ± 2 mg/kg for amikacin, gentamicin, and tobramycin, respectively, and the median dosing interval was 26 (23.5–43.5) hours. TDM of C_{max} and C_{min} was performed in 47% and 57% of the patients, respectively. After the first dose 68% of patients achieved a C_{max}/MIC >8, suggesting that efforts to optimize the first AG dose are warranted, and 71% of the patients had C_{min} above the recommended thresholds.

Tsuji BT, Pogue JM, Zavascki AP, et al. International consensus guidelines for the optimal use of the polymyxins: Endorsed by the American College of Clinical Pharmacy (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Society of America (IDSA), International Society for Anti-infective Pharmacology (ISAP), Society of Critical Care Medicine (SCCM), and Society of Infectious Diseases Pharmacists (SIDP). *Pharmacotherapy*. 2019;39(1):10–39.

The first ever consensus therapeutic guidelines for optimal therapeutic use of polymyxins, colistin (polymyxin E), and polymyxin B in adult patients endorsed by the IDSA, ISAP, SCCM, and SIDP. Also endorsed by ESCMID as a consensus statement and the overall document conclusions endorsed by the European Committee on Antimicrobial Susceptibility Testing (EUCAST). The document was developed based on evidence by a diverse international expert panel aiming to make therapeutic recommendations regarding PK/PD properties and PK targets of polymyxins, polymyxin agent selection, dosing, dosage adjustment, TDM, polymyxin-based combination therapy, intrathecal therapy, inhalation therapy, toxicity, and prevention of renal failure.

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Antimicrobial Agents With Primary Activity Against Gram-Positive Bacteria

Kelli A. Cole and Diane M. Cappelletty

Nosocomial infections continue to pose a significant burden on the healthcare system. The most recent summary of data reported to the National Healthcare Safety Network (NHSN) showed that gram-positive organisms remained a leading cause of healthcare–associated infections (HAIs) between 2015 and 2017.[1] Similarly, the EPIC II study in 2007 demonstrated that gram-positive organisms were associated with 47% of infections in the intensive care unit (ICU).[2] *Staphylococcus aureus* and coagulase-negative staphylococci were the most commonly isolated pathogen in nosocomial bacteremia, and the former was responsible for the greatest proportion of ventilator-associated pneumonia and surgical site infections in hospital ICUs. Along with the increase in prevalence of gram-positive cocci in the ICU, staphylococci are becoming multidrug resistant. This chapter addresses gram-positive organisms and resistance issues associated with each of the antimicrobials with activity against these pathogens.

VANCOMYCIN

Vancomycin was discovered in 1956 and marketed in 1958. Early preparations of the drug contained pyrogens and impurities that produced a brownish, muddy appearance that provided vancomycin's nickname, "Mississippi mud." In addition, these pyrogens and impurities caused high fevers, hypotension, severe phlebitis, and possibly nephrotoxicity.[3]

Mechanisms of Action and Resistance

Vancomycin is a glycopeptide that inhibits synthesis of the cell wall by binding to the D-alanyl-D-alanine terminus of cell wall precursor units and is bactericidal against most gram-positive organisms. In the mid-2000s, the Clinical and Laboratory Standards Institute (CLSI) and the U.S. Food and Drug Administration (FDA) changed the vancomycin breakpoints against *S. aureus* from less than or equal to 4 μg/mL to less than or equal to 2 μg/mL for susceptible strains. Intermediate susceptibility is now 4–8 μg/mL, and resistance to vancomycin is greater than or equal to 16 μg/mL.[4] The European Committee on Antimicrobial Susceptibility Testing (EUCAST) changed their vancomycin interpretations against *S. aureus* to less than or equal to 2 μg/mL as susceptible and greater than 2 μg/mL as resistant. These changes in breakpoints will alter how literature is interpreted with respect to the frequency or prevalence of vancomycin-intermediate or vancomycin-resistant *S. aureus* over the past 30 years.

Vancomycin-intermediate *S. aureus* (VISA), defined using the previous breakpoints of minimum inhibitory concentration (MIC) 8–16 μg/mL, was first reported from Japan in 1996; by June 2002, eight cases were confirmed in the United States.[5] A precursor to VISA, known as *heteroresistant vancomycin-intermediate S. aureus* (hVISA), was described around the same time.[6] A systematic review and meta-analysis from 2015 found that both phenotypes are increasing in prevalence.[7] In June 2002, the first case of vancomycin-resistant *S. aureus* (VRSA) with an MIC greater than 32 μg/mL was identified in Michigan, and to date, 14 clinical isolates have been reported.[5,8,9] Although the exact mechanism leading to reduced susceptibility in VISA isolates has yet to be determined, many agree that a common element involves thickening of the cell wall, whereas all VRSA strains possessed the VanA gene.

Nine types of resistance for vancomycin have been isolated from enterococci: VanA, VanB, VanC, VanD, VanE, VanG, VanL, VanM, and VanN. The VanA phenotype, inducible by vancomycin, confers high-level resistance to both teicoplanin (MICs: 16–512 μg/mL) and vancomycin (MICs: 64 to greater than 1000 μg/mL), whereas VanB confers low-level resistance primarily to vancomycin. Both have been identified in *Enterococcus faecium* and *Enterococcus faecalis*. VanA, B, D, and E are all transferable to other organisms. In contrast, the VanC phenotypes are endogenous (constitutively produced) and are components of *Enterococcus gallinarum, Enterococcus casseliflavus,* and *Enterococcus flavescens* and confer resistance to vancomycin alone.

Spectrum of Activity

Vancomycin is active primarily against aerobic gram-positive cocci, including streptococci and staphylococci. Although it is considered the drug of choice for most methicillin-resistant *S. aureus* (MRSA) infections, it has been shown to be inferior to nafcillin or oxacillin for the treatment of methicillin-susceptible *S. aureus* (MSSA), and similarly should be considered an agent of last resort against streptococci.[10,11] It has reliable activity against *Corynebacterium* spp. and is also considered first-line for such infections. The activity of vancomycin against enterococci varies greatly with the species. *E. faecium* is the most resistant, with approximately 80% of strains demonstrating resistance compared with only ~10% of *E. faecalis* strains.[1]

Vancomycin is active against anaerobic gram-positive organisms such as *Peptostreptococcus* spp., *Propionibacterium* spp., *Eubacterium* spp., *Bifidobacterium* spp., and most *Clostridium* spp., including *C. difficile*.[12]

Pharmacokinetics and Pharmacodynamics

Vancomycin is administered orally and parenterally. The drug is poorly absorbed after oral administration, and although the majority of the drug is excreted unchanged in feces, inflammation of the gastrointestinal tract may result in increased absorption.[13] Intramuscular injections are extremely painful and should not be used. Intraperitoneal, intrathecal, or intraventricular administration may be needed in certain circumstances. Vancomycin is approximately 55% bound to plasma proteins. The volume of distribution (V_d) corrected for weight ranges is 0.4–0.9 L/kg.[14–17] Vancomycin does not penetrate well into aqueous humor or noninflamed meninges; however, penetration ranges from 1% to 37% of serum concentrations in the setting of meningeal inflammation.[18–20] Penetration is greater than 75% serum concentrations into ascitic,

pericardial, and synovial fluids; approximately 50% into pleural fluid; and 30%–50% into bile.[16] Elimination of vancomycin is 80%–90% unchanged drug in the urine via glomerular filtration and the remaining via nonrenal elimination (up to 40 mL/min in healthy individuals).[21] The half-life of the drug increases with decreased renal function; in patients with creatinine clearances (CrCl) greater than 80 mL/min, the half-life is 4–6 hours. The pharmacodynamic target predicting efficacy has received much attention and is suggested to be an area under the concentration time curve to MIC (AUC/MIC) ratio of 400.[22]

Dosage Regimens and Therapeutic Monitoring

Therapeutic Drug Monitoring

Routine monitoring of vancomycin serum concentrations has become a highly debated issue over the years. Those who advocate routine monitoring cite the need to ensure therapeutic concentrations and to minimize toxicities.

Studies have shown that peak concentrations of vancomycin are not associated with safety or clinical efficacy. Therefore monitoring peak serum concentrations has largely fallen out of favor. On the other hand, vancomycin troughs have been heavily studied for their correlation with efficacy and toxicity. And although a few publications found improved outcomes when targeting vancomycin troughs of 15–20 μg/mL for serious MRSA infections, mounting evidence suggests that vancomycin troughs of this magnitude (greater than or equal to 15 μg/mL) are associated with an increased risk of nephrotoxicity.[23–25] Because of this, greater attention has been given to AUC-based dosing strategies, with recent literature finding that an AUC/MIC target ratio of ≥400 was associated with decreased mortality and clinical failure while at the same time lower rates of nephrotoxicity and overall vancomycin exposure.[26–29] Unfortunately, AUC monitoring is not routinely performed in clinical practice, and most critically ill patients are inappropriate for AUC-based dosing. Thus it still remains prudent to measure serum trough concentrations until more definitive guidance is provided to address these patient populations.[30]

Intravenous Administration in Adults

In nonobese adults with normal renal function, the usual dose of vancomycin is 1 g (~15 mg/kg actual body weight) intravenously (IV) every 12 hours. For severe MRSA infections, 15–20 mg/kg every 8–12 hours has been recommended to achieve serum trough concentrations of 15–20 μg/mL, and loading doses of 25–30 mg/kg are proposed for critically ill patients in order to achieve higher concentrations sooner (both grade IIIB recommendations).[30] Several dosing nomograms using body weight and CrCl have been developed to accurately and easily dose vancomycin; however, significant interpatient variability exists in both volume of distribution and renal clearance estimation in the critically ill population, so use of these nomograms is limited.[31–34] Similarly, use of continuous infusion has been proposed, but with limited data on its benefit over intermittent infusion.[35,36] Table 108.1 lists dosing regimens for the antimicrobials discussed in this chapter.

Dosing in the Setting of Obesity

Morbidly obese, critically ill patients are difficult to dose given the lack of pharmacokinetic studies. Although actual body weight and CrCl continue to be the best correlate to volume of distribution and vancomycin clearance in the obese population, use of traditional weight-based dosing has led to overexposure and toxicity.[37] This has prompted various alternative dosing strategies, including AUC-targeted nomograms, but these have yet to be studied in the combined critically ill and obese cohort.[38–40] Because of this, therapeutic drug monitoring (TDM) remains a key tool in managing vancomycin dosing in this population.[41,42]

Dosing in Renal Failure/Dialysis

Dose reduction is recommended for patients with renal dysfunction.[15] In patients receiving intermittent hemodialysis, vancomycin pharmacokinetics vary depending on the patient's actual body weight, timing of administration, residual renal function, and type of dialysis membrane used. With older, low-flux membranes, less frequent and lower postdialysis supplemental doses are required.[43] With high-flux membranes, as much as 50% of vancomycin is removed.[44–49] In these situations, common practice involves administration of a weight-based loading dose followed by maintenance doses given during the last hour of each dialysis session.[50] Use of trough levels before each dialysis session may further guide dosing.

When continuous renal replacement therapy (CRRT) is being used, vancomycin dosing again depends on patient- and dialysis modality–related factors. Continuous venovenous hemodialysis (CVVHD) and continuous venovenous hemodiafiltration (CVVHDF) result in a greater total body clearance of vancomycin than does continuous venovenous hemofiltration (CVVH); therefore dosing every 12–24 hours and every 24–48 hours has been proposed for each modality, respectively.[21,51–53] For patients receiving sustained low-efficiency dialysis (SLED), a newer modality combining intermittent hemodialysis and CRRT, it appears that an initial weight-based loading dose followed by maintenance doses coupled with TDM may be appropriate.[54] Overall, a review of several pharmacokinetic studies in patients receiving various forms of CRRT showed an association between effluent flow rate and vancomycin clearance. However, these findings require additional validation.[55] Based on the variability in clearances achieved with each of these methods depending on blood flow rate, ultrafiltration rate, and the membranes used, TDM remains an effective method of ensuring appropriate vancomycin dosing when CRRT is used.

Dosing in Cardiopulmonary Bypass/Extracorporeal Membrane Oxygenation

Cardiopulmonary bypass (CPB) was found to significantly affect the pharmacokinetic parameters of vancomycin in several small studies over the past 20 years. For example, Ortega and colleagues observed an immediate decrease in vancomycin serum concentration by 7 μg/mL after initiation of CBP, followed by gradual and steady decreases over the next 30 minutes.[56] However, a recent prospective, comparative evaluation of vancomycin pharmacokinetics found no difference in maximum plasma concentration (C_{max}), area under the curve ($AUC_{0–8}$), V_d, and clearance (Cl) between patients undergoing cardiac surgery with and without CBP.[57]

Three studies in adult patients receiving extracorporeal membrane oxygenation (ECMO) found no significant differences in pharmacokinetic parameters compared with matched controls, reflecting vancomycin's relative stability in ECMO circuits.[58]

Oral Administration

Oral administration of vancomycin is only for treating *C. difficile* colitis. The dose is 125–500 mg orally every 6 hours depending on severity and is not adjusted for renal dysfunction. Two oral formulations (capsules or liquid) can be used, or the IV solution can be administered orally to treat *C. difficile*. In cases of ileus or toxic megacolon, administration via rectal tube (as a retention enema) or ileostomy can be considered.

Adverse Effects

The most notable adverse effects associated with vancomycin include nephrotoxicity, ototoxicity, and infusion-related reactions.

Initial reports of nephrotoxicity were thought to be related to impurities in the early formulations.[3] After improved purification methods,

TABLE 108.1 Dosages for Agents With Primary Activity Against Gram-Positive Bacteria

Drug	Dosage	Adverse Effects	Considerations
Vancomycin	Oral (PO) and intravenous (IV) administration Dose based on actual body weight (ABW) PO: 125–500 mg q6h IV: 1 g (~15 mg/kg) q12h for average-weight adult or 15 mg/kg loading dose followed by 30 mg/kg/day continuous infusion IV: For morbidly obese adult, dose on ABW ~15 mg/kg/dose	Red man syndrome: erythema, pruritus, flushing of upper torso Thrombophlebitis Ototoxicity: rare Nephrotoxicity: rare Maculopapular or erythematous rashes	Intramuscular injections painful Poorly absorbed orally Half-life of drug increases with decreased renal function Optimal target to be determined For obese patients and patients on dialysis, consider therapeutic drug monitoring
Teicoplanin	PO and IV administration PO: 200 mg BID (*Clostridium difficile*–associated diarrhea) Moderate infections: 400 mg (6 mg/kg) once followed by maintenance dose 200 mg (3 mg/kg) q24h Severe infections: 400–800 mg (6–12 mg/kg) q12h for 2–3 doses, followed by 400–800 mg q24h	Nephrotoxicity: rare Ototoxicity: rare Hypersensitivity	Special dosage considerations for patients with renal failure, patients on dialysis Compassionate use only in the United States (not FDA approved)
Telavancin	IV: 10 mg/kg once daily	Nausea and vomiting Taste perversion Foamy urine Renal impairment	Teratogenic in animal models, further information needed in humans Interferes with common anticoagulation and urine protein dipstick testing
Daptomycin	IV: 4 mg/kg q24h for average-weight adult for skin and skin structure infection 6 mg/kg q24h for bacteremia/endocarditis	Transient muscle weakness Myalgia CPK elevations	Contraindicated in pneumonia 8–12 mg/kg considered for serious infections
Linezolid	Bioequivalence between PO and IV formulations Moderate infections: 600 mg twice daily Uncomplicated infections: 400 mg twice daily	Reversible myelosuppression Anemia Neutropenia Thrombocytopenia Monoamine oxidase interactions Peripheral and optic neuropathy	Oral formulation is bioequivalent to IV formulation Caution with prolonged use and in patients on selective serotonin reuptake inhibitors (SSRIs)
Tedizolid	Bioequivalence between PO and IV formulations 200 mg daily for acute bacterial skin and skin structure infections	Nausea, vomiting, diarrhea Headache Dizziness	Less myelosuppressive and risk for monoamine oxidase interaction
Quinupristin/dalfopristin	IV: 7.5 mg/kg q8–12h infused over 1 hr	Arthralgia Myalgia Infusion-related Nausea, vomiting, diarrhea, rash	Last-line agent because of significant toxicities

the rate is generally accepted to be between 5% and 10% when vancomycin is not administered with other nephrotoxic agents and trough concentrations are less than 10 μg/mL.[59–61] Factors that may increase the risk of nephrotoxicity include trough concentrations >15 μg/mL, higher total daily doses (≥4 g/day), larger patient weight, prolonged durations (>7 days), and concomitant nephrotoxins (i.e., aminoglycosides).[23,61–67] Recently, piperacillin-tazobactam in combination with vancomycin has also been associated with increased risk of acute kidney injury when compared with either agent alone and when compared with combinations of vancomycin with other beta-lactams.[68,69] On the other hand, use of continuous infusion appears to lower these risks.[35] Although vancomycin-associated nephrotoxicity is usually reversible, it can lead to increased hospital length of stay, healthcare costs, and even mortality.[62]

Ototoxicity is rare and ranges from vertigo and tinnitus to hearing loss.[3,59] Correlation between vancomycin exposure and risk of ototoxicity is lacking, suggesting that early reports of toxicity may have been caused by either another drug or the combination of another drug with vancomycin.[59,70] In the majority of cases, ototoxicity symptoms disappear within a month of discontinuing vancomycin.

Red man syndrome comprises erythema, pruritus, and flushing of the upper torso and is often associated with too rapid an infusion of the drug. In general, the infusion rate should not exceed 1 g/hr. Less frequently, hypotension and angioedema can occur. It is thought that increased histamine release is the cause of this syndrome, and the effects can be relieved by antihistamines.[3,59,71–74]

Other toxicities associated with vancomycin include maculopapular or erythematous rashes (2%–8%)[17,75,76] and anecdotal reports of neutropenia and thrombocytopenia.[75,77]

TEICOPLANIN

Teicoplanin is a glycopeptide antibiotic and is not approved for use in the United States. It is available for use in Europe, some Asian countries,

Mexico, New Zealand, and Australia. It has a more favorable adverse effect profile than vancomycin; however, there is concern over teicoplanin's clinical efficacy in the treatment of severe gram-positive infections.

Mechanisms of Action and Resistance

Teicoplanin, like other glycopeptide antibiotics, inhibits synthesis of the cell wall by binding to the d-alanyl-d-alanine terminus of cell wall precursor units. Resistance has been reported in both staphylococci and enterococci. The VanA phenotype confers high-level resistance to both teicoplanin (MIC: 16–512 μg/mL) and vancomycin (MIC: 64 to >1000 μg/mL). The VanB phenotype has also been identified in both *E. faecium* and *E. faecalis* and usually confers low-level resistance to vancomycin but not to teicoplanin. This resistance may limit the utility of teicoplanin for some vancomycin-resistant enterococcal infections. Several reports of *S. aureus* resistance developing during therapy with teicoplanin have been reported.[78–81] The mechanism of the resistance was determined in one patient to be constitutive and non–plasmid-mediated.[79] Most phenotypes of hVISA and VISA demonstrate cross-resistance to teicoplanin.[82]

Spectrum of Activity

Teicoplanin is only active against gram-positive organisms. Activity against MSSA and MRSA is comparable to that of vancomycin. Coagulase-negative staphylococci have a varied pattern of susceptibility to teicoplanin. *Staphylococcus haemolyticus* is the most resistant species to teicoplanin (30%).[76] For methicillin-resistant coagulase-negative staphylococci, 39% of isolates have teicoplanin MICs greater than 8 μg/mL compared with 1% with vancomycin.[76,83] Teicoplanin is active against other aerobic and anaerobic gram-positive organisms such as *Corynebacterium* spp.; *Clostridium* spp., including *C. difficile* and *C. perfringens; Peptostreptococcus* spp.; and *Propionibacterium acnes*.

Pharmacokinetics and Pharmacodynamics

Teicoplanin is administered orally and intravenously. The drug is poorly absorbed after oral administration, and approximately 40% of the drug is excreted unchanged in feces. IV administration of 400 mg (6 mg/kg) should provide a peak serum concentration of 20–50 μg/mL attained 1 hour after administration.[84] The volume of distribution is large, at 0.9–1.41 L/kg, and teicoplanin is 90%–95% protein bound.[84] Tissue distribution is variable; most notably, penetration is poor into noninflamed meninges and fat but good into myocardium and pericardium.[85] Teicoplanin is primarily eliminated via glomerular filtration, and only 3% is metabolized.[84] The half-life is approximately 150 hours in patients with normal renal function.[84] In patients with mild to moderate renal dysfunction, the half-life was found to be 157–567 hours.[85,86]

Dosage Regimens and Therapeutic Monitoring

Despite the long half-life in patients with normal renal function, teicoplanin should be administered daily, and the dose is dependent on the severity of infection. For less serious infections involving the urinary tract, skin, soft tissue, and lower respiratory tract, a loading dose of 400 mg (6 mg/kg) × 1 is administered, followed by a maintenance dose of 200 mg (3 mg/kg) every 24 hours. For severe infections such as septicemia, endocarditis, and osteomyelitis, 400 mg of teicoplanin is administered every 12 hours for 3 doses, followed by 400 mg every 24 hours. For specific clinical scenarios such as *S. aureus* endocarditis, levels between 20 and 30 mg/L have been recommended. Therefore higher doses (up to 12 mg/kg) are suggested.[84,87]

Dosing in Renal Failure/Dialysis

Teicoplanin is not removed by hemodialysis or continuous ambulatory peritoneal dialysis (CAPD).[88,89] The amount removed by high-flux membranes such as CVVH, CVVHD, and CVVHDF can be significant.[90–92] For renal dysfunction, several dosing regimens exist, with doses even as high as 600–1800 mg/day during CVVH.[91] Even with such high doses, therapeutic drug monitoring is still recommended, given the variability in protein binding and ultrafiltration rates when using CRRT.

Dosing in Venoarterial Extracorporeal Membrane Oxygenation

Limited data are available on the use of teicoplanin in patients receiving venoarterial extracorporeal membrane oxygenation (VA-ECMO). Eleven patients received a median loading dose of 11.6 mg/kg every 12 hours × 3 then a fourth dose 24 hours after the third dose. The range of trough concentrations was 14.85–44.84 μg/mL.[93]

Adverse Effects

Nephrotoxicity associated with teicoplanin is much lower than with vancomycin. The incidence from published and unpublished studies found the nephrotoxic rate to be 4%.[71] Ototoxic rates with teicoplanin are similar to those with vancomycin.[71] Hypersensitivity reactions are the most common adverse reaction to teicoplanin (2%–15%).[71]

TELAVANCIN

Mechanisms of Action and Resistance

Telavancin is a lipoglycopeptide derivative of vancomycin that has a dual mechanism of action. It binds to the d-alanyl-d-alanine terminus of the cell wall precursors, as does vancomycin, but additionally binds to bacterial membranes, resulting in depolarization and increased permeability of the membrane.[94,95] This dual mode of action, in addition to structural differences, allows for enhanced activity against MRSA and some enterococci.[96] The acquired VanA phenotype in enterococci confers resistance to telavancin. However, susceptibility is retained with the VanB phenotype.[97] Van-mediated resistance in *S. aureus* leads to reduced telavancin activity but not as great as for vancomycin. In vitro studies have shown a low rate of de novo resistance development in both staphylococci and enterococci, even with previous vancomycin exposure, and currently only one case of elevated telavancin MIC has been reported with clinical use.[98–104]

Spectrum of Activity

Telavancin is active against MSSA, MRSA, coagulase-negative staphylococci, vancomycin-susceptible enterococci, *Streptococcus pyogenes, Streptococcus agalactiae,* and *Streptococcus anginosus*. The MIC_{90} against both MSSA and MRSA is 0.06 μg/mL, and despite higher MICs, telavancin does have activity against vancomycin-intermediate and vancomycin-resistant strains (MIC ranges of 0.03–0.25 μg/mL, 0.06–0.5 μg/mL, and 0.25–8 μg/mL against hVISA, VISA, and VRSA, respectively).[105–110] Against *Enterococcus* spp., telavancin is slightly less potent, and greater activity is seen against vancomycin-resistant strains, with VanB over those with VanA.[97,105–110] Telavancin is active against most anaerobic gram-positive organisms, including *C. difficile* and *C. perfringens*.[111]

Pharmacokinetics and Pharmacodynamics

Telavancin is administered IV and demonstrates linear pharmacokinetics over doses of 7.5–15 mg/kg. In healthy subjects, doses of 7.5 and 15 mg/kg at steady state resulted in mean C_{max} serum concentrations of 88 and 186 μg/mL and trough concentrations of 6 and 16 μg/mL, respectively.[112] Approximately 70% of telavancin is renally eliminated, and the half-life was dose dependent and ranged from 6 to 7.5 hours.[112] Telavancin is 90% protein bound to albumin and has a volume of distribution of approximately 0.14 L/kg.[113] Telavancin penetrates lung epithelial lining fluid and alveolar macrophages well, and concentrations

exceeded 0.5 μg/mL during the entire dosing interval.[114] Penetration into blister fluid is approximately 40% of serum concentrations but only 1%–2% into inflamed meninges.[115,116]

Telavancin exhibits rapid concentration-dependent killing. The pharmacodynamic parameter identified in animal models as the best predictor of efficacy is the AUC/MIC ratio, with a target of 219 resulting in optimal killing.[117,118]

Dosage Regimens and Therapeutic Monitoring

For both complicated skin and skin structure infections and hospital-acquired/ventilator-associated pneumonia, telavancin is dosed 10 mg/kg IV every 24 hours when CrCl is over 50 mL/min.

Dosing in Renal Failure/Dialysis

Because of the high urinary elimination of telavancin, dosage reductions are required when the patient's CrCl falls below 50 mL/min. If CrCl is 30–50 mL/min, the dose of telavancin is 7.5 mg/kg every 24 hours; when less than 30 mL/min, the dose is further reduced to 10 mg/kg every 48 hours.[113,118] Hemodialysis does not have a significant impact on telavancin removal.[119] In vitro studies evaluated the effect of CRRT on telavancin elimination and found high ultrafiltrate or dialysate rates can remove a significant amount of telavancin, which could require supplemental dosing.[120]

Dosing in the Setting of Obesity

A linear relationship is seen between body weight and clearance, thus supporting the milligram per kilogram dosing strategy; however, further investigation is warranted, given the potential overestimation of CrCl using total body weight.[121,122]

Adverse Effects

Little information is available about the safety of telavancin in pregnant women. In three animal species, telavancin was found to have fetal effects including decreased birth weight and increased digit and limb malformations. A serum pregnancy test should be performed in women of childbearing age before starting telavancin. A pregnancy exposure registry is available should there be a need to use telavancin in a pregnant woman.[113]

The most common adverse effects associated with telavancin are nausea, vomiting, diarrhea, taste disturbance, foamy urine, and renal impairment.[113,123–126] Telavancin interferes with urine protein qualitative dipstick tests and several anticoagulation tests, including prothrombin time (PT), activated partial thromboplastin time (APTT), international normalized ratio (INR), activated clotting time (ACT), and factor X activity assays.[113] For this reason, concomitant use with unfractionated heparin is contraindicated.[113,127] When measuring anticoagulation, these tests should be performed as close as possible before a patient's next dose or alternative monitoring methods considered.[113]

DAPTOMYCIN

Daptomycin is a lipopeptide that was first discovered in the 1980s and was approved in 2003 by the FDA for complicated skin and skin structure infections and in 2006 for *S. aureus* bloodstream infections, including right-sided endocarditis.

Mechanisms of Action and Resistance

Daptomycin has a unique mechanism of action targeting the cell membrane in the presence of calcium.[128,129] To date, there have been several case series and case reports describing daptomycin resistance in patients with *S. aureus*.[130] The mechanism appears to be multifactorial, with cell membrane changes being largely implicated. Development of resistance in enterococcus has been observed as well.[131] However, in contrast to *S. aureus,* genetic pathways appear to be the key alterations explaining this phenomenon. Clinically, the development of resistance has led to treatment failures and the need for salvage therapy.

Spectrum of Activity

Daptomycin's rapid, concentration-dependent antibacterial activity encompasses most gram-positive bacteria (staphylococci, pneumococci, and enterococci), including vancomycin-resistant and penicillin-resistant strains. Because of the calcium-dependent nature of daptomycin activity, all in vitro testing must be supplemented with physiologic concentrations of calcium.[132] The breakpoint for susceptibility is less than or equal to 1 μg/mL for staphylococci and beta-hemolytic streptococci. Isolates with higher MICs are considered nonsusceptible. Although rare, 0.03% and 0.06% of *S. aureus* strains were found to be nonsusceptible in the United States and Europe, respectively.[133] Daptomycin initially appeared active against vancomycin-intermediate and vancomycin-resistant strains of *S. aureus*. However, a recent analysis of 33 VISA isolates found 70% resistance to daptomycin.[134] Interestingly, 100% of VRSA isolates were susceptible, possibly because of the difference in resistance mechanisms. The FDA breakpoint for susceptibility against enterococci is less than or equal to 4 μg/mL, whereas EUCAST is currently reviewing and CLSI has recently established new cutoffs.[135,136] This includes a definition of susceptible dose-dependent (MIC ≤ 4 μg/mL), warranting higher doses of 8–12 mg/kg, or resistant (≥8 μg/mL) for all *E. faecium* isolates. On the contrary, ≤2 μg/mL is considered susceptible, 4 μg/mL intermediate, and ≥8 μg/mL resistant for all other *Enterococcus* spp. Daptomycin resistance is more common in enterococci compared with staphylococci and is higher among *E. faecium* than *E. faecalis*.[133]

Pharmacokinetics and Pharmacodynamics

Daptomycin given as either a 30- or 2-minute infusion demonstrates linear kinetics at dosing from 4 to 12 mg/kg.[136,137] The drug is 90%–95% protein bound and has a lower affinity for tissue proteins, leading to a small volume of distribution and relatively low rate of central nervous system (CNS) penetration.[136] Although it does distribute to lung parenchyma, it is inactivated by pulmonary surfactant, rendering it ineffective in bronchoalveolar pneumonia. It is primarily eliminated by the renal route, and the half-life is 7–9 hours in patients with normal renal function.[136] In patients with CrCl less than 30 mL/min, end-stage renal disease, hemodialysis, or peritoneal dialysis, a 4 mg/kg dose should provide peak serum concentrations around 25–30 μg/mL and a half-life of about 30 hours.[136]

Daptomycin is rapidly bactericidal and exhibits concentration-dependent killing against gram-positive organisms, including enterococci.[128,129] Daptomycin also exhibits a postantibiotic effect that allows for once-daily dosing.[138]

Dosage Regimens and Therapeutic Monitoring

Intravenous Administration in Adults

For complicated skin and skin structure infections, dosing of daptomycin is 4 mg/kg every 24 hours. Dosing for *S. aureus* bacteremia or right-sided endocarditis is 6 mg/kg every 24 hours.[136] Limited clinical evidence suggests consideration of higher doses (8–12 mg/kg) in specific scenarios such as MRSA bacteremia or deep-seated enterococcal infections.[139,140]

Dosing in the Setting of Obesity

Daptomycin exposure is greater in obese patients, but does not exceed safety thresholds.[141,142] Based on this, recommendations have been to base daptomycin dosage on total body weight. However, recent data

demonstrate greater risk for toxicities in this population, such as creatine phosphokinase (CPK) elevations, and some may advocate for alternative dosing strategies.[143–147] Despite this, there is currently insufficient evidence to routinely use other weight measurements, such as ideal body weight or adjusted body weight, when determining daptomycin dosage, especially in critically ill obese patients.

Dosing in Renal Failure/Dialysis

In patients with CrCl less than 30 mL/min or undergoing hemodialysis or chronic peritoneal dialysis, the dose should be reduced and given every 48 hours according to the underlying infection.[136] In patients undergoing CRRT, the amount of daptomycin removed is dependent on the type of filter and the flow rates.[148] Dosing recommendations for patients undergoing CRRT are 4–6 mg/kg every 48 hours, although there is some speculation that doses may need to be increased to 8–10 mg/kg every 48 hours or 4–6 mg/kg every 24 hours.[52,149–154] Similarly, a dose of 6 mg/kg every 24 hours has been proposed for patients receiving extended daily dialysis (EDD).[155] Despite this, until more data are obtained, the use of higher doses should be balanced with the risk of adverse effects.

Dosing in Cardiopulmonary Bypass/Extracorporeal Membrane Oxygenation

Daptomycin administered at a dose of 8 mg/kg to patients undergoing cardiopulmonary artery bypass grafting requiring CPB produced mean concentrations greater than 30 μg/mL throughout the procedure and until sternum closure.[156] In a single ex vivo study examining daptomycin concentrations after passage through pediatric and adult ECMO circuits, no significant daptomycin loss was observed at 24 hours.[157]

Dosing in Burn Patients

One study evaluated single-dose pharmacokinetics (4 mg/kg) in burn patients and found the C_{max} was 44% lower, with 47% lower AUC and an increase in volume of distribution and clearance.[158] The authors suggest a dose of 10–12 mg/kg in burn patients should provide the same drug exposure as 6 mg/kg in healthy volunteers.

Adverse Effects

CPK concentrations increased in 2.8% of patients treated with daptomycin in the complicated skin and skin structure infection studies and 9.2% in the bacteremia/endocarditis trial.[129,136] Elevations in CPK can occur 2–3 days before clinical signs or symptoms of myopathy present but generally return to normal upon discontinuation of the drug.[138] Daptomycin minimal concentrations (C_{min}) above 24.3 mg/L and concomitant statin therapy have been associated with increased risk of this adverse effect.[144,159]

LINEZOLID

Linezolid was approved in 2000 by the FDA for several indications involving susceptible gram-positive organisms, including skin and skin structure infections, community-acquired and nosocomial pneumonia, and vancomycin-resistant *E. faecium* infections (including those with concomitant bacteremia).

Mechanisms of Action and Resistance

Linezolid is an oxazolidinone antibiotic, a newer class of synthetic agents. Linezolid binds to the 50S ribosome and inhibits the binding of messenger RNA (mRNA), thereby preventing protein synthesis.[160] Clinical isolates of *S. aureus, E. faecium,* and *E. faecalis* resistant to linezolid have been identified, but rates are low (≤1.5%) and have remained relatively stable.[161] The most common mechanism of resistance is chromosomal alteration of the 23S ribosomal RNA (rRNA).[161] Other emerging mechanisms involve acquisition of the natural resistance gene, *cfr,* and a newly identified gene, *optrA,* both of which have been increasing in linezolid nonsusceptible isolates in recent years.[162–165] This finding is worrisome because the *cfr* gene confers resistance to other antimicrobial classes, including chloramphenicol and clindamycin, and both genes are transmissible.[163] These resistance issues, although rare, do raise concern and emphasize the importance of appropriate use of linezolid.

Spectrum of Activity

The FDA and CLSI breakpoint for susceptibility to linezolid is less than or equal to 4 μg/mL for staphylococci and less than or equal to 2 μg/mL for enterococci and streptococci. EUCAST breakpoints are less than or equal to 4 μg/mL for staphylococci and enterococci and less than or equal to 2 μg/mL for streptococci. It is active against both MSSA and MRSA and VISA and VRSA.[134,161,166,167] Linezolid is equally active against both vancomycin-susceptible and vancomycin-resistant enterococci and both penicillin-susceptible and penicillin-resistant *S. pneumoniae*.[161,168] Linezolid is also active against a variety of other organisms, including *Pasteurella multocida, Peptostreptococcus* spp., *Fusobacterium* spp., and *Prevotella* spp.

Pharmacokinetics and Pharmacodynamics

Linezolid is available in both oral and IV formulations. Oral absorption is over 90%, making the oral formulation bioequivalent to the IV formulation. The peak serum concentration and half-life at steady state after 600 mg twice daily are 14–18 μg/mL and 5–6 hours.[169–171] Linezolid is approximately 30% protein bound and penetrates quickly into bone, fat, and muscle, achieving 50%–60% of serum concentrations in bone and 90%–95% in muscle.[172] Cerebrospinal penetration has been documented in patients with meningitis at a fluid/plasma ratio around 1, and pulmonary distribution is excellent.[173–177] Elimination of linezolid is 30% renal and 70% metabolized to inactive metabolites, with essentially no linezolid eliminated in feces as unchanged drug.[171] Linezolid is not an inducer of the cytochrome P-450 enzyme system.

Linezolid is bacteriostatic against staphylococci and enterococci and is bactericidal against streptococci. It demonstrates time-dependent pharmacodynamics, and the parameters that best model the killing activity are an AUC/MIC ratio >100 and %T > MIC of ≥85%.[178]

Dosage Regimens and Therapeutic Monitoring

Intravenous Administration in Adults

The usual dose of linezolid is 600 mg twice daily, and for uncomplicated skin and skin structure infections, the dose is 400 mg twice daily. In critically ill patients, linezolid pharmacokinetics have been found to vary significantly and may lead to insufficient levels in those receiving standard dosing.[179–183] For this reason, alternative dosing strategies (i.e., continuous infusion, increased frequency, higher doses) coupled with TDM have been proposed; however, further studies are needed to assess the efficacy and safety of this.[179,184]

Dosing in the Setting of Obesity

Body weight has been associated with alterations in linezolid kinetics; however, no concrete dose adjustments have been recommended for critically ill, obese patients.[178,185,186]

Dosing in Renal Failure/Dialysis

Hemodialysis removes approximately 30% of linezolid during a 3- to 4-hour session, and limited data exist on peritoneal dialysis removal. However, no dosage adjustment is needed in patients with

renal dysfunction or end-stage renal disease. During different modalities of CRRT, linezolid removal is variable and has the potential to lead to subtherapeutic levels; however, further studies are warranted to determine the optimal dosing regimen when CRRT is used.[187,188]

Dosing in Burn Patients

In a small study of severe burn patients, the volume of distribution and renal clearance were similar to healthy controls; however, total clearance was higher, likely the result of increased nonrenal clearance in those with thermal injuries (323 + 191 vs. 80.4 + 27.5 mL/min, $P = 0.063$).[189]

Adverse Effects

Reversible myelosuppression is the most significant adverse effect associated with linezolid therapy. Anemia, neutropenia, and thrombocytopenia have all been reported, and the incidence increases with durations of therapy exceeding 14 days.[190,191] Renal dysfunction and elevated linezolid concentrations have also been associated with this toxicity.[192] Complete blood cell counts should be monitored weekly, especially in patients in whom the duration of therapy is likely to exceed 2 weeks.

Linezolid is a reversible, nonselective inhibitor of monoamine oxidase; therefore the potential for interaction with adrenergic and serotonergic agents exists. Several case reports of serotonin syndrome (fever, agitation, tremors, and mental status changes) secondary to an interaction between linezolid and selective serotonin reuptake inhibitors (SSRIs) have been identified.[193]

Serious reactions, including optic or peripheral neuropathy, have been increasingly reported and are generally seen after longer durations of linezolid therapy.[193] Optic neuropathy tends to be reversible upon discontinuation of linezolid, but peripheral neuropathy tends to be permanent.[193] The mechanism underlying this neuropathy is thought to involve the inhibition of mitochondrial protein synthesis.[193,194] Lactic acidosis, another potentially fatal effect, is also thought to be caused by prolonged therapy and mitochondrial disruption.[195]

TEDIZOLID

FDA-approved in 2014 and European Medicines Agency (EMA)–approved in 2015, tedizolid is currently indicated only for the treatment of acute bacterial skin and skin structure infections.

Mechanisms of Action and Resistance

Tedizolid phosphate, the prodrug of the active moiety tedizolid, is a second-generation oxazolidinone. It acts via a mechanism similar to linezolid in preventing protein synthesis by binding to the 50S ribosome.[196] Owing to the incorporation of a D-ring substituent and a hydroxymethyl group, however, tedizolid exhibits fourfold to eightfold greater potency against staphylococcal, streptococcal, and enterococcal isolates.[197,198] These structural changes are also responsible for tedizolid's ability to maintain activity against some oxazolidinone-resistant organisms expressing the *cfr* gene.[199,200] Cross-resistance to tedizolid can occur, however, and is likely mediated by a combination of alterations at the ribosomal binding site or acquisition of the *otprA* gene.[165,200,201] Overall, the spontaneous development of resistance to tedizolid is low.[202]

Spectrum of Activity

The FDA breakpoint for susceptibility to tedizolid is less than or equal to 0.25 μg/mL for streptococci in the *S. anginosus* group and less than or equal to 0.5 μg/mL for *S. pyogenes, S. agalactiae, E. faecalis,* and *S. aureus* (including both methicillin-resistant and methicillin-susceptible isolates).[203] Against hVISA, VISA, and daptomycin-nonsusceptible (DNS) *S. aureus,* tedizolid demonstrates activity with an MIC_{90} value of 0.5 μg/mL against all pathogens.[166] Higher MICs were seen when tedizolid was tested against linezolid-resistant isolates of *S. aureus* (range: 1–8 μg/mL), albeit much lower than the MICs to linezolid (range: 8–64 μg/mL).[204] Tedizolid is equally active against both vancomycin-susceptible and vancomycin-resistant enterococci with an MIC_{90} of 0.5 μg/mL, and against linezolid-resistant enterococci, the MIC ranged from 1 to 4 μg/mL.[203,204] Tedizolid exhibited similar potency against penicillin-susceptible and penicillin-resistant *S. pneumoniae* with an MIC_{90} of 0.25 μg/mL.[203]

Pharmacokinetics and Pharmacodynamics

Tedizolid is available in both oral and IV formulations as tedizolid phosphate, a prodrug that is rapidly converted by serum phosphatases to the active tedizolid compound. Oral absorption is approximately 90%.[205,206] The mean maximum plasma concentration ranged from 1.8 to 2.4 μg/mL at 2–3 hours after oral administration, with a mean half-life of approximately 11 hours.[205] Tedizolid is 90% protein bound and is widely distributed into soft tissues (V_d = 108 L), including significant accumulation in epithelial lining fluid (ELF).[207,208] Elimination of tedizolid is 20% renal and 80% via the liver as an inactive sulfate conjugate.[209,210] Tedizolid has low affinity for cytochrome P-450 enzymes, and weak, reversible inhibition of monoamine oxidase (MAO) was seen in vitro.[196,211]

Tedizolid is bacteriostatic, and early models suggest that the AUC/MIC ratio is the pharmacodynamic parameter most reflective of tedizolid killing of staphylococci.[212–215]

Dosage Regimens and Therapeutic Monitoring

The usual dose of tedizolid is 200 mg once daily for the treatment of acute bacterial skin and skin structure infections and is not affected by obesity.[216] At this time, there have been no completed studies exclusively in critically ill patients. However, a phase III study is currently ongoing comparing tedizolid with linezolid for the treatment of hospital-acquired bacterial pneumonia (HABP) and ventilated nosocomial pneumonia (VNP).[217]

A study of patients with extensive renal and hepatic impairment suggested that no adjustment of tedizolid dosage is required for these populations.[210] Additionally, neither hemodialysis nor CRRT significantly removes the drug.[210,218]

Adverse Effects

The potential for myelosuppression, similar to that observed with linezolid, exists with tedizolid; however, it was not observed in healthy adults receiving 200 mg of tedizolid daily for 21 days.[219] Similarly, a pooled analysis of two phase III trials found a lower incidence of thrombocytopenia compared with those receiving linezolid.[220] These results suggest that tedizolid may have less harmful hematologic effects than linezolid.

MAO inhibition by tedizolid was also evaluated in human and animal studies, yet no significant rise in blood pressure or serotonergic effect was seen.[211] Similarly, no evidence of optic or peripheral neuropathy was found after a 21-day course of tedizolid in healthy adults.[221] Despite these findings, the true impact of these untoward reactions remains to be seen as more widespread use of tedizolid takes place.

QUINUPRISTIN/DALFOPRISTIN

Mechanisms of Action and Resistance

Quinupristin/dalfopristin is a streptogramin antibiotic and is a mix of two different streptogramin components from groups A and B. The individual components are bacteriostatic, but the combination is often

bactericidal except against *E. faecium*. Each component binds to different sites on the 50S subunit of the ribosome, inhibiting translation of mRNA at the elongation step, thereby inhibiting protein synthesis.[222]

Streptogramins share similar sites of action with macrolide and lincomycin antibiotics. As a result, mechanisms of resistance are also shared. The most common type of resistance to streptogramins involves the erythromycin resistance methylase *(erm)* genes, termed MLS_B.[223] These genes decrease the binding of antibiotics such as streptogramins group B, erythromycin, and clindamycin by dimethylating a residue on the 23S ribosome. Group A streptogramins are not affected, and the combination often retains its synergistic activity.[223] Enzymatic modification of both components is another mechanism of resistance to the drug.[224,225] The third mechanism involves efflux pumps: one that pumps out both macrolides and streptogramins and one specific for streptogramins.[224,226,227]

Spectrum of Activity

Quinupristin/dalfopristin is active against a wide variety of gram-positive organisms in addition to many anaerobes and oral flora organisms. An MIC of 2 μg/mL or less indicates susceptibility. Against vancomycin-intermediate and vancomycin-resistant *S. aureus,* the drug is active with MICs of 0.25–1 μg/mL.[228,229] Both vancomycin-susceptible and vancomycin-resistant *E. faecium* are susceptible to quinupristin/dalfopristin (MIC_{90}: 1–4 μg/mL); however, *E. faecalis* is resistant to quinupristin/dalfopristin (MIC_{90}: 4–32 μg/mL).[229–231]

Pharmacokinetics and Pharmacodynamics

In healthy volunteers and in patients undergoing CAPD, the mean peak serum concentration of quinupristin was 2.6 and 2.9 μg/mL, respectively, and for dalfopristin it was 7.1 and 8.5 μg/mL, respectively, after a single 7.5-mg/kg dose.[232] Quinupristin/dalfopristin is hepatically metabolized to several active metabolites, and both the parent components and the metabolites are primarily eliminated via bile into feces.[233] Urinary excretion of quinupristin/dalfopristin and metabolites is 15%–19%. The mean half-life ranges from 1.2 to 1.5 hours. The drug is 90% protein bound.[234]

Dosage Regimens and Therapeutic Monitoring

The dose of quinupristin/dalfopristin is 7.5 mg/kg every 8–12 hours and infused over 1 hour. Dosage reduction is likely required in patients with severe liver dysfunction, although specific recommendations are not available.

Dosing in Renal Failure/Dialysis

Neither hemodialysis nor peritoneal dialysis removes any appreciable amount of quinupristin/dalfopristin.[232,235] Penetration into the peritoneal cavity is negligible in CAPD patients. No dosage adjustment is needed in patients with renal insufficiency or on dialysis.

Adverse Effects

Myalgias (6%–7%) and arthralgias (9%–9.5%) are the most severe adverse effects and are often the reason for discontinuation of the drug.[236,237] Elevations in direct and conjugated bilirubin and gamma-glutamyl transferase are common. Infusion-related adverse effects occur in 30%–45% of patients with peripheral lines used for the infusion.[236] The reactions include pain, burning, inflammation, and thrombophlebitis. Other toxicities include nausea, diarrhea, vomiting, and rash.

KEY POINTS

- Vancomycin is a first-line agent for most gram-positive infections, including those caused by staphylococci, streptococci, and enterococci. Resistance to vancomycin in *S. aureus* is rare but much more common in *Enterococcus* spp.
- Significant attention has been drawn to the challenge of dosing vancomycin, especially in the critically ill population. TDM is recommended, and the optimal target for safety and efficacy is a continued source of debate.
- Red man syndrome, nephrotoxicity, and, rarely, ototoxicity are the most common adverse effects associated with vancomycin use.
- Telavancin can be used as an alternative for skin and skin structure infections or nosocomial pneumonia; however, use of this agent is plagued by teratogenicity and interference with anticoagulation tests.
- Daptomycin is a lipopeptide with gram-positive activity, including several vancomycin-resistant strains. It is approved for bacteremia, right-sided endocarditis, and complicated skin and skin structure infections.
- Dosing concerns exist with critically ill patients, and traditional weight-based dosing has led to subtherapeutic and supratherapeutic concentrations in different populations. Alternative dosing strategies need to balance efficacy with the risk of toxicity, most commonly manifested as myopathy and CPK elevations.
- Linezolid is an oxazolidinone used both intravenously and orally for skin and skin structure infections and for pneumonia. The most common side effects include myelosuppression, MAO interactions, and peripheral and optic neuropathy.

References for this chapter can be found at expertconsult.com.

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109

Antimicrobial Agents Active Against Anaerobic Bacteria

Itzhak Brook

Infections caused by anaerobic bacteria are common and may be serious and life-threatening. Anaerobes are predominant components of the bacterial flora of the normal human skin and mucous membranes[1] and are a common cause of endogenous bacterial infections. Because of their fastidious nature, they are difficult to isolate and are often overlooked. Their isolation requires appropriate methods of collection, transportation, and cultivation.[2–5] Treatment of anaerobic bacterial infections is complicated by the relatively slow growth of these organisms, frequent polymicrobial nature, and growing resistance to antimicrobials.

Antimicrobial resistance among anaerobes has increased in the past three decades, and their susceptibility has become less predictable.[6–14] The most commonly isolated antibiotic-resistant anaerobes are those that belong to the *Bacteroides fragilis* group.[15] This increase makes the choice of appropriate empiric therapy more difficult. Resistance patterns have been monitored through national and local surveys, but susceptibility testing of anaerobic bacteria at individual hospitals is rarely done.[10,11] This chapter describes the antimicrobials effective against anaerobic bacteria and the resistance of these organisms against them.

ANTIMICROBIAL AGENTS EFFECTIVE AGAINST ANAEROBIC BACTERIA

Table 109.1 illustrates the antimicrobials effective against anaerobic bacteria and their efficacy against both aerobic and anaerobic bacteria. Table 109.2 illustrates the resistance of bacteria from the *B. fragilis* group and other anaerobes to antimicrobials.

Beta-Lactam Antibiotics

Penicillin G is the classical drug of choice when the infecting strains are susceptible. Most *Clostridium* strains (except some *C. ramosum, C. clostridioforme,* and *C. innocuum*) and *Peptostreptococcus* spp. remain susceptible to penicillin. Most *B. fragilis* groups are resistant to penicillin. Other strains that may show resistance are growing numbers of anaerobic gram-negative bacilli (AGNB), such as pigmented *Prevotella* and *Porphyromonas* spp., *Prevotella oralis, P. bivia, B. disiens*, strains of *Clostridia, Fusobacterium* spp. (*F. varium* and *F. mortiferum*), and microaerophilic streptococci. Some of these strains show minimum inhibitory concentration (MIC) of 8–32 units/mL of penicillin G. In these instances, administration of very high dosages of penicillin G (for non–beta-lactamase producers) may eradicate the infection.

Ampicillin, amoxicillin, and penicillin are generally equal in activity to penicillin G, but the semisynthetic penicillins are less active. **Methicillin, nafcillin,** and the isoxazolyl penicillins (**oxacillin, cloxacillin,** and **dicloxacillin**) are ineffective against the *B. fragilis* group, have unpredictable activity, and are frequently inferior to penicillin G against anaerobes.[16]

Penicillin and ampicillin/amoxicillin are of limited utility because of the production of beta-lactamases by many oral and most intraabdominal anaerobes. Clavulanate, sulbactam, and tazobactam irreversibly inhibit beta-lactamase enzymes produced by beta-lactamase–producing *Fusobacterium* spp. and AGNB.[16–18] When used in combination with a beta-lactam antibiotic (e.g., **ampicillin-sulbactam, amoxicillin-clavulanate,** and **piperacillin-tazobactam**), they are effective in treating anaerobic infections caused by beta-lactamase–producing bacteria (BLPB).

Beta-lactam/beta-lactamase inhibitor combinations (BL-BLICs) are appropriate choices for mixed aerobic-anaerobic infections. They have maintained good activity against most anaerobes. Whereas 89% of *B. fragilis* are susceptible to ampicillin-sulbactam, 98% are susceptible to piperacillin-tazobactam[8] compared with 86% and 92%, respectively, for *B. thetaiotaomicron* isolates. Recently, the Infectious Diseases Society of America (IDSA) removed ampicillin-sulbactam from the recommended list of drugs for intraabdominal infections because of increased *Escherichia coli* resistance.[19] Amoxicillin-clavulanate remains the agent of choice for human and animal bite wound infections,[20] especially when anaerobes may be involved. Piperacillin-tazobactam is also a frequently and appropriately prescribed agent for serious intraabdominal infections. It has also maintained good activity against most anaerobes.[8]

The semisynthetic penicillins, the carboxy-penicillins (**carbenicillin** and **ticarcillin**) and ureidopenicillins (**piperacillin, azlocillin,** and **mezlocillin**), generally are administered in large quantities to achieve high serum concentration. These drugs are effective against Enterobacteriaceae and have good activity against most anaerobes at these concentrations. However, up to 30% of the bacteria in the *B. fragilis* group is resistant.[21]

Many anaerobes possess cephalosporinases, and therefore cephalosporins have limited utility.[22] The activity of **cephalosporins** against the beta-lactamase–producing AGNB varies. The antimicrobial spectrum of the first-generation cephalosporins against anaerobes is similar to penicillin G, although on a weight basis, they are less active. Most strains of the *B. fragilis* group and many *Prevotella, Porphyromonas,* and *Fusobacterium* spp. are resistant to these agents.[23] Cephalosporinases have little or no hydrolytic activity against the second-generation **cefoxitin** (a cephamycin), which is the most effective cephalosporin against the *B. fragilis* group. However, susceptibility may vary by geographic location and is generally directly related to its clinical use. Cefoxitin is relatively inactive against most species of *Clostridium,* including *C. difficile,* with the exception of *C. perfringens*.[23–25]

Cefoxitin is often used for surgical prophylaxis at most body sites that involve mucous membranes. With the exception of moxalactam, the third-generation cephalosporins are not as active against *B. fragilis*.

Currently, approximately 85% of *B. fragilis* isolates are susceptible to cefoxitin, but the other *B. fragilis* group species are more resistant.[8]

TABLE 109.1 Antimicrobial Agents Effective Against Mixed Infections

	ANAEROBIC BACTERIA		AEROBIC BACTERIA	
Antimicrobial Agent	Beta-Lactamase–Producing AGNB	Other Anaerobes	Gram-Positive Cocci	Enterobacteriaceae
Penicillin[a]	0	+ + +	+	0
Chloramphenicol[a]	+ + +	+ + +	+	+
Cephalothin	0	+	+ +	±
Cefoxitin	+ +	+ + +	+ +	+ +
Carbapenems	+ + +	+ + +	+ + +	+ + +
Clindamycin[a]	++	+ + +	+ + +	0
Ticarcillin	+	+ + +	+	+ +
Amoxicillin + clavulanate[a]	+ + +	+ + +	+ +	+ +
Piperacillin + tazobactam	+ + +	+ + +	+ +	+ +
Metronidazole[a]	+ + +	+ + +	0	0
Moxifloxacin	++	++	++	+++
Tigecycline	++	+++	+++	++

AGNB, Anaerobic gram-negative bacilli.
Degrees of activity: 0 to + + +.
[a]Available also in oral form.

TABLE 109.2 Percent Resistance of *Bacteroides fragilis* Group and Other Anaerobes to Antimicrobial Agents (Includes Intermediate-Resistant Strains)

	Amp-Sulb	Amx-Clav	Pip-Tazo	Fox	Erta	Imi	Mero	Dori	Clinda	Moxi	Tige
Suscept. breakpoint	<8/4	<4/2	<32/4	<16	<4	<4	<4	<4	<2	<2	<4
Resistant	>32/16	>16/8	>128/4	>64	>16	>16	>16	>16	>8	>8	>16
Organism											
Bacteroides fragilis	2.8–11	4–37	0–5	4–25	1.4–10	0.3–7	1.2–22	1.3–12	10–42	10–41	2–11
B. thetaiotaomicron	4.9–15	12–37	0–12	6.8–68	1.3–3	0–7	0–3	0–3	39.8–60	13–75	0–5.8
Parabacteroides distasonis	15–20.6	21	0–14	11–60	0–6	0–1	0–1	0	14.3–64	12.5–52	0–3.2
B. ovatus	2–8	18	0	18–59	2–2.2	0	0	0	36–45.5	8–87	2–5.2
B. vulgatus	3–25	14	1.1–7	11–20	0–2	0–7	0	0	40–54	21–74	0–5
B. fragilis group		10–20	0–8	17–33		<1–1			32–52	14–57	2–13
Prevotella spp.	0	0–19	0–1	0–3	0	0–6			13–33	11–42	0
Fusobacterium spp.		0–11	0	0	0	4	8	0	8–31	10–25	0
Clostridium spp.	0	0–5	0	16–35	0–4	15	0–5	0	16–25	7–53	14
Anaerobic gram-positive cocci	0	0–6	0–3	0–2	0	0	0	0	5–27	3–36	0

Amx-Clav, Amoxicillin/clavulanate; *Amp-Sulb,* ampicillin/sulbactam; *Clinda,* clindamycin; *Dori,* doripenem; *Erta,* ertapenem; *Fox,* cefoxitin; *Imi,* imipenem; *Mero,* meropenem; *Moxi,* moxifloxacin; *Pip-Tazo,* piperacillin/tazobactam; *Tige,* tigecycline.
Metronidazole is not included because >99% of gram-negative strains are susceptible.
Adapted from Mazuski JE, Solomkin JS. Intra-abdominal infections. *Surg Clin North Am.* 2009;89(2):421-ix.

Cefotetan is less effective than cefoxitin against *B. fragilis* and other members of the *B. fragilis* group. Recently, the IDSA removed cefotetan from the recommended list of drugs against intraabdominal infections because of poor *B. fragilis* group activity and resultant clinical failures.[26–28]

The carbapenems (imipenem, meropenem, doripenem, and ertapenem) have excellent activity against anaerobes.[29] **Imipenem,** a thienamycin, is a beta-lactam antibiotic that is effective against a wide variety of aerobic and anaerobic gram-positive and gram-negative organisms, including *B. fragilis*.[30,31] It is also effective against most Enterobacteriaceae, with about 5%–15% of *Pseudomonas* spp. resistance.[32] To overcome the problem of renal metabolism of imipenem, it is combined at a 1:1 ratio with an inhibitor of the renal dipeptidase, cilastatin. This agent is an effective single agent for the treatment of mixed aerobic-anaerobic infections. Recarbrio (imipenem, cilastatin, and the beta-lactamase inhibitor relebactam) has been approved by the Food and Drug Administration (FDA) for the treatment of complicated intraabdominal infections. Relebactam is active against both class A and class C beta-lactamases and restores imipenem susceptibility to many imipenem-resistant isolates of AmpC-producing *Pseudomonas aeruginosa* and Enterobacteriaceae expressing *Klebsiella pneumoniae* carbapenemases (KPC) or combinations of impermeability and extended-spectrum beta-lactamases (ESBLs)/AmpCs.[33]

Meropenem antibacterial activity is similar to imipenem. However, it is less active against staphylococci and enterococci and provides better coverage of aerobic and facultative gram-negative bacteria.[34] Meropenem has been effective in abdominal infections, meningitis in children and adults, community-acquired and nosocomial pneumonia, and neutropenic fever.[35]

Ertapenem, a newer 1-beta-methyl carbapenem, is stable to dehydropeptidase and has a broad antibacterial spectrum for aerobic and anaerobic bacteria, including *C. perfringens, Fusobacterium* spp., *Peptostreptococcus* spp., and AGNB.[36] Compared with other available carbapenems, ertapenem has a long half-life of 4.5 hours and is given as a single daily dose. It is not active against *P. aeruginosa, Enterococcus* spp., and *Acinetobacter* spp.

Doripenem, a synthetic 1-beta-methyl carbapenem, possesses a similar antimicrobial spectrum to meropenem and imipenem.[31] It has significant in vitro activity against aerobic and anaerobic bacteria, including the *B. fragilis* group. In vitro, resistant *P. aeruginosa* mutants appear to be harder to select with doripenem than with other carbapenems.

Carbapenems are generally employed in more serious anaerobic infections such as intraabdominal and skin and soft tissue infections.[26–28] Recent reports have noted the development of some carbapenem resistance among anaerobes,[13] ranging from 1.1% to 2.5% in a multicenter US survey but higher in a small number of isolates from Taiwan.[37]

Resistance to Beta-Lactam Antibiotics

Anaerobes manifest three major resistance mechanisms to beta-lactam antibiotics: inactivating enzymes, mainly beta-lactamases (BLAs), which include penicillinases and cephalosporinases; low-affinity penicillin binding proteins (PBPs); and decreased permeability through alterations in the porin channel.[38] The production of BLAs is the most common mechanism of resistance to beta-lactam antibiotics in anaerobes, especially among the *B. fragilis* group and *Prevotella* spp.[39] Typically, the cephalosporinases belong to the 2e class type and can be inhibited by three beta-lactamase inhibitors: clavulanic acid, sulbactam, and tazobactam. Each individual cephalosporin may have either a class or specific inhibitor enzyme that is able to inactivate it.

Carbapenemases are active against the carbapenems and all beta-lactam antibiotics. Carbapenem resistance occurs in <1% of US isolates, and up to 3% of *Bacteroides* strains harbor one of the genes that is expressed at a very low level.

With a few exceptions among some *Clostridium* spp., strains of *Clostridium, Porphyromonas,* and *Fusobacterium* have also been found to express resistance by one or more of the BLAs. BLA-producing *Fusobacterium* and *Clostridium* spp. express enzymes that are generally inhibited by clavulanic acid.[40] Resistance to beta-lactam antibiotics through changes in the OMP/porin channels, decreased PBP affinity, and efflux pumps[41] is less well studied. The bacteria in the *B. fragilis* group are generally resistant to penicillins (average 90%), piperacillin (25%), cefoxitin (25%), cefotetan (30%–85%), and third-generation cephalosporins.[42,43] The combinations of BL-BLICs inhibitors and carbapenems have maintained their excellent antibacterial activity. The combination of ampicillin-sulbactam, amoxicillin-clavulanate, ticarcillin-clavulanate, and piperacillin-tazobactam is generally very active against members of the *B. fragilis* group.[42] However, species-to-species variation in susceptibility occurs.[44] Resistance to co-amoxiclav (8%) was reported in Slovania.[45] *B[6]. fragilis* group resistance rates for piperacillin-tazobactam is generally <1%.[42] However, resistance of *Parabacteroides distasonis* to ampicillin-sulbactam has risen to 20% in 2002–2004 but continued to be low for the other *B. fragilis* group species.

The carbapenems (imipenem, meropenem, doripenem, and ertapenem) are very effective against all members of the *B. fragilis* group, and resistance is rare at <0.1%.[41,44,46] Geometric mean MICs for imipenem and meropenem for *P. distasonis, B. thetaiotaomicron,* and *B. ovatus* have been reported to be onefold dilution lower than those for ertapenem[42] in 2004. The non–*B. fragilis* group (including *B. intestinalis, B. nordii, B. pyogenes, B. stercoris, B. salyersiae,* and *B. cellulosilyticus*) was found resistant to meropenem (14%) between 2014 and 2016 in Korea.[47] Imipenem resistance was found in a quarter of metronidazole-resistant isolates.[48]

Beta-lactams are generally effective against non–*B. fragilis* group species, and resistance to them is generally low, except that more than half of *Prevotella* spp. may also produce BLAs. A multicenter survey[30] found penicillin resistance for *Fusobacterium* spp., *Porphyromonas* spp., and *Peptostreptococcus* spp. at 9%, 21%, and 6%, respectively. No resistance was found to cefoxitin, cefotetan, beta-lactam/BLA inhibitor combinations, and carbapenems in that survey, with the exception of *Peptostreptococcus* spp. and *Porphyromonas* spp. (4% and 5% resistance to ampicillin-sulbactam, respectively). BLAs were identified in several *Prevotella* and *Porphyromonas* spp. recovered from pediatric intraabdominal infections.

Chloramphenicol

Chloramphenicol, a bacteriostatic agent, is active against most anaerobic bacteria but is rarely used in the United States.[3,23] Resistance is rare. Although several failures to eradicate anaerobic infections with chloramphenicol have been reported,[49] this agent has been used for over 65 years for treatment of anaerobic infections. In the past, it was the drug of choice for the treatment of serious anaerobic infections, including the central nervous system (CNS). However, the drug has potential significant toxicity. The risk of fatal aplastic anemia with chloramphenicol is estimated to be approximately 1 per 25,000–40,000 patients treated. This serious complication is unrelated to the reversible, dosage-dependent leukopenia. Other side effects include the production of the potentially fatal "gray baby syndrome" when given to neonates, hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, and optic neuritis in those who take the drug for a prolonged time.[50]

Chloramphenicol has a unique property of lipid solubility to permit penetration across lipid barriers. Levels in the cerebrospinal fluid, with or without meningitis, usually are one-third to three-fourths the serum concentrations. Levels in brain tissue may be substantially higher than serum levels.[51]

Macrolides: Erythromycin, Azithromycin, and Clarithromycin

The macrolides, which possess low human or animal toxicity, have moderate to good in vitro activity against anaerobic bacteria other than the *B. fragilis* group and *Fusobacterium*.[23] Macrolides are active against pigmented *Prevotella* and *Porphyromonas* and microaerophilic streptococci, gram-positive non–spore-forming anaerobic bacilli, and certain clostridia. They are less effective against *Fusobacterium* and *Peptostreptococcus* spp.[52] They show relatively good activity against *C. perfringens* and poor or inconsistent activity against AGNB.

Clarithromycin is the most active of the macrolides against gram-positive oral cavity anaerobes, including *Actinomyces* spp., *Propionibacterium* spp., *Lactobacillus* spp., and *Bifidobacterium dentium*. Azithromycin is slightly less active than erythromycin against these species.[52] Azithromycin is the most active macrolide against AGNB: *Fusobacterium* spp., *Bacteroides* spp., *Wolinella* spp., and *Actinobacillus actinomycetemcomitans,* including those resistant to erythromycin. Clarithromycin showed similar activity to erythromycin against most AGNBs.[53]

Erythromycin resistance during therapy can occur.[54,55] Erythromycin is effective in the treatment of mild to moderately severe anaerobic soft tissue and pleuropulmonary infections when combined with adequate débridement or drainage of infected tissue. Phlebitis is reported

to develop in one-third of the patients receiving intravenous erythromycin, but the oral preparation is well tolerated.

Clindamycin

Clindamycin has a broad range of activity against anaerobes. It is used to treat dental infections, especially in patients allergic to penicillin, and to treat aspiration pneumonia. Clindamycin hydrochloride is rapidly absorbed from the gastrointestinal tract.[56–58] It rapidly penetrates into body tissues and fluids, including saliva, sputum, respiratory tissue, pleural fluid, soft tissues, prostate, semen, bones, and joints,[59] and into fetal blood and tissues. Clindamycin does not efficiently cross the blood-brain barrier or eye and should not be administered in CNS infections.

The side effect of most concern is *C. difficile*–associated colitis.[60,61] Colitis has also been associated with a number of other antimicrobials, such as ampicillin, cephalosporins, and quinolones, and occasionally also in the absence of previous antimicrobial therapy.

Because *B. fragilis* resistance to clindamycin is increasing, it is no longer recommended as an empiric therapy for intraabdominal infecti ons.[13,42,46,62] Clindamycin resistance was found in 31.6% of *B. fragilis* group isolates among isolates recovered from 2013 to 2015 in a study done in South India.[63] High rates of resistance were reported to clindamycin, in particular among isolates of the *Bacteroides fragilis* group (22.1%–48.1%) and *Prevotella* spp. (10.9%–32.2%) in a study of nine European countries between 2010 and 2016.[64] Clindamycin resistance was found in 54% of *Finegoldia* genera, 49% of *Bacteroides* spp., and 40% of *Prevotella* spp. recovered in Spain in 2018.[65] An 8-year study revealed that 19.3% of 2721 *B. fragilis* group isolates, 29.6% of *P. distasonis,* 33.4% of *B. ovatus,* 33.3% of *B. thetaiotaomicron,* and 35.6% of *Bacteroides vulgatus* strains were clindamycin resistant. This is a significant increase compared with only 3% clindamycin resistance in 1987.[43]

Clindamycin resistance was detected in 46.6% of *B. fragilis* and 17.6% of *Propionibacterium acnes* isolates recovered from pulmonary empyema.[66] Resistance has also increased for many non-*Bacteroides* anaerobes. Up to 10% resistance was noted in *Prevotella* spp., *Fusobacterium* spp., *Porphyromonas* spp., and *Peptostreptococcus* spp., with higher rates for some *Clostridium* spp. (especially *C. difficile*).[30] *P. acnes* isolates have also become more resistant to clindamycin, and this has been associated with prior therapy for acne.[67]

Clindamycin has lost some of its activity against anaerobic gram-positive cocci (*Finegoldia magna*, 30% resistant; *Peptoniphilus* spp.; etc.) and *Prevotella* spp. (*P. bivia,* 70% resistant; *P. oralis* and *P. melaninogenica*, both 40% resistant), although its activity against *Fusobacterium* and *Porphyromonas* spp. remains good.[68]

Among the other resistant anaerobes are various species of *Clostridium,* especially *C. difficile*. Approximately 20% of *C. ramosum* are resistant to clindamycin, as are a smaller number of *C. perfringens.*

Metronidazole and Tinidazole

Metronidazole and tinidazole have excellent in vitro activity against most obligate anaerobic bacteria, such as the *B. fragilis* group, other species of *Bacteroides, Fusobacterium*, and *Clostridium*.[36] Only six strains of the *B. fragilis* group were ever reported to be clinically resistant and associated with therapeutic failure.[2]

Resistance of anaerobic gram-positive cocci is rare, and nonsporulating bacilli are common. Microaerophilic streptococci, *P. acnes,* and *Actinomyces* spp. are almost uniformly resistant.[69] Aerobic and facultative anaerobes are usually highly resistant. Because of its lack of activity against aerobic bacteria, an antimicrobial effective against these organisms (e.g., a cephalosporin, a fluoroquinolone) needs to be added when treating a polymicrobial infection.

Adverse reactions to metronidazole are rare and include CNS toxicity, ataxia, vertigo, headaches, convulsions, and peripheral neuropathy. Peripheral neuropathy is associated with prolonged metronidazole use. Gastrointestinal side effects are common and include nausea, vomiting, metallic taste, anorexia, and diarrhea. Other adverse reactions include reversible neutropenia, phlebitis at intravenous infusion sites, and drug fever.

Some studies in mice[70,71] have shown possible mutagenic activity associated with administration of large doses of metronidazole. Other experiments[71] in rats and hamsters did not show any pathology. In addition, no evidence of mutagenicity was found in humans.[72]

Metronidazole is effective in the treatment of anaerobic infections, including those of the CNS.[73,74] Valid data on the safety of metronidazole in pregnancy are still needed. The nonteratogenicity of metronidazole is difficult to prove, but the existing data indicate no major risks.[75]

Resistance to metronidazole among the *B. fragilis* group is rare.[35,76] Half of the resistant *B. fragilis* group isolates carry one of nine known *nim* genes (nim A–I) on either a chromosome or a mobilizable plasmid. This gene encodes a nitroimidazole reductase that converts 4- or 5-nitroimidazole to 4- or 5-aminoimidazole, preventing the formation of toxic nitroso residues necessary for the agent's activity. Resistance among gram-positive organisms that are not strict anaerobes is frequent, especially for *P. acnes* and *Actinomyces* spp. A significant increase in metronidazole resistance of *Bacteroides* spp., from 12.3% in 2010–2011 to 17.5% in 2017, was found in a study done in Pakistan.[48]

Tetracyclines

Tetracycline is of limited use because of the development of resistance to it by most anaerobes. Resistance to *P. acnes* has been related to previous use.[67] Only about 45% of all *B. fragilis* strains presently are susceptible to this drug.[23] The tetracycline analogues, doxycycline and minocycline, are more active than the parent compound. Because of significant resistance to these drugs, they are useful only when susceptibility tests can be performed or in less severe infections in which a therapeutic trial is feasible. The use of tetracycline is not recommended before 8 years of age because of its adverse effect on teeth.

Tigecycline is a glycylcycline, a direct analog of minocycline with a 9-glycylamide moiety. It has activity against both aerobic gram-negative and gram-positive bacteria, anaerobes,[77,78] and certain drug-resistant pathogens.[79] It is active against the ***Streptococcus anginosus*** group (which includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), *B. fragilis*, *B. thetaiotaomicron*, *B. uniformis*, *B. vulgatus*, *C. perfringens*, *C. difficile*, and *Parvimonas micra* (*Peptostreptococcus micros*).[77] Resistance of tigecycline for members of the *B. fragilis* group varied from 3.3% to 7.2%.[13,42]

Omadacycline (OMC), a broad-spectrum aminomethylcycline, has shown clinical efficacy in anaerobic acute bacterial skin and skin structure infections and in animal models of intraabdominal anaerobic infections. The in vitro activity of OMC against anaerobes was similar to that of tigecycline.[80]

Eravacycline is fully synthetic fluorocycline antibiotic of the tetracycline class with in vitro activity against clinically important gram-positive and gram-negative aerobic and anaerobic bacteria, including most of those resistant to cephalosporins, fluoroquinolones, beta-lactam/beta-lactamase inhibitors, multidrug-resistant strains and carbapenem-resistant Enterobacteriaceae, and most anaerobic pathogens.[81] It has been approved by the FDA for the treatment of complicated intraabdominal infections.

Fluoroquinolones

Quinolones with low activity against anaerobes include ciprofloxacin, ofloxacin, levofloxacin, fleroxacin, pefloxacin, enoxacin, and lomefloxacin. Compounds with intermediate antianaerobic activity include sparfloxacin and grepafloxacin.[82] **Trovafloxacin, gatifloxacin,** and

moxifloxacin yield low MICs against most groups of anaerobes.[83] The use of trovafloxacin has been limited because of hepatotoxicity. Quinolones with the greatest in vitro activity against anaerobes include clinafloxacin and sitafloxacin.[84]

Moxifloxacin has been studied as monotherapy in intraabdominal infections in adults[26,62] and has shown activity against intraabdominal anaerobic isolates.[85,86] However, the increasing fluoroquinolone resistance in both the *E. coli* and *B. fragilis* groups has reduced its use in intraabdominal infections.[9,13,62,86]

The use of quinolones is restricted in growing children because of their possible adverse effects on cartilage. The major concerns with the use of fluoroquinolones to treat anaerobic infections have been the increasing resistance in the *B. fragilis* group and anaerobic gram-positive cocci and the impact of these antibiotics on the growing incidence of *C. difficile*–associated disease.[84]

Bacteroides spp. resistance to fluoroquinolone has been attributed to either an alteration in efflux of the antibiotic or a mutation in the quinolone resistance determining region (QRDR) of the gyrase A gene *(gyrA)* from either single or multiple mutations.[87] High-level resistance can be caused by both mechanisms.

Other Agents

Bacitracin was active in vitro against pigmented *Prevotella* and *Porphyromonas* spp. but is inactive against *B. fragilis* and *Fusobacterium nucleatum*.[23] Vancomycin and daptomycin are effective against all gram-positive anaerobes but are inactive against AGNB.[88] Quinupristin/dalfopristin shows antibacterial activity against some anaerobic organisms that were tested, including *C. perfringens, Lactobacillus* spp., and *Peptostreptococcus* spp.[89] Linezolid is active against *Fusobacterium nucleatum* and other *Fusobacterium* spp., and *Porphyromonas* spp., *Prevotella* spp., and *Peptostreptococcus* spp.[53] Little clinical experience has, however, been gained in the treatment of anaerobic infections using these agents.

GENERAL CONSIDERATION OF ANTIMICROBIAL SELECTION

Because anaerobic infection is often polymicrobial, antimicrobials effective against both aerobic and anaerobic components of the infection should be administered. When such therapy is not given, the infection may persist, and serious complications may occur.[2,3,90] A number of factors should be considered when choosing appropriate antimicrobial agents: they should be effective against all target organisms, induce little or no resistance, achieve sufficient levels in the infected site, have minimal toxicity, and have maximum stability and longevity.

When selecting antimicrobials for the therapy of mixed infections, their antibacterial spectrum and their availability in oral or parenteral form should be considered (see Table 109.1). Some antimicrobials have a limited range of activity. For example, metronidazole is only active against anaerobes and therefore cannot be administered as a single agent for the therapy of mixed infections. Other antimicrobials, such as carbapenems, tigecycline, and BL-BLICs, possess a broader spectrum of activity against aerobic and anaerobic bacteria.

Selecting antimicrobials is simplified when a reliable culture result is available. However, this may be particularly difficult in anaerobic infections because of the difficulties in obtaining appropriate specimens. For this reason, many patients are treated empirically on the basis of suspected, rather than established, pathogens. Fortunately, the types of anaerobes involved in many anaerobic infections and their antimicrobial susceptibility patterns tend to be predictable.[2,3] However, some anaerobes have become resistant to antimicrobials, and many can develop resistance during therapy.[41,91]

Aside from susceptibility patterns, other factors influencing the choice of antimicrobial therapy include the pharmacologic characteristics of the various drugs, their toxicity, their effect on the normal flora, and bactericidal activity.[2,3] Although identification of the infecting organisms and their antimicrobial susceptibility may be needed for selection of optimal therapy, the clinical setting and Gram stain preparation of the specimen may indicate the types of anaerobes present in the infection and the nature of the infectious process.

Typically, antimicrobial therapy for anaerobic infections should be given for prolonged periods because of their tendency to relapse. This may range from 3 weeks to 3 months, depending on the site and severity of the infection.

RESULTS/DISCUSSION

Hastey and colleagues,[92] who reported the changes in the antibiotic susceptibility of anaerobic bacteria in the United States from 2007–2009 to 2010–2012, illustrated the importance of the annual generation of an institutional-specific antibiogram of anaerobic bacteria for tracking of resistance trends over time. The authors illustrated that increased resistance led to most of the significant changes noted between the two periods. Significant increases in antimicrobial resistance was seen overall with anaerobic gram-positive cocci to ampicillin/sulbactam, cefoxitin, and moxifloxacin. Small increases in resistance rates were noted for meropenem against the *B. fragilis* group without *B. fragilis* and for metronidazole against the *B. fragilis* group, whereas moderate increases in resistance rates were seen in both for ampicillin-sulbactam and piperacillin-tazobactam. For organisms other than *B. fragilis,* there was a similar pattern of moderate increases in resistance to ampicillin-sulbactam and ertapenem but smaller increases in metronidazole resistance rates. In contrast, the resistance rate decreased in the *B. fragilis* group without *B. fragilis* for cefoxitin. Moxifloxacin resistance rates were also lower for some *B. fragilis* group isolates and for certain other anaerobes such as *Prevotella* spp.

KEY POINTS

- Because anaerobic infection is often polymicrobial, antimicrobials effective against both aerobic and anaerobic components of the infection should be administered. When such therapy is not given, the infection may persist, and serious complications may occur.
- Anaerobes are often involved in mixed infections, which present unique situations for antimicrobial use. The interactions between the different bacteria and the various antibiotics can be difficult to distinguish and/or predict.
- Selecting antimicrobials is simplified when a reliable culture result is available. However, this may be particularly difficult in anaerobic infections because of the difficulties in obtaining appropriate specimens.
- Susceptibility patterns of anaerobes have been changing over the years, and susceptibility to metronidazole cannot be assumed. Although susceptibility testing of anaerobes is difficult, clinicians must realize the importance of performing and analyzing the susceptibility tests.
- Several beta-lactam antibiotics, fluoroquinolones, clindamycin, and tigecycline possess activity against anaerobic organisms. However, resistance is a concern with all of these classes of antibiotics. A few investigational agents have the potential for use in anaerobic infections, but clinical data are needed.

References for this chapter can be found at expertconsult.com.

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Selective Decontamination of the Digestive Tract

Evelien A.N. Oostdijk, Jeroen A. Schouten, and Anne Marie G.A. de Smet

Infections acquired in the intensive care unit (ICU) often occur during the treatment of critically ill patients, increasing their morbidity, mortality, and healthcare costs.[1,2] Several studies suggest that the use of prophylactic antibiotic regimens such as selective decontamination of the digestive tract (SDD)[3–6] and selective oropharyngeal decontamination (SOD) can reduce the incidence of nosocomial infections and mortality in ICU patients.[5,7,8] The SDD approach[9,10] is directed toward the following: prevention of secondary colonization with gram-negative bacteria, *Staphylococcus aureus,* and yeasts through application of nonabsorbable antimicrobial agents in the oropharynx and gastrointestinal tract; preemptive treatment of possible infections caused by commensal respiratory tract bacteria through systemic administration of cephalosporins during the patient's first 4 days in the ICU; and maintenance of anaerobic intestinal flora through selective use of antibiotics (administered both topically and systemically) without antianaerobic activity.[10]

BACKGROUND

The intestinal flora is highly diverse and consists primarily of anaerobic bacteria. Intact anaerobic flora is considered an important defense mechanism against intestinal colonization by potentially pathogenic microorganisms. The commensal flora of the oropharynx consists of hundreds of bacterial species, including enterococci and anaerobic bacteria, which are replaced by gram-negative bacteria during the first week of hospitalization in the ICU. Gastric acidity usually prevents bacterial overgrowth in the stomach. Yet in ICU patients, reduced acid production caused by underlying diseases, use of acid-modifying medication (stress ulcer prophylaxis), and intragastric administration of enteral nutrition (with a pH of 6) leads to a gastric environment that favors bacterial growth, especially of gram-negative bacteria.

Anaerobic bacteria grow well on the mucosa of the gut and actively line the epithelium.[11] Disruption of this layer by antibiotics that destroy the anaerobic flora may create a portal of entry for pathogenic microorganisms.

Combinations of nonabsorbable antibiotics have been used to selectively decontaminate the digestive tract and reduce the load of pathogenic aerobic microorganisms while maintaining the anaerobic flora. This concept was first investigated in mice[9] and later developed into an infection prevention strategy for neutropenic leukemia patients, which the investigators called *selective decontamination of the digestive tract,* or SDD.[12,13]

From Concept to Practice in the ICU

The earlier experience with SDD in leukemia patients suggested that some infections in ICU patients might have an endogenous source and could be prevented in the same way. After a 2-year observational microbiologic study of trauma patients, an infection classification was proposed (Table 110.1) that included definitions for colonization and the use of SDD for infection prevention in trauma patients in the ICU.[10,14,15] These studies resulted in the establishment of an SDD regimen consisting of the application of nonabsorbable antimicrobial agents in the oropharynx and gastrointestinal tract to prevent acquired colonization with gram-negative bacteria, *S. aureus,* and yeasts, in combination with 4 days of intravenous administration of a third-generation cephalosporin to preemptively treat incubating respiratory tract infections with gram-positive and gram-negative bacteria. Topical and systemic antibiotics were selected based on their antibacterial spectrum and presumed absence of activity on the anaerobic intestinal flora.[14,15]

CLINICAL RESULTS

Earlier Studies

The first study of SDD in ICU patients was performed in 63 trauma patients, using a historical control group of 59 trauma patients.[10] Because of its design and use of a historical control group, this study not only triggered many critical comments and editorials but also led to additional studies in more heterogeneous ICU patient populations, with different combinations of absorbable and nonabsorbable antibiotics, with or without parenteral antibiotics.[3,16–18] The conflicting results of these clinical trials led to the conclusion that there was insufficient scientific evidence to recommend SDD as a routine infection control measure in ICU patients.[19]

SDD was also used early as a prophylactic strategy in major gastrointestinal surgery and showed a decreased rate of postoperative infections and anastomotic leakage.[20] SDD has been reported to reduce gram-negative colonization and to decrease postoperative infection rates after esophagectomy.[21] This study included a very limited patient group from a single center, and the surgical technique, perioperative care, and SDD protocols have changed over time.

Randomized ICU Studies

A Dutch single-center, prospective, controlled, randomized, unblinded study in 2003 reported significantly lower ICU and hospital mortality rates (35% and 22%, respectively), shorter length of stay, and lower incidence of antibiotic resistance in patients with an expected duration of mechanical ventilation of ≥2 days and/or expected length of stay in the ICU of ≥3 days and receiving SDD.[4,22] A subsequent multicenter, controlled, crossover study using cluster randomization and identical inclusion criteria that compared SDD with SOD was performed in the Netherlands. SOD was included because of the hypothesis that the main

TABLE 110.1 Definitions

Colonization resistance	The strong protective effect of the endogenous anaerobic fraction of the intestinal microflora in resisting colonization by aerobe microorganisms along the alimentary canal. Suppression of the anaerobic flora increases the risk of overgrowth by gram-negative bacteria.
PPM	Potentially pathogenic microorganisms
SDD	*Selective decontamination of the digestive tract* is the selective elimination of PPM from the oral and intestinal flora by topical, nonabsorbable antibiotics.
SOD	*Selective oropharyngeal decontamination* is the selective elimination of PPM from the oral flora by topical, nonabsorbable antibiotics.
Primary endogenous infections	Caused by PPM with which the oropharynx and/or digestive tract of the patient was colonized at admission. These PPM are part of the "normal" flora of the patient.
Secondary endogenous infections	Caused by PPM with which the oropharynx and/or digestive tract of the patient was not colonized at admission but acquired during ICU stay.
Exogenous infections	Caused by PPM not present at admission and developing without preceding colonization.
Colonization	Presence of the same species of PPM in an organ system for more than 3 days (≥2 positive cultures) without signs of infection.

ICU, Intensive care unit.

effect of SDD—a reduction in the incidence of ventilator-associated pneumonia (VAP)—could be achieved by oropharyngeal decontamination only, without intestinal decontamination and without the routine prophylactic use of systemic antibiotics during the first 4 days of ventilation.[7,8] The results of this first Dutch multicenter trial (DMT-I) with almost 6000 patients showed that SDD and SOD groups were associated with a reduction in mortality at day 28 of 13% and 11% relative to controls, respectively, corresponding to an absolute reduction of 3.5% and 2.9%.[5] There were several noteworthy limitations to this study; in particular, as with most SDD studies, it was not blinded, so all physicians were aware of the treatment patient participants would receive. Because inclusion was based on several criteria, this created the possibility of selection bias. To minimize the occurrence of selection bias, patient eligibility and inclusion rates were monitored frequently and immediately followed by feedback to the participating investigators. Yet despite the use of these measures next to the objective inclusion criteria, there were baseline differences between the control and the two intervention groups. Patients in the intervention groups (SDD and SOD) were more frequently intubated, were less likely to be surgical patients, and had a higher baseline APACHE score. Further, SDD patients were older compared with SOD and control patients.[5]

A second Dutch open cluster, randomized, crossover, multicenter trial (DMT-II: 11,997 patients) compared 12 months of SDD with 12 months of SOD. Again, there was a baseline difference, with SDD patients being more severely ill. Mortality at day 28 was significantly higher in the SOD group (25.7% compared with 23.8%, respectively, with corresponding adjusted odds ratios (ORs) of 0.85 (95% confidence interval [CI] 0.77–0.93).[23]

Various meta-analyses were published. In 2009 a Cochrane meta-analysis was published on the effects of topical antibiotics (with or without systemic antibiotics) and their effects on mortality and the incidence of respiratory tract infections (RTIs).[6] This meta-analysis included 36 trials, with a total of 6914 patients (without DMT-I and DMT-II). They concluded that a combination of topical and systemic antibiotics as compared with controls resulted in a significant reduction in both RTIs (16 studies; OR, 0.28; 95% CI 0.20–0.38) and mortality (17 studies; OR, 0.75; 95% CI, 0.65–0.87).

Topical antibiotics alone as compared with controls or comparing topical plus systemic with systemic alone resulted in a significant reduction in RTIs (17 studies; OR, 0.44; 95% CI, 0.31–0.63) but not in mortality (19 studies; OR, 0.97; 95% CI, 0.82–1.16).

Another systemic review and meta-analysis published in 2014 compared SDD, SOD, and oropharyngeal chlorhexidine for the prevention of death and concluded that SDD had a favorable effect on mortality with a less certain effect of SOD. Both were superior to chlorhexidine, with a remark that chlorhexidine might be associated with increased mortality.[24] In 2018 an individual patient data meta-analysis was published. It included all patients of six randomized controlled studies (including DMT-I and DMT-II) and found significantly lower hospital mortality during SDD and SOD as compared with control, with an OR of 0.82 (95% CI 0.72–0.93) and 0.84 (95% CI 0.73–0.97), respectively. In a head-to-head comparison, in-hospital mortality was lower during SDD than during SOD (adjusted odds ratio [aOR], 0.90; 95% CI, 0.82–0.97).[25]

It has been a consistent critique that no large randomized controlled trials (RCTs) had been performed in countries with higher levels of antibiotic resistance. All Dutch trials were carried out in ICUs with low levels of antibiotic resistance. Wittekamp and colleagues performed a cluster randomized trial in a diversity of European countries in settings with moderate to high levels of antibiotic resistance.[26] In 13 European, non-Dutch or Scandinavian ICUs, SDD, SOD, or a chlorhexidine mouthwash were used for 6-month periods. Only ICUs with an extended-spectrum beta-lactamase prevalence of at least 5% among Enterobacteriaceae-causing bloodstream infections were eligible. The order of interventions was randomized.

The difference with the trials performed in the Netherlands was the use of the chlorhexidine and omitting the standard systemic prophylaxis (4 days of intravenous [IV] cephalosporin) during SDD. Another difference with the Dutch randomized studies is that there were no protocol modifications for patients with tracheostomy, jejunostomy, or colostomy or for those with persistent respiratory tract colonization with yeasts or gram-negative bacteria. In total 8665 patients were included. No significant differences were found in the incidence of ICU-acquired bacteremias with multidrug-resistant, gram-negative bacteria and for mortality at day 28 between the three groups.

The "what, when, and why" of the different parts of the SDD regimen as it is used in the two Dutch randomized studies are shown in Table 110.2.

TABLE 110.2 Selective Decontamination of the Digestive Tract Regimen

What	When	Why
BASELINE		
Oropharyngeal application of 0.5 g of a paste containing polymyxin E, tobramycin, and amphotericin B, each in a 2% concentration*	Four times daily until ICU discharge	Selective decontamination of the oropharynx
Administration of 10 mL of a suspension containing 100 mg polymyxin E, 80 mg tobramycin, and 500 mg amphotericin B via the nasogastric tube	Four times daily until ICU discharge	Selective decontamination of the gut from stomach to rectum
Cefotaxime 1 g intravenously during the first 4 days of study (or other third-generation cephalosporins)	Four times daily during the first 4 days	Preemptive treatment of primary endogenous infections
Avoidance of systemic antibiotics that might impair the colonization resistance (i.e., antibiotics with antianaerobic activity)	During treatment with SDD, until ICU discharge	Avoidance of penicillins, carbapenems, etc. No addition of antibiotics for patients with colonization without clinical signs suggestive of infection
Cultures of endotracheal* aspirates, oropharyngeal* and rectal swabs	On admission and surveillance cultures twice weekly	Determination of colonization pattern at admission and during treatment, including monitoring of effectiveness of SDD Detection of infection
Oropharyngeal care*	Four times daily using sterile water or chlorhexidine† mouthwash, preceding application of oropharyngeal paste; includes brushing of teeth twice daily. Clean visually contaminated oropharyngeal cavity with swab moistened with 1.5% hydrogen peroxide	Cleansing of mouth and teeth Removing residue of paste Preparing mouth for (next) application of paste
Use of normal hygiene guidelines*	Always	Preventing transmission of pathogens in the patient Prevention of (exogenous) cross-contamination and infections from and to other patients Control of outbreak
MODIFICATIONS FOR PATIENTS WITH		
Tracheostomy*	0.5 g of paste applied around the tracheostomy 4 times daily	Selective decontamination of the oropharynx
Duodenal tube or jejunostomy	Divide the 10 mL of suspension into 5 mL suspension via the gastric tube and 5 mL via the duodenal tube or jejunostomy	Selective decontamination of the gut from stomach to rectum
Colostomy or ileostomy	SDD suppositories (containing 100 mg polymyxin E, 40 mg tobramycin, and 500 mg amphotericin B) twice daily in the distal part of the gut	Selective decontamination of the gut from stomach to rectum
Documented cephalosporin allergy	Cefotaxime can be replaced by ciprofloxacin (twice daily 400 mg)	Avoidance of allergic reaction
MODIFICATIONS FOR PATIENTS WITH PERSISTENT RESPIRATORY TRACT COLONIZATION WITH YEASTS OR GRAM-NEGATIVE BACTERIA		
If a surveillance culture (>48 h after admission culture) of the throat yields yeasts and/or gram-negative bacteria*	Increase application of oropharyngeal paste to 8 times daily until two surveillance cultures are negative	Decolonization
If a sputum surveillance (>48 h after admission culture) culture yields yeasts*	Nebulize 5 mL (5 mg) amphotericin B 4 times daily until two sputum cultures are negative	Decolonization
If a sputum surveillance culture (>48 h after admission culture) yields gram-negative bacteria*	Nebulize 5 mL (80 mg) polymyxin E 4 times daily until two sputum cultures are negative	Decolonization

ICU, Intensive care unit; *SDD*, selective decontamination of the digestive tract.
*The SOD regimen from de Smet AM, Kluytmans JA, Cooper BS, et al. Decontamination of the digestive tract and oropharynx in intensive care patients. *N Engl J Med.* 2009;360:20–31.
†Chlorhexidine was not used in the Dutch SDD-SOD trial (*N Engl J Med.* 2009;360:20–31).

MICROBIOLOGIC EFFECTS OF SELECTIVE DECONTAMINATION

Decontaminating Effect

The DMT-I showed that the proportion of SDD patients colonized with gram-negative bacteria isolated from rectal swabs decreased from 56% at day 3 to 25% at day 8 and 15% at day 14. Oropharyngeal colonization rates with gram-negative bacteria decreased from 18% at day 2 to 4% at day 8 among SDD patients. The same trial showed a comparable decrease in oropharyngeal colonization rates with gram-negative bacteria in SOD patients from 20% at day 2 to 7% at day 8.[5] These results are comparable to those reported in other studies.[10,27,28] Further, it was

shown that SDD could eradicate cephalosporin-resistant Enterobacteriaceae from the intestinal tract.[29]

The positive effects of SDD and SOD on respiratory tract colonization and infection have been described extensively.[4,6–8] The DMT-I showed significantly a lower incidence of ICU-acquired bacteremia during SOD and SDD for *S. aureus* gram-negative rods as *Pseudomonas aeruginosa* and other nonfermenters and Enterobacteriaceae as compared with controls. The incidence of ICU-acquired candidemia was lower in the SDD group compared with either SOD or control groups.[5] Patients receiving SDD had a lower incidence of ICU-acquired bacteremia with Enterobacteriaceae than those receiving SOD,[5,30] a result that was confirmed in the DMT-II.[23]

Emergence and Selection of Antibiotic Resistance in Gram-Negative and Gram-Positive Microorganisms During Selective Decontamination

Enhanced selection of antibiotic-resistant microorganisms has been suggested to occur as a result of the application of SDD and SOD and as such is considered an important threat to SDD and SOD.[31] Consistent use of surveillance cultures as part of SDD and SOD protocols makes it possible to assess the efficacy of enteral decontamination and to detect the emergence of antibiotic-resistant pathogens early.

Gram-Negative Microorganisms

To the contrary of what has been suggested, several studies showed an overall decrease in antibiotic-resistant, gram-negative microorganisms in patients during the episode when they were receiving SDD, including a significantly beneficial effect on colonization with resistant gram-negative bacteria, such as *P. aeruginosa* resistant to ceftazidime, imipenem, and ciprofloxacin and other aerobic gram-negatives resistant to imipenem, ciprofloxacin, and tobramycin.[4,18,32] One prospective Dutch study determined the effect of SDD on colonization with antibiotic-resistant gram-negative bacteria (ARGNB) after ICU discharge (T = 0) on day 3, 6 and 10. They found lower ARGNB rates at ICU discharge during SDD as compared with SOD and in addition the risk to acquire ARGNB after ICU discharge was found to be lower as well (hazard ratio, 0.61; 95% CI, 0.40–0.91; $P = .02$).[33] Patients receiving SDD during the DMT-I had a lower incidence of ICU-acquired candidemia and a lower incidence of bacteremia with Enterobacteriaceae and with highly resistant microorganisms (HRMOs; as defined in Dutch guidelines[34]) than those receiving SOD. Apart from candidemia, this was all confirmed in the DMT-II.[35]

Analysis of the rates of colistin resistance during SDD and SOD in DMT-I showed that during persistent intestinal carriage of gram-negative bacteria and during intestinal colonization with tobramycin-resistant gram-negative bacteria, the risk of acquisition of colistin-resistant gram-negative bacteria and conversion rates to colistin resistance increased. The overall risk of acquisition of colistin-resistant gram-negative bacteria and conversion rates to colistin resistance were, however, low.[36] This finding was confirmed by a Dutch study analyzing colistin-resistant *Enterobacter cloacae* in two ICUs during SDD using detailed microbiologic techniques, including whole-genome sequencing. They found low acquisition rates for colistin-resistant *E. cloacae* and no trend in time during their 5-year study period. Conversion from colistin susceptibility to colistin resistance occurred, yet the main route of acquisition of colistin-resistant *E. cloacae* was via clonal transmission, stressing the need for detailed microbiologic surveillance during SDD.[37]

A post hoc analysis in five Dutch ICUs using SDD or SOD over 7 years showed no increase in the prevalence of resistance against colistin or tobramycin.[38] A Dutch single-center study determined the ecologic effects of SDD over a 21-year period. SDD was used throughout the whole 21 years. No increase was observed in incidence rates of ICU-acquired antibiotic-resistant bacteria.[39] On the other hand, an increase in colistin resistance in extended-spectrum beta-lactamase (ESBL)–producing *Klebsiella pneumoniae* was reported when SDD was used to control an outbreak.[40]

The incidence of candidemia and bacteremia caused by HRMO was low in both the DMT-I and DMT-II, so whether the difference between SDD and SOD will translate into a difference in clinical outcome depends on the overall incidence of candidemia and HRMO bacteremia, the appropriateness of empiric antimicrobial therapy in such patients, and the attributable effects of such events on the outcome and length of stay.

All these findings do not support the concern that the use of topical antibiotics, with or without systemic prophylaxis with third-generation cephalosporins, increases the prevalence levels of antibiotic resistance in gram-negative bacteria. This conclusion is further supported by two 5-year prospective studies and a recent meta-analysis.[31,41,42]

Finally, a post hoc analysis of the European SDD (without systemic antibiotics)-SOD-chlorhexidine study on the eradication and acquisition of third-generation cephalosporin and carbapenem-resistant gram-negative bacteria showed in mechanically ventilated patients that SDD was associated with less acquisition and more eradication of both the cephalosporin- and carbapenem-resistant bacteria in the rectum compared with the SOD and chlorhexidine group. Both SDD and SOD were associated with less acquisition and more eradication of cephalosporin- and carbapenem-resistant bacteria in the respiratory tract compared with the chlorhexidine group.[43]

Gram-Positive Microorganisms

Methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE) are highly prevalent in ICUs in many countries, unlike the Netherlands, where the last three major studies were carried out. The use of topical antibiotics for SDD or SOD is generally considered to be contraindicated in such settings, as such regimens may increase colonization and infection rates with these bacteria. The effects of SDD and SOD are studied in settings with high levels of MRSA.[41] In one study, a shift toward gram-positive organisms was detected after the introduction of SDD in trauma patients, including an outbreak and increased carriage rates with MRSA 2 years after the introduction of SDD.[44,45] This shift was successfully addressed by implementation of control measures.[44] To prevent infections with MRSA, some investigators add vancomycin to the SOD or SDD regimen.[7,46] When applied topically, vancomycin is not absorbed and reaches high concentrations in the intestinal tract. In a Spanish burn unit, SDD with topical vancomycin was associated with improved patient outcome and lower colonization rates with MRSA.[46]

The results of the DMT-I and DMT-II indicate that both SDD and SOD are associated with higher rates of acquired respiratory tract colonization (DMT-I), but not with higher rates of bacteremia caused by enterococci or rectal colonization with VRE (DMT-I and DMT-II). In ICU patients, enterococci will colonize all body sites (especially the skin) and contaminate the inanimate environment. Enterococci are now among the most frequent causes of hospital-acquired infections worldwide, and the proportion of infections caused by ampicillin-resistant enterococci (ARE) has increased substantially in Western countries, including the Netherlands.[47] In the United States, approximately 35% of all ICU-acquired enterococcal bacteremias are caused by VRE. The clinical relevance of ARE and VRE infections is unclear.

Widespread use of topical vancomycin in units with high levels of MRSA will increase the selective pressure for VRE. This factor should be carefully balanced against the benefits of applying SDD or SOD with

vancomycin added to oral paste and/or suspension. In the United States, ICUs with high levels of MRSA frequently also have high endemic levels of VRE. In such settings, the addition of oropharyngeal chlorhexidine oral washings and/or chlorhexidine body washings may help to control spread and bloodstream infections caused by VRE and MRSA.[48,49]

Ecologic Effects

During the DMT-I, surveillance cultures from the respiratory and intestinal tract were obtained each month on a fixed day from all patients present in the ICU, regardless of whether they were included in the study.[5] These 18 point-prevalence studies in 13 ICUs allowed analysis of the effects of SDD and SOD on the bacterial ecology in these ICUs together. The effect of SDD (over a 6-month period) and SDD/SOD (combined over a 12-month period) on intestinal and respiratory tract carriage with gram-negative bacteria was determined by comparing results from consecutive point-prevalence surveys using intervention to consecutive point-prevalence data in the preintervention and intervention periods.[50] The average proportion of patients colonized with ceftazidime-, tobramycin-, or ciprofloxacin-resistant gram-negative bacteria in the intestinal tract decreased during the use of SDD in the ICU and increased again after discontinuation. During combined SDD/SOD, resistance levels in the respiratory tract were low (≤6%) for all three antibiotics but seemed to increase gradually, with a significant increase only for ceftazidime resistance ($P < .05$). After discontinuation of SDD/SOD, the resistance levels increased to 10% or higher. Clearly, both SDD and SOD have marked ecologic effects that are supported by the results of a 4-year ecologic study published in 2014.[51] According to the DMT-II, SDD showed significantly lower rectal carriage of ARGNB than did SOD.[23] Further, a gradual increase in tobramycin resistance was observed during both the SOD and SDD periods, but more clearly during SDD; however, the incidence of acquired bacteremia with aminoglycoside-resistant GNB was lower in the SDD group than in the SOD group.[23] Of note, some of these patients were in the ICU only briefly and not receiving SOD or SDD, and the incidence of resistance in other hospital wards was unknown. An increasing incidence of resistance in the participating hospitals might have influenced these results.

Overall, the ecologic effects (i.e., lowest resistance levels during interventions) corroborate the positive effects of SOD and even more of SDD on antibiotic resistance in individual patients. One might regard this effect as a herd effect of the use of SDD or SOD.[4,31]

Other Issues

Effectiveness of SDD in Specific Patient Groups

Evidence suggests that SDD might not be equally effective in all ICU patient groups. In one meta-analysis, increased SDD efficacy was observed in surgical patients.[17] Further, studies on the preoperative use of SDD suspension and other oral antibiotics in patients undergoing gastrointestinal surgery report lower rates of surgical site infections (SSIs) and anastomotic leakage.[20,52,53] In 2019 a Dutch multicenter RCT was published that included patients with colorectal cancer who electively underwent curative surgery with a primary anastomosis. Both the control and SDD group patients received perioperative IV cefazolin and metronidazole. The SDD group received standard SDD (i.e., tobramycin, colistin, and amphotericin B). SDD was started 3 days before surgery and continued until patients had normal bowel motion with a minimum of 3 days after surgery. Four hundred and fifty-five patients were included, and no significant differences were found for the incidence of anastomotic leakage (6.1% during SDD versus 9.7% in the control group). Yet infectious complications were less frequent during SDD as compared with control (14.9% versus 26.9%, respectively).[54] The individual patient data meta-analysis did show comparable treatment effects for SOD and SDD in surgical versus nonsurgical patients.[25]

Hospital-Acquired Infections After Treatment With SOD and SDD

In the SDD study by De Jonge and colleagues, the relative risk reduction in ICU mortality of 35% decreased to 22% at hospital discharge.[4] Triggered by these findings, it was hypothesized that this reduction in survival benefit after ICU discharge might be related to an increased incidence of hospital-acquired infections (HAIs) in patients who had received SDD in the ICU. Nested within the DMT-I, the incidence of HAI was prospectively monitored during the first 14 days after ICU discharge in all patients transferred to regular wards in two university hospitals.[55] Most HAIs were in the respiratory tract, with a similar incidence and duration of infection in all three posttreatment study groups. The incidence of bloodstream infections was also similar in the three posttreatment groups, but the time until infection tended to be longer in the post-SOD and post-SDD groups compared with the post-control group. On the other hand, the incidence of SSIs increased in the postintervention groups. The low rates of HAI, the overall low mortality rates after ICU discharge, and the low prevalence of infections among those who succumbed after ICU discharge refute the hypothesis that discontinuation of SDD and SOD post-ICU increases the infection rate and thus affects clinical outcomes.[55]

Antibiotic Use and Cost-Effectiveness

De Jonge and colleagues determined that the total cost of antibiotics, topical and systemic, was 11% lower in the SDD group than in the control group. This difference was primarily attributed to the decrease in the use of antibiotics such as ciprofloxacin, ceftazidime, imipenem, and antifungal treatment.[4] These results were confirmed by the DMT-I, with a decrease of 12% and 10% in the use of daily defined doses (DDDs) of systemic antibiotics in the SDD and SOD groups, respectively, as compared with controls.[5] Although the increase in the use of third-generation cephalosporins in SDD patients was obvious, DMT-1 showed a remarkable decrease in more broad-spectrum antimicrobial use such as ciprofloxacin, ceftazidime, and imipenem and in antifungal treatment. As such, SDD may be considered a potentially powerful intervention in antimicrobial stewardship programs. It may be hypothesized that the lack of an effect on antimicrobial resistance (AMR) by SOD/SDD is caused by a decrease in the Defined Daily Dose (DDD) of broad-spectrum antibiotics used in these same patients.

A cost-effectiveness individual patient data meta-analysis included DMT-I and DMT-II. It reported significantly lower hospital mortality during SDD as compared with SOD, with no difference in costs.[56]

Adverse Events

Three patients are reported to have suffered large clots from accumulation of the buccally applied oral SDD/SOD paste, causing obstruction of the esophagus or jejunum. This complication can be prevented by regular and appropriate oral care.[57]

Toxic serum concentrations of tobramycin caused by enteral absorption has been reported as an adverse event of prolonged use of SDD. As tobramycin is renally eliminated, patients with kidney failure are most at risk for toxic levels. A prospective study in 19 SDD patients treated with renal replacement therapy could detect serum tobramycin concentrations in 63% of the patients.[58] They reported a toxic concentration (≥2.0 mg/L) in one patient (5%). The highest concentrations of tobramycin were found in patients with bowel ischemia. It is hypothesized that ischemia may lead to decreased intestinal barrier function, in turn leading to detectable serum tobramycin concentrations.

The use of chlorhexidine 2% mouthwash has been associated with the development of oral mucosal lesions, including ulcerations and bleeding mucosa.[59] Replacement with 1% mouthwash resulted in reported intolerance in less than 1% of the patients.

KEY POINTS

- SOD and SDD improve survival in ICU patients.
- Both SDD and SOD lower the incidence of ICU-acquired bacteremia, RTIs, and the use of systemic (broad-spectrum) antibiotics. SDD reduces the incidence of ICU-acquired bacteremia compared with SOD. Only SDD lowers the incidence of candidemia compared with controls.
- No evidence supports the concern that the use of topical antibiotics with or without systemic prophylaxis increases the prevalence of antibiotic resistance to gram-negative bacteria. In particular, SDD decreases the rate of antibiotic resistance to gram-negative bacteria.
- Both SDD and SOD are cost-effective.
- More studies are needed to determine the long-term effects of SOD and SDD on antibiotic resistance, with special attention to the changes in antibiotic resistance among gram-negative bacteria in surroundings with high antibiotic resistance levels.
- During the use of SDD, strict surveillance should be carried out to monitor effectiveness and to detect colonization with resistant bacteria.

References for this chapter can be found at expertconsult.com.

ANNOTATED REFERENCES

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Intravascular Catheter-Related Infections

Niccolò Buetti and Jean-François Timsit

INTRODUCTION

Intravascular catheters are essential in the care of critically ill patients in order to allow safe intravenous administration of medications, help in the monitoring of hemodynamic parameters, and aid in the intravenous administration of fluid resuscitation. In European intensive care units (ICUs), the central venous catheter (CVC) utilization rate was, on average, 71 CVC days per 100 patient days.[1] Moreover, bloodstream infections (BSIs) were catheter-related in 42.6% of cases,[1] and rates of catheter-related BSIs (CR-BSI) ranged to levels as high as 1–6.2 per 1000 catheter days.[1] In the United States, 15 million CVC days are estimated to occur each year in ICU patients, in addition to about 40,000 CVC-related BSIs, leading to a rate of more than 2 per 1000 CVC days.[2] However, peripherally inserted central venous catheters (PICCs) are less frequently placed for central access in critically ill patients, and their use in the ICU setting remains debated.[3]

CR-BSIs are associated with a significantly increased mortality.[4] However, recent studies describe a nonincreased risk of mortality in a cohort of patients where catheters were systematically removed.[5] The excess of ICU length of stay is estimated at 9–12 days.[6,7] Early adequate antimicrobial therapy and catheter removal are key components of therapy in the case of CR-BSI with severe sepsis or shock. Data on duration of antimicrobial therapy are scarce and will be discussed.

In contrast to other hospital-acquired infections, the majority of the risk factors for intravascular catheter infection are linked to the device itself and can be prevented efficiently.[8,9] Healthcare worker education and training and continuous unit–based improvement programs are therefore instrumental.[9,10] We will discuss the potential interests of new technical developments and put them into perspective according to the available recommendations. Our focus will be mostly on short-term CVC use in critically ill patients, though other catheters are also mentioned.

PICCs, arterial, and short-term dialysis catheters will be discussed separately in the electronic supplemental material.

PATHOPHYSIOLOGY AND MICROBIOLOGY

The colonization of the catheter can occur by two main pathways: the extraluminal route or the intraluminal route. Colonization of the catheter from its dermal surface is the predominant route of colonization for short-term CVCs (<15–30 days), whereas colonization via the intraluminal route resulting from hub contamination predominates for long-term CVCs.[11] These main differences should be kept in mind when choosing between different diagnostic options and preventive strategies.

The occurrence of bacteremia caused by common skin organisms (e.g., coagulase-negative staphylococci [CoNS] or *Staphylococcus aureus*) is a major criterion for the diagnosis of CR-BSI, although Enterobacteriaceae and *Pseudomonas aeruginosa* are increasingly observed these last years,[12] especially in case of femoral site of insertion.[13,14]

DEFINITIONS

Definitions that are currently accepted are displayed in Table 111.1 and apply to all types of vascular catheters. Having them in mind is important to better interpret clinical evidence. Two major definitions are used to define BSIs caused by vascular catheters: central line associated–BSI (CLA-BSI) and catheter-related BSI (CR-BSI). The CLA-BSI definition requires a single positive blood culture for a typical pathogen (or two positive blood cultures for a skin commensal) without positive tip culture or positive peripheral blood cultures. Although this definition is accepted for surveillance, it overestimates the true incidence of catheter infections and remains subjective in assigning the source of infection.[2,15] A recent meta-analysis illustrated that the consistency between CLA-BSI and CR-BSI definitions was rather poor.[16] Indeed, the CR-BSI definition is a more specific clinical definition that requires specialized microbiologic data (e.g., differential time to positivity [DTP], catheter tip culture) and positive peripheral blood cultures.[17]

DIAGNOSIS OF CATHETER INFECTIONS

Clinical Diagnosis

An old study showed that inflammation signs (e.g., erythema or redness) at the exit site are nonspecific and are rarely present in case of CR-BSI.[20] However, an analysis including four randomized controlled trials (RCTs) with more recent data illustrated that local signs at removal were significantly associated with CR-BSI and were highly predictive for catheter infection, especially in the first 7 catheter days.[21] Usually, when CR-BSI is suspected, the common practice in the ICU is to remove the CVC and replace it at a new site. However, only about 15%–25% of CVCs so removed indeed proved infected upon quantitative tip culture.[22–24]

Diagnosis of CR-BSI After Catheter Removal

Cultures at catheter removal should only be performed if an intravascular catheter infection is suspected (see Table 111.1).[18] Although the qualitative broth tip culture has a high sensitivity, its specificity is very low, and contamination cannot be discriminated from infection; it should therefore be abandoned. Quantitative culture techniques have been developed and explore either the extraluminal part of the catheter (semiquantitative Maki technique) or the extraluminal and intraluminal parts via vortex wash or sonication.[25–28] The semiquantitative culture techniques appear to be as accurate as the quantitative methods for diagnosis of catheter-related infections.[29] Of note, the sensitivity of the

TABLE 111.1 Proposed Definitions

	Definition	Comments
Catheter tip colonization	Positive culture of the catheter tip that grew to ≥15 cfu/mL (semiquantitative), 10^2 cfu/mL (quantitative sonication), or 10^3 cfu/mL (quantitative vortexing).	Qualitative culture should no longer be used.
Exit site infection	Tenderness, erythema, or induration > 0.5 cm at the exit site. It may be associated with other signs and symptoms (e.g., fever or purulent drainage).	Positive culture of exudate confirms the exit site infection microbiologically.
Catheter-related bloodstream infection (CR-BSI)	One positive blood culture obtained from peripheral vein and clinical manifestation of infection and (1) a catheter tip colonization or (2) a differential time to positivity of more than 120 min and no obvious source of bacteremia except the catheter or (3) simultaneous quantitative cultures of blood with a ratio of >3:1 cfu/mL of blood (catheter vs. peripheral blood).	Simultaneous quantitative culture from a peripheral vein and the catheter of 3–5: 1 ratio is rarely used.
Central line associated–bloodstream infection (CLA-BSI)	One positive blood culture and clinical manifestation of infection in a patient with a catheter in place with no other source of bacteremia except the catheter.	Easy to use for surveillance purposes. However, this definition can lead to an overestimation of the BSI incidence caused by catheter infection, especially in ICU and in onco-hematologic patients.
Catheter-related clinical sepsis	Clinical manifestation of infection that disappears within 48 hours of catheter removal and a positive catheter tip culture and no other obvious treated source of infection.	Represent 30%–50% of catheter-related infections with general manifestation. Not easy to collect routinely, but may need antimicrobial treatment.
Suspected intravascular catheter infection	The presence of one of the following signs: elevation of inflammatory signs (fever or organ dysfunction) after catheter placement without other infectious or noninfectious explanations; exit site infection signs (purulent discharge, redness, or cellulitis >0.5 cm diameter, abscess); positive blood culture without identification of infectious focus.	This definition is based on expert opinion.[18] The exclusion of other sources of infection can lead to important variability in the final classification in ICU patients. The purulence of the exit site of the catheter is a strong argument to impute the catheter as the source of infection.
Clinical/laboratory signs or risk factors for complicated catheter infection	• Hemodynamic instability. • Neutropenia (<500/mm^3) or immunosuppression (including organ transplantation). • Local exit site signs (purulent discharge or redness/cellulitis >0.5 cm diameter).	This definition is based on exclusion criteria used in a study investigating a watchful waiting strategy versus immediate catheter removal in ICU patients with suspected catheter-related infection.[19]
Noncomplicated intravascular catheter infection	• Favorable clinical course without persistence of fever and negative blood cultures after 72 hours of adequate treatment. • No septic metastasis, endocarditis, or septic thrombophlebitis. • Without other intravascular devices or immunosuppression.	In contrast, a persistent CR-BSI is defined as the presence of positive blood cultures after 72 hours of adequate antimicrobial therapy.
Catheter-related thrombophlebitis	Clinical definition: induration or erythema, warmth, and pain or tenderness along the tract of a catheterized or recently catheterized vein. Alternatively, imaging evidence of vascular thrombosis and clinical manifestations concordant with location of a catheterized or recently catheterized vein.	

BSI, Bloodstream infection; *cfu*, colony-forming unit; *CoNS*, coagulase-negative staphylococci; *ICU*, intensive care unit.
Adapted from Timsit JF, Rupp M, Bouza E, et al. A state of the art review on optimal practices to prevent, recognize, and manage complications associated with intravascular devices in the critically ill. *Intensive Care Med*. 2018;44(6):742–759; and Buetti N, Timsit JF. Management and prevention of central venous catheter-related infections in the ICU. *Semin Respir Crit Care Med*. 2019;40(4):508–523.

catheter culture may be decreased in case of prior use of antimicrobials.[30,30a] This point should be kept in mind when interpreting negative or borderline culture results. Therefore the need to perform diagnostic tests (blood and catheter cultures) before starting any new antimicrobials should be always emphasized.

Diagnosis of CR-BSI With Catheter in Place

In the case of severe sepsis or shock, the catheter should be promptly removed.[17,31] However, most of the suspected catheter infections are not life-threatening, and diagnostic techniques allowing an accurate diagnosis while keeping the catheter in place are an attractive option[19] (see "Management of Catheter-Related Infections").

Quantitative Culture of the Catheter Exit Site

A negative culture of the catheter exit site in case of suspicion of infection may rule out the diagnosis of CR-BSI or colonization but their role remains debated in the literature.[32,32a] Alternatively, the combination of skin and flushed needleless connectors culture (i.e., connectors closing catheter hubs requiring a less invasive microbiologic diagnostic) may be a valuable option for ruling out catheter colonization,[33] thus avoiding any unnecessary catheter replacement.

Differential Time to Positivity

Simultaneous blood cultures, drawn through the catheter and a peripheral vein without removal or exchange of the catheter, are accurate

means for predicting CR-BSI. The time to positivity (TTP) of a blood culture is related to the magnitude of the bacterial inoculum: if a catheter is the source of bacteremia, blood cultures sampled through this catheter will likely have an increased inoculum than peripheral samples and should yield bacterial growth more quickly.[34] Therefore the *differential* time to positivity (DTP) of hub-drawn blood cultures as compared with peripherally drawn blood cultures has been proposed as a means to diagnose CR-BSI[35] (i.e., the difference in the time to positivity between hub blood and peripheral blood cultures). If a cutoff of 120 minutes is used, sensitivity and specificity are greater than 90%[35]; moreover, for short-term catheters, a meta-analysis documented a sensitivity of 89% and specificity of 87%.[27] Theoretically, this technique only explores the intraluminal route of infection, but other authors showed that it can be used for both short-term and long-term CR-BSI diagnosis,[36,37] thus indirectly suggesting a good yield for the extraluminal route diagnosis. However, aspiration of blood cultures drawn through the catheter lumen is technically impossible in one case out of four.[38] Furthermore, each lumen may represent a source of infection. It has been shown that the sampling of one out of three lumens of triple-lumen catheters misses 37% of the CR-BSI cases.[39] Moreover, the role of DTP for the diagnosis of several specific microorganism CR-BSIs remains debated. For diagnosis of *Candida* CR-BSI, one retrospective study showed good sensitivity (85%) and specificity (82%),[40] whereas other investigators reported a specificity of only 40%.[41] Similar controversies are observed for the diagnosis of *S. aureus,* CoNS, or non-AmpC Enterobacteriaceae CR-BSI with DTP.[42–45]

Paired Quantitative Blood Cultures

A diagnosis of CR-BSI can be made if the microorganism colony count is higher in blood cultures obtained from the CVC versus percutaneously obtained peripheral blood.[17] Although it is an accurate method to diagnose CR-BSI,[27] this technique is limited by the lack of standardized cutoff points. In addition, most laboratories rarely perform quantitative blood cultures.[17,27]

PREVENTION

The only sure way to prevent CR-BSI, in addition to other catheter-related complications, is to avoid unnecessary intravascular catheters.[46,47] An increasing body of studies indicates the safety of peripheral intravenous lines for administration of low-dose vasoactive medication.[48,49] Therefore a minimization of catheter use or the use of alternatives are important tools for CR-BSI prevention. The need for CVCs should be assessed daily, and unnecessary CVCs should be removed.[15]

Guidelines on CR-BSI prevention have been recently updated.[8,9,18,31,50,50a] They belong to two categories: studies applying multimodule programs to improve general infection control measures when using catheters, such as surveillance, education, and quality management strategies, and studies that have tested new biomaterials, antiseptic dressings, and catheter locks. Their key points are illustrated in Figs. 111.1, 111.2, and 111.3.

Catheter Insertion

Sterile Barrier Precautions

Full barrier precautions using sterile gloves, long-sleeved sterile gown, procedure mask, cap, and large sterile sheath drape during catheter insertion are essential for the prevention of CR-BSI and should represent the standard during CVC and pulmonary catheter insertion.[51,52] Only one prospective randomized study in surgical patients did not show any additional benefit for full sterile barrier precautions.[53] Nevertheless, most available evidence suggests risk reduction with this intervention. A bedside checklist should be used to improve the compliance with appropriate insertion procedures.[54]

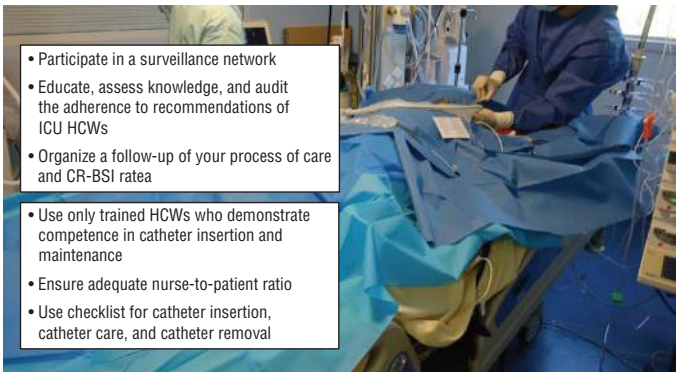

Fig. 111.1 Structure and Process of Care for Prevention of Catheter-Related Bloodstream Infections (*CR-BSI*) in the Intensive Care Unit (*ICU*). *HCWs,* Healthcare workers.

Fig. 111.2 Catheter Insertion. Strongly recommended preventive measures are written in **bold**. *CHG*, Chlorhexidine gluconate; *CR-BSI*, catheter-related bloodstream infection; *CVC,* central venous catheter.

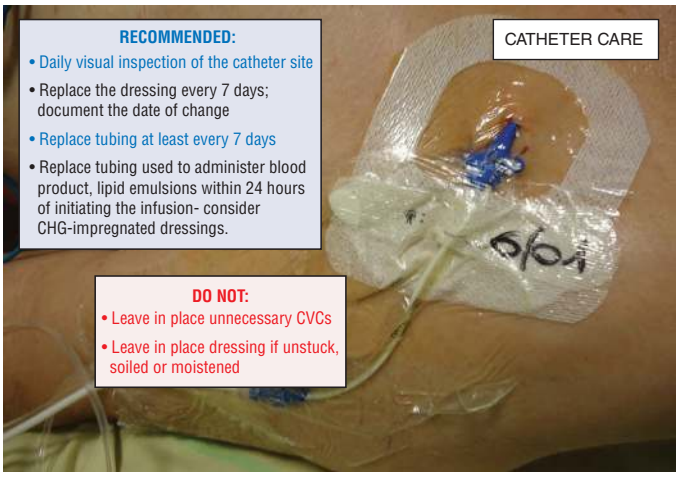

Fig. 111.3 Catheter Care. Strongly recommended preventive measures are written in **bold**. *CVC,* Central venous catheter.

Skin Antisepsis

Skin antisepsis is one of the most important preventive measures. An old in vitro study postulated that antiseptic detergent before application of an antiseptic solution may decrease the amount of bacteria and (potentially antiseptic-inhibiting) protein-rich biomaterials on the skin.[55] However, an RCT demonstrated that cleansing of the skin with a detergent is unnecessary; therefore this measure should be abandoned unless the skin is obviously contaminated.[24]

Adequate skin decontamination requires correct application technique, including the dose for the skin surface area and allowing adequate drying time. The optimal modality of antiseptic application remains controversial.[56] The application of the antiseptic either using applicators or sterile gauze handled with a pincer may increase antiseptic diffusion into the deeper layers of the skin while keeping the hands of the operator away to reduce the risk of contamination.[31] Single-use vials containing sterilized antiseptic further reduce the risk of contaminated solutions from multiuse bottles but may increase costs.[31]

Numerous studies have been conducted to identify the best antiseptic solution for skin decontamination. In patients without contraindications (e.g., chlorhexidine allergy), a sterile 2% (w/v) chlorhexidine gluconate (CHG) solution should be used to decontaminate the skin before the insertion of a vascular catheter, and neither aqueous nor alcoholic povidone-iodine (PVI) should be used as a first-line agent for skin decontamination.[24,57–59] The CHG superiority is probably because of its rapid bactericidal activity. The majority of these studies were conducted using 2% alcoholic CHG. Interestingly, one prospective cohort study found no difference in catheter colonization by CR-BSI between 0.5% alcoholic chlorhexidine and 2% aqueous chlorhexidine.[60] In contrast, another observational study found a similar risk for catheter-related infections between alcoholic CHG <1% and alcoholic PVI, suggesting less benefit using lower concentrations of CHG.[59] The potential benefit of the 2% alcoholic CHG compared with 0.5% alcoholic CHG has been demonstrated in vitro[61] and suggested by one before-and-after study evaluating *S. aureus* bacteremia in patients receiving hemodialysis.[62] Given the widespread use of CHG in medicine, the development of CHG resistance, and especially cross-resistance, to clinically relevant antibiotics has raised concerns.[63] For example, gram-negative bacteria can exhibit a high level of intrinsic resistance to CHG (e.g., *P. aeruginosa, Proteus* spp., and *Providencia stuartii*).[63,64] Moreover, efflux pumps' gene-resistance mechanisms are present in both gram-positive (e.g., *Enterococcus* spp.) and gram-negative microorganisms (e.g., *Acinetobacter* spp. or *Klebsiella pneumoniae*), thus raising the concern that the resistance to CHG with widespread clinical use may simultaneously increase the antibiotic resistance.[63,65] Moreover, CHG tolerance has been associated with methicillin-resistant *S. aureus* (MRSA) decolonization protocol failure.[66] However, the clinical impact of this is uncertain, and a possible cross-resistance between CHG and antibiotics remains controversial.[65] Ubiquitous use of CHG, including patient bathing, oral care, and decontamination of medical devices, however, warrants closer monitoring for emergence of resistant strains to CHG and cross-resistance to antibiotics.[31,63,65] CHG is probably the most effective disinfectant; however, it is associated with more cutaneous skin reactions,[24,67] and rarely, severe anaphylaxis has been reported.[68] *Sequential* use of PVI-containing and CHG cutaneous antiseptics may be beneficial, particularly for high-risk cases, but prospective, multicentered RCTs should be conducted to more rigorously address the utility of this approach to preventing intravascular catheter-related infections.[69]

Chlorhexidine Patient Bathing

Important RCTs have found that routine patient washing with CHG or universal decolonization protocols result in significant CLA-BSI reduction.[70–72] However, in a meta-analysis, the effect was evident in the gram-positive subgroup and became nonsignificant after removal of a high-risk-of-bias study.[73] The impact on gram-negative BSI was not significant.[73] The last cluster-RCT conducted in more than 70 German ICUs showed no benefit of chlorhexidine bathing on CLABSI.[73a] Considering the existing concerns about the risk of emergence of CHG resistance and antibiotic cross-resistance,[65] the implementation of universal skin decolonization with CHG warrants caution and further evaluation.[74]

Catheter Insertion Site

Selection of the insertion site should be based on both the benefits and the risks of the procedure. These include infection, thrombosis, and mechanical complications. The subclavian site is the preferred insertion site for reducing infectious complications.[75,76] An old RCT demonstrated that the subclavian site was associated with lower risk of infectious and thrombotic complications than femoral catheterization in ICU patients.[73] The three-site multicentric RCT confirmed the superiority of the subclavian site compared with the femoral site, and based on results of the per-protocol analysis, a decreased risk for the subclavian site was observed compared with the jugular site.[72] Of note, the impact of systematic ultrasound-guided catheter insertion has not been routinely considered in the previously mentioned analyses.

Several meta-analyses compared the differences in the infectious risk between femoral and jugular sites.[77–80] Two of them showed a superiority for the jugular insertion site. However, when considering RCTs only, the femoral and internal jugular accesses were associated with similar risk of infection.[78,79,81] Two studies using individual data of RCTs suggested that catheter colonization and infection were higher for the femoral site in females, in patients with elevated body mass index (>28.4),[81] or if the catheter dwell time was ≥5 days.[80]

Catheter Fixation

Application of sutures disrupts the skin at the insertion site and may serve as a nidus for microbial growth. An innovative approach using a suture-free system has been proposed by Karpanen and colleagues.[82] This securement system performed similarly in terms of CVC migration and unplanned removal of CVC; however, to date, its effect on CR-BSI reduction has not been demonstrated.

Ultrasound-Guided Placement

The use of ultrasound compared with anatomic landmarks is associated with greater procedural success, lower number of attempts, shorter time of catheterization, and a reduction of mechanical complication, especially for internal jugular and subclavian veins.[83,84] Moreover, this technique may allow prompt recognition of complications (e.g., pneumothorax).[85] However, the impact of ultrasound on the rate of catheter infections is uncertain. Only a few studies have assessed the infectious risk associated with ultrasound guidance, and a prospective study did not show any effect of ultrasound guidance on CVC-associated BSIs or mortality.[86] A recent large post-hoc analysis including data until 2014 showed that ultrasound guidance may be associated with an increased risk of infection. In hospitals where ultrasound equipment is available and the physician has a sufficient training level, combining the anatomic landmarks with ultrasound catheter insertion procedures should be considered to reduce the risk of mechanical complications.

Thrombosis and Infection

Some clinical data suggested a close relationship between catheter thrombosis and infection.[87] A fibrin sheath surrounding the catheter enhances catheter colonization,[88] and therefore the diagnosis of catheter thrombosis should increase the suspicion for catheter infection. Anticoagulant and antithrombotic agents have been used to prevent and manage complications of CVCs. However, the role of heparin in

preventing CR-BSI remained controversial: a recent meta-analysis showed that heparin saline is not superior to regular saline in reducing CR-BSI.[89] Data supporting the specific use of systemic anticoagulant therapy to prevent catheter-related thrombosis in ICU patients are scarce. In selected patient populations (e.g., cancer patients) with CVCs, anticoagulation administration should balance the possible benefit of reduced thromboembolic complications with the possible harms of anticoagulants.[31,90] To date, routine use of systemic anticoagulation cannot be recommended.

Few data exist regarding the use of heparin-bonded catheters in adult patients in the ICU. A meta-analysis including two studies performed in pediatric patients concluded that heparin-bonded catheters did not reduce the rate of catheter-related thrombosis.[91] One study reported a reduction in the rate of CR-BSI and colonization after the use of heparin-bonded catheters.[91] Another study including patients with hemato-oncologic disease illustrated that the use of heparin-coated catheters can be a safe and effective approach for prevention of CR-BSI.[92] However, the potential interest of heparin-coated catheters might be balanced by the risk of heparin-induced thrombocytopenia.

Catheter Care

Replacement

Repeated catheterizations of the same vein are associated with an increased risk of catheter infection.[22] However, the scheduled replacement of catheters as a preventive strategy has not lowered catheter infection rates in many trials in the 1980s to 1990s.[93,94] These findings argue in favor of avoiding any routine replacement of CVCs for catheters that are functioning and have no evidence of local or systemic complications.[95] Importantly, such a statement might not hold true for arterial catheters, whose daily risk of colonization might increase with duration of catheter maintenance.[96]

Dressing

Semipermeable transparent dressings are widely used; they allow continuous observation of the skin insertion site and reduce the risk of extrinsic colonization. Gauze dressing is preferred if blood is oozing from the catheter insertion site. Catheter dressings should be changed immediately if the dressing becomes damp, loosened, or soiled. The risk of CR-BSI increases by more than threefold after the second dressing disruption and by more than tenfold if the final dressing is disrupted.[97] The optimal frequency of routine changes of a CVC dressing is not well-established. However, an RCT demonstrated that the interval of scheduled dressing changes could be safely increased to 7 days in the ICU, provided the dressings are closely monitored.[98] New dressings combining high adhesiveness and permeability and good skin tolerance were not able to decrease the risk of catheter infection and overall catheter complications in a large monocentric RCT.[99] The application of a new acrylic terpolymer skin-protective barrier film around the catheter insertion site resulted in fewer dressing disruptions and skin integrity issues. However, the effect on CR-BSI was not demonstrated, and this technology was tested only in CHG-impregnated dressing.[100]

Both CHG-impregnated sponges and CHG-gel dressings were associated in two RCTs with a 60% decrease in the risk of catheter infections, including CR-BSIs.[98,101] The limitations of these studies included the use of skin antisepsis with PVI at insertion and when changing dressings (first study) and the lack of a double-blind design and a manufacturer's financial participation (second study). Moreover, CHG-impregnated sponges and CHG-gel dressings triggered contact dermatitis at a low rate, <10/10,000 catheters in adult patients. Two meta-analyses confirmed that CHG-impregnated dressings were beneficial in preventing catheter colonization and CR-BSI.[102,103] In light of these considerations, CHG-impregnated dressings should probably be used to decrease CR-BSI in adults.

Administration Set Replacement (Tubing)

Administration sets that do not convey lipids, blood, or blood products may be left in place for intervals of up to 96 hours without increasing the risk of infection.[104] A large RCT conducted in several ICUs in Australia showed that infusion set use can be safely extended to seven days.[105,105a] Nevertheless, tubing used to administer blood, blood products, or lipid emulsions (including propofol infusions) should probably be replaced at least every 24 hours.[106,107]

Catheter Hubs and Needleless Connectors

Any excessive manipulation of CVCs increases the risk for subsequent bacterial ingress into the catheter lumen, and therefore CR-BSI, and must be avoided.[10] Any intravascular access point with a surface open to the environment requires disinfection before use, as it acts as the immediate portal of entry.[108] Before accessing catheter hubs or needleless connectors, an appropriate antiseptic (alcoholic CHG, 70% alcohol) should be used.[8,15,108] Applying mechanical friction for at least 5 seconds was associated with reduced contamination[109,110] and should therefore be implemented. However, it is unclear whether this minimum scrub time can be generalized to needleless connectors.[109] Although some needleless systems appear to be associated with a greater risk of BSI, probably related to their features (i.e., transparency, displacement, flow dynamic, fluid pathway, difficulty of cleaning),[15,111–114] needleless intravascular connector valves may be introduced into clinical practice to minimize the risk of needlestick injury during intermittent use.

The catheter hub should be appropriately disinfected to prevent catheter infections; however, the compliance with this time-consuming manual disinfection process is low. New antiseptic barrier caps have been developed that clean the catheter hub by continuous passive disinfection and may be associated with a lower CLA-BSI incidence.[115]

Antimicrobial-Coated or -Impregnated Catheters

The efficacy of catheters impregnated with CHG and silver sulfadiazine was tested in many RCT studies in the 1990s. A meta-analysis including 57 studies and 11 types of impregnations showed that catheter impregnation significantly reduced CR-BSI and colonization.[116] However, catheter impregnation did not significantly influence the rates of clinically diagnosed sepsis, all-cause mortality, and catheter-related local infections.[116] In terms of microbiologic outcomes (e.g., catheter colonization) minocycline-rifampicin impregnation appeared to be superior to chlorhexidine–silver sulfadiazine impregnation, which was in turn superior to silver impregnation.[116] However, many of the studies were performed in the era before infection preventive bundles became routinely used; whether impregnated catheters are still cost-effective in such settings is uncertain.[31,116] Although the emergence of antimicrobial resistance is of concern, particularly with the minocycline-rifampin–coated catheter, the available data suggest that the long-term use of antimicrobial-coated CVCs is not associated with increased resistance against staphylococcal species.[117] However, no clear conclusion could be drawn regarding the impact of the use of rifampin-minocycline–impregnated catheters on the development of antimicrobial resistance or on the selection of resistant flora and *Candida* spp.[118,119] Therefore the use of such catheters should be limited to hospital units with an infection rate above the institutional goals despite their compliance with basic catheter infection prevention practices.[8,15] Other catheters impregnated with silver

zeolite, oligon, platinum, and carbon have been tested but have not proven their efficacy.[120]

Systemic Antibiotic or Antiseptic Lock Solutions

The prophylactic use of systemic antibiotics at the time of catheter insertion has not proven to be effective in reducing CR-BSI. However, only a few studies investigated the role of systemic antibiotic prophylaxis in short-term catheters. A meta-analysis including three relatively small studies demonstrated that the routine use of prophylactic systemic antibiotics in newborns during the full period of CVC maintenance reduced the rate of "proven" or "suspected" septicemia and of clinical sepsis without any effect on mortality.[121] Only a few studies investigated the role of systemic antibiotic prophylaxis in adults. Concurrent systemic antibiotics at catheter insertion and intravascular catheter-related infection in the ICU: a post hoc analysis using individual data from five large RCTs.[123,123a] The prophylactic use of systemic antibiotics at catheter insertion has not proven to be effective in reducing the incidence of CR-BSI and is therefore discouraged.

Antimicrobial lock therapy (ALT) consists of instilling a supratherapeutic concentration of an antimicrobial solution into a catheter lumen and leaving it in place until the catheter hub is reaccessed. ALT is intended for catheters not used continuously and targets endoluminal catheter infections. Importantly, most available data evaluating this strategy are derived from long-term catheters.[31] In a meta-analysis, the use of antimicrobial lock solutions led to a reduction of CLA-BSI rate and a decrease of exit-site infections compared with the use of heparin.[124] However, this meta-analysis identified a significant publication bias.[124] Moreover, lock solutions may lead to the emergence of antibiotic-resistant organisms[125] and could lead to systemic toxicity caused by lock solution spillage from catheters.[31] Some fibrinolytics reduced the rate of catheter infection and dysfunction in tunneled dialysis catheters[126]; however, the extrapolation of these studies to short-term catheters inserted in ICU patients is debatable because of differences in catheter type, use, and accessibility for ALT.[31] To date, the use of prophylactic ALT for short-term catheters cannot be recommended.

Role of Nursing Care

The intravenous catheter care bundle includes a checklist for catheter insertion, appropriate postinsertion catheter care, and prompt removal of the catheter when no longer required.[8,50] Nursing staff and any personnel involved with the care of intravascular catheters have an essential role during these processes.[31] The checklist is a tool to assure that the catheter insertion procedure is followed correctly, and it empowers healthcare workers to challenge and stop the procedure if this is not executed appropriately.[8,31] Finally, it is essential to assure an appropriate nurse-to-patient ratio and limit the use of float nurses in ICUs.[8,127]

Bundles of Care

Several insertion and maintenance prevention measures can be combined to create a bundle. Implementation of such bundles has been demonstrated to reduce the median incidence of CLA-BSI from 6.4 per 1000 catheter days to 2.5 per 1000 catheter days after their implementation.[128]

Proposed bundles should result from available recommendations and be adapted locally.[129] The key components include (1) improvement of hand hygiene compliance; (2) use of maximal barrier precautions during the insertion; (3) preferential use of subclavian access; (4) use of alcoholic 2% CHG for skin antisepsis and catheter care; (5) daily inspection of the insertion site; (6) immediate change of unstuck, soiled, or moistened catheter dressings; and (7) removal of the catheters as soon as no longer requested. Although nearly 50% of US ICUs reported having a CLA-BSI prevention bundle policy, only 38% of institutions that monitored bundle implementation reported full bundle compliance.[130] Therefore hospitals must target improving bundle implementation and compliance as opposed to simply instituting policies.[130] Several success stories were published using these recommendations, most of which were observed in ICUs.[47,131–134]

Knowledge, Education, and Behavioral Interventions

Practice change was one of the most important interventions that reduced the incidence of CLA-BSI.[128] In particular, the implementation of central-line bundles has the potential to reduce the incidence of CLA-BSI.[128] Knowledge, education, and training are the cornerstones of any behavior change strategy. Individual experience is instrumental in explaining behavior compared with the evidence base or formal education.[135] Therefore isolated knowledge delivery by ex cathedra teaching or handing out of written protocols is not sufficient to change behavior.[31] In this context, a systematic review on organization and structure of infection control identified three essential components addressing knowledge, education, and behavioral interventions: (1) guidelines should be used in combination with practical education and training; (2) education and training should involve frontline staff and should be team- and task-oriented; and (3) implementation should follow a multimodal strategy, including tools such as checklists and bundles, developed by multidisciplinary teams, taking into account local conditions.[124,125,136–138]

MANAGEMENT OF CATHETER-RELATED INFECTIONS

Catheter Removal or a More Conservative Attitude?

When CR-BSI is suspected, in the case of hemodynamic instability, immunosuppression, or if local signs of infection are observed, the catheter should be removed[31] (see Table 111.1 and Fig. 111.4). Otherwise, the decision of catheter removal should take into account the ease of a new catheter insertion and the severity of the comorbidities of the patient. In this context, there are few relevant data, especially from RCTs. Moreover, cautious decisions about catheter removal and type and length of antibiotic therapy should be made after each case is examined in light of these variables. An RCT including a relatively low number of hemodynamically stable critically ill patients without proven bacteremia and without local signs of CR-BSI illustrated that a *watchful waiting strategy* (versus immediate catheter removal) permitted a substantial decrease in the number of unnecessarily removed CVCs without increasing morbidity.[19] Another strategy for patients with limited venous access (e.g., patients with a hemodialysis catheter) is the *change of catheter over a guidewire* (GWX).[139] An old systematic review comparing GWX with new site replacement showed a trend toward fewer mechanical complications but increased infections using GWX.[140]

When conservative strategies have been initiated, the catheter should be removed depending on microorganisms recovered and on the clinical course within the first 72 hours (see Table 111.1).

Catheter removal is strongly recommended in patients with CR-BSI caused by *S. aureus,* gram-negative bacilli, enterococci, fungi, or multidrug-resistant (MDR) bacteria.[17,141–145] If CoNS are identified and if blood culture contamination is ruled out, the catheter should also be removed: CVC retention does not have any impact on the resolution of CoNS bacteremia but is a significant risk factor for recurrence.[146] For CR-BSI (i.e., *bacteremic* intravascular catheter infection) in the ICU, the catheter removal is usually preferable, as it allows a complete removal of the source of infection. Overall, conservative strategies are associated with an increased risk, and critically ill patients have to be cautiously monitored. Of note, if GWX is performed in the setting of a catheter infection, the newly

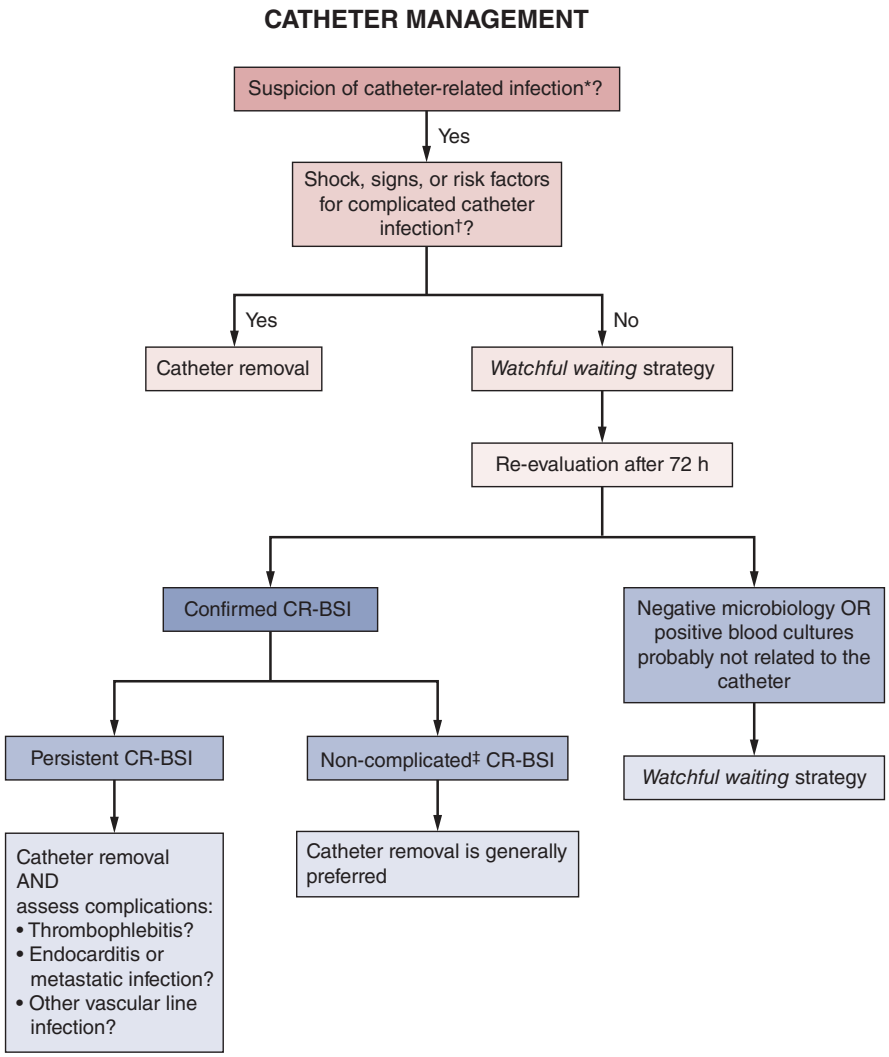

Fig. 111.4 Algorithm for the Management of Suspected Catheter-Related Infections. *Elevation of inflammatory signs after catheter placement without other infectious or noninfectious explanations, or exit site infection signs (purulent discharge, redness/cellulitis >0.5 cm diameter, abscess), or positive blood culture without identification of infectious focus. †Hemodynamic instability; or neutropenia (<500/mm^3) or immunosuppression (including organ transplantation); or local exit site signs (purulent discharge or redness/cellulitis >0.5 cm diameter). ‡Favorable clinical course without persistence of fever and negative blood cultures after 72 hours of adequate treatment; and no septic metastasis, endocarditis, or septic thrombophlebitis; and no other intravascular devices or immunosuppression. *CR-BSI*, Catheter-related bloodstream infection.

placed catheter should be removed. The optimal timing of antimicrobial therapy administration in this specific case has not been evaluated.

Positive Catheter Tip Culture With No Positive Blood Cultures

The Infectious Diseases Society of America (IDSA) guidelines recommend that catheter cultures be performed each time a catheter is removed for suspected CR-BSI.[17] However, in the ICU, at the time of any catheter removal, the body temperature is abnormal in more than half of the patients, and two of the four systemic inflammatory response syndrome (SIRS) criteria are present in about 90% of patients.[98,101] Thus most catheter tips would end up by being cultured on the sole basis of these criteria. There are limited data on the clinical significance of positive tip culture without concomitant bacteremia or fungemia.[147] Considering all microorganisms, the prevalence of *subsequent BSI* (i.e., delayed BSI with the same microorganism as the one recovered from the catheter tip) ranges from 1.3% to 4.1%.[147–151] However, a comparison between studies is difficult because of the lack of a generally accepted definition of subsequent BSI.[150] Therefore the management of a positive catheter culture without positive blood cultures in a patient without specific symptoms is a challenge at bedside. The decision of whether antibiotic treatment should be administered depends on the identified microorganism. Overall, the risk of subsequent BSI is the highest for *S. aureus*, followed by gram-negative microorganisms, whereas it is low for *Enterococcus* spp. and CoNS.

In patients with suspicion of infection and positive catheter tip culture with *S. aureus* though without demonstrated bacteremia within 24 hours after intravascular catheter removal, the risk of subsequent *S. aureus* bacteremia is 24% if they do not receive immediate antistaphylococcal antibiotics.[152] Interestingly, a treatment within

24 hours after intravascular catheter removal led to a reduction in the incidence of subsequent bacteremia,[152] and therefore the majority of authors supported the role of antibiotics for *S. aureus*.[153–156] An important percentage of subsequent BSI has also been found for *P. aeruginosa,*[157] extensively resistant *Acinetobacter baumannii,*[158] *Serratia marcescens,*[150] and more generally for gram-negative microorganisms.[159] The risk is probably lower for CoNS and enterococci.[151] Little is known about the significance of a fungal colonization of a catheter tip (i.e., candidemia). Whereas some authors found a low risk of developing subsequent fungemia,[160,161] other studies hypothesized an increased risk of developing a delayed fungal infection.[162] These findings are supported by two other studies investigating subsequent fungemia and bacteremia.[147,151] All these retrospective studies suffer from important methodologic flaws and did not demonstrate that subsequent BSI was directly related to the positive catheter tip culture. It makes sense to treat critically ill patients with sepsis whose catheter tip reveals a significant growth of *S. aureus, P. aeruginosa, A. baumannii,* or *Candida* spp., especially if they are immunocompromised or if a thrombosis of the catheterized vein was observed at removal.[87] For these microorganisms, follow-up blood cultures should be drawn, and an ultrasound examination may be considered.[31] When the catheter tip culture yields CoNS, *Enterococcus* spp. or Enterobacteriaceae, management without any antimicrobial treatment may be considered. The duration of therapy is not known: a maximum of 3–5 days is generally accepted[18] (Table 111.2).

Empiric Treatment

Empiric therapy should be individualized to the patient's characteristics, clinical stability, risk factors, and local epidemiology (Fig. 111.5). Once an intravascular catheter infection is suspected and associated with clinical or laboratory signs for complicated infection (see Table 111.1), empiric antimicrobial therapy should be administered immediately after appropriate samples are drawn for culture.

CR-BSI are frequently caused by gram-positive microorganisms and, accordingly, intravenous vancomycin (or daptomycin in patients with acute renal failure or when organisms have reduced susceptibility to vancomycin) is recommended in healthcare settings with a high prevalence of MRSA.[22] Empiric therapy for gram-negative pathogens, particularly *P. aeruginosa,* should be based on clinical (e.g., severity of disease, neutropenia, immunosuppression, or hematologic malignancy) and epidemiologic factors (e.g., known colonization or exposure to high-prevalence healthcare settings).[17,31] It is usually recommended to use a fourth-generation cephalosporin, beta-lactam/beta-lactamase inhibitor combination, or carbapenem.[15] Moreover, having had a previous MDR gram-negative infection, sharing a room with a known MDR carrier, critical illness, neutropenia and immunosuppression, and prior antibiotic therapy are recognized risk factors for MDR gram-negative infections.[163,164] Especially in patients with documented recent colonization with MDR gram-negative bacilli, a combination therapy with two different classes of antimicrobials against MDR gram-negative bacilli is indicated.[15] Empiric coverage for fungal infections should be considered only in a limited subpopulation of septic *and* severely ill immunocompromised patients (e.g., bone marrow or organ transplants, hematologic malignancy, or other immunosuppression) and if multiple sites are colonized with *Candida* spp., or for patients with total parenteral nutrition or prolonged administration of broad-spectrum antibiotics.[17,31,165] Empiric treatment consists mainly of an echinocandin, whereas fluconazole may represent an option in patients without risk of azole-resistant fungal infections (i.e., without previous identification of *C. glabrata* or *C. krusei* or without exposure to fluconazole in the previous 3 months).[31,165] Among other critically ill patients with ICU-acquired sepsis (e.g., nonsevere immunocompromised with risk factors for invasive *Candida* infections), an empirical treatment with echinocandin did not improve the fungal infection–free survival at day 28 and is therefore discouraged.[166]

TABLE 111.2 Proposed Targeted Therapy After Catheter Removal for Suspected Infection and Positive Catheter Tip Culture

Microbiologic Findings	Duration of Antimicrobial Therapy
Staphylococcus Aureus, Candida spp.	
Negative blood cultures	3–5 days
Positive blood cultures, without complications*	14 days
Positive blood cultures, with complications*	4–6 weeks
***Enterococcus spp., CoNS,*[a] Enterobacteriaceae[b]**	
Negative blood cultures	No therapy[b]
Positive blood cultures, without complications*	5–7 days
Positive blood cultures, with complications*	4–6 weeks
Pseudomonas Aeruginosa, Acinetobacter Baumannii	
Negative blood cultures	3–5 days
Positive blood cultures, without complications*	7 days
Positive blood cultures, with complications*	4–6 weeks

*See Table 111.1 for complications.
[a]Withholding antimicrobial therapy for CoNS may be considered.
[b]In the case of positive catheter tip with *Serratia* spp. without concurrent positive blood cultures a short course of antimicrobial therapy should be considered.
CoNS, Coagulase-negative staphylococci.

Targeted Antimicrobial Treatment According to the Specific Pathogen Isolated

Once the antimicrobial susceptibility patterns are available, a de-escalation to the most appropriate therapy with the narrowest possible spectrum is recommended. The targeted treatment depends on the causative pathogen, presence of complications, catheter management, and host factors.[15,165] In general, in noncomplicated intravascular catheter infections (for definition, see Table 111.1), a short course of antimicrobial treatment should be administered.[15,165,165a] The therapy duration may range from 5–7 days to 6 weeks[165] (see Table 111.2). Recommendations on duration of treatment for CR-BSI are often extrapolated from hospital-acquired bacteremia literature. A systematic review that included bacteremic critically ill patients showed no significant differences in clinical cure, microbiologic cure, and survival among bacteremic patients receiving shorter (5–7 days) versus longer duration (7–21 days) antibiotic therapy.[167] To date, the results from a large Canadian multicentric RCT in critically ill patients with bacteremia (BALANCE Trial) are not available.[168]

S. aureus is frequently responsible for CR-BSI. Standard therapy for methicillin-susceptible *S. aureus* (MSSA) consists of an antistaphylococcal penicillin or first-generation cephalosporin.[169] The addition of an aminoglycoside is not recommended, as it does not offer clinically significant benefit and increases the risk for renal impairment.[170] For MRSA, and based on long-term clinical experience and trial results, vancomycin (with trough levels of 15–20 μg/mL) or daptomycin are the agents of choice.[171] For uncomplicated *S. aureus* infection (i.e., not associated with endocarditis or metastatic infection, negative follow-up

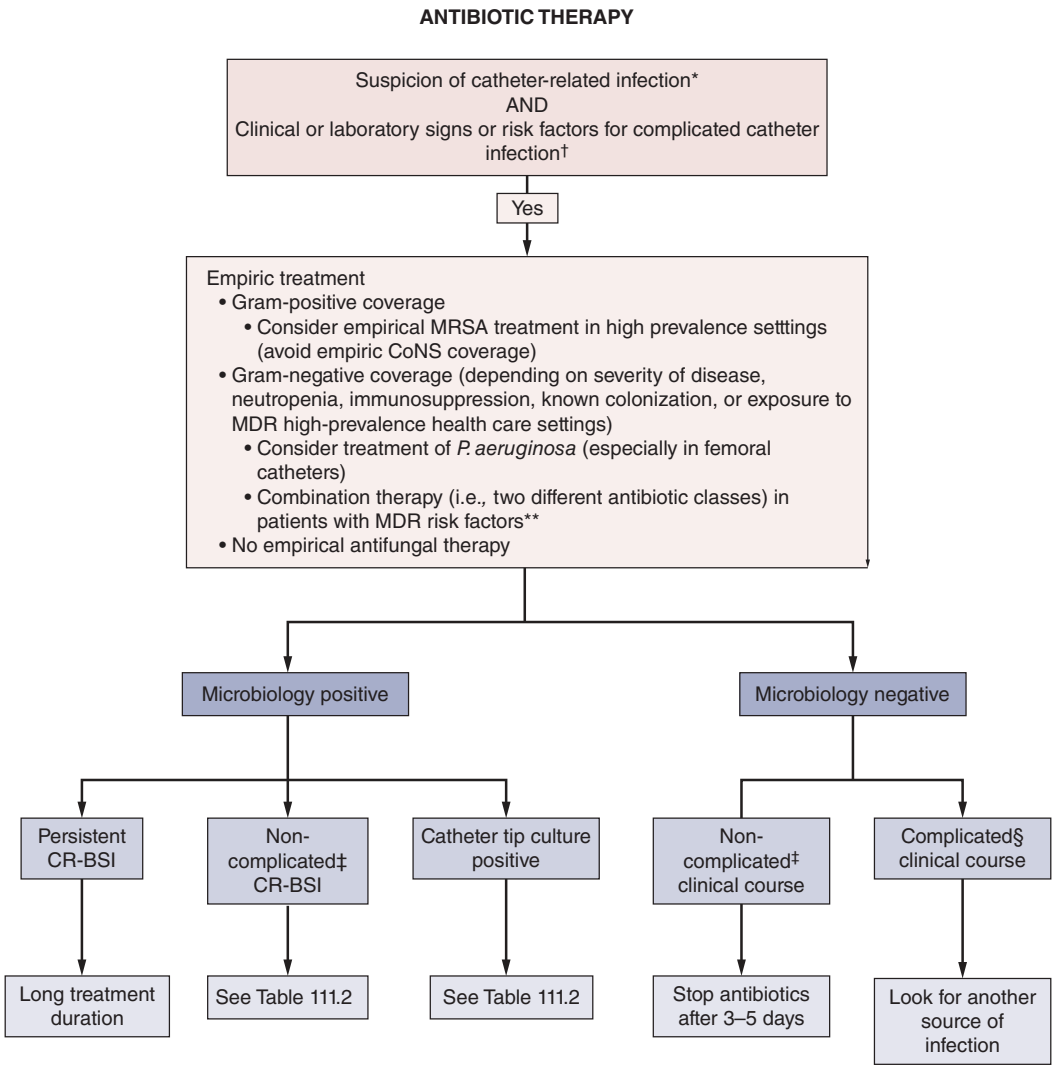

Fig. 111.5 Algorithm for Antibiotic Therapy in Suspected Catheter-Related Infections. *Elevation of inflammatory signs after catheter placement without other infectious or noninfectious explanations; or exit site infection signs (purulent discharge, redness/cellulitis >0.5 cm diameter, abscess); or positive blood culture without identification of infectious focus. †Hemodynamic instability; or neutropenia (<500/mm^3) or immunosuppression (including organ transplantation); or local exit site signs (purulent discharge or redness/cellulitis >0.5 cm diameter). **Previous multidrug-resistant (MDR) gram-negative infection or colonization, sharing a room with a known MDR carrier (e.g., neutropenic and immunosuppressed patients). ‡Favorable clinical course without persistence of fever and negative blood cultures after 72 hours of adequate treatment; and no septic metastasis, endocarditis, or septic thrombophlebitis; and without other intravascular devices or immunosuppression. §Persistence of fever or inflammatory signs after 72 hours or septic metastasis, endocarditis, or septic thrombophlebitis. *CoNS,* Coagulase-negative staphylococci; *CR-BSI,* catheter-related bloodstream infection; *MRSA.* methicillin-resistant *Staphylococcus aureus.*

blood cultures, prompt response to institution of therapy, no indwelling intravascular devices), 14-day therapy may be administered.[171] Otherwise, 4–6 weeks of antibiotic treatment should be given.

The optimal treatment for CoNS has not been addressed in clinical trials. A recent retrospective study that included a large number of ICU patients after catheter removal showed that withholding antimicrobial therapy in CoNS-CR-BSI was not associated with either short-term complications or long-term recurrences.[172] However, other experts advocate short antibiotic treatment courses (5–7 days).[17] Of note, *Staphylococcus lugdunensis* should be treated similarly to *S. aureus.*[173]

For enterococcal CR-BSI, ampicillin is the first choice for ampicillin-susceptible strains, vancomycin for those that are ampicillin-resistant, and daptomycin or linezolid for vancomycin-resistant enterococci (VRE) strains.[174] The role of combination therapy for treating enterococcal CR-BSI without endocarditis is unresolved, especially for VRE.[175] A 7-day course of therapy is recommended for uncomplicated enterococcal CR-BSI if the catheter is removed.[18]

Most of the recommendations for the management of CR-BSI caused by gram-negative bacilli have been limited by their small numbers of cases. Among gram-negative bacteria infections, the risk for metastatic complications is lower compared with *S. aureus* infections.

The antibiotic therapeutic course should be administered for at least 7 days with a single agent if the catheter is removed.[18,31]

Among *Candida* CR-BSI, echinocandins have the advantage of their fungicidal activity and their activity against yeasts in biofilm.[176] Fluconazole is an alternative for patients who are stable, have had no prior azole exposure,[176] and whose catheter is removed. Lipid formulation of amphotericin B and voriconazole are alternatives that may be considered, especially if *C. krusei* is identified.[176] The recommended minimal duration of therapy for candidemia without metastatic complications is 14 days after documented clearance of *Candida* from the bloodstream.[176,177]

In exceptional circumstances, catheter salvage therapy might be proposed in the ICU, especially for long-term catheter inserted before the ICU stay. This treatment should only be discussed in the absence of severe sepsis and when fungi, *S. aureus, Pseudomonas* spp., *A. baumannii,* or MDR bacteria are not involved. Compared with parenteral therapy alone, therapy including antibiotic lock was significantly more likely efficient for catheter salvage.

Complicated Courses

Persistent fever or bacteremia after catheter removal and despite an adequate antimicrobial therapy (i.e., *persistent* CR-BSI; see Table 111.1) may reflect a persisting infection focus. This must trigger an active search for another vascular line infection, metastatic abscess, septic thrombophlebitis (e.g., with ultrasound examination), or endocarditis (e.g., with transesophageal echocardiography).[17,31] A prolonged antibiotic course combined with adequate management of the complication may be required (4–6 weeks of therapy).

Failure resulting from the poor pharmacokinetic-pharmacodynamic properties of the antimicrobial are mainly encountered when treating MRSA with glycopeptides. The volume of distribution of hydrophilic antimicrobials is always increased in case of septic shock and might explain the failure of treatment with beta-lactams or vancomycin.[178] Therefore therapeutic drug monitoring for the pharmacokinetic optimization of antimicrobial doses, particularly vancomycin, is strongly recommended.[179] A trough level of vancomycin between 15 and 20 mg/L should be reached. Daptomycin might be an alternative,[180] particularly when the minimum inhibitory concentration (MIC) to vancomycin reaches 1.5 mg/mL.[181]

An infected intravascular thrombus after catheter removal may explain the persistence of severe sepsis despite adequate antibiotic therapy. The most common causal microorganism is *S. aureus,* whereas *Candida* spp. and gram-negative bacilli are less frequently observed. The optimal choice and duration of therapy are based on retrospective studies and expert recommendations. A 4- to 6-week course of antibiotic treatment is usually administered. In addition, the available literature suggests that early administration of heparin should be considered in the management of patients with septic thrombophlebitis.[182,183]

CONCLUSION

Intravascular catheter-related infections remain a leading cause of nosocomial infections, particularly in ICUs. They are the most frequent cause of hospital-acquired bacteremia and can be prevented if rigorous policies are implemented. They should be one of the main targets of a quality improvement program. The management of CR-BSI requires catheter removal in most critically ill patients. In noncomplicated intravascular catheter infections, a short course of antimicrobial treatment is usually appropriate.

KEY POINTS

- Catheters are the leading source of bloodstream infections in critically ill patients.
- Comprehensive, unit-based improvement programs are effective in decreasing the rate of CR-BSI.
- A locally adapted checklist of preventive measures should include hand hygiene, cutaneous antisepsis with 2% alcoholic CHG preparation, maximal barrier precautions, preferential use of a subclavian venous insertion site, a strict policy of catheter maintenance, and prompt ablation of useless catheters.
- A conservative approach might be attempted in mild infections, whereas the catheter should always be removed in cases of severe sepsis or septic shock.
- In case of persistence of fever or positive blood culture after 3 days despite adequate antimicrobial therapy and catheter removal, endocarditis or thrombophlebitis should be ruled out.

References for this chapter can be found at expertconsult.com.

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PERIPHERALLY INSERTED CENTRAL CATHETERS

The use of PICCs has increased in ICU patients.[184,185] Compared with CVCs, PICCs exhibit several advantages, including (1) a convenient placement procedure via the upper extremity without pleural-pulmonary damage; (2) low cost; (3) placement performed by nurse-led vascular access teams; and (4) clinical advantages in specific patient populations (e.g., with coagulopathies, morbid obesity).[186–188] A systematic review found no significant difference in rates of CR-BSI between PICCs and CVCs in hospitalized patients (including ICU patients).[189] However, PICCs are associated with several risks, particularly in critically ill patients. Probably because of their insertion in smaller veins, PICCs are prone to venous stasis; a systematic review showed that PICCs were associated with a higher risk of deep vein thrombosis than are CVCs, especially in critically ill patients.[3] Moreover, because of their small diameter and length, PICCs appear to be more prone to catheter tip malpositioning, catheter dysfunction, and thrombophlebitis than CVCs.[190] In general, PICC infections were strongly associated with multilumen catheters,[189,191] which are frequently used in the ICU setting. Moreover, PICCs placed at the bedside in the ICU setting are associated with higher complication rates (e.g., infectious complications) than those placed by interventional radiology in non-ICU patients.[192] For all these reasons, PICCs cannot be strongly recommended for short-term (<15–20 days) catheterization in the ICU.[193] Exceptions may be made in patients with severe obesity or with an elevated hemorrhagic risk.

ARTERIAL CATHETERS

Arterial catheters (ACs) are essential in the care of critically ill patients to facilitate hemodynamic monitoring and frequent blood sampling. Frequent complications of ACs include transient vascular occlusion, hemorrhage, hematoma, iatrogenic pseudoaneurysm, air embolism, and neurologic injury.[194] The risk of mechanical complication is decreased by ultrasound-guided access.[195–197]

To date, the duration of catheter maintenance of ACs is similar to CVCs, thus increasing the infection risk among ACs.[198] The infection risk associated with ACs is similar to that observed for CVCs.[99,199,200] However, a nationwide survey showed that clinicians significantly underestimated the infection risk associated with ACs.[201] In contrast to CVCs, the daily colonization risk appeared to increase during catheter maintenance.[96] The infection risk is lower for radial as compared with femoral ACs[200]; therefore radial access should be preferred. The microorganisms responsible for colonization and infection of ACs appeared similar to those identified in CVCs.[14,202] Reducing the duration of AC insertion may also limit the risk of arterial thrombi and infection occurrence.

SHORT-TERM HEMODIALYSIS CATHETERS

About one-third of critically ill patients have acute kidney injury (AKI), of whom approximately 20% receive renal replacement therapy (RRT).[203] In the ICU, vascular access for RRT for AKI management is usually granted by means of a large-bore, short-term dual-lumen catheter (DC) inserted in a central vein.[204] On one hand, extrapolating the DC data regarding catheter-related infections from long-term dialysis patients is debatable, as procedures applied in dialysis centers and in the ICU differ in terms of catheter types, patient populations, modalities, and catheter duration.[204] On the other hand, data on the epidemiology of standard CVCs cannot be extrapolated to DCs, as the latter differ substantially from CVCs in design and use (e.g., different use with frequent hub disconnections, other insertion sites, and different lumens).[204] For example, the subclavian site is discouraged to preserve the vascular network. The most information and recommendations on DC are based on data on the use of CVCs in the ICU.[205,206] A recent post hoc analysis of four RCTs showed that the infection risk was higher for DCs than for CVCs within the first 7 catheter days and appeared to be similar to CVCs later on. These findings suggest that targeted prevention strategies for DCs should focus on the period after catheter insertion.[207] The risk of DC colonization was demonstrated to remain stable over time for intermittent hemodialysis but to increase after 10 days for continuous RRT.[208] There is no difference in CR-BSI between the jugular and the femoral insertion sites; however, the risk of colonization is higher at the femoral site in obese patients.[81] An old small RCT showed that minocycline-rifampicin–coated DCs failed to decrease the rate of colonization but reduced CR-BSIs.[209] Studies conducted in chronic dialysis patients have suggested that locks might be associated with lower rates of thrombotic and infective complications, particularly if associated with antimicrobial solutions.[210] However, only a few studies were conducted in critically ill patients.[23,211,212] Souweine and colleagues demonstrated that a 2-minute 60% ethanol lock was not able to decrease the rate of intravascular catheter infections in short-term hemodialysis catheters of ICU patients.[23] A large study comparing interdialytic lock with unfractionated heparin and citrate as a catheter locking solution for nontunneled central venous hemodialysis catheters showed no significant difference in catheter-related infections between the two groups.[213] To date, the use of prophylactic ALT for short-term DC cannot be recommended. Skin antisepsis before catheter insertion should be performed with 2% CHG for DC,[24] but the impact of CHG dressings on DC catheter infections was not evaluated. However, in light of recent published data, the introduction of CHG dressing in the first 7 days for DC may be of value.[207] Empirical treatment therapies for DCs did not differ from CVCs: new data suggested that microorganisms associated with CR-BSI were similar between CVCs and DCs.[14] The risk of catheter colonization for DCs replaced because of dysfunction did not differ between DCs inserted by new puncture or exchanged over a guidewire.[214]

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112

Septic Shock

Jean-Louis Vincent

INCIDENCE

Septic shock is a form of acute circulatory shock that occurs secondary to severe infection. The incidence of septic shock may be rising, partly related to medical progress that allows individuals to survive longer, resulting in increased numbers of older, debilitated, or immunocompromised patients passing through the intensive care unit (ICU). Some 15% of ICU patients develop septic shock at one time or another, and the mortality rate is 40%–50%.[1,2] Somewhat lower mortality rates have been reported in some trials evaluating the effects of new therapeutic interventions, but such studies include a number of exclusion criteria that are often associated with high mortality rates—cirrhosis, immunosuppression, and "do-not-resuscitate orders," for example—so it is perhaps not surprising that mortality rates are lower in these therapeutic trials than in "real life."

ETIOLOGY OF SEPTIC SHOCK

Septic shock is most often bacterial, but it can also be caused by a fungal, parasitic, or viral[3] infection. In one-third of patients, no infectious agent is identified.[1] About half of the infections are nosocomial in origin. Although an infection can originate anywhere, the lung is the most common source of infection (40%), followed by the abdomen (20%), indwelling venous and arterial catheters and primary bacteremias (15%), and the urinary tract (10%).[1]

PATHOPHYSIOLOGY OF SEPTIC SHOCK

The pathophysiology of septic shock is complex. Essentially, the systemic sepsis response starts with the body's recognition of an invading organism or its toxins. Among the bacterial factors, one of the best known toxins is lipopolysaccharide, which is part of the outer gram-negative bacterial membrane, but other bacteria-derived factors include lipoteichoic acid and peptidoglycan. In certain cases, especially infections involving *Staphylococcus aureus* or beta-hemolytic group A streptococcus, the formation of superantigens results in toxic shock syndrome.

The early humoral response involves the complement and contact (kinin-kallikrein) systems. Immune cells, principally monocytes/macrophages and polymorphonuclear neutrophils (PMNs), are not only able to recognize pathogenic agents and their products so they can phagocytose and destroy them but also to release a series of mediators that can activate other cells. Among cell membrane receptors implicated in the recognition of pathogenic agents are the Toll-like receptors. In response to cellular stimulation, intracellular signaling is activated, resulting largely in the activation of transcriptional factors, including nuclear factor kappa B, which in turn are responsible for the initiation of proinflammatory reactions. A number of cytokines that interact synergistically are released by macrophages and other cells. Two of the key players are tumor necrosis factor alpha (TNF-α) and interleukin (IL)-1. TNF-α and IL-1 are particularly important proinflammatory cytokines whose administration in animals can reproduce all features of septic shock, including hypotension and development of multiple organ failure. A host of secondary mediators, including lipid mediators, oxygen free radicals, proteases, and arachidonic acid metabolites, are also released by macrophages, PMNs, and other cells. Vasodilator substances such as nitric oxide (NO) and prostaglandins are released by endothelial cells and are responsible for the early hemodynamic changes of sepsis. NO, in particular, acts as a powerful vasodilator on vascular smooth muscle. Increased NO production is essentially the result of the induction of inducible NO synthase by proinflammatory cytokines. The formation of large quantities of NO can also have secondary toxic effects on cells. It is important to note that the inflammatory response also causes release of vasoconstrictor substances, including thromboxane and endothelins.

Other effects of the inflammatory reaction that accompanies septic shock include expression of adhesion molecules on vascular endothelium and circulating cells (platelets, PMNs, and monocytes), allowing adhesion of activated leukocytes and their migration to subendothelial tissues. Alterations in intercellular endothelial junctions result in increased capillary permeability and generalized edema. Alterations in coagulation and fibrinolysis complete the picture, with proinflammatory mediators creating a procoagulant state. In addition, sepsis causes a significant reduction in plasma levels of natural anticoagulants such as protein C, protein S, and antithrombin by reducing their synthesis and increasing their consumption and clearance. Thrombolysis is also stimulated with an increase in the levels of plasminogen activator inhibitor-1. The net result is a balance that favors procoagulant processes, often leading to disseminated intravascular coagulation and contributing to the microcirculatory disorder that leads to multiple organ failure and death in many patients with sepsis. Antiinflammatory mediators including IL-4 and IL-10 are also released, which limit the effects of proinflammatory mediators and can lead to a state of relative immunosuppression sometimes called *immunoparalysis*.[4] Many patients are already immunosuppressed when sepsis is diagnosed.[5]

CLASSIFICATION

Patients with septic shock may be classified according to the letters *PIRO*[6]:

P = Predisposing Factors

Each patient has specific characteristics. For example, an individual receiving long-term immunosuppressant therapy requires a different

approach than someone who was previously healthy. Factors associated with lifestyle, such as alcoholism, may influence the course of septic shock.[7] Patient age and gender may also be important. Increasingly, genetics is being considered, and studies are discovering the genetic factors that can influence the development of and survival from sepsis.[8–10] Improved understanding of these aspects should help better direct therapeutic strategies.

I = Infectious Insult

This refers to the specific characteristics of the infection, that is, the agent or pathogen involved (e.g., gram-positive vs. gram-negative, bacteria vs. virus or fungus), the source of sepsis (e.g., urinary tract vs. respiratory tract), and the degree of extension of the infection (e.g., pneumonia confined to one lobe of one lung vs. generalized bilateral lung involvement, appendicitis vs. generalized peritonitis). All of these factors can influence the severity of sepsis response and the patient's likely response to therapy.

R = Host Response

This refers to factors involved in the inflammatory response of the host to the infection and is assessed largely by the presence or absence of the signs and symptoms of sepsis (e.g., degree of elevation of white blood cell count, C-reactive protein [CRP], or procalcitonin). Each patient mounts a different response dependent on various factors, including those previously discussed, and a patient's response will vary with his or her clinical course and treatment.

O = Organ Dysfunction

This refers to the degree of organ dysfunction related to sepsis and can be evaluated using the Sequential Organ Failure Assessment (SOFA) score,[11] which uses objective, readily available measures to quantify the dysfunction of six organ systems (Table 112.1). Dysfunction of each organ is rated according to a scale (0 [normal function] to 4 [organ failure]), and individual scores can then be summed to provide a total. Individual organ function and a composite score can thus be followed during the course of the disease and treatment.

CLINICAL PRESENTATION

It has been suggested that sepsis progresses in a continuum through to septic shock, but in the clinical situation, such a progression is not always so clear-cut or constant, and it is difficult to predict which patients are going to develop septic shock and when. Septic shock can develop very abruptly, without evidence of signs of sepsis in the preceding hours.

Septic shock is characterized by the persistence of severe arterial hypotension requiring vasopressor support, despite adequate fluid resuscitation, and the presence of perfusion abnormalities manifested by oliguria, reduced peripheral perfusion, and altered mental status. Septic shock is typically associated with hyperlactatemia (blood lactate concentrations greater than 2 mEq/L).[12]

One may anticipate that patients with septic shock will have fever, leukocytosis, and other typical features of sepsis, but this is not always true. Fever may be an important clue, but moderate fever can be found in other types of shock as well. More importantly, fever is often absent in patients with septic shock; in fact, hypothermia may be present in 10%–15% of cases, and this feature is associated with higher mortality rates.[13] Tachycardia can be the result of circulatory alterations associated with any type of shock. Leukocytosis is also nonspecific and can be found in other types of circulatory failure; moreover, acute leukopenia may occur in sepsis because of peripheral trapping of activated leukocytes and is also associated with a worse prognosis. Lactic acidosis, a hallmark of all types of circulatory failure, is usually compensated for by hyperventilation, so tachypnea is not specific for septic shock.

A more typical characteristic of septic shock is the hyperkinetic pattern characterized by high cardiac output. Although such a hemodynamic pattern is not entirely specific—it can be found in other inflammatory states such as polytrauma, pancreatitis, or even anaphylactic

TABLE 112.1 The Sequential Organ Failure Assessment Score

SOFA Score	0	1	2	3	4
Respiration PaO_2/FiO_2, mm Hg	>400	≤400	≤300	≤200 with respiratory support	≤100 with respiratory support
Coagulation Platelets × $10^3/mm^3$	>150	≤150	≤100	≤50	≤20
Liver Bilirubin, mg/dL (μmol/L)	<1.2 (<20)	1.2–1.9 (20–32)	2.0–5.9 (33–101)	6.0–11.9 (102–204)	>12.0 (>204)
Cardiovascular Hypotension	No hypotension	MAP <70 mm Hg	Dopamine ≤5 *or* dobutamine (any dose)*	Dopamine >5 *or* epinephrine ≤0.1 *or* norepinephrine ≤0.1*	Dopamine >15 *or* epinephrine >0.1 *or* norepinephrine >0.1*
Central Nervous System Glasgow Coma Score	15	13–14	10–12	6–9	<6
Renal Creatinine, mg/dL (μmol/L) *or* urine output	<1.2 (<110)	1.2–1.9 (110–170)	2.0–3.4 (171–299)	3.5–4.9 (300–440) *or* <500 mL/d	>5.0 (>440) *or* <200 mL/d

From Vincent JL, de Mendonca A, Cantraine F, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units. Results of a multicenter, prospective study. *Crit Care Med.* 1988;26:1793–1800.
*Adrenergic agents administered for at least 1 hour (doses given are in μg/kg/min).

shock—it should alert the attending physician to a likely diagnosis of septic shock.

HEMODYNAMIC CHANGES

The inflammatory reaction causes intense vasodilation that increases vascular capacity and results in a fall in arterial blood pressure. Hypovolemia caused by fluid loss (e.g., diarrhea, vomiting, or sweating) and alterations in capillary permeability contribute to hypotension, and reduced myocardial contractility can further aggravate the hemodynamic situation, although it is completely reversible when the septic shock resolves. The pathophysiology of reduced myocardial contractility includes alterations in endothelial function, beta-adrenergic receptors, and myocardial calcium metabolism. These effects are caused largely by sepsis mediators such as TNF-α and IL-1, oxygen free radicals, platelet activating factor, and NO, which all have negative inotropic effects.

After vascular filling as a result of volume resuscitation, the hemodynamic status in septic shock is characterized by reduced vascular tone associated with reduced systemic vascular resistance and a raised cardiac output. In addition, impaired myocardial contractility causes a fall in the ventricular ejection fraction. Ejection volume and cardiac output may be maintained by an increase in diastolic volumes. Hence, there is myocardial depression or dysfunction without any true cardiac failure (which would be associated with reduced cardiac output).

MONITORING

Any patient with septic shock requires monitoring with an arterial catheter to enable reliable and continuous assessment of arterial pressure. Changes in systolic and pulse pressures in mechanically ventilated patients during the respiratory cycle may also indicate a greater likelihood of response to a fluid challenge; however, this sign is not reliable when the patient triggers the ventilator.[14] The arterial catheter also facilitates blood sampling, notably for blood gas analysis.

Invasive Versus Less Invasive Monitoring

The use of the pulmonary artery catheter (PAC) has decreased substantially in recent years, primarily because of the development of less invasive techniques, especially echocardiography. Echocardiography can provide useful additional information, largely to visualize the degree of ventricular filling and ejection volume. However, echocardiography provides no information on the adequacy of cardiac output for the patient's needs and is difficult to perform continuously, so information is usually intermittent. Other less invasive methods of monitoring cardiac output include PiCCO, LidCO, transesophageal Doppler techniques, and even bioimpedance or bioreactance techniques.[15,16] However, measurement of cardiac output in isolation is not very helpful in most critically ill patients.

Blood Lactate Levels

The blood lactate level is an important biologic variable for determining the adequacy of perfusion and oxygenation. The normal blood lactate level is around 1 mEq/L, and hyperlactatemia becomes clearly pathologic above a level of 2 mEq/L. Although hyperlactatemia is the result of cellular hypoxia in other forms of circulatory shock, in septic shock, additional mechanisms may play an important role in raising blood lactate levels. In sepsis, blood lactate levels may be raised by an increase in cellular metabolism, inhibition of pyruvate dehydrogenase, and reduced clearance. Repeated measurements enable one to assess the efficacy of treatment[17] and have a predictive value superior to derived oxygenation parameters. The evolution of blood lactate levels enables a global evaluation of the state of shock in response to treatment, although in view of the relatively slow rate of change, blood lactate levels cannot be used to guide resuscitation.

Peripheral Perfusion Parameters

Measurements of the gastric intramucosal pH or its derivatives (mucosal PCO_2 or the difference between the mucosal and arterial PCO_2 [the PCO_2 gap]) reflect splanchnic perfusion and hence provide an idea of the adequacy of regional oxygenation. However, these techniques may be influenced by technical considerations, including the influence of gastric acid and enteral nutrition, and are not used clinically.

Other techniques for monitoring peripheral perfusion have been developed. Although the sublingual tissue is not a region that would immediately seem to be of most interest, it is easily accessible. Using techniques of orthogonal polarization spectral or side stream darkfield imaging, the heterogeneity of microcirculatory flow and the proportion of perfused vessels can be observed (Fig. 112.1) and quantified in patients with sepsis.[18] Moreover, the impact of therapeutic interventions on such vessels can be monitored,[19,20] opening the possibility that monitoring the microcirculation could be used to guide treatment.

Near-infrared spectroscopy is a technique that uses the differential absorption properties of oxygenated and deoxygenated hemoglobin to evaluate tissue oxygenation (StO_2). Analysis of changes in StO_2 during a circulatory stress test, such as a brief episode of forearm ischemia (venous or arterial occlusion), may be more useful to quantify sepsis-induced microvascular dysfunction than an isolated StO_2 value.[21] The

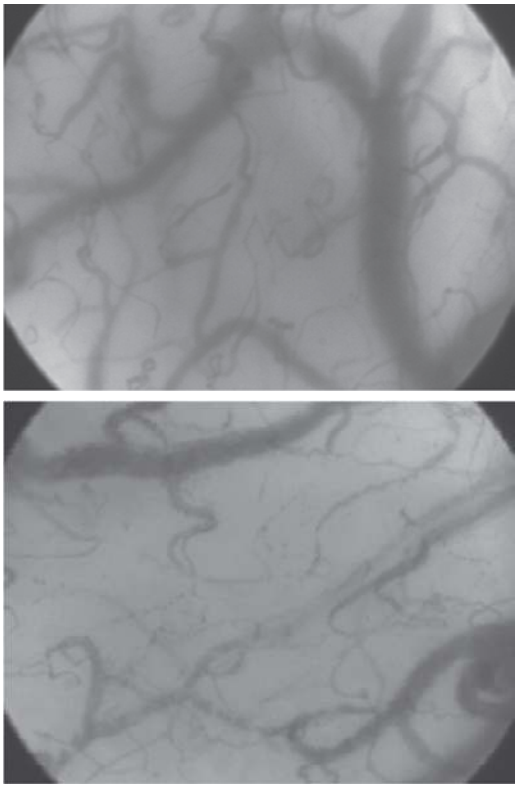

Fig. 112.1 Representative examples of sublingual microvasculature in a healthy volunteer *(top panel)* and in a patient with septic shock *(lower panel)*. Note decrease in density of small vessels in sepsis. (From De Backer D, Creteur J, Preiser JC, et al. Microvascular blood flow is altered in patients with sepsis. *Am J Respir Crit Care Med.* 2002;166:98–104, with permission.)

cutaneous perfusion can also be assessed objectively using Doppler techniques.[22]

Although all these techniques have demonstrated clearly the presence of an altered microcirculation in patients with sepsis, findings which are associated with prognosis,[23] further research is needed to fully evaluate the relevance of these values to the early resuscitation and care of critically ill patients.

MANAGEMENT

Septic shock, which both causes and reflects dysfunction of vital organs, is a serious condition, and patients must be stabilized as a matter of urgency. Management of the patient with septic shock involves three inseparable components: treatment of the infection, cardiovascular resuscitation, and modulation of the host response (Fig. 112.2).[24]

Treatment of Infection

Infection must be treated effectively and rapidly. Antibiotic therapy should be started as early as "reasonably possible." In all cases, sampling of blood and other material for culture is very important. In severe cases, including septic shock, antibiotic administration is urgent. In less severe cases, a bit more time could be taken to further evaluate the patient and sometimes in complex cases to consult with infectious disease specialists to determine the optimal agents. The choice of antibiotics may depend on local microbiologic flora and resistance patterns. Often, however, the microorganisms responsible for sepsis in an individual patient are not known for sure, and empiric broad-spectrum antibiotics must be given to ensure adequate coverage. Such empiric therapy must then be modified as soon as microbiology culture results become available.

In addition to antibiotic treatment, any focus of infection must be removed or drained without delay. If no source is identified, a systematic search should be made based on the "big five": lungs, abdomen, urine, wounds, and catheters.

Cardiovascular Resuscitation

The VIP rule proposed by Weil and Shubin[25] should be followed. Each patient is, in fact, a VIP, but the letters refer here to *Ventilation, Infusion,* and *Pump*.

V = Ventilation

All patients with septic shock must be generously oxygenated, with the aim of correcting any hypoxemia, regardless of whether it is caused by inadequate cardiac output, pulmonary edema, or pulmonary disease.

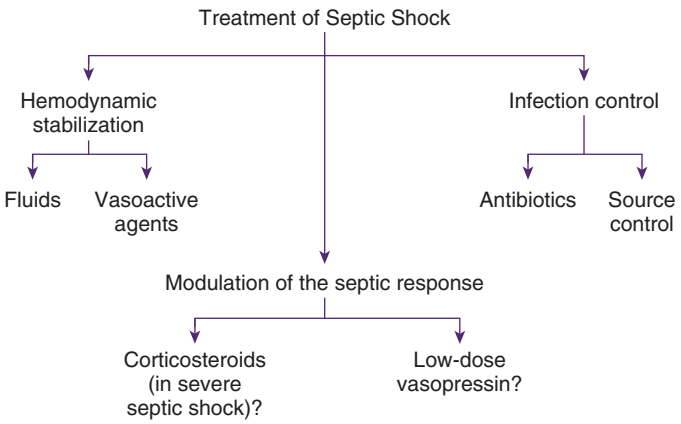

Fig. 112.2 The three aspects of the treatment of septic shock.

Severe cases require endotracheal intubation and mechanical ventilation. Noninvasive ventilation is not recommended in such hemodynamically unstable patients. Even though it may represent a temporary support rather than a treatment per se, mechanical ventilation allows not only an improvement in gaseous exchange but also has beneficial hemodynamic effects, notably by reducing the oxygen requirement of the respiratory muscles. As soon as the situation becomes more stable, hyperoxemia should be avoided. A reasonable rule is to target an SpO_2 of around 94%–97%.

I = Infusion

Septic shock is accompanied by absolute and relative hypovolemia, the result of various mechanisms:

- External losses, which may be obvious, such as vomiting and diarrhea, or less apparent, such as sweating
- Internal losses via an increase in capillary permeability with development of edema and sometimes liquid effusions (peritoneal, pleural effusion)
- Increase in plasma volume associated with arterial and venous dilatation

Hypovolemia needs to be corrected rapidly, as it causes hemodynamic instability both at the level of cardiac output and in terms of peripheral perfusion.

Assessment of an adequate volume state is essentially clinical: restoration of arterial pressure, improvement of cutaneous perfusion, improved urine output, and improved mental state. The central venous pressure (CVP) can be a useful guide, but it is not possible to define in advance the CVP that should be reached in any individual patient. Measurements of cardiac filling are primarily used as a limit to fluid administration in order to minimize the risk of pulmonary edema. In fluid replacement, it is preferable to use a fluid challenge technique, in which filling pressures are measured at regular intervals during fluid administration (Table 112.2).[26] If cardiac output is monitored, one should ensure that it increases with fluid boluses, and such fluid administration should be stopped when cardiac output reaches a plateau. The passive leg raising test represents a form of mini-fluid challenge without giving fluids. Raising the legs sounds easy, but there are limitations. Importantly, the test should not trigger a stress response in the patient, which would result in an increase in cardiac output, arterial pressure, and heart rate in any individual. In any case, it is not the blood pressure that counts, but the transient increase in stroke volume associated with the maneuver that must be assessed properly.[27]

There has been considerable debate as to which fluid should be used in sepsis, but it is the quantity of fluid rather than the type of fluid per se that is of greatest importance. Because of their propensity for leakage into the extravascular space, greater volumes of crystalloids are needed to achieve the same effect as colloids,[28] thus potentially increasing the risk of edema, but colloids are more expensive and carry their own risks. Although this is still controversial, the current evidence

TABLE 112.2 The Fluid Challenge Technique (With the TROL Mnemonic)

Define	Example
Type of fluid	Ringer's lactate
Rate of infusion	200 mL in 10 min
Objective	Mean arterial pressure >75 mm Hg
Limits	Central venous pressure 16 mm Hg

supports the administration of some albumin in septic patients with significant hypoalbuminemia and risks of multiple organ failure.

P = Pump (Vasoactive Agents)

If fluid administration alone is unable to restore an adequate perfusion pressure, vasoactive agents are required. Catecholamines are preferred for their rapid action and efficacy and their short half-lives. Adrenergic agents stimulate beta-1 (positive inotropes), beta-2 (essentially vasodilators and bronchodilators), and alpha- (essentially vasoconstrictors) receptors to varying degrees. Dopamine also stimulates dopaminergic receptors, causing vasodilation primarily in the splanchnic and renal regions, but the clinical relevance of this effect is doubtful.

A randomized controlled study showed that dopamine use is associated with increased adverse effects, notably arrhythmias, in patients with shock,[29] and a meta-analysis indicated that dopamine administration is associated with higher mortality rates than norepinephrine in septic shock.[28] Norepinephrine is therefore the preferred first-line vasopressor in patients with septic shock. Epinephrine should not be used as a first-line vasopressor in patients with septic shock; it can have deleterious effects on splanchnic circulation and increase cellular metabolism. Dobutamine is often added to vasopressor therapy, particularly when using norepinephrine, to increase cardiac output by its positive inotropic effects.

Angiotensin II has strong vasopressor activity. Initially proposed (also called "hypertensin") in the early 1960s,[30] therapeutic interest was revived with the commercial development of a new preparation (angiotensin II).[31] The beneficial effects need to be better defined before generalized use can be recommended.

The place of vasopressin derivatives is also not well defined. Patients with septic shock usually have a degree of relative vasopressin deficiency so that vasopressin supplementation may be warranted. The primary risk is that of excessive vasoconstriction, with reduced blood flow to the splanchnic and coronary circulation. Therefore vasopressin should never be administered when cardiac output is low. Doses should not exceed 0.03 U/min, and cardiac output should be monitored. Vasopressin may be involved in endothelial protection so that its early administration may limit edema formation.[32] This hypothesis, however, requires confirmation by further study.

Maintaining oxygen delivery (DO_2), and therefore cardiac output, is fundamental, because septic shock is typically a hyperkinetic state. Mixed venous oxygen saturation (SvO_2) is typically normal or high. Attempts to maintain central venous oxygen saturation ($ScvO_2$) at least at 70% may be beneficial, although taking this approach should not be routine.[33] In patients who do not improve with initial resuscitation, $ScvO_2$ should be checked.[33] A low $ScvO_2$ should prompt the administration of more fluids and possibly dobutamine. A transfusion may be useful.[34] Decreasing oxygen demand by administering sedatives has its own problems because sedatives can decrease DO_2 and alter the microcirculation.

Immunomodulation

Clinical trials assessing drugs that limit the effects of proinflammatory cytokines such as TNF-α (anti-TNF antibodies, TNF receptors) and IL-1 (IL-1 receptor antagonist inhibitors) have not given convincing results regarding the beneficial effects of these agents on outcome, probably largely because such cytokines have multiple effects, beneficial and harmful. Administration of activated protein C (drotrecogin alfa [activated]) early in septic shock reduced mortality and morbidity in initial studies,[35] but the drug was withdrawn from the market after negative results were obtained in a placebo-controlled study.[36] A trial of thrombomodulin in patients with sepsis-associated coagulopathy[37] gave promising results[38] but further study is needed to confirm this effect.

The administration of large doses of corticosteroids for patients with septic shock was proposed many years ago and not shown to be beneficial. More recently, the concept of relative adrenal insufficiency has emerged, and administration of moderate doses of corticosteroids (200 mg hydrocortisone in 24 hours) in patients with septic shock may be effective.[39]

The treatment of fever is controversial. Increased body temperature increases oxygen requirements, but the increased cellular metabolism may form part of the body's natural defense. Animal studies have suggested that control of fever is detrimental[40] and that the release of heat shock proteins in fever may have important cell-protective effects.[41] A multicenter study of acetaminophen in febrile ICU patients with suspected infection showed that the drug was well tolerated but did not reduce mortality.[42]

High-flow hemofiltration techniques can remove a range of bacterial products and mediators. These techniques appear to improve hemodynamic status and decrease vasopressor requirements. However, clinical studies have provided conflicting data regarding the effects of these techniques on outcomes.[43]

Nutritional Support

Malnutrition can prolong the course of sepsis and increase the risk of complications. When considering nutritional support in patients with septic shock, several factors should be remembered:

- There is no urgency to start nutritional support unless the patient is malnourished.
- The enteral route is preferable to the parenteral route.
- Enteral nutrition should not be started during the initial phase of resuscitation. Although studies are limited, increasing the oxygen requirements of the gut is probably unwise in circulatory shock. However, as soon as the patient has achieved a degree of hemodynamic stability (after a maximum of 24–48 hours), enteral nutrition should be started.
- There is no urgency to start parenteral nutrition. Waiting a few days is acceptable.
- Careful control of blood glucose levels is recommended. It is suggested that the glucose concentration be kept below 180 mg/dL or, even better, below 150 mg/dL.[44] This can be achieved quite easily with modern equipment. Variability in glucose levels should also be avoided.[45]

Organ Support

Organ dysfunction can involve any organ and can be quantified using the SOFA score (see Table 112.1). Techniques for individual organ support are covered in separate chapters, but an overview is given here.

Respiratory Alterations

Respiratory failure is a common complication of sepsis and is usually characterized by hypoxemia. The diagnosis of acute respiratory distress syndrome (ARDS) is made when the PaO_2/FiO_2 ratio is less than 300 mm Hg in the presence of bilateral infiltrates on a chest radiograph, with no evidence of left heart failure.[46] There is no specific therapy for ARDS, and treatment relies on respiratory support and management of the underlying cause (e.g., sepsis).[47]

When starting a patient on mechanical ventilation, several factors need particular attention:

- Worsening of arterial hypotension when starting mechanical ventilation suggests the presence of hypovolemia because of a reduction in venous return (and hence in cardiac output) when intrathoracic pressures are increased.
- As in all mechanically ventilated patients, the use of large tidal volumes and high inflation pressures must be avoided not only for

hemodynamic reasons but also to avoid a major inflammatory reaction from ventilator-induced lung injury (VILI).

- Sedation must be avoided whenever possible. Administration of effective analgesia can help reduce sedative needs, which in turn can improve patient comfort and shorten the duration of mechanical ventilation and ICU stay.[48] This approach can be summarized in the mnemonic, eCASH: early Comfort using Analgesia, minimal Sedatives and maximal Humane care.[49]

Renal Alterations

Sepsis is the leading cause of acute renal failure in the ICU.[50] Renal function can worsen as a result of combined circulatory changes and inflammation. In addition, management of septic patients may involve administration of nephrotoxic agents, such as aminoglycosides or contrast material used for radiologic examinations.

Unfortunately, there is no prophylactic approach to renal failure other than to try to maintain adequate renal perfusion and overall volume state. Administration of dopaminergic agents is ineffective at preventing renal failure,[51] and the indiscriminate use of diuretics may be harmful.[52]

Renal replacement therapy is frequently necessary in septic patients. In septic shock, continuous venovenous hemofiltration techniques, with or without dialysis, are generally preferred over intermittent techniques to facilitate control of fluid balance.

Coagulation Alterations

Coagulopathy is common in septic shock. A low platelet count is common and may be associated with a prolonged prothrombin time and an activated partial thromboplastin time. Treatment of these alterations revolves primarily around the cause, and there is no indication for heparin administration other than for thromboembolism prophylaxis. In severe cases associated with significant bleeding, administration of fresh frozen plasma or platelet infusions may be indicated.

Hepatic Alterations

Circulatory shock of any cause frequently results in the elevation of liver-associated enzyme levels, but the contribution of various organs (e.g., muscles) to increased enzyme levels is difficult to quantify. Often there is a rise in bilirubin levels after several days, without evidence of hemolysis, major hematomas, or biliary pathology. Supplementary examinations such as ultrasound may be indicated to exclude any associated biliary pathology.

Cerebral Function Alterations

Circulatory shock is typically accompanied by an alteration in cognitive function, initially manifested as confusion without coma. Cerebral alterations can be prolonged, and the patient is then said to have septic encephalopathy. The exact cause of the encephalopathy is unclear, although various mediators of sepsis have been implicated. Sedative agents, especially benzodiazepines, can contribute to delirium. Investigations are of little use except to exclude other causes. The electroencephalogram generally shows a diffuse slowing,[53] whereas cerebral computed tomography and cerebrospinal fluid examination are normal. These alterations are usually fully reversible with the resolution of shock.

CONCLUSION

Optimal treatment of a patient with septic shock requires a rapid and effective management plan with the assistance of the full ICU team. Infection control and achieving hemodynamic stability must be tackled simultaneously. Other interventions are currently undergoing clinical trials, with the hope that they will improve the microcirculatory changes of sepsis or beneficially modulate the host response. A better characterization of patients with septic shock—for example, by using the PIRO system—is necessary to appropriately titrate therapeutic interventions to individual patients.

KEY POINTS

- Septic shock affects about 15% of ICU patients and has a mortality rate of close to 40%–50%.
- Septic shock is most commonly caused by a bacterial infection, although fungi, viruses, and parasites can all be implicated. The most common source of such serious infection is the lung, followed by the abdomen.
- Patients with sepsis can be classified according to their predisposing factors, the nature of the infection, degree of immune response, and associated organ dysfunction.
- Septic shock is defined as sepsis with organ dysfunction with persistent arterial hypotension requiring vasopressor administration despite adequate fluid resuscitation in the presence of perfusion abnormalities manifested by oliguria, reduced peripheral perfusion, and/or altered mental status.
- Blood lactate levels are typically raised in septic shock, and persistently raised levels are a poor prognostic sign.
- Management of septic shock includes infection control, hemodynamic stabilization, and modulation of the host response.

References for this chapter can be found at expertconsult.com.

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Infections of the Urogenital Tract

Florian M.E. Wagenlehner, Adrian Pilatz, and Kurt G. Naber

Infections in the intensive care unit (ICU) contribute significantly to patient morbidity. Depending on the type of ICU, nosocomial infections may account for 70% of infections.[1] Nosocomial infections of the urogenital tract are frequent and sometimes underestimated in the ICU.[2]

DEFINITION

Urinary tract infection (UTI) can be the primary cause for admission to the ICU or can be acquired after intensive care procedures. Because patients are frequently sedated in the ICU, clinical diagnosis of UTI is often difficult. Nevertheless, UTI is an important cause of morbidity and antibiotic resistance in the ICU. Complicated UTI is a highly heterogeneous entity, with a common pattern of the following factors[3,4]:

- Anatomic, structural, or functional alterations of the urinary tract, which significantly impede urodynamic properties (e.g., stents, urine transport disturbances, instrumentation of the urinary tract, stones, tumors, or neurologic disorders)
- Impaired renal function caused by parenchymal diseases or prerenal, intrarenal, or postrenal nephropathies (e.g., acute and chronic renal insufficiencies, cardiac insufficiency)
- Accompanying diseases impairing the patient's immune status (e.g., diabetes mellitus, liver insufficiency, use of immunosuppressive agents such as corticosteroids, acquired immunodeficiency syndrome [AIDS], hypothermia)

ETIOLOGY

Causative pathogens of UTI are almost exclusively bacteria and yeast. Viral pathogens are only found in patients with severe immunosuppression, such as after bone marrow transplantation. High antibiotic pressure and special circumstances in the ICU modulate the microbial spectrum. *Escherichia coli* is the most frequent pathogen but occurs less frequently in nosocomial UTI than in uncomplicated community-acquired UTI. Other Enterobacteriaceae may also be uropathogenic (e.g., *Klebsiella, Proteus*, *Enterobacter*, *Serratia*, *Citrobacter,* or *Morganella* species). Nonfermenters such as *Pseudomonas aeruginosa,* gram-positive cocci such as staphylococci and enterococci, and *Candida* species may also play an important role. The microbial spectrum is likely to differ over time and from one institution to the other. To follow the spectrum and development of antibiotic resistance, each ICU has to update its own surveillance analyses (Table 113.1, Fig. 113.1).

EPIDEMIOLOGY

The Extended Prevalence of Infection in Intensive Care (EPIC II) study[1] revealed that 51% of patients were infected on the study day and that 71% of all patients were receiving antibiotics. The most frequent types of ICU-acquired infections with their total occurrence were respiratory tract infections, 63.5%; abdominal infections, 19.6%; bloodstream infections, 15.1%; and renal or UTIs, 14.3%.[1] The true incidence of UTI, however, may be even higher if more meticulously looked for. In a prospective study specifically evaluating nosocomial UTI, nosocomial UTIs accounted for 28% of nosocomial infections, lower respiratory tract infections for 21%, pneumonia for 12%, and bloodstream infections for 11%. The rates of urinary catheter–associated UTIs varied between 4.2% (symptomatic UTI) and 14.0% (asymptomatic UTI), which shows that asymptomatic bacteriuria is frequent in ICU patients, although symptoms of UTIs in intensive care patients are frequently difficult to assess.[2] In the global one-day point prevalence study in urologic hospitalized patients (GPIU study), asymptomatic bacteriuria accounted for 27% of healthcare–associated (HA) UTIs (HAUTIs), followed by cystitis (26%), pyelonephritis (20%), urosepsis (11%), and other urogenital infections (16%),[7] showing that HAUTI is present in high frequency in certain patient groups. In a recent infection control program HAUTI caused by indwelling urinary catheters (CAUTI) rates were assessed in ICUs in order to prevent CAUTI by educational means. Before the intervention, the CAUTI rate in ICU patients was 2.48 CAUTIs/1000 catheter days. In non-ICUs the CAUTI rate was 2.28/1000 catheter days.[8]

UTIs in the ICU are divided into two groups:

1. UTIs with nonurologic complicating causes: diabetes mellitus, renal insufficiency, immunodeficiency, infectious foci contiguous to the urogenital tract, or trauma patients
2. UTIs with urologic complicating causes: renal transplantation, neurogenic bladder dysfunction, procedures in the urogenital tract, urinary stones or foreign bodies in the urogenital tract (e.g., CAUTI)

In UTIs with primary nonurologic complicating causes, antimicrobial therapy is generally sufficient. However, in UTIs with primary urologic causes, the complicating factors must be identified and treated. In such cases, antimicrobial therapy is only one component of the treatment.

Urinary Tract Infections With Nonurologic Complicating Causes

Individuals with diabetes are at higher risk of UTIs.[9,10] Increased susceptibility in patients with diabetes is positively associated with the increased duration and severity of diabetes as a result of impaired granulocyte function, decreased excretion of the Tamm-Horsfall protein, low levels of interleukin (IL)-6 and IL-8 in the urine that lead to lower "cidality" of the urine, and altered microflora in the genital region. Furthermore, diabetic cystopathy and nephropathy may be complicating factors in the urinary tract. In addition to antibiotics, treatment must address the metabolic situation. In pyelonephritis, usually a switch to insulin or insulin-analogous therapy is necessary.

TABLE 113.1 Bacterial Spectrum of Healthcare–Associated Uropathogens (≥2%) From Distinct Surveillance Studies

Name of Study	SENTRY[5]	SENTRY[5]	SENTRY[5]	ESGNI-003[6]	GPIU-Study[7]
Regions of the world	North America	Latin America	Europe	Europe	Global
Year of surveillance	2000	2000	2000	2000	2003–2010
Type of surveillance	Longitudinal	Longitudinal	Longitudinal	Cross-section	Cross-section
Origin of samples	Microbiology laboratories	Microbiology laboratories	Microbiology laboratories	Different departments in the hospital	Urology departments
Number of pathogens	*n* = 1466	*n* = 531	*n* = 783	*n* = 607	*n* = 1371
SPECIES, %					
Escherichia coli	43%	60%	46%	36%	40%
Klebsiella spp.	12%	12%	9%	8%	11%
Pseudomonas spp.	7%	6%	9%	7%	11%
Proteus spp.	6%	7%	10%	8%	6%
Enterobacter spp.	3%	4%	4%	4%	5%
Citrobacter spp.	4%	2%	2%	2%	n.r.
Enterococcus spp.	16%	4%	13%	16%	12%
Staphylococcus spp.	6%	3%	3%	4%	6%
RESISTANCE RATES OF ANTIBIOTICS FOR THE TOTAL BACTERIAL SPECTRUM TESTED, %					
Ampicillin	59%[e]	62%[e]	65%[e]	66%[e]	n.r.
Ampicillin + BLI	31%[e]	36%[e]	36%[e]	29%[a]	53%
TMP/SMZ	43%[e]	38%[e]	48%[e]	32%[a]	53%
Ciprofloxacin	29%[e]	32%[e]	29%[e]	17%[b]	51%
Gentamicin	n.r.	n.r.	n.r.	18%	42%
Ceftazidime	n.r.	n.r.	n.r.	13%[c]	38%
Amikacin	n.r.	n.r.	n.r.	19%[c]	n.r.
Piperacillin/tazobactam	n.r.	n.r.	n.r.	n.r.	30%
Imipenem	n.r.	n.r.	n.r.	14%[c]	10%
Vancomycin	n.r.	n.r.	n.r.	1%[d]	n.r.

BLI, Beta-lactamase inhibitor; *n.r.*, not reported; *TMP/SMZ*, trimethoprim-sulfamethoxazole.
[a]Gram-negative bacteria excluding *Pseudomonas aeruginosa*.
[b]Gram-negative bacteria.
[c]*P. aeruginosa*.
[d]Enterococci.
[e]*E. coli*, *Klebsiella* spp., *P. aeruginosa*, enterococci.

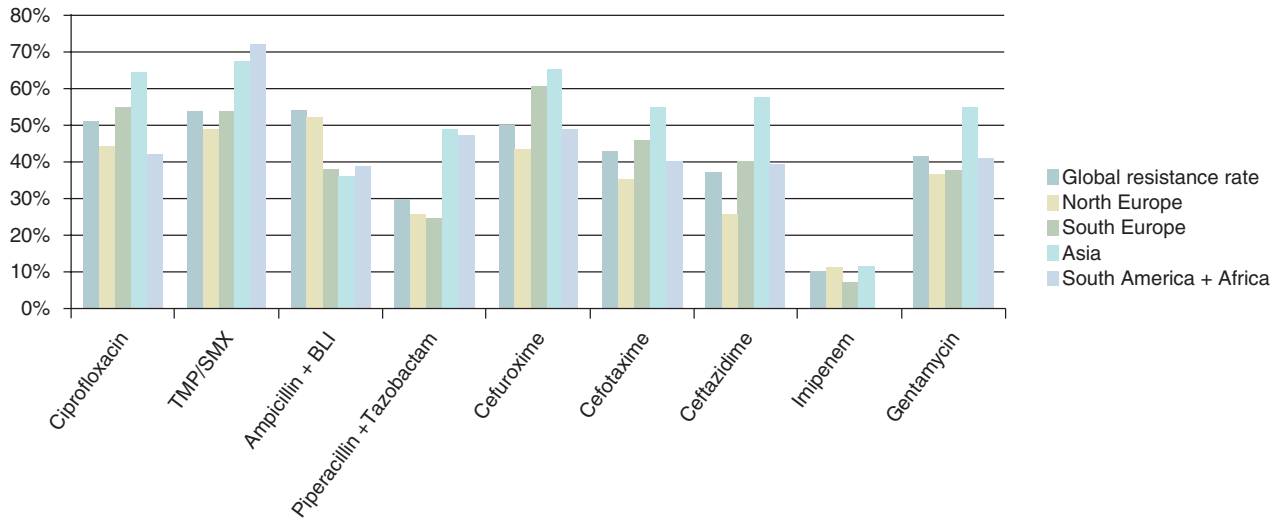

Fig. 113.1 Global and Regional Resistance Rates of the Total Bacterial Spectrum from Healthcare–Associated UTI.[7] *BLI*, Beta-lactamase inhibitor; *TMP/SMZ*, trimethoprim-sulfamethoxazole.

The place of immunosuppression per se in the development of UTI remains unresolved.[11] Patients with end-stage renal failure are generally not particularly susceptible to the usual gram-negative urinary pathogens, although they may acquire unusual and granulomatous infections. Patients have evidence of reduced cellular and humoral immunity. However, the situation is a little clearer in male patients with human immunodeficiency virus (HIV) and AIDS, where there is a close relationship between CD4 counts and the risk of bacteriuria, particularly in those whose counts are less than 200 cells/mL.[12]

Pathogens may be translocated into the urinary tract from contiguous infectious foci (e.g., appendicitis, sigmoid diverticulitis, or translocation by ileus). Symptoms and localization of pain can be misleading and may delay the diagnosis. Operations or trauma may cause hypothermia, tissue hypoxia, and hemodynamic alterations that result in kidney dysfunction and impaired mucosal perfusion. The use of latex catheters in these critical situations (e.g., operations with heart-lung machine) can also lead to urethral strictures. Silicone catheters or suprapubic catheters are recommended in these patients.[13] Suprapubic catheters cannot prevent UTIs. They can, however, lower the rate of UTIs from 40% to 18%.[14]

Urinary Tract Infections With Urologic Complicating Causes

Patients show a high risk of developing bacteriuria after renal transplantation, threatening clinical outcomes for both the patient and transplant. Early infections (up to 3 months after transplantation) are differentiated from late infections (more than 3 months after transplantation). Early infections may present with no symptoms. In this phase, occult bacteremia (60% of bacteremias after renal transplantation originate from the urinary tract), allograft dysfunction, and recurrent UTIs after antibiotic therapy are frequently seen.[4] Sometimes, it can be quite difficult to distinguish rejection from infection. Patients must also be investigated for surgical complications.

UTIs caused by *Candida* species are frequently asymptomatic. There is, however, a risk of obstructive fungal balls leading to candidemia or invasion of the anastomosis in renal transplant recipients. Asymptomatic candiduria should therefore be treated in these patients.[4] Urine transport disturbances (e.g., from an obstructive ureteral stone) require specific urologic therapy such as percutaneous nephrostomy or stenting. In case of bladder obstruction, an indwelling urinary catheter (suprapubic or transurethral) will be the primary therapy in the ICU. Long-term indwelling catheters (more than 30 days) are associated with a selected microbial spectrum of difficult-to-treat uropathogens (e.g., *Providencia* spp., *Proteus* spp., or *Pseudomonas* spp.).[15] After initiation of antimicrobial therapy, the catheter should be replaced to remove the biofilm material.[4]

PATHOPHYSIOLOGY

UTIs generally occur from organisms invading the urinary tract via the urethra. Pathogens originate from endogenous or exogenous nosocomial flora. Hematogenous spread to the urinary tract is rare.

In uncomplicated UTIs, pathogens need to have specific virulence factors enabling them to initiate an infection after invasion of the urinary tract. The medical conditions of an ICU patient may weaken physiologic barriers and defenses, thus facilitating the entry of pathogens. In addition, the nosocomial environment in the ICU, including antibiotic pressure and decreased supply of oxygen or nutrients (e.g., iron) to tissues, can select pathogens with specific resistance patterns. A general adaptation strategy is the formation of hypermutator strains, which show 100- to 1000-fold increased mutation frequencies, enabling the pathogens to rapidly adapt to challenging environments and thus develop effective mechanisms for antibiotic resistance.[16,17]

An important mechanism contributing to UTI is the formation of biofilms, which are associated with the increased number of biomaterials used in medical practice. Biofilm infections develop not only around foreign bodies such as urinary catheters or stents but also in urinary stones, scarred or necrotic tissue, obstructive uropathies, or even chronic bacterial prostatitis. A biofilm has been defined as an accumulation of microorganisms and their extracellular products forming a structured community on a surface. The formation of a biofilm generally consists of three steps:

1. Deposition of a host conditioning film
2. Attachment of microorganisms followed by microbial adhesion and anchorage to the surface by exopolymer production
3. Growth, multiplication, and dissemination of the organisms

The basic structural unit of a biofilm is a microcolony—that is, a discrete matrix-enclosed community consisting of bacteria of one or more species. The biofilm is usually built up of three layers[13,14]:

1. Linking film that attaches to the surface of a tissue or biomaterial
2. Base film of compact microorganisms
3. Surface film as an outer layer, where planktonic organisms can be released to float freely and spread on the surface

Bacteria within biofilms differ both in behavior and phenotypic form from the planktonic, free-floating bacteria. The failure of antimicrobial agents to treat biofilms has been attributed to a variety of mechanisms:

- Organisms encapsulated in biofilms grow more slowly than planktonic ones, probably because encapsulated bacteria have a decreased nutrient and oxygen supply, leading to a decreased metabolic rate and antimicrobial susceptibility. This may select a less susceptible genotype, forming a resistant population. Furthermore, antimicrobial binding proteins are poorly expressed in these slow-growing bacteria.
- The biofilm matrix delays or impedes the diffusion of antibiotic molecules into the deeper layer of the film (extrinsic resistance).
- Bacteria within the biofilm are phenotypically so different from their planktonic counterparts that antimicrobial agents fail to eradicate them. Bacteria within a biofilm activate many genes that alter the cell envelope and molecular targets by altering the susceptibility to antimicrobial agents (intrinsic resistance). These phenotypic changes are likely to play a more important role in the development of antimicrobial resistance than external resistance (biofilm matrix, glycocalyx).
- Bacteria within a biofilm can sense the external environment, communicate with each other, and transfer genetic information and plasmids within biofilms.
- Bacteria in biofilms can usually survive antibacterial concentrations 100–150 times higher than those needed to kill planktonic bacteria of the same species.[18–20]

Antimicrobial treatment can be effective in only "young" biofilms (<24 hours). At present, combination therapy with fluoroquinolones and macrolides or fosfomycin seems to be most effective against biofilm infections. During an acute febrile phase of biofilm infection, antimicrobial therapy is essential and can be effective because the planktonic bacteria are responsible for the febrile reactions and not the bacteria covered in the biofilm. However, to eradicate pathogens from the biofilm, the biofilm itself has to be removed (e.g., catheter change or extraction of infectious stones).

DIAGNOSIS

Medical History and Physical Examination

Sedated intubated patients are often difficult to evaluate regarding their signs and symptoms of UTIs. The patient or a family member should be asked about previous episodes of UTIs and urologic diseases (e.g., stones or tumors) or operations.

The physical examination should include inspection and palpation of the costophrenic area, lower abdomen, pubic region, inguinal lymph nodes, and genitals and a digital transvaginal or transrectal examination. Ultrasound is an important diagnostic device, and its use should be frequently considered because of the close proximity of the urogenital organs to the intestine, spleen, liver, pancreas, gallbladder, ovary, or uterus.

Urinary Examinations

Urine specimens in ICU patients are almost exclusively collected from catheters. Because urine from catheters has to be collected into a closed system, the urine specimen should be taken from the puncture site at the catheter after disinfection, without opening the closed system. There are different complementary methods for laboratory examination of the urine specimen.

Dipstick Test

The dipstick test is performed with undiluted urine and investigates the following infection-related parameters[21]:

- pH: An alkaline urine (pH >8.0) points to urease-producing organisms such as *Proteus* or *Providencia* spp. and is associated with magnesium-ammonium-phosphate stones.
- Nitrate: Most Enterobacteriaceae harbor a nitrate reductase that reduces nitrate to nitrite. Some common uropathogens such as *Enterococcus* and *Staphylococcus* lack nitrate reductase and will therefore not be detected using this parameter, independent of their urinary concentration. The positive detection of nitrate requires its inclusion in the patient's diet.
- Leukocytes (positive leukocyte esterase): Granulocytes are the most frequently detected leukocytes in the urine of UTI patients. Macrophages appear fairly often in patients with UTIs, but their significance remains unknown.
- Erythrocytes (positive hemoglobin): Hematuria remains a major sign of urinary tract and renal disease.
- Specific gravity/osmolality (degree of urine dilution).
- Protein: Total protein in urine is a mixture of high- and low-molecular-weight plasma proteins from the kidney and urinary tract or bacteria.
- Glucose (metabolic condition of the patient).

Microscopy

There are two possibilities of a microscopic evaluation[21]:

1. Chamber counting of uncentrifuged urine (standard values for urine are shown in Table 113.2).
2. Urinary sediment findings; at least 10 fields of vision at 400× magnification are counted, and the mean value of particles is registered. However, centrifugation methods are never quantitative in counting erythrocytes and leukocytes because of variable loss during centrifugation.

Urine Flow Cytometry

Flow cytometry usually combines impedance method detection with the identification and quantification of urinary particles, such as leukocytes and bacterial cells, available for real-time assessment. Urine flow cytometry has not been specifically evaluated in critical care patients. However, existing data suggest that flow cytometry is beneficial in real-time assessment of uropathogens and leukocytes.[22]

Microbiology

To differentiate contamination in urine from significant bacteriuria, quantitative microbiology is needed. The microbial count has to be interpreted in relation to the urinary dilution.

Clinical Diagnosis

To survey and compare infection rates in different institutions, UTIs should be classified according to widely accepted definitions, such as the definitions of the US Centers for Disease Control and Prevention (CDC). The CDC/National Healthcare Safety Network definitions[23] stratify HAUTIs into symptomatic, asymptomatic, and other infections of the urinary tract. To be of value in determining a nosocomial infection, urine specimens must be obtained aseptically using an appropriate technique such as clean catch collection, bladder catheterization, or suprapubic aspiration.

THERAPY

General Principles

Not all bacteriuric patients in the ICU need to be treated. In general, asymptomatic bacteriuria does not have to be treated.[24] Therapy should only be started in patients with significant symptoms and morbidity and in whom asymptomatic bacteriuria may be deleterious (e.g., before traumatizing intervention of the urinary tract and in pregnant women). In the ICU, indications for treatment of asymptomatic UTIs might include some other circumstances such as renal transplant, severe diabetes mellitus, or severe immunosuppression. In complicated UTIs, antibiotic therapy can only be successful when complicating factors can be eliminated or urodynamic functions restored. Treatment of complicated UTIs therefore comprises adequate antibiotic treatment and successful urologic intervention.

Antibiotic Therapy

For therapy of complicated UTI, antibiotics must possess appropriate pharmacodynamic and pharmacokinetic prerequisites: high renal unmetabolized clearance with good antibacterial activity, both in acidic and alkaline urine. Moreover, microbial resistance patterns must be considered in the choice of antibiotics. Increasing antibiotic resistance, especially among Enterobacteriaceae, makes prudent antibiotic therapy increasingly difficult. The increasing appearance of quinolone-resistant and extended-spectrum beta-lactamase (ESBL)–forming enterobacteria will inevitably lead to the increased use of carbapenems in empiric therapy, thus increasing antibiotic pressure on these highly potent antibiotics. To diminish the selection pressure for resistant pathogens, antibiotics from different classes should be used. Multiple antimicrobial agents are available for therapy for complicated UTIs (see Table 113.2): second- or third-generation cephalosporins, broad-spectrum penicillins with beta-lactamase inhibitors, cephalosporins with beta-lactamase inhibitors, carbapenems, carbapenems with beta-lactamase inhibitors, monobactams, fluoroquinolones, and aminoglycosides. For empiric therapy of severe UTIs, broad-spectrum antibiotics should be used (e.g., broad-spectrum penicillins with beta-lactamase inhibitors, third-generation cephalosporins with or without beta-lactamase inhibitors, fluoroquinolones, or carbapenems). Aminoglycosides as monotherapy have recently been shown to be noninferior to carbapenems or colistin and in severe infections.[25,26] Synergism with aminoglycosides, which inhibit protein synthesis and thus block the formation of toxins or virulence factors, might also be useful for initial therapy, but side effects have to be considered.

Candiduria is a common problem in ICUs. It may represent harmless colonization, but it can also be an early sign of systemic candidosis.[27] A second urine culture after replacing the urethral catheter can rule out contamination. In critically ill patients, systemic therapy for *Candida* species should be started according to susceptibility testing or species differentiation (see Table 113.2). Complicating factors such as diabetes mellitus or urologic abnormalities should be treated concomitantly. Systemic antimycotic therapy is preferred to local instillation therapy because of the potentially systemic nature of candiduria in ICU patients.

TABLE 113.2 Division and Dosage of Distinct Antibiotics Recommended for Treatment of Urinary Tract Infections

		DOSAGE	
Antibiotic Group	**Substance**	**Oral**	**IV**
Aminopenicillin + BLI	Ampicillin/sulbactam	0.750 g twice daily	0.75–3 g 3 times daily
	Amoxicillin/clavulanic acid	1 g twice daily *or* 0.625 g 3 times daily	1.2–2.2 g 3 times daily
Acylureidopenicillin + BLI	Piperacillin/tazobactam	—	2.5–4.5 g 3 times daily
	Piperacillin/sulbactam	—	5 g 3 times daily
Cephalosporin Gr. 1	Cephalexin	Prophylaxis only	—
Cephalosporin Gr. 2	Cefuroxime axetil	500 mg twice daily	—
	Cefuroxime	—	0.75–1.5 g 3 times daily
	Cefotiam	—	1–2 g 2–3 times daily
Cephalosporin Gr. 3	Cefpodoxime proxetil	200 mg twice daily	—
	Ceftibuten	200–400 mg daily	—
Cephalosporin Gr. 3a	Cefotaxime	—	1–2 g 2–3 times daily
	Ceftriaxone	—	1–2 g daily
Cephalosporin Gr. 3b	Ceftazidime	—	1–2 g 2–3 times daily
Cephalosporin Gr. 4	Cefepime	—	2 g twice daily
Cephalosporin + BLI	Ceftolozane/tazobactam	—	Ceftolozane/tazobactam 1.5 g 3 times daily
	Ceftazidime/avibactam	—	Ceftazidime/avibactam 2.5 g 3 times daily
Carbapenem Gr. 1	Imipenem	—	0.5–1 g q6–8h
	Meropenem	—	0.5–1 g 3 times daily
	Doripenem		0.5 g 3 times daily
Carbapenem Gr. 2	Ertapenem	—	1 g daily
Fluoroquinolone Gr. 2	Ciprofloxacin	500–750 mg twice daily	400 mg twice daily
	Ciprofloxacin XR	1000 mg daily	—
Fluoroquinolone Gr. 3	Levofloxacin	500–750 mg daily	500–750 mg
Aminoglycoside	Plazomicin	—	15 mg/kg/body weight once daily
Antimycotic Group			
Azole derivatives	Fluconazole	400–800 mg daily	400–800 mg daily
	Voriconazole	4–6 mg/kg BW daily	4–6 mg/kg BW daily
Pyrimidine analog	Flucytosine		100–150 mg/kg BW 4 times daily
Echinocandin	Caspofungin		50–70 mg daily

BLI, Beta-lactamase inhibitor; *BW,* body weight, *IV,* intravenous.
Data adapted from Grabe M, Bartoletti R, Bjerklund-Johansen TE, et al. *Guidelines on Urological Infections. European Association of Urology Guidelines, Arnhem.* The Netherlands: European Association of Urology; 2015.

Urologic Therapy

Urologic interventional therapy of complicated UTIs is divided into acute therapy and control of the infectious focus with delayed definitive therapy. The primary aim of acute therapy is early focus control, with minimal tissue necrosis. In primary therapy, catheters, stents, or drains are frequently used. Delayed definitive therapy of the urinary tract (e.g., lithotomy, prostatic resection, or ureter reimplantation) is frequently performed after days or weeks of stabilization.

Prophylaxis of Catheter-Associated Urinary Tract Infections

Some 80%–90% of nosocomial UTIs are associated with urinary catheters or instrumentation of the urinary tract. The best prophylaxis is to avoid a catheter or, if catheterization is necessary, to minimize catheter duration. Unfortunately, prevention programs with the aim of reducing CAUTIs by educational activities were not able to reduce CAUTI rates in ICUs compared with non-ICUs.[8] Various techniques have been used to avoid catheter-related infections.

Silver coating of catheters may exert a bactericidal effect, but the concentration of free silver ions must be high, whereas the exposure to albumin and chloride ions has to be low because silver-chloride complexes can precipitate.[28] A multicenter randomized controlled trial using silver alloy– or nitrofural-coated catheters in adults requiring short-term catheterization in the hospital could not demonstrate a sufficiently high reduction in symptomatic UTIs to recommend routine use of antimicrobial-impregnated catheters.[29] Suprapubic catheterization can initially decrease the rate of UTIs from 40% to 18% because proximity to the anal region and irritation of the urethral mucosa with ensuing mucopurulent discharge are avoided.[14] Urinary drainage should be performed with a closed system that should not be opened either for emptying or for urinary sampling. The sites used for urinary sampling must be adequately sterilized. General hygienic procedures such as aseptic catheter insertion, wearing of disposable gloves, and hygienic hand disinfection to prevent cross-contamination or cross-infection are mandatory. International consensus recommendations for the use of urinary catheters to prevent HA infections have been described.[30]

Recommended Evidence-Based Measurements for Preventing Catheter-Associated Urinary Tract Infections

The primary methodologies for preventing CAUTIs[30] include:

- Limiting unnecessary catheterization and discontinuing use of the catheter as early as possible.
- Policies and procedures for recommended catheter insertion indications, insertion and maintenance techniques, discontinuation strategies, and replacement indications should be developed and closely followed.
- Alternatives to indwelling urethral catheterization should be considered, such as condom catheterization, intermittent catheterization, or suprapubic catheterization, although data are insufficient to recommend one alternative over another.
- Closed catheter drainage systems should be used.
- Most other measures for the prevention of CAUTIs, such as prophylaxis with systemic antimicrobials, methenamine salts, cranberry products, enhanced meatal care, and catheter irrigation with either antimicrobials or saline, are not recommended.[30]
- It is also unclear whether routine catheter changes reduce the risk of catheter-associated bacteriuria or UTIs.

SPECIAL CLINICAL ISSUES

Infections of the Upper Urinary Tract and Contiguous Organs

Pyelonephritis

The high osmolality of the renal medulla has a negative effect on leukocyte function. For this reason, the interstitium of the renal medulla is more affected in pyelonephritis than the cortex. Clinical symptoms are unilateral or bilateral flank pain, painful micturition, dysuria, and fever (>38°C). Focal nephritis is limited to one or more renal lobules, which is comparable to that in lobular pneumonia. Ultrasonographic findings are circumscribed lesions with interrupted echoes that break through the normal cortex/medulla organization. A computed tomography (CT) scan with contrast medium shows typical oval-shaped, poorly limited areas of diminished contrast perfusion. As differential diagnoses, renal abscess, tumor, and renal infarction must be taken into account. Emphysematous pyelonephritis characteristically shows gas formation in the renal parenchyma and perirenal space. Diabetes mellitus or obstructive renal disease is the predisposing factor. The most frequently isolated organisms are *E. coli*, *Klebsiella pneumoniae,* and *Enterobacter cloacae*. Fermentation of glucose in Enterobacteriaceae occurs via two different metabolic pathways: mixed acid fermentation and the butylene glycol pathway. Organisms of the *Klebsiella-Enterobacter-Hafnia-Serratia* group and, to a lesser extent, *E. coli* use the butylene glycol pathway and produce copious amounts of CO_2, which appears clinically as gas formation.[31] Aggravated by diminished tissue perfusion, the contralateral side is often affected as well.

Renal and Perirenal Abscess

Clinical symptoms are rigor, fever, back or abdominal pain, flank tenderness, mass lesion and redness of the flank, and tenderness of the upper lumbar and paraspinal muscles. Respiratory insufficiency, hemodynamic instability, or reflectory paralytic ileus occurs frequently. Frequent signs of renal abscess formation are fever and leukocytosis for more than 72 hours, despite antibiotic therapy. The urinary culture may be negative in 14%–20% of cases.[32] Frequently isolated organisms are *E. coli*, *K. pneumoniae, Proteus* spp., and *Staphylococcus aureus* from hematogenous spread. The fascial limitations are open toward the pelvis, and the perirenal fat is in close contact with the pelvic fat tissue. A perinephritic abscess may therefore point to the groin or perivesical tissue or to the contralateral side, thus penetrating the peritoneum. Inflammation of the flank, thigh, back, buttocks, and lower abdomen may occur. Because of the late diagnosis, the mortality can be as high as 57%. Blood cultures are positive in 10%–40% of cases, and urinary cultures are positive in 50%–80%.[33]

Infections of the Lower Urinary Tract and Contiguous Organs

Cystitis

Cystitis is frequently limited to the bladder mucosa and hence shows no systemic signs or symptoms. An ascending infection can, however, clinically result. Cystitis in the ICU is almost exclusively catheter-associated and can cause hematuria. Spontaneous elimination is frequently found after removal of the indwelling catheter but is less frequent in elderly patients.[4]

Epididymitis/Orchitis

Epididymitis in the ICU is usually an ascending infection and can also involve the testis. Possible causes are subvesical obstruction, transurethral resection of the prostate, or an indwelling transurethral urinary catheter, in which case the pathogens are identical with the pathogens in the urine. Of note, epididymitis is frequently involved in urogenital tuberculosis. Orchitis with the formation of a sterile hydrocele can appear during the course of polyserositis or cardiac failure and may point to a generalized systemic disease.

Cavernitis

Cavernitis of the penis is a rare phlegmonous infection of the cavernous bodies. Possible causes are indwelling transurethral urinary catheters, penile operations, autoinjection for erectile dysfunction, pelvic operations, or trauma. Pathogens may represent skin flora or uropathogens. Treatment consists of suprapubic catheterization, broad-spectrum antibiotic therapy, and, if needed, operative débridement.

Acute Prostatitis and Prostatic Abscess

Acute prostatitis and prostatic abscess are bacterial infections of the prostate gland. Prostate biopsy is currently one of the most frequent causes for development of acute bacterial prostatitis. The bacterial spectrum consists of 53%–80% *E. coli* and other enterobacteria, 19% gram-positive bacteria, and 17% anaerobic bacteria.[34] In regions with a high incidence of *Neisseria gonorrhoeae*, the prostate may be involved. Symptoms are high fever, rigor, dysuria, urinary retention, and perineal pain. Rectal palpation reveals an enlarged, tender prostate. Prostate massage is contraindicated. In acute prostatitis, the pathogens are usually detected in the urine. However, the urine may be sterile in prostatic abscess formation. Therapy consists of a combination of antibiotic therapy with broad-spectrum antibiotics and the insertion of a suprapubic catheter. In case of a prostatic abscess, urologic drainage is necessary.[34]

Fournier Gangrene

Fournier gangrene is a necrotizing fasciitis of the dartos and Colles fascias. It is mainly seen in men in the fourth to seventh decades but also occurs in women or newborns. Causes are operations or trauma in the genital or perineal region, including microlesions, or infectious processes from the rectal or urethral areas. Important predisposing factors are diabetes mellitus, liver insufficiency, chronic alcoholism, hematologic diseases, or malnutrition. Patient-related predictors of mortality are increasing age; increased Charlson comorbidity index; preexisting conditions such as congestive heart failure, renal failure, or coagulopathy; and hospital admission via transfer.[35] Fatality rates were

7.5% in one large study.[36] The infectious process follows anatomically preformed spaces. The superficial perineal fascia is fixed dorsally at the transverse deep perineal muscle and laterally at the iliac bone and merges ventrally in the superficial abdominal fascia. Hence, a ventrally open and craniodorsally and laterally closed space is formed (Colles space), which facilitates the spread of infection. In contrast to gas gangrene, the fascial borders are respected in Fournier gangrene. A mixed bacterial flora is seen, consisting of gram-positive cocci, enterobacteria, and anaerobic bacteria. The released toxins facilitate platelet aggregation and complement activation, which, in conjunction with the release of heparinase by anaerobic bacteria, lead to small vessel thrombosis and tissue necrosis. The destruction of tissue enhances the potential of acute renal failure. Fournier gangrene is a rapidly progressing infection that leads to septic shock if not treated in time.

Therapy for Fournier gangrene consists of immediate operative débridement, followed by subsequent operations until the infectious process has been controlled. A suprapubic catheter is advisable, and colostomy may have to be performed in cases where fecal contamination of the wound is inevitable. A combination of antibiotic therapy with broad-spectrum beta-lactam antibiotics, fluoroquinolones, and clindamycin is recommended.

Urosepsis

In 20%–30% of all septic patients, the initial infectious focus is in the urogenital tract. The most frequent causes of urosepsis are obstructive diseases of the urinary tract such as ureteral stones, anomalies, stenosis, or tumor. Early relief from the obstruction controls the infectious focus and improves organ perfusion. This is one reason why mortality in urosepsis is usually lower than that in other septic forms (Fig. 113.2).[37]

Biomarkers such as procalcitonin and/or midregional proadrenomedullin, in addition to lactate, should be included into the early diagnostic work-up. The initial levels of procalcitonin or midregional proadrenomedullin are positively correlated with signs of severity, such as bacteremia or length of hospital stay, but do not predict treatment outcome in urosepsis.[38] C-reactive protein is not discriminatory at all.

Immediately after microbiologic sampling of urine and blood, empiric broad-spectrum antibiotic therapy should be started parenterally. Adequate initial (e.g., in the first hour) antibiotic therapy ensures improved outcome in septic shock.[39,40] Inappropriate antimicrobial therapy in severe UTIs is linked to a higher mortality rate.[41] Empiric antibiotic therapy is based upon the expected bacterial spectrum, institution-specific resistance rates, specific pharmacokinetic and pharmacodynamic factors in UTIs, and individual patient characteristics.

The bacterial spectrum in urosepsis predominantly consists of Enterobacteriaceae such as *E. coli*, *Proteus* spp., *Enterobacter* and *Klebsiella* spp., nonfermenting organisms such as *P. aeruginosa*, and gram-positive organisms.[42,43] *Candida* spp. and *Pseudomonas* spp. occur as causative agents in urosepsis mainly if the host defense is impaired. Patients with candiduria show frequently invasive candidiasis and candidemia.[44,45] Candiduria at any time in an ICU is associated with higher mortality rates (odds ratio [OR], 2.86).[45] Viruses are not common causes of urosepsis.

Although urosepsis is a systemic disease, the activity of an antibiotic at the site of the infection is critical. A variety of studies have shown that inflammatory mediators such as IL-6, CXC chemokines, endotoxin, or HMGB1 are produced and released in the urinary tract.[46–48] Therefore predominantly antimicrobial substances with high activities in the urogenital tract are recommended.[49,50]

The increasing antibiotic resistance rates of pathogens causing urosepsis significantly diminish the choice of antibiotics available for adequate empiric initial therapy in urosepsis. In particular, the increasing rates of Enterobacteriaceae producing ESBL pose clinically relevant problems.[5,51–53] Other recent developments of concern include increased rates of fluoroquinolone-resistant enterobacteria and vancomycin-resistant enterococci.[54,55] Currently, there are no specific pharmacokinetic/pharmacodynamic parameters available for the treatment of patients with urosepsis.

Correct dosing in urosepsis has to consider the altered systemic and especially renal pathophysiology that exists in patients with urosepsis. Sepsis and the treatment thereof result in higher clearances of antibacterial drugs.[56] The increased volume of distribution as a result of peripheral edema in sepsis will lead to underexposure, especially of hydrophilic antimicrobials such as beta-lactams and aminoglycosides, which exhibit a volume of distribution mainly restricted to the extracellular space.[57] Increased dosing is therefore necessary. On the other hand, urosepsis may also cause multiple organ dysfunction such as hepatic or renal dysfunction, resulting in decreased clearance of antibacterial drugs. In such a case, dosing adjustment has to be considered. As beta-lactams are time-dependent antibacterials, optimal administration would be by continuous infusion. Fluoroquinolones, on the other hand, display largely concentration-dependent activity. The volume of distribution of fluoroquinolones in sepsis is not greatly influenced by fluid shifts, and therefore no alterations of standard doses are necessary, unless renal dysfunction occurs.[56,57] Antimicrobial resistance in patients with UTI and urosepsis is generally higher than antimicrobial resistance in patients with nonseptic UTI.[58] Depending on local susceptibility patterns, a third-generation cephalosporin with or

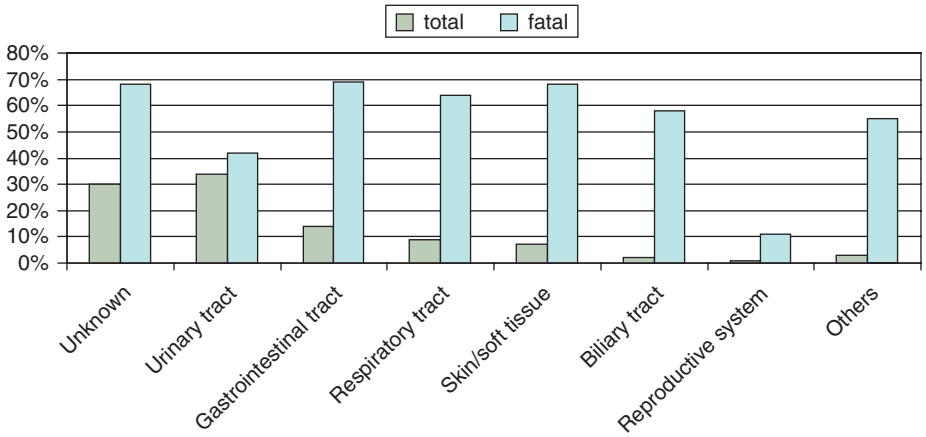

Fig. 113.2 Six Hundred and Twelve Episodes of Gram-Negative Bacteremia 1965–1974.[3]

without a beta-lactamase inhibitor, piperacillin, in combination with a beta-lactamase inhibitor or a carbapenem may be appropriate for empiric therapy.[4,59–62] In areas with a high (>10%) rate of Enterobacteriaceae producing ESBL, initial treatment with a carbapenem might be advisable.[59–63] Aminoglycosides as monotherapy might be an alternative.[26] In case of candiduria with signs of sepsis, antifungal treatment is recommended.[44,45]

KEY POINTS

- Complicated UTI is a highly heterogeneous entity with a common pattern of complicating factors.
- The bacterial spectrum of complicated UTIs is much broader than that of uncomplicated UTIs, comprising a variety of gram-negative and gram-positive pathogens and, among these, frequently multiresistant pathogens. Patients with urosepsis have higher antimicrobial resistance rates than patients with nonseptic UTI.
- UTIs are frequent in ICUs. It would be pragmatic to stratify UTIs into those with nonurologic complicating causes, in which antimicrobial therapy is the primary therapy, and those with urologic complicating causes, in which the complicating urologic anomaly has to be effectively treated as well.
- Pathogens of nosocomial complicated UTIs may be characterized by certain properties such as adaptation strategies to changing environments (i.e., hypermutator strains) or propensity to biofilm formation.
- The diagnosis of UTIs is based on medical history and a thorough physical examination, including bedside ultrasound and investigations of urine (dipstick test, microscopy, and microbiology). For clinical diagnosis, general accepted criteria should be employed. Symptomatic UTIs in ICU patients are especially difficult to evaluate.
- Not all bacteriuric patients in ICUs need to be treated. Therapy should, however, be started early in those with significant symptoms and morbidity. Management of complicated UTIs comprises adequate antibiotic therapy and successful treatment of complicating factors.
- Prophylaxis of UTIs is important. However, the percentage of infections that can be prevented is not known. Important points in prophylaxis encompass training of staff, hygiene measures, type of catheter and drainage, and patient care.
- Special clinical pictures of UTIs and infections of contiguous organs are seen in the ICU. UTIs of the upper urinary tract are distinguished from those of the lower urinary tract and infections of the male adnexal glands and fasciitis of the perineum and scrotum. All these pictures can potentially merge into urosepsis if the UTI is not treated adequately. The urogenital tract is the source of sepsis in 20%–30% of cases.

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Central Nervous System Infections

Michael J. Bradshaw and Karen C. Bloch

Central nervous system (CNS) infections represent life-threatening conditions that require emergent evaluation and frequently treatment in a critical care unit.[1] These infections may be challenging to identify, as numerous noninfectious conditions mimic CNS infections. Even when an infectious syndrome is suspected, it may take several days before a specific microorganism is identified, necessitating the use of broad empiric therapy directed against the most likely causative pathogens based on clinical, epidemiologic, and demographic clues. Pharmacologic considerations in selecting appropriate antimicrobials include the ability of the agent to cross the blood-brain barrier and achieve bactericidal levels at the site of infection. Clinical outcomes associated with CNS infections are directly related to the rapidity with which appropriate medical or surgical interventions can be provided, adding urgency to the diagnostic and therapeutic evaluation.[2]

CNS infections may be caused by bacteria, fungi, viruses, protozoa, and prions. The risk of infection with these pathogens varies based on the host immune status (e.g., human immunodeficiency virus [HIV] infection, immunosuppression), epidemiology (e.g., time of year, travel to endemic regions), and acquisition site (e.g., community acquired vs. healthcare acquired). The microbiology and pathophysiology of CNS infections differ based on the specific anatomic site of infection. The major CNS syndromes covered in this chapter include meningitis, brain abscess, encephalitis, and myelitis. These syndromes may occur in isolation or may be found as overlapping conditions (e.g., meningoencephalitis or encephalomyelitis). Localizing the site of infection is often the first step in guiding the diagnostic evaluation and initiating empiric therapy. An interdisciplinary approach with colleagues from critical care, infectious disease, and neurology is important in addressing diagnostic and treatment considerations and potential complications.

MENINGITIS

Infections of the meninges can be subclassified by the acuity of onset of symptoms. Bacterial infections cause an acute meningitis syndrome, characterized by rapid (<48 hours) progression of fever, headache, and neck stiffness or meningismus. In contrast, subacute meningitis syndrome, caused by viruses, fungi, or mycobacteria, is more slowly evolving, with symptoms developing over several days to weeks (Box 114.1). The following sections outline approaches to acute and subacute meningitis. These approaches prioritize the competing needs of obtaining a precise microbiologic diagnosis versus instituting early antimicrobial therapy.

Anatomy

Bacterial meningitis is a pyogenic infection of the meninges and subarachnoid space, with bacteria usually confined to the nutrient-rich cerebrospinal fluid (CSF), although brain and spinal cord parenchyma can be involved, given their anatomic proximity. In adults, CSF is produced at a rate of approximately 500 mL/day, yet the CSF space averages only 140 mL in volume; therefore there is rapid production and reabsorption. CSF is formed in the choroid plexus of the ventricles, flows into the subarachnoid space at the cisterna magna and around the cerebral hemispheres, and is reabsorbed by the arachnoid villi (Fig. 114.1). The cerebral and spinal subarachnoid spaces connect at the cisterna magna, and the flow of CSF through the spinal subarachnoid space is of variable velocity and direction.

There are numerous potential and actual spaces among the layers of the meninges (see Fig. 114.1). Meningitis involves the actual space (i.e., the subarachnoid space), which consists of multiple interconnected compartments. The small size of the foramina of Luschka and Magendie allows for a unidirectional caudal flow toward the cisterna magna, where the CSF then moves into the spinal canal. This compartmentalization has implications in therapy because the movement of medications and infectious agents is influenced by the rate and direction of CSF flow. Obstruction of CSF flow can produce hydrocephalus and may restrict the entry of antibiotics into sites of ongoing infection.

Infectious agents can invade the CSF by at least three routes (Box 114.2). First, the vascular structures of the choroid plexus and pia and the vessels that traverse the subarachnoid space may serve as conduits during bacteremia.[3] A second less common route is by direct invasion across the protective meninges. Physical disruption of the dura by trauma or surgery allows for the direct invasion of the subarachnoid space and should be considered in patients with a history of CSF leakage or clear, watery rhinorrhea, in addition to those who have undergone recent neurosurgical interventions. Emissary veins provide another pathway for bacteria to spread from contiguous foci into the subarachnoid space. These veins traverse the skull and dura, directly connecting the soft tissues of the head and neck with the venous system of the brain and meninges, including the arachnoid villi. Although blood in the emissary veins usually flows away from the brain, the CNS veins and dural sinuses do not contain valves, and retrograde flow of bacteria is possible. Rarely, organisms may reach the ventricles or subarachnoid space from within the neural tissue; for example, rupture of a brain abscess into the ventricles may have disastrous effects. Until 2015, it was thought that the brain has no lymphatic drainage, and these recently identified vessels may prove to be another route of infectious contamination of the CNS.[4,5]

Pathophysiology

Despite complex host-cellular and anatomic defense mechanisms, including immune surveillance of the CSF,[6,7] microorganisms have evolved a number of virulence factors that contribute to the development of

BOX 114.1 Causes of Acute and Subacute Central Nervous System Infection Syndromes

Acute Meningitis Syndrome

Rapid onset (<24–48 h) of fever, headache, or meningismus, with early cognitive impairment

Common

Pyogenic meningitis (pneumococcal, meningococcal, *Listeria,* other)

Uncommon

Viral encephalitis (especially herpes simplex), subarachnoid bleed, brain abscess (with rupture)

Rare

Viral meningitis, granulomatous meningitis (cryptococcal, mycobacterial), carcinomatous meningitis, brain tumor

Subacute Central Nervous System Infection Syndrome

Subacute onset (>24–48 h) of fever, headache, or meningismus, with no or gradual cognitive impairment

Common

Viral meningitis, viral encephalitis, rickettsial infection

Uncommon

Brain abscess, brain tumor, granulomatous meningitis

Rare

Cerebrovascular accident, carcinomatous meningitis

bacterial meningitis. Meningeal inflammation causes vasospasm or vasculitis with occlusion of cerebral arteries/arterioles, cerebral venous thrombosis, damage to nerve roots that traverse the subarachnoid space, and impaired CSF flow (see Fig. 114.1). The activation of leukocytes leads to an inflammatory cascade, with the release of cytokines, oxidants, and proteolytic enzymes, which contribute to the damage caused by the infection. This can lead to increased intracranial pressure and a risk of herniation, especially when there is focal parenchymal edema.[8]

Epidemiology

The epidemiology of bacterial meningitis in the United States has changed in the past 20 years because of the widespread use of vaccines active against *Haemophilus influenzae* type B, *Neisseria meningitidis,* and *Streptococcus pneumoniae.*[9] Simultaneously, the incidence of nosocomial bacterial meningitis caused by increasingly resistant strains of Enterobacteriaceae, *Pseudomonas aeruginosa,* and *Staphylococcus aureus* is increasing.[10]

Meningococcal meningitis presents unique public health and infection control challenges. This diagnosis is suggested by the presence of a petechial or purpuric rash; however, this finding is neither sensitive nor specific.[11] To prevent secondary cases among healthcare workers, all patients with presumed bacterial meningitis should initially be placed on droplet precautions to prevent the spread of infection by inhalation. This can be discontinued after an alternative pathogen is identified or after 24 hours of antibiotics effective against this organism.

Before the availability of antibiotics, bacterial meningitis was universally fatal. However, even with administration of effective antimicrobial

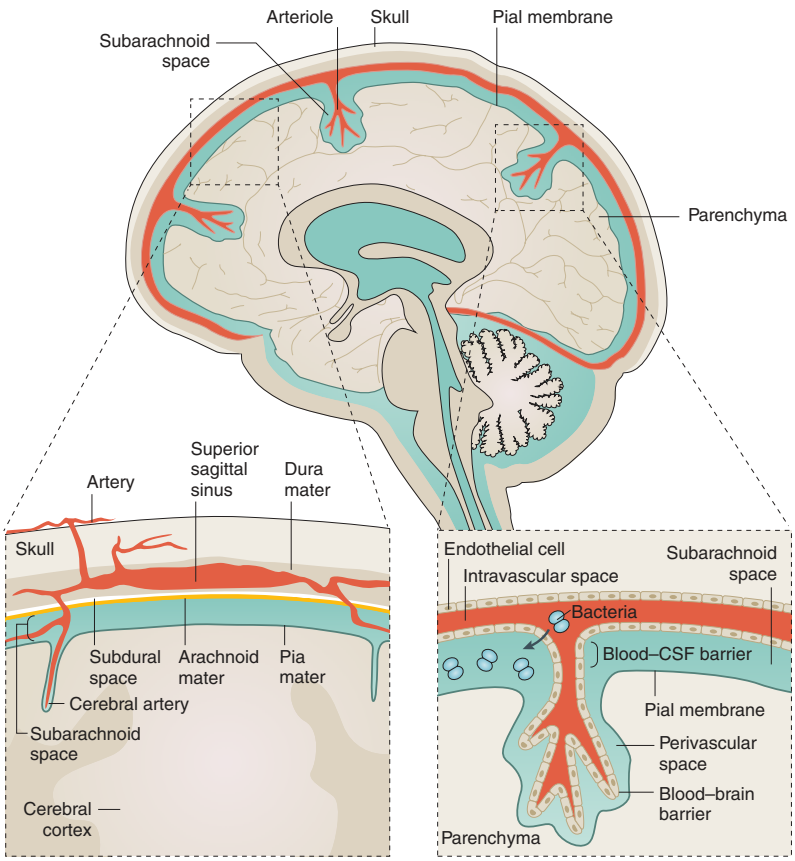

Fig. 114.1 Anatomic Considerations in the Pathophysiology of Bacterial Meningitis. (From van de Beek D, Brouwer M, Hasbun R, et al. Community-acquired bacterial meningitis. *Nat Rev Dis Primers.* 2016;2:16074.)

BOX 114.2 Routes by Which Bacteria May Enter the Subarachnoid Space

Vascular (Blood-Brain Barrier)
- Mostly likely pathogens: pneumococci, meningococci, *Listeria, Escherichia coli* (neonates), group B streptococci (neonates), *Haemophilus influenzae*
- Choroid plexus: may be common site of invasion for *H. influenzae*
- Meningeal blood vessels: throughout the subarachnoid space; may be usual route for pneumococci
- Arachnoid villi: possible route of invasion, located between the sagittal sinus and subarachnoid space

Transdural
- Most likely pathogens: pneumococci, gram-negative enteric bacilli, staphylococci (including coagulase-negative), *H. influenzae*
- Surgery: including ventriculoatrial or ventriculoperitoneal shunts
- Trauma: especially when cribriform plate or petrous bone is fractured
- Parameningeal infective focus: including sinusitis, mastoiditis, otitis, or osteomyelitis; emissary veins may serve as conduit
- Congenital defects: including myelomeningocele and spinal dermal sinus

Transparenchymal
- Mostly likely pathogens: anaerobic bacteria, enteric gram-negative bacilli
- Occurs when brain abscess ruptures directly into ventricles or subarachnoid space

therapy, the case fatality of bacterial meningitis remains significant, with a high incidence of neurologic sequelae among survivors. The fatality rate of pneumococcal meningitis ranges from 16% to 37% in developed countries. Neurologic sequelae, including hearing loss, epilepsy, focal neurologic deficits, and cognitive dysfunction, develop in 30%–52% of survivors.[7,12]

Clinical Manifestations

Bacterial Meningitis

Bacterial meningitis is a medical emergency, and patients with complications such as seizures or decreased level of consciousness are best managed in the intensive care setting.[13] The initial manifestations may be subtle, with a low-grade headache, nausea, and fever. However, once meningeal signs and symptoms (vomiting, severe headache, and stiff neck) develop, clinical decompensation is often rapid. The classic clinical triad associated with bacterial meningitis (fever, neck stiffness, and altered mental status) is present in only 44% of cases.[14] Signs of meningeal inflammation, including nuchal rigidity, Kernig sign, or Brudzinski sign, are neither sensitive nor specific for bacterial meningitis.[15] However, 95% of patients present with at least two of four of the most common symptoms of meningitis: i.e., headache, fever, neck stiffness, and altered mental status.[14] A petechial or purpuric skin eruption suggests meningococcal or pneumococcal meningitis, but skin lesions may be absent at the time of presentation, and other infections such as Rocky Mountain spotted fever encephalitis can also produce a rash.[11,16] Bacterial meningitis may present atypically in the elderly or immunocompromised patients, with minimal focal findings.[17–19] In addition, these populations have a higher incidence of noninfectious conditions that may mimic acute meningitis (e.g., subarachnoid bleeding and malignancies involving the CNS), complicating the initial evaluation.

The diagnosis of meningitis is confirmed through the evaluation of CSF, assuming there is no contraindication to lumbar puncture (see later). Prompt transportation and processing of CSF are important to maximize specimen integrity, as concentrations of neutrophils degrade by up to 50% after an hour post lumbar puncture.[20] Opening pressure is often elevated to the range of 20–50 cm H_2O. Other CSF findings in bacterial meningitis include moderate to high pleocytosis (hundreds to thousands of cells/uL) with a neutrophil predominance, hypoglycorrhachia (low glucose), and elevated protein levels (often >100 mg/dL). The CSF lactate level is a useful adjunct for differentiating bacterial meningitis from viral meningitis, but may be elevated in other CNS diseases that cause meningeal inflammation.[21,22] A positive Gram stain is diagnostic of bacterial meningitis, with a specificity of more than 99%, although the sensitivity varies based on concentration of bacteria in the CSF and the antecedent use of antibiotics.[23,24]

TABLE 114.1 Pathogens Included in the BioFire FilmArray Meningoencephalitis Panel

Bacteria	Viruses	Fungi
Escherichia coli K1	Cytomegalovirus (CMV)	*Cryptococcus neoformans/gattii*
Haemophilus influenzae	Enteroviruses	
Listeria monocytogenes	Herpes simplex virus 1 and 2 (HSV-1 and HSV-2)	
Neisseria meningitidis	Human herpesvirus 6 (HHV-6)	
Streptococcus agalactiae	Human parechovirus	
Streptococcus pneumoniae	Varicella-zoster virus (VZV)	

Molecular microarray panels for the diagnosis of meningoencephalitis are increasingly available and offer the advantage of rapid diagnosis and directed antibiotic therapy. Currently, the only commercially available product tests for 14 common CNS pathogens, including *Escherichia coli* K1, *H. influenzae*, *Listeria monocytogenes*, *N. meningitidis*, *S. pneumoniae,* and *Streptococcus agalactiae* (group B streptococcus) (Table 114.1). In a large retrospective multicenter trial, molecular testing performed comparably to conventional culture for detection of bacterial meningitis.[25] However, questions remain about the sensitivity of this assay after antibiotic treatment, and false positives may be seen because of the potential for contamination.

Management

Delay in antibiotic therapy increases the risk of an adverse outcome or death, particularly when progressive neurologic impairment occurs before receiving therapy.[26,27] For this reason, guidelines recommend the expedited administration of empiric antibiotics to patients with a presumptive diagnosis of bacterial meningitis.[28,29] Even in patients with profoundly abnormal Glasgow Coma Scale scores at presentation, complete recovery may be seen with directed therapy and intensive supportive care.[30]

Coupled with the need for emergent treatment is the need for microbial diagnosis. Identification of a pathogen allows a clinician to narrow the antibiotic regimen based on susceptibility patterns and has prognostic and therapeutic implications. However, in some cases, lumbar puncture is unavoidably delayed. When this is the case, antibiotics should be given immediately after peripheral blood cultures are obtained. The yield of CSF culture decreases within as little as 15 minutes after the administration of antibiotics.[31] Despite the inhibitory effect of prior antibiotics on bacterial culture and Gram stain, the absolute neutrophil count and differential are not initially affected by antibiotics and remain suggestive of bacterial meningitis.[32,33] A full course of empiric therapy should be completed if CSF parameters and the clinical presentation are consistent with this diagnosis.

Historically, neuroimaging has been recommended before lumbar puncture to exclude the presence of a mass lesion or any other risk factor for brain herniation. Studies have challenged this practice, citing the potential deleterious effect of computed tomography (CT) scan–related delays in the initiation of therapy or the sterilizing effect of antecedent antibiotics on CSF cultures.[26,27,31,34] Even among patients with an abnormal CT scan, only a minority of patients have radiographic findings precluding lumbar puncture.[35] For this reason, neuroimaging before lumbar puncture should be reserved for patients with compromised immune systems (e.g., HIV infection, use of immunosuppressive medications, or organ transplantation), new-onset seizures, severely altered mental status (defined as Glasgow Coma Scale of <10), or focal neurologic deficits/optic disc edema.[36] Signs of impending herniation such as deteriorating level of consciousness (particularly with Glasgow Coma Scale ≤11), brainstem signs, or very recent seizure are also important to identify.[37] In the absence of these features, it is generally safe to proceed directly to lumbar puncture, followed by immediate administration of empiric antibiotics.[28]

Antibiotics

The choice of empiric antibiotics is based on the assessment of the most likely causative agents. Recommendations for empiric therapy are listed in Table 114.2, with dosages commonly used for the treatment of CNS infections listed in Table 114.3.[28,29,38]

Empiric therapy should be directed against the most common causes of bacterial meningitis. In immunocompetent adults younger than 50 years,[10,39] *S. pneumoniae* and *N. meningitidis* are the most common causes of community-acquired bacterial meningitis, and therefore initial therapy should include a third-generation cephalosporin such as cefotaxime or ceftriaxone in combination with vancomycin. Strains of *S. pneumoniae* that are increasingly resistant to penicillin have emerged as important pathogens; however, most isolates remain sensitive to third-generation cephalosporins, and all are susceptible to vancomycin.[40]

Empiric therapy for *L. monocytogenes* should be included for adults aged 50 years or older, patients with T-cell immunocompromise (e.g., on chronic steroid therapy), pregnant women, or patients with significant use of alcohol.[28,39] If the CSF Gram stain shows gram-positive rods suggestive of *Listeria,* high-dose ampicillin plus intravenous (IV) gentamicin should be given. For patients with immediate sensitivity reaction to penicillin, meropenem or parenteral trimethoprim-sulfamethoxazole are acceptable alternatives.

In contrast to community-acquired meningitis, organisms causing nosocomial meningitis reflect the highly resistant strains endemic to the hospital.[29] Empiric therapy for patients suspected to have healthcare–associated meningitis should be directed against staphylococcal species (both coagulase-positive and -negative strains) and multidrug-resistant strains of gram-negative bacilli, including *P. aeruginosa* and *Acinetobacter baumannii*. Empiric therapy in this population includes vancomycin in addition to an antipseudomonal cephalosporin (ceftazidime or cefepime) or an antipseudomonal carbapenem. Imipenem is active against *Pseudomonas* and achieves therapeutic levels in the CSF; however, because this agent lowers the seizure threshold, it is relatively contraindicated for meningitis. Meropenem, a related carbapenem, is less epileptogenic and is therefore preferred for this indication.[38]

Initial antibiotic choices can be refined when sensitivity patterns become available, typically in 2–3 days. The duration of therapy varies based on the pathogen and clinical response. Although there have been few randomized studies evaluating the optimal duration of therapy, 7 days of treatment for *H. influenzae* and *N. meningitidis* meningitis is typically sufficient,[41] whereas *S. pneumoniae* requires 10–14 days of therapy.[28,42] Adults with pneumococcal meningitis may have predisposing infections, including pneumonia, sinusitis, otitis, or rarely, endocarditis, in which case prolonged therapy with bactericidal antibiotics is indicated.

Abnormalities of the CSF (e.g., pleocytosis and elevated protein) may persist for days to weeks after the eradication of infection. The resolution of infectious signs and symptoms (e.g., fever, meningismus, and leukocytosis) should serve as adequate evidence of successful therapy. In a patient who fails to respond to 48–72 hours of empiric therapy, lumbar puncture may be repeated, and head imaging, preferably magnetic resonance imaging (MRI) with and without contrast, is indicated. A repeat lumbar puncture is particularly important for detecting clearance of bacteria from the CSF in patients with cephalosporin-resistant pneumococcal meningitis who demonstrate a slow clinical response.[43] Patients with culture-negative pyogenic meningitis and suboptimal clinical response should also have repeat lumbar puncture to ensure response to empiric antibiotics. Worsening CSF parameters suggest infection with resistant bacteria, with a pathogen more typically associated with a subacute meningitis syndrome, or a noninfectious condition (see Box 114.1).

TABLE 114.2 Empiric Antimicrobial Therapy for Adult Patients With Presumed Bacterial Meningitis

Site of Acquisition	Predisposition	Organisms	Antimicrobial Agents
Community	Age 16–50 years	*Streptococcus pneumoniae*	Vancomycin plus third-generation cephalosporin*
		Neisseria meningitidis	
	T-cell deficiency	*S. pneumoniae, N. meningitidis*	Vancomycin plus third-generation cephalosporin*
		Listeria monocytogenes	*plus* ampicillin
	Age >50 years	*S. pneumoniae, N. meningitidis*	Vancomycin plus third-generation cephalosporin*
		L. monocytogenes	*plus* ampicillin
Nosocomial		Staphylococcal species	Vancomycin plus fourth-generation cephalosporin†
		Gram-negative bacilli (including *Pseudomonas aeruginosa*)	*or* meropenem

*Ceftriaxone or cefotaxime.
†Cefepime, ceftazidime.

TABLE 114.3 Antimicrobial Dosages for Central Nervous System Infections*

Drug	Dosage (by Total Body Weight)	Usual Dosage (for 70-kg Adult)
Acyclovir	10 mg/kg IV q8h	700 mg IV q8h
Ampicillin	30 mg/kg IV q4h	2 g IV q4h
Ceftazidime	30 mg/kg IV q8h	2 g IV q8h
Cefepime	30 mg/kg IV q8h	2 g IV q8h
Ceftriaxone	30 mg/kg IV q12h	2 g IV q12h
Meropenem	40 mg/kg IV q8h*	2 g IV q8h
Metronidazole	7.5 mg/kg IV/po q6h	500 mg IV q6h
Nafcillin	30 mg/kg IV q4h	2 g IV q4h
Penicillin G	60,000–70,000 units/kg IV q4h	4 million units IV q4h
Tobramycin or gentamicin	2-mg/kg IV load, then 1.7 mg/kg q8h‡	140 mg IV load, then 120 mg IV q8h‡
Intraventricular		4–8 mg/day
Trimethoprim-sulfamethoxazole	5 mg/kg IV q6h	350 mg IV q6h§
Vancomycin	15 mg/kg IV q6h	500 mg IV q6h‡ or 1 g IV q12h
Intraventricular dosing of vancomycin		5-20 mg/day

*These doses are for patients with normal renal function and modifications may be necessary for patients with reduced creatinine clearance.
‡Adjust dosage based on serum levels, with goal trough 15–20. For both gentamicin and tobramycin, the target peak is 8-10 mcg/mL and target trough <1-2 mcg/mL
§Dosage indicates trimethoprim component.

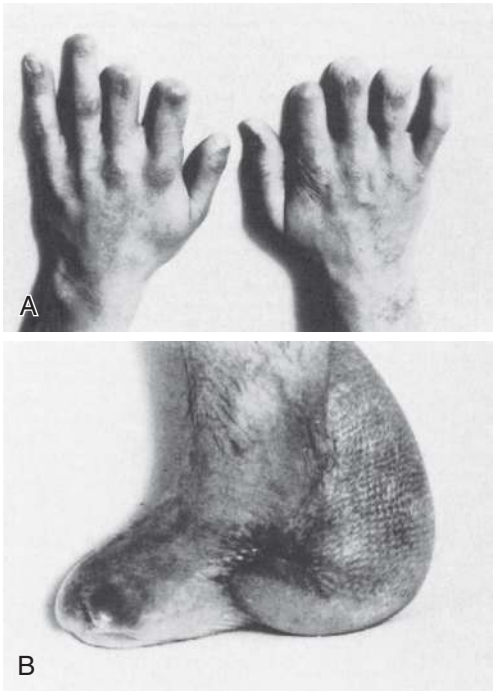

Fig. 114.2 Extremities—hands **(A)** and foot **(B)**—of a 14-year-old boy observed by two physicians as his petechial rash progressed to "bruises" (purpura fulminans). Purpura were not recognized as the hallmarks of *Neisseria meningitides*–induced sepsis. In addition to the loss of extremities from the necrotizing vasculitis of meningococcemia, the patient rapidly developed signs and symptoms characteristic of the acute meningitis syndrome.

Corticosteroids

Much of the morbidity from bacterial meningitis is caused by the host inflammatory response. Corticosteroids decrease inflammation, and animal studies have shown an improvement in outcome when corticosteroids are given as adjuvant therapy with antibiotics. A Cochrane Database review from 2013 evaluated 25 randomized controlled clinical studies on the effect of adjuvant corticosteroids for bacterial meningitis.[44] There was no reduction in overall mortality; however, there was a significant decrease in mortality among the subgroup of patients infected with *S. pneumoniae* meningitis. Administration of steroids was associated with a lower incidence of hearing loss and neurologic sequelae as well. US treatment guidelines recommend adjuvant dexamethasone (0.15 mg/kg IV every 6 hours for 2–4 days) given concomitantly with the first dose of antibiotics for adult patients with suspected or proven pneumococcal meningitis.[28] More recent guidelines by the European Society of Clinical Microbiology and Infectious Diseases suggests that adjuvant corticosteroids be started within 4 hours of antibiotic initiation for all patients with presumed bacterial meningitis beyond the neonatal age.[36]

Complications

Complications specific to meningococcal meningitis include purpura fulminans and necrotizing vasculitis leading to skin necrosis and digital gangrene (Fig. 114.2). Nonspecific complications associated with meningococcal and other forms of meningitis include adrenal insufficiency caused by infarction (Waterhouse-Friderichsen syndrome), renal failure (caused by acute tubular necrosis in the setting of hypotension), deafness, hydrocephalus, seizures, and cognitive impairment.

Other Causes of Meningitis

Other organisms, including viruses, fastidious bacteria (e.g., *Rickettsia rickettsii*, *Treponema pallidum*), fungi (e.g., *Cryptococcus*), or mycobacteria may also infect the meninges (see Box 114.1). These organisms are often classified as causes of aseptic meningitis to differentiate them from the more fulminant syndrome of bacterial meningitis. In contrast to acute bacterial meningitis, patients with aseptic meningitis are less likely to require admission to the intensive care unit (ICU), and in the case of viral meningitis, usually improve spontaneously without antimicrobial therapy.

Differentiating bacterial and nonbacterial etiologies of meningitis may be challenging at the time of presentation, and laboratory data play an important role in making this distinction. Peripheral blood leukocytosis (>10,000/mm^3), CSF white blood cell counts over 1000/mm^3, CSF protein concentration over 100 mg/dL, and CSF glucose concentrations below 40 mg/dL favor a bacterial cause. Patients with these findings should be given empiric antibiotics until a specific diagnosis is made or bacterial cultures return negative. A lymphocytic predominance in the CSF, particularly in the absence of prior antibiotic therapy, argues against a bacterial etiology. Several models incorporating these variables have been developed to predict the likelihood of bacterial meningitis, although these have been best studied in pediatric patients.[15] The measurement of CSF lactate levels has been shown to discriminate bacterial and aseptic meningitis; however, the sensitivity is decreased with prior receipt of antibiotics.[21,22,45] Clinical judgment supersedes results from prediction models or biomarkers, particularly given the possibility of a fatal outcome when antibiotic therapy is deferred.

Viruses are the most common cause of aseptic meningitis, with enteroviruses predominating.[42,46] Other viral causes of meningitis include arboviruses (including West Nile virus), herpesviruses (especially herpes simplex virus [HSV] type 2, which when recurrent is often referred to as *Mollaret meningitis*), acute HIV infection, and lymphocytic choriomeningitis virus. Viral meningitis is typically a self-limited syndrome and does not require treatment. Laboratory testing may be useful if there is diagnostic uncertainty or to aid in epidemiologic evaluations. Commercially available meningoencephalitis molecular array panels include testing for a number of viral pathogens, allowing rapid, point-of-care diagnosis.

Other causes of culture-negative meningitis may be more aggressive or require directed therapy. These include tickborne infections (such as with *Borrelia, Ehrlichia,* or *Rickettsia*), secondary syphilis, mycobacterial or fungal infections, irritation from a parameningeal focus (such as an epidural abscess), or partially treated bacterial infections. In these cases, additional diagnostic studies are indicated but should be individualized based on epidemiologic risk factors and clinical findings. Despite intensive diagnostic testing, a pathogen is identified in only two-thirds of patients with subacute meningitis syndrome.[42]

BRAIN ABSCESS

A pyogenic brain abscess is a localized suppurative infection of the brain parenchymal tissue and may be caused by infection with bacteria, fungi, mycobacteria, or parasites. In immunocompetent adults, 95% of brain abscesses are the result of bacterial pathogens.[47] Differentiating a brain abscess from other CNS infections or brain tumors may be challenging, as there is significant overlap in the clinical and radiologic presentations (Table 114.4). Optimal treatment often requires biopsy to identify the causative organism and obtain susceptibility testing. Even with a combined medical and surgical approach, mortality is significant. Rapid progression of symptoms and impaired mental status at presentation are predictors of an adverse outcome, with rupture of the abscess into the ventricles associated with significant mortality.[48]

Pathophysiology

A brain abscess begins as a localized area of parenchymal infection (cerebritis) that evolves to necrosis and frank suppuration. As cerebritis progresses, a capsule-like hyperemic zone surrounding the area of inflammation develops. In time, liquefactive necrosis leads to abscess formation, with the capsule typically appearing as a ring-enhancing lesion on contrast MRI. In relatively avascular areas such as the cerebral white matter of the brain, capsule formation is delayed, and these sites have higher rates of spontaneous rupture.

Brain abscesses arise thorough several different mechanisms. The most frequent cause is the extension of infection from a contiguous focus (middle ear, mastoids, or sinuses). In approximately one-third of cases, seeding arises through hematogenous spread, and microabscesses typically develop in the distribution of the middle cerebral artery.[49] Filtration of bacteria by the pulmonary vasculature provides some protection for the brain from hematogenous seeding. Therefore when cardiac shunts or pulmonary arteriovenous fistulae are present, as is the case with hereditary hemorrhagic telangiectasia, the risk of brain abscess is increased. Finally, direct inoculation may occur after neurosurgery or intracranial trauma.[50] In approximately 20% of patients, no obvious source of infection is identified.[51,52]

The pathogens causing brain abscesses differ according to the route of infection. Abscesses that arise from contiguous sites are frequently polymicrobial. In contrast, brain abscesses associated with hematogenous spread are usually caused by a single pathogen. Infections after neurosurgery reflect nosocomial flora and often include multidrug-resistant organisms such as methicillin-resistant *S. aureus* (MRSA), enteric bacteria, or *Acinetobacter*. The bacteria most often isolated from brain abscesses include Enterobacteriaceae, streptococci, staphylococci, and pneumococci.[49] Fastidious bacteria such as *Nocardia,* fungi such as *Aspergillus,* and even protozoa such as *Toxoplasma* can also be etiologic agents, particularly in immunosuppressed patients.

Clinical Manifestations

The signs and symptoms of a brain abscess relate to the anatomic location, size, and rapidity of development. At one extreme, the course may span weeks, with few constitutional symptoms. In this setting, signs and symptoms of a space-occupying lesion predominate. In contrast, a previously asymptomatic brain abscess may rupture into the subarachnoid space, causing death within hours. The differential diagnosis in this setting includes an acute cerebrovascular event and pyogenic meningitis. However, brain abscesses usually progress subacutely over 7–14 days,

TABLE 114.4 Differential Diagnosis of CNS Infection and Tumor

	Brain Abscess	Bacterial Meningitis	Herpetic Encephalitis	Brain Tumor
HISTORY				
Headache	Severe, often focal	Severe, generalized	Mild to severe	Absent to severe
Focal defect	Often	Occasional	Occasional	Often
Progression	Days to weeks	Hours to days	Days	Days to months
PHYSICAL EXAMINATION				
Fever	Variable	>90%	>90%	Rare
Early focal signs	Often	Occasional	Occasional	Often
Pressure signs	Often	Rare	Occasional	Often
Extra-CNS infection	Often	Often	No	No
CT OR MRI SCAN				
Focal	Always*	No	Often	Always
Ring effect/onset	Often/late†	No	No	Often/early

CNS, Central nervous system; *CT,* computed tomography; *MRI,* magnetic resonance imaging.
*May be negative or nonspecific during first 48 hours of illness.
†Development of abscess wall may be delayed by steroid therapy.

which is temporally atypical for malignancy and inconsistent with stroke. The most common symptom is headache, present in approximately 70% of cases. Other signs and symptoms include fever (53%), focal neurologic deficits (48%), nausea or vomiting (47%), altered mentation (43%), papilledema (35%), nuchal rigidity (32%) and seizures (25%), and focal neurologic signs (48%).[51,52] The classic clinical triad of fever, headache, and focal neurologic deficit is present in only 20% of patients.[47] CSF findings are often nonspecific and may be normal in approximately 15% of cases. Lumbar puncture is contraindicated if there is clinical or radiographic evidence of increased intracranial pressure, given the risk of herniation.

Imaging

Neuroimaging plays an important role in diagnosis and in monitoring response to therapy. Maturation of a brain abscess is associated with encapsulation, and this is visualized as ring enhancement on CT or MRI.[53] MRI is superior to CT in assessing brain abscesses, as the latter may miss small lesions or those localized to the brainstem or cerebellum. Misinterpretation can occur, particularly when the abscess is in the white matter, where decreased vascularity may result in delayed encapsulation with minimal ring enhancement. Similarly, steroid therapy may decrease local inflammation, resulting in resolution of the ring enhancement. Ring enhancement is not specific for bacterial abscesses and may be seen with other infections or brain tumors. Diffusion-weighted imaging is useful for differentiation of a brain abscess from other cystic brain lesions.[54] Ring-enhancing neoplasms often exhibit facilitated diffusion in the central, nonenhancing area, whereas abscesses typically demonstrate diffusion restriction.[53] When differentiating abscess from other pathologies, diffusion-weighted imaging has a sensitivity of 72%–95% and a reported specificity of 96%–100%.[55,56]

Management

In general, a combination approach of antimicrobials coupled with surgical drainage remains the standard approach for the management of pyogenic brain abscesses. The choice of antimicrobials should be guided by culture results, given the diversity of potential pathogens and the need for prolonged therapy (e.g., 6–8 weeks). Because of the difficulty in achieving therapeutic concentrations of antibiotics across the blood-brain barrier, CNS penetration should be considered when selecting an agent. Empiric therapy should be guided by the most likely microbiology based on origin of the infection. In cases in which the source is unknown or a metastatic spread from a distant focus is likely, empiric therapy with vancomycin, metronidazole, and a third-generation cephalosporin is suggested.[52] An antipseudomonal cephalosporin should be substituted for postneurosurgical infections or for an abscess arising from an otogenic site. Meropenem may be substituted for cephalosporins and metronidazole when there is a contraindication to one of these agents.

Neurosurgical aspiration is invaluable in identifying specific pathogens, and sensitivity testing is crucial for narrowing therapy. Use of stereotactic biopsy allows minimally invasive drainage for both diagnostic and therapeutic purposes. Bacterial, fungal, and mycobacterial cultures should be obtained on all aspirates. Positive cultures from blood or extra-CNS suppurative foci can occasionally establish a presumptive etiologic agent. Ancillary testing for a culture-negative brain abscess includes HIV serology, serum cryptococcal antigen, and *Toxoplasma* titers.

Medical management without drainage may be necessary when the lesion is inaccessible or surgical intervention poses unacceptable risks. However, open or stereotactic drainage is indicated when deterioration from increased intracranial pressure occurs or there is no improvement on medical therapy.[52] Patients treated without drainage may require a longer duration (e.g., 12 weeks) of parenteral antibiotics and should be followed closely for clinical and radiographic improvement. Steroids should be reserved for cases in which significant edema is present.

ENCEPHALITIS

Encephalitis is inflammation of the brain parenchyma accompanied by neurologic dysfunction.[57] Clinical findings include altered mental status (such as disorientation, confusion, and behavioral/cognitive changes), seizures, fever, and focal neurologic dysfunction. The worldwide incidence of encephalitis is estimated at 0.07–12.6 cases/100,000 persons,[58] with mortality in the range of 7%–18% and severe disability reported in approximately half of all survivors.[59–61]

Encephalitis presents a diagnostic challenge to the clinician, and a specific etiology is only identified in approximately 50% of all cases.[62] A myriad of noninfectious etiologies can cause or mimic encephalitis, including direct parenchymal infection, postinfectious autoimmune reactions including acute disseminated encephalomyelitis (ADEM), other immune-mediated etiologies such as autoimmune encephalitis related to neuronal cell surface/synaptic autoimmunity (most commonly anti-*N*-methyl-D-aspartate receptor [NMDAR] autoantibody encephalitis), multiple sclerosis, neuromyelitis optica spectrum disorders, neuro-Behçet, neurosarcoidosis, and others.[1,63]

Infection is the most common cause of encephalitis and constitutes approximately 50% of identifiable etiologies.[63] HSV-1 is the single most common cause of sporadic encephalitis worldwide; this pathogen is of particular importance, as specific treatment is available.[64] Varicella-zoster virus (VZV) is another important cause of encephalitis that is associated with high mortality and treated with parenteral acyclovir, similar to HSV. In the United States, West Nile virus neuroinvasive disease is the leading cause of epidemic encephalitis during the summer and early fall.

Recent epidemiologic studies suggest that the incidence and prevalence of autoimmune encephalitides are comparable with infectious encephalitis.[65]

Infectious Encephalitides

Pathophysiology

The blood-brain and brain-CSF barriers help protect the CNS from the free diffusion of potentially harmful biological and chemical agents.[66] Most vascular endothelial cells in the CNS are sealed by tight junctions and are unfenestrated. These contribute to the protection afforded by the basement membrane, which functions as an acellular barrier to CNS penetration. Within the CNS, astrocytic foot processes form a dense basal lamina surrounding the brain and spinal cord that contributes to the blood-brain barrier.[67] Juxtavascular microglial cells and perivascular macrophages within the brain parenchyma surveil the perivascular spaces. In the choroid plexus, endothelial cells are fenestrated but supported by a second layer of epithelial cells.

Inhaled viruses such as VZV or measles and ingested viruses such as enteroviruses penetrate mucosal membranes and establish infection in the local lymphoid tissue. Viruses that are inoculated into subcutaneous tissue (e.g., arboviruses) are transported by Langerhans cells to the draining lymph nodes. From the secondary lymphoid tissues, the viruses are shed into the bloodstream and thereby disseminate. Many viruses (including West Nile virus, human T-lymphotropic virus type-1 [HTLV-1]), and some bacteria such as *R. rickettsii,* have been shown to directly infect microvascular endothelial cells in vitro.[68,69] Some viruses are capable of entering vascular endothelial cells by binding to endothelial cell-expressed molecules—for example, HTLV-1 can use glucose transporter 1 in order to enter the endothelial cell.[68] Once within the endothelial cell, some agents can alter cellular physiology

(e.g., promoting chemokine expression and altering expression of adhesion molecules), leading to increased vascular permeability and allowing the agent to bypass the first layer of CNS protection.[67]

Although the brain is protected by both the blood-brain and brain-CSF barriers, many neurotropic infectious agents have developed mechanisms for gaining entry into the CNS.[70] Infection of host leukocytes, which are capable of entering the CNS, can serve as a "Trojan horse" neuroinvasive mechanism for viruses such as HIV.[71] Another means of entry is direct neuronal invasion through peripheral nerves.[72] Rabies virus and some enteroviruses, such as poliovirus, are examples of agents that reach the CNS through this mechanism. Poliovirus initially infects mucosal epithelial cells before gaining access to the CNS via retrograde transport in motor neurons,[73] and rabies infects epithelial cells and myocytes at the site of inoculation before gaining access to the nervous system. Once in the motor neurons, rabies virus is transported to the CNS by retrograde axonal transport and through synapses until it reaches the CNS.[74] HSV-1 infects keratinocytes before entering peripheral sensory nerves and may also gain access to the CNS through olfactory sensory neurons (as may several other viruses).[75]

Individual infectious agents demonstrate variable affinities for different anatomic areas of the CNS. Those with a tropism for the meninges cause meningitis, whereas those capable of infecting the brain parenchyma can cause meningoencephalitis or encephalitis. Many agents can affect the spinal cord, causing myelitis (discussed later) as well. In older children and adults, HSV-1 characteristically causes temporal lobe encephalitis, whereas HSV-2 more typically causes meningitis or a lumbosacral radiculomyelitis (Elsberg syndrome).[76] A number of infectious agents have a tropism for the brainstem and can cause a syndrome of brainstem encephalitis. Findings of brainstem encephalitis include cranial nerve palsies, crossed hemiparesis (ipsilesional face/contralesional body from corticospinal tract lesions) or sensory changes (medial lemniscus or spinothalamic tracts), ataxia (cerebellum/cerebellar peduncles), decreased alertness (ascending arousal system), and unusual symptoms such as recalcitrant nausea/vomiting and hiccoughs (area postrema). Infectious etiologies that have been associated with brainstem encephalitis include *L. monocytogenes*,[77] tuberculosis, Whipple disease,[78] herpes group viruses,[79,80] enteroviruses (particularly enterovirus 71), and flaviviruses (especially Japanese encephalitis virus and West Nile virus). There are a number of immune-mediated causes of brainstem encephalitis as well, such as multiple sclerosis, neuromyelitis optica spectrum disorders, neuro-Behçet, neurosarcoidosis, chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS), Fisher-Bickerstaff encephalitis, and others.[1,81–83]

Clinical Manifestations

In the approach to assessing a patient with possible encephalitis, it is important to first distinguish between encephalitis and encephalopathy without brain inflammation. Encephalopathy without inflammation can result from metabolic derangements (hypoglycemia, hypoxia, electrolyte disturbances, renal or liver disease) or toxin exposure (alcohol, illicit drugs, prescription medications, and environmental contaminants). A clinical case definition for encephalitis that has been proposed by an international working group[57] includes a major criterion of altered mental status for longer than 24 hours and at least two of the following: fever, seizures not attributable to a previously identified seizure disorder, new focal neurologic findings, CSF white cell count more than 5/mm^3, and abnormalities on neuroimaging or electroencephalogram (EEG) suggesting inflammation. This definition was designed for research and epidemiologic purposes but also provides a standardized case definition for clinicians. Notably, this definition may fail to identify patients with focal encephalitis, which may not produce altered mentation.

Management

The history and physical examination are critically important in the diagnostic evaluation of the patient with suspected encephalitis. Particular attention should be given to recent infectious symptoms, risk factors for tuberculosis or other infectious agents, unusual insect or toxin exposures, travel, rash, a history of autoimmunity, and neuropsychiatric manifestations. Full neurologic and general examinations are important in guiding the diagnostic approach. Given the broad differential diagnosis, a diagnostic algorithm has been proposed that emphasizes the most common causes, those that benefit from targeted therapies, and those that pose a particular public health threat.[57,84] Once a clinical diagnosis of encephalitis is suspected, empiric therapy with appropriate antimicrobial agents should be initiated while the diagnostic evaluation is under way.

Routine testing for adults with encephalitis includes complete blood count (CBC) with differential, measures of renal and liver function, blood cultures, HIV testing, and treponemal testing. In addition, *Mycoplasma pneumoniae* antibodies and Epstein-Barr virus (EBV) serologies (VCA immunoglobulin G [IgG] and immunoglobulin M [IgM] and EBNA IgG) should be obtained in children with encephalitis. Serum should be reserved from presentation, and convalescent serum collected 10–14 days later for paired antibody testing as indicated. CSF analysis should be pursued in all patients with encephalitis with routine testing, including opening pressure; cell count and differential; protein; glucose; oligoclonal bands; IgG index; Gram stain; bacterial cultures; HSV-1/2 polymerase chain reaction (PCR); VZV PCR; and if available, VZV IgG and IgM, enterovirus PCR, cryptococcal antigen, and Venereal Disease Research Laboratory (VDRL). In the last several years, molecular multiplex panels targeting the most common causes of community-acquired meningoencephalitis have become commercially available, allowing targeted testing for multiple pathogens, with results available within hours. Autoimmune antibody panels from the serum and CSF should be considered depending on the presentation.

Neuroimaging, preferably MRI with and without contrast, should be obtained in all patients and may reveal meningeal and/or parenchymal contrast enhancement, limbic edema, or other important diagnostic clues. EEG should be obtained in all patients with encephalitis, and when available, continuous EEG monitoring should be considered, as nonconvulsive status epilepticus is a common mimic and complication of encephalitis.[85]

Patients with depressed consciousness, increased intracranial pressure, or seizures are best managed in an intensive care setting. All patients with encephalitis should be treated with IV acyclovir pending CSF PCR result for HSV. Empiric antibiotics should be given if there is concern for meningoencephalitis or a bacterial etiology such as *Listeria* brainstem encephalitis. Anticonvulsant therapy should be initiated in patients with clinical or subclinical seizures but not prophylactically. With the exception of encephalitis caused by herpes group viruses and a few other agents (see later), the management of most viral encephalitides is focused on supportive care.[86]

Herpesvirus Encephalitis

Herpes Simplex Virus Encephalitis

HSV-1 and -2 are two of eight human herpesviruses (HHVs), which also include VZV (HHV-3), EBV (HHV-4), cytomegalovirus (CMV; HHV-5), HHV-6, HHV-7, and HHV-8. HSV-1 and -2 infections are common; HSV-1 seropositivity among adults is 80%–90% worldwide.[87] HSV-1 is the most common cause of sporadic encephalitis in the United States, responsible for approximately 90%

of HSV encephalitis in adults and children (with HSV-2 responsible for the remainder).[64] The mortality caused by untreated HSV-1 encephalitis is roughly 70%, and neurologic sequelae are almost universal in the absence of treatment.[64] Recent epidemiologic studies indicate mortality in the range of 6.2%–18.7% (higher numbers are seen for those admitted to the ICU) in the United States, with significant health and economic impact among survivors.[88,89] Early administration of acyclovir has been shown to significantly improve survival and outcomes.[90,91]

HSV-1 encephalitis may be caused by reactivation of the dormant virus or may occur in the setting of primary infection.[92] The virus has a tropism for the orbitofrontal and temporal lobes; however, no combination of clinical, laboratory, or radiographic findings is sufficiently sensitive to confirm the diagnosis, and empiric acyclovir therapy should be given to all patients with possible HSV-1 encephalitis until all definitive diagnostic studies are completed.[86]

Signs and symptoms typical of HSV-1 encephalitis reflect viral replication and inflammation in the mesial temporal and orbitofrontal lobes and include personality change, confusion, memory loss, hallucinations, aphasia, and seizures; fever is almost universally present.[1,64] Progressive temporal lobe edema can lead to uncal herniation with mydriasis (usually ipsilateral), which can progress to complete third nerve palsy, herniation, and death. When HSV-2 affects the CNS, it primarily causes meningitis, which may be recurrent (Mollaret meningitis) but may rarely cause encephalitis as well. In addition, HSV-2 can cause a triad of brainstem encephalitis, myelitis, and radiculomyelitis (Elsberg syndrome).[76]

The MRI is abnormal in most cases of HSV-1 encephalitis and may disclose unilateral or bilateral abnormalities within the mesial temporal and orbitofrontal lobes, the two most commonly affected structures, and the insular cortex.[93] Diffusion-weighted imaging may be more sensitive for HSV-1 encephalitis, particularly early in the course of the illness.[93] EEG is significantly more likely to demonstrate periodic discharges or focal slowing in frontotemporal leads in patients with HSV-1 encephalitis compared with those with encephalitis from other causes.[94]

The CSF exhibits lymphocytic pleocytosis in over 90% of patients but may appear normal early in the course and is nonspecific. The CSF protein is usually elevated, and glucose level is generally normal. CSF PCR for HSV-1 and -2 remains the diagnostic test of choice with a high sensitivity (96%) and specificity (99%).[95,96] Empiric acyclovir therapy can usually be discontinued if the PCR result is negative, although there have been reports of false-negative results early in the course of the disease; therefore if the clinical suspicion for HSV encephalitis is high, repeat lumbar puncture and PCR for HSV should be performed >3 days after the initial negative test, with continuation of empiric acyclovir.[97]

IV acyclovir 10 mg/kg every 8 hours is the treatment of choice for HSV-1 and -2 encephalitis and should be continued for a minimum of 14–21 days.[98] Dose adjustment is necessary with renal impairment. The safety and efficacy of adjunctive corticosteroids have not been rigorously investigated, and these are typically reserved for use in patients with significant edema.[99] Cognitive deficits and seizures are significant sequelae among survivors. A recent trial of long-term valacyclovir after standard treatment for HSV encephalitis, although well tolerated, did not improve outcomes.[100]

Although HSV-1 encephalitis is typically monophasic, roughly 27% of patients will suffer a secondary autoimmune encephalitis days to months after the initial presentation that can mimic a relapse of the HSV encephalitis.[101] Clinical features of the autoimmune relapse are age dependent. Children generally present with encephalopathy and movement disorders such as choreoathetosis, whereas adults typically present with neuropsychiatric manifestations.[101–103] HSV has been associated with a number of autoantibodies, including those targeting the NMDA receptor, and a number of other antibodies targeting identified or unidentified neuronal antigens.[101,104,105] Patients with clinical relapse after viral encephalitis should be evaluated for autoimmune antibodies and consideration given to empiric immunosuppression after infectious etiologies have been excluded.

Varicella-Zoster Virus Encephalitis

VZV is an important cause of encephalitis and was responsible for 5% of cases in one recent study, with a high case-fatality rate.[59] VZV can also cause brainstem encephalitis, meningitis, myelitis, and vasculopathy that may lead to multifocal ischemic strokes, which may be recurrent. The diagnosis is confirmed by demonstrating VZV PCR positivity or elevated VZV IgM or IgG in the CSF in the appropriate clinical context. Treatment is similar to that for HSV encephalitis and consists of IV acyclovir for 10–14 days. With VZV vasculopathy, concomitant steroid therapy may be indicated. Cutaneous zoster in the setting of encephalitis warrants empiric therapy while diagnostic evaluation is under way, although rash may not be present (zoster sine herpete).

Immune-Mediated Encephalitides

Although viral infections have historically been the most common identifiable etiologic category of encephalitis, a 2018 epidemiologic study from Olmstead County found that the incidence and prevalence of autoimmune encephalitis (AIE) were comparable to infectious encephalitis,[65] and it is increasingly recognized that immune-mediated encephalitis accounts for a substantial burden of disease.[106,107] In one large-scale study, NMDAR encephalitis was the most commonly identified cause of encephalitis in patients who were 30 years or younger.[108]

In 2005 six patients with encephalitis were reported, all of whom had unidentified neural cell surface antibodies and improved with immunotherapy and/or tumor removal.[109] Together with previous studies on paraneoplastic neurologic disorders, this small case series ushered in the characterization of a number of autoimmune encephalitides, a growing area of interest that has had a significant impact in the fields of medicine, neurology, and psychiatry. Since the discovery of NMDAR encephalitis in 2007,[110] roughly one to two novel autoantibody syndromes have been identified yearly. Among these, NMDAR encephalitis is the most common, followed by LGI-1 encephalitis.[106]

Pathophysiology

The AIEs associated with neuronal antibodies can be divided roughly into two categories: those with antibodies targeting cell surface/synaptic antigens and those with antibodies targeting intracellular antigens.[106] Broadly speaking (and with some exceptions), AIE associated with antibodies targeting *cell surface/synaptic antigens* may or may not be paraneoplastic, generally develop in younger patients, and tend to respond to immunotherapy, whereas AIE with antibodies targeting *intracellular antigens* are more often paraneoplastic, more common in older adults, and are less likely to respond to immunotherapy. In addition, whereas IgG antibodies targeting cell surface/synaptic antigens are often directly pathogenic, those targeting intracellular antigens generally are not directly pathogenic and are considered a marker of autoimmunity primarily affected by T cells. This paradigm is useful and has implications for the treatment of AIE, as discussed later.

Binding of autoantibodies to their target extracellular epitopes on neural cell surface or synaptic proteins can lead to alteration of the structure or function of the target antigen.[111] NMDAR encephalitis is the best studied of the autoimmune encephalitides. The NMDAR is localized to the postsynaptic membrane and clustered at the postsynaptic density. In cultured neurons, the binding of patient IgG antibodies to the GluN1

subunit of the NMDAR leads to selective cross-linking and internalization of the NMDAR in a titer-dependent, reversible manner.[112,113] GABAbR and AMPAR antibodies have also been shown to cause selective internalization of their respective receptors in cultured neurons.[114,115] Planaguma and colleagues demonstrated in vivo pathogenicity of NMDAR antibodies by continuously infusing CSF from patients with NMDAR encephalitis into the ventricles of mice, which caused memory and behavioral deficits.[116] Hippocampal analysis demonstrated accumulation of bound antibodies over time with a decrease in the number of synaptic NMDARs. Both the clinical and pathologic consequences improved with the cessation of antibody infusion.

Clinical Manifestations

The importance of the clinical history and examination cannot be overstated, and there has been a tendency to be overreliant on antibody testing in AIE. A 2016 position paper from experts in the field outlines a clinical approach to AIE.[117] The criteria for possible AIE include subacute, progressive deficits in memory, altered mental status or psychiatric symptoms with new focal CNS findings, unexplained seizures, CSF pleocytosis, or MRI suggesting encephalitis in patients in whom reasonable alternative causes have been excluded. Here we will briefly discuss NMDAR encephalitis, but interested readers are referred to several recently published reviews of immune-mediated encephalitides from several different institutions.[106,107,118–120]

NMDAR encephalitis most commonly occurs in young females, with a median age of 21 years (0.6–85 years) although all ages and both genders can be affected. The syndrome develops over stages, with approximately 70% experiencing a viral prodrome consisting of headaches, fevers, vomiting, diarrhea, and/or upper respiratory tract symptoms.[121,122] Within 2 weeks, behavioral and neuropsychiatric manifestations develop and can easily be misinterpreted as evidence of a primary psychiatric condition. This is followed by a depressed level of consciousness that may alternate with episodes of agitation and catatonia. Dissociative responses such as passive resistance to eyelid opening and no reaction to noxious stimulation may be observed, similar to findings in pharmacologic NMDAR antagonism such as ketamine.[123] In this stage, patients develop a variety of abnormal movements (dystonias, dyskinesias, etc.) and autonomic dysfunction that may lead to respiratory failure requiring mechanical ventilation.

Seizures are common throughout the illness, and EEG is abnormal in most patients. The extreme delta brush pattern, which consists of 1- to 3-Hz delta activity with superimposed 20- to 30-Hz beta activity, may be observed in 33% of patients and is relatively unique to NMDAR encephalitis.[124] Brain MRI is abnormal in only 23%–50% of patients and may reveal nonspecific T2 hyperintense lesions in the frontal, parietal, medial temporal, or posterior fossa and occasionally the basal ganglia.[125] A positron emission tomography (PET) scan may demonstrate frontotemporal hypermetabolism with occipital hypometabolism.[126] The detection of anti-NMDAR antibodies confirms the diagnosis, and autoantibodies should be sought in both the serum and CSF, as 6%–13% of patients will only have autoantibodies detectable in the CSF, depending on the method used for antibody detection.[127] There is also a risk of false-positive results if testing is limited to the serum.[128] When AIE is suspected or confirmed, search for an underlying malignancy should be aggressively pursued. Up to half of patients with NMDAR encephalitis have an underlying tumor; although neoplasia is less common in males and younger patients, appropriate diagnostic evaluation should still be pursued.[129,130]

Management

Management includes immunotherapy and the removal of any underlying tumor. With treatment, 70%–80% of patients with anti-NMDAR encephalitis will attain complete or near-complete recovery, and signs and symptoms of the disease generally abate in reverse order.[131] Any tumor should be promptly removed, particularly ovarian or testicular masses. A retrospective analysis of 501 patients treated for anti-NMDAR encephalitis provides the most comprehensive data regarding outcomes.[130] Treatment varied among patients and included first-line regimens consisting of tumor removal (when present), corticosteroids, IV immunoglobulin (IVIg), or plasmapheresis and second-line treatment with rituximab (anti-CD20 monoclonal antibody) and/or cyclophosphamide. For patients who received first-line therapy, 53% improved within 4 weeks. Among patients who did not respond to first-line therapy, 57% were given second-line therapy, which was associated with improved outcomes compared with those who were continued on first-line therapy alone. Patients may require hospitalization for months while undergoing evaluation and treatment.

Although no data have demonstrated the superiority of one regimen over another, one approach is to combine 1g IV methylprednisolone (IVMP) daily for 5–7 days with plasma exchange (1 volume every other day for five sessions) as first-line treatment. IVIg (0.4 g/kg/day for 5 days) can be used after plasma exchange if needed, but should not precede plasma exchange. IVIg antibodies are removed by plasma exchange, potentially decreasing the efficacy of this costly treatment. If improvement is not noted within 10 days, rituximab or cyclophosphamide can be considered. We prefer rituximab for patients with antibodies targeting cell surface/synaptic antigens and generally reserve cyclophosphamide for patients with intracellularly targeted antibodies (wherein the antibody is generally a marker of autoimmunity but not directly pathogenic). Once substantial clinical improvement is noted, treatment can be discontinued in most patients; however, 20%–25% of patients (usually those without a teratoma) may relapse, and longer immunosuppression should be considered in these patients.

Acute Disseminated Encephalomyelitis

ADEM is an immune-mediated inflammatory demyelinating disease of the CNS that is generally monophasic and can be difficult to prospectively distinguish from other causes of encephalitis. ADEM most often affects children, with an annual incidence of 0.07–0.6/100,000 people.[132–134] ADEM generally presents within 2–4 weeks of an infectious illness or, occasionally, vaccination, but antecedent exposure may be absent in 26% of patients.[135] This observation, combined with data from an animal model of demyelination (experimental AIE), suggests that the pathogenesis is related to molecular mimicry in which antigenic epitopes are shared between pathogens or vaccines and host myelin. Alternatively, CNS infection with the subsequent inflammatory cascade may lead to disruption of the blood-brain barrier, exposing CNS antigens to the host immune system, which may lead to breakdown of tolerance.

The syndrome clinically presents with fever, encephalopathy (42%–83%), headache with or without vomiting (15%–37%), meningeal signs (13%–43%), seizures (4%–48%), focal weakness (17%–77%), ataxia (10%–52%), cranial nerve palsies (11%–48%), and/or visual impairment (7%–23%).[136–138] CSF analysis may disclose a variable degree of lymphocytic pleocytosis with mildly to moderately elevated protein levels, normal glucose levels, normal Gram stain with sterile cultures, and transient oligoclonal bands in up to 29%.[137]

The MRI findings in ADEM typically include multiple large (>1–2 cm) asymmetric T2 and fluid-attenuated inversion recovery (FLAIR) hyperintense lesions randomly distributed in the cerebral hemispheres, cerebellum, brainstem, and spinal cord.[139–141] Lesions classically involve the white matter but commonly develop in the deep gray matter as well, particularly the thalamus and basal ganglia, where they tend to be more symmetric.[135] The frequency and patterns of gadolinium

enhancement are highly variable in ADEM (8%–100%), depending on the stage of inflammation, although all lesions tend to be at the same stage at the same time (in contrast to the lesions seen with multiple sclerosis). ADEM is classically a monophasic illness, and signs and symptoms generally resolve over time; however, "multiphasic ADEM" has been reported. There is no standard treatment for ADEM, and the current suggested therapy is based on level IV evidence. After infectious and other causes of encephalitis have been excluded, most authors suggest high-dose IVMP (20–30 mg/kg/day to maximum of 1 g/day) for 3–5 days followed by oral prednisone tapered over 4–6 weeks.[137,140,142,143] For patients who are not responding to steroids, IVIg has been reported to be successful in several case studies and can be considered. A reasonable regimen is 2 g/kg IV divided into doses given daily over 2–5 days (e.g., 0.4 mg/kg given daily for 5 days). In cases of fulminant ADEM unresponsive to steroids, plasma exchange can be considered and has been shown to be effective in aggressive CNS demyelination.[144]

MYELITIS AND MYELOPATHY

Myelopathy refers to any pathology of the spinal cord with associated neurologic dysfunction and includes noninflammatory etiologies such as nutritional deficiency and malignancy. Myelitis is an inflammatory cause of myelopathy and may occur in isolation (e.g., poliovirus myelitis or herpesvirus myelitis) or coexist with encephalitis as an overlap syndrome (e.g., acute flaccid paralysis associated with West Nile virus [WNV] encephalomyelitis, progressive encephalomyelitis with rigidity and myoclonus, or ADEM). The differential diagnosis of myelitis includes infectious and immune-mediated etiologies in addition to noninflammatory causes of myelopathy such as vitamin or mineral deficiencies (e.g., vitamin B_{12}, copper), vascular myelopathies, and neurodegenerative conditions.[1]

The differential diagnosis for myelitis is shown in Box 114.3. Some causes, such as ADEM and other postinfectious myelitides, are monophasic, whereas others, such as multiple sclerosis, neuromyelitis optica, lupus myelitis (now recognized to be often associated with neuromyelitis optica), and neurosarcoidosis, can be progressive and/or relapsing.

A thorough history and neurologic examination are critical for defining the temporal profile and localization. Back or neck pain (especially funicular pain), bowel or bladder dysfunction, saddle anesthesia, and bilateral upper or lower extremity weakness are historic features that suggest a spinal localization. The temporal profile is helpful in determining etiologic probabilities. For example, a hyperacute presentation is suggestive of a vascular or traumatic etiology, whereas an acute-subacute temporal profile suggests inflammatory or infectious etiologies, and a subacute-chronic course implies nutritional deficiency or malignancy.

Identifying a spinal level is a key step in localizing a lesion to the spinal cord, and the pattern of localization may assist in determining the etiology (e.g., weakness and loss of pain/temperature with preserved vibration and proprioception in cases of anterior spinal artery occlusion or loss of vibration and proprioception with preserved pain/temperature and motor function in tertiary syphilis). In the acute setting, patients may present with hyporeflexia that can mimic Guillain-Barré syndrome, a finding that can mislead the diagnostician to a peripheral localization. Although a localization can usually be identified, none of the features on the examination or history is sufficiently sensitive or specific to differentiate between inflammatory, vascular, or compressive causes. Therefore all patients with myelitis should be managed as true emergencies using a standardized approach.

The first step in the diagnostic approach to possible myelitis is to exclude extrinsic cord compression that might warrant surgical intervention.[145] Emergent imaging is indicated if cord compression is suspected, as early decompression dramatically improves functional outcomes. The preferred modality is spinal MRI with and without contrast, although CT myelography is a reasonable alternative if MRI is contraindicated. Once compression is excluded, lumbar puncture with cell count and differential, total protein, glucose, Gram stain/cultures, IgG index, and oligoclonal bands should be obtained, with an extra sample reserved for future studies. In addition, antiaquaporin-4 autoantibodies, Sjögren syndrome A antibodies/ Sjögren syndrome B antibodies (SSA/SSB), antinuclear antibodies (ANA), anticardiolipin antibodies, copper, vitamin B_{12}, treponemal antibody, CSF varicella-zoster PCR and IgG, and enterovirus PCR should be considered. Inflammation of the spinal cord is supported by contrast enhancement on MRI, CSF pleocytosis, or elevated CSF IgG index.

There are four key steps in the management of myelitis: (1) recognizing the syndrome, (2) extinguishing acute inflammation, (3) determining the etiology, and (4) providing long-term management. While the diagnostic evaluation is under way, high-dose steroids (typically with 1 g IVMP daily for 3–7 days) should be given in order to decrease the acute inflammation.[146]

BOX 114.3 Differential Diagnosis of Myelitis

Viral
- HIV
- HSV-1 and -2
- VZV
- CMV
- EBV
- WNV
- HTLV

Bacterial
- *Mycoplasma pneumoniae*
- *Borrelia burgdorferi*
- *Treponema pallidum*
- Pyogenic bacteria
- *Mycobacterium tuberculosis*

Fungal
- *Coccidioides immitis*
- *Actinomyces*
- *Aspergillus*
- *Blastomyces dermatitidis*
- Histoplasmosis

Immune-Mediated
- Multiple sclerosis
- Neuromyelitis optica
- Connective tissue disorders (neuro-lupus, neuro-Sjögren)
- Neurosarcoidosis
- Paraneoplastic

Noninflammatory Myelopathies
- Vitamin B_{12} deficiency
- Folic acid deficiency
- Copper deficiency
- Vitamin E deficiency
- Nitrous oxide toxicity
- Heroin
- Radiation myelopathy
- Traumatic/compressive myelopathy
- Vascular myelopathy

When infectious etiologies are suspected or confirmed, appropriate antimicrobial agents should be given. Patients with longitudinally extensive myelitis associated with lupus may benefit from the addition of cyclophosphamide to corticosteroids and plasma exchange.[147,148] Those with myelitis as a result of neuromyelitis optica should be treated with steroids and plasma exchange, a regimen associated with improved outcomes.[149,150] When neurosarcoidosis presents with myelitis, corticosteroids are usually effective,[151] and severe or refractory cases generally respond to tumor necrosis factor-alpha (TNF-α) antagonism (such as with infliximab).[152] No specific regimen for infliximab in this setting has been validated, as only small case series exist, but doses range from 3 to 5 mg/kg, including induction with doses at 0, 2, and 6 weeks and maintenance dosing every 4–6 weeks thereafter. Notably, TNF-α antagonism can worsen multiple sclerosis and is contraindicated in these patients.[153] In managing patients with severe myelitis of unknown etiology, consideration should be given to concomitant steroids and plasma exchange, which were associated with improved outcomes in at least one retrospective review.[148]

Myelopathy from vitamin B_{12} deficiency should be treated with 1000 μg intramuscular vitamin B_{12} daily for a week, weekly for a month, and then monthly thereafter. Depending on the cause of deficiency, some patients can eventually be treated with oral vitamin B_{12}.[154] Hypocupremic myeloneuropathy should be treated with oral elemental copper 8 mg by mouth daily for a week, then 6 mg daily for a week, then 4 mg daily for a week, followed by 2 mg daily thereafter.[150,155,156] The underlying cause of deficiency should be identified (often associated with excessive zinc consumption, gastrointestinal surgeries, or malabsorption syndromes). Nitrous oxide toxicity may present with subacute-acute myelopathy and has been reported after a single exposure.[157] Nitrous oxide inactivates vitamin B_{12} by oxidizing the cobalt center of the molecule; therefore treatment is with vitamin B_{12}. Heroin use may cause an acute myelopathy, the treatment of which is supportive.

Ischemic myelopathy secondary to spinal cord infarction is managed with lumbar drainage and hemodynamic augmentation with vasopressors in order to increase perfusion of the spinal cord.[158] Guidelines from the Congress of Neurological Surgeons in 2013 recommended against the use of steroids in acute spinal cord infarction,[159] unless caused by vasculitis. Physical and occupational therapy are important interventions in the care of all patients with myelopathy. Long-term medical management is contingent upon the etiology of the myelitis.

CENTRAL NERVOUS SYSTEM INFECTION AND THE ACQUIRED IMMUNODEFICIENCY SYNDROME PATIENT

Patients with HIV/AIDS are susceptible to an array of opportunistic infections in addition to the more common causes of CNS infection. Differentiating neurocognitive dysfunction associated with HIV from neurologic dysfunction related to malignancy or opportunistic infections requires a thoughtful and systematic diagnostic approach to allow rapid and appropriate treatment of what are frequently life-threatening infections.

Pathophysiology

Opportunistic infections of the CNS are common in patients with advanced HIV, including cryptococcus, toxoplasmosis, and progressive multifocal leukoencephalopathy (PML). Advanced HIV infection is associated with *HIV-associated neurocognitive disorders* (HANDs), which comprise a spectrum of disease, with HIV-associated dementia (HAD) reserved for the most severe cases of cognitive dysfunction.[160] Before the availability of highly active antiretroviral therapy (HAART), it was estimated that 20%–30% of patients with uncontrolled HIV suffered from HAD.[161] The prevalence of HAD has decreased to 2%–8% in patients treated with HAART.[162] Over 40% of patients with HIV will present with neurologic manifestations, either related to the direct involvement of HIV itself or related to opportunistic infections over the course of their lives.[163] The neuropathogenesis of HIV has recently been reviewed, to which interested readers are referred.[164] Here we focus on opportunistic infections associated with HIV.

Clinical Manifestations

The most important factor in assessing a patient with HIV and neurocognitive changes is the degree of immunosuppression.[165] This framework can be used to establish the most likely etiologies in the differential diagnosis. Patients with CD4 counts higher than 500/μL are more likely to present with noninfectious conditions or infections common to immunocompetent patients. The exception is tuberculous meningitis, which can occur at any CD4 count. Those with CD4 counts between 200 and 500/μL are more likely to present with HIV-associated cognitive and motor disorders, whereas patients with CD4 counts lower than 200/μL are more likely to have CNS mass lesions, HIV-associated malignancy (such as CNS lymphoma), and opportunistic infections.

Management

In the evaluation of the patient with HIV and neurologic manifestations, a systematic approach is important. Imaging should be performed before lumbar puncture, given the increased risk of mass lesion such as toxoplasmosis or lymphoma in this population. A brain MRI with and without gadolinium contrast is the preferred method and can assist in securing the diagnosis.[166] In addition to the standard diagnostic studies, CSF analysis in HIV/AIDS patients should include cytology, cryptococcal antigen testing, VDRL (for syphilis), and, when indicated, PCR for herpesviruses, JC virus, and *Mycobacterium tuberculosis*.[167] The clinical manifestations and management of several of the most common CNS infections in patients with HIV are briefly reviewed next.

Toxoplasmosis

An obligate intracellular protozoan, *Toxoplasma gondii* is the most common HIV-associated opportunistic infection of the CNS.[168] It is found in cat feces and undercooked meat, and in immunocompetent patients, results in an acute but self-limited, nonspecific febrile illness. Seroprevalence studies suggest infection rates in the United States between 15% and 25%.[169] In patients with CD4 counts lower than 100/μL, CNS reactivation of prior toxoplasmosis infection may occur, and patients present with acute to subacute encephalitis.[170] Brain MRI with and without gadolinium contrast is more sensitive than CT.[166,171] MRI findings suggestive of *Toxoplasma* encephalitis include multiple nodular or ring-enhancing lesions, usually with extensive surrounding vasogenic edema, with a predilection for the basal ganglia and corticomedullary junction.[172] On noncontrast images, the appearance of lesions is highly variable; they may be isointense or hypointense on T1-weighted images and hypointense, isointense, or hyperintense on T2-weighted sequences. The "eccentric target sign" is an infrequent, but highly specific (95%), finding.[173] Most patients with *Toxoplasma* encephalitis have positive serologies for toxoplasmosis, but their absence does not exclude the infection. PCR of the CSF for toxoplasmosis is highly specific but insensitive and is not universally available. Treatment consists of sulfadiazine, pyrimethamine, and leucovorin (given to prevent pyrimethamine-induced hematologic toxicity). Patients who are unable to take sulfadiazine can substitute clindamycin. Maintenance therapy should be given to prevent further episodes of infectious reactivation. Corticosteroids

should be reserved for patients with a significant mass effect. Surgical intervention is typically reserved for patients with signs of impending herniation or lack of radiographic response after 2 weeks of empiric therapy for toxoplasmosis, in which case a biopsy to exclude an alternative cause, such as CNS lymphoma, is indicated.

Cryptococcus

Cryptococcus neoformans, an encapsulated budding yeast, is commonly found in soil contaminated by bird feces. Cryptococcal meningitis is the second most common CNS infection in patients with HIV. Cryptococcus typically presents as subacute (1–2 weeks) meningitis, but can rarely present with fulminant disease progressing to death over several days. A high index of suspicion is warranted in patients with low CD4 counts (especially <100/μL). Neuroimaging findings are highly variable and are often normal. Involvement of the basal ganglia may be present. Some features that suggest cryptococcal meningoencephalitis include dilated Virchow-Robin spaces, pseudocystic and cystic masses, meningitis, or hydrocephalus.[166] Many patients present with evidence of elevated intracranial pressure (>20 cm H_2O) that is characterized by decreased consciousness, papilledema, and sixth nerve palsy. The CSF classically reveals a low white blood cell count (<50/μL), with a mononuclear predominance, elevated protein, and low glucose levels but is normal in up to 30% of infected patients.[174,175] The CSF should be tested for the presence of cryptococcal antigen.[176] Commercially available molecular diagnostic panels include testing for *Cryptococcus,* but importantly, the sensitivity of PCR is only 52%.[177]

Opening pressure should be checked in all patients undergoing lumbar puncture, as elevated pressure is a poor prognostic sign. Patients with elevated intracranial pressure should be treated with repeated lumbar puncture or lumbar drain placement for decompression.[178] Patients with moderately elevated intracranial pressure present with an opening pressure of less than 20 cm H_2O. When symptomatic patients have an extremely high pressure, the pressure target should generally be 50% of the initial value. Daily lumbar puncture may be necessary until normalization/stabilization of pressures. Antifungal therapy includes an induction phase with liposomal amphotericin B (amphotericin B deoxycholate is an alternative if the liposomal form is unavailable) and flucytosine for at least 2 weeks, followed by prolonged consolidation therapy with fluconazole.[179,180]

Herpesviruses

Immunocompromised patients with herpetic infections of the CNS present a diagnostic challenge, and the index of suspicion should be high in order to avoid missing the diagnosis. Immunocompromised patients with herpes encephalitis are less likely to present with prodromal symptoms or focal neurologic deficits, have more extensive radiographic involvement (often distributed outside the temporal lobes), and have CSF pleocytosis.[181] Even with modern treatment and supportive care, mortality among the immunocompromised is significantly higher than among the immunocompetent, with reported mortalities of 35.7% and 6.7%, respectively. As in immunocompetent patients, acyclovir is the preferred agent.

CMV is another herpesvirus that is latent in the majority of the population but may reactivate in immunocompromised persons. CMV can cause encephalitis, retinitis, myelitis, polyradiculopathy, and peripheral neuropathy and is most likely to manifest when the CD4 count is less than 50/μL. Findings on MRI are neither sensitive nor specific. MRI may reveal diffuse or focal T2 hyperintense lesions predominantly involving the periventricular white matter and possibly evidence of ventriculoencephalitis, characterized by T2 hyperintense lesions along the ependymal lining of the lateral ventricles that may enhance with the administration of gadolinium.[182] Analysis of the CSF may reveal neutrophilic pleocytosis (unusual for viral infection) and elevated protein and low glucose levels, though these findings are variably present.[182] CMV PCR should be obtained from the CSF, and high levels of viral DNA in the proper clinical context confirm the diagnosis, although low levels may be difficult to interpret. Several treatment regimens are in use for neurologic infections with CMV. Most clinicians use a combination of ganciclovir and foscarnet for patients with CNS infection, but patients who are unable to tolerate combination therapy can be treated with either agent alone.

Progressive Multifocal Leukoencephalopathy

PML is a life-threatening demyelinating disease of the CNS that results from reactivation of JC virus.[183] Primary infection usually occurs in childhood, with up to 86% of adults seropositive for the virus.[184] In most patients, the virus remains latent in the kidneys and the lymphoid organs, but in an immunocompromised individual, reactivation may occur with secondary spread to the CNS, where it causes a lytic infection of oligodendrocytes. PML usually manifests with subacute, progressive neurologic deficits, including personality change, altered mental status, and focal neurologic deficits referable to the localization of the infection. Seizures may occur in up to 18% of patients and are likely related to cortical or juxtacortical involvement.[185] Most patients with HIV who present with PML have CD4 counts of less than 100 μL, but PML has been associated with immunosuppression related to a number of medications, including mycophenolate mofetil,[186] rituximab,[187,188] and natalizumab.[189,190] PML classically affects the white matter, manifesting on MRI as symmetric or asymmetric T1-hypointense/T2-hyperintense lesions that may become confluent.[166] In patients with a profound immunocompromised status,[191] there may be minimal or no enhancement with gadolinium, but in the setting of PML-immune reconstitution inflammatory syndrome or with medications such as natalizumab, contrast enhancement is more common.[192] JC virus PCR from the CSF should be obtained when PML is suspected and is highly specific. However, the sensitivity may be decreased because of low viral burden with HAART.[177,193] Consequently, in rare cases, brain biopsy may be required to establish the diagnosis. There remains no specific treatment for PML; therefore therapy is aimed at restoring immune function. In patients with HIV, initiation or optimization of antiretroviral therapy is the best option and can prolong survival.[194,195] As the serotonin receptor 5HT2A can serve as a receptor for the virus, the addition of mirtazapine may be beneficial, but evidence is limited to case reports.[196–198] PML is associated with a bleak prognosis and is almost uniformly fatal in patients with AIDS.[199,200]

Central Nervous System Lymphoma

Patients infected with HIV are predisposed to several malignancies, including primary CNS lymphoma (PCL),[201] which are strongly linked to EBV infection.[202] PCL can mimic an opportunistic infection, and MRI may be helpful in differentiating the etiology of mass lesions in patients with AIDS. AIDS-related PCL is often associated with a high degree of contrast enhancement, which is typically irregular and inhomogeneous.[203,204] Lesions that involve the corpus callosum and periventricular or periependymal areas are more likely to represent PCL, whereas PCL involves the posterior fossa in less than 10% of cases in this population.[203,205] Among the conditions discussed here, PCL and toxoplasmosis are most likely to cause a mass effect.[206] As there is clinical and radiologic overlap with opportunistic infections, these should be thoroughly evaluated as outlined earlier with the inclusion of CSF EBV PCR, cytology, and flow cytometry. In the absence of a pathologic diagnosis, empiric corticosteroids should be used with caution, as these may decrease the diagnostic yield for CNS lymphoma.

EXTRACRANIAL INFECTIONS

Paradural Abscess

The epidural space is between the dura and the bony structures of the skull and vertebral column; the subdural space is between the subarachnoid membrane and the dura (see Fig. 114.1). Unlike the subarachnoid space, the paradural tissues are only potential spaces, with the arachnoid membrane and the dura limiting the spread of infection across their surfaces. Although subdural abscesses are more common within the cranium and epidural abscesses are more common within the vertebral column, the microbiology, pathophysiology, and treatment are similar. These abscesses usually develop from a contiguous infection, surgery, or trauma.

Cranial Paradural Abscess

In the skull, the epidural tissues are dense and abscess formation is unusual. The subarachnoid membrane is less adherent to the dura, making the subdural space the more likely site of infection. Intracranial paradural abscesses tend to evolve rapidly, often producing irreversible damage to underlying intracranial tissue. Antibiotics alone are inadequate, and neurosurgical drainage remains the mainstay of therapy. MRI has greatly aided in the rapid identification and management of intracranial paradural abscesses.

Cranial epidural abscesses most commonly occur adjacent to the frontal sinus, but if left untreated, infection can spread into the subdural space or even brain parenchyma. Infection may be the result of trauma or surgery, but, most commonly, is a complication of sinusitis, which is reflected in the microbiology of cranial epidural abscesses.[207] Treatment requires emergent surgical drainage followed by antibiotics tailored against the bacteria cultured intraoperatively.

Cranial subdural empyema may be clinically indistinguishable from meningitis or a brain abscess, with the triad of fever, headache, and altered consciousness seen at presentation in approximately 50% of patients.[208] A subdural abscess is most commonly a complication of a prior neurosurgical procedure but can also occur after infection of the paranasal sinuses and, less commonly, the ears or mastoids.[209] Rarely, spontaneous development of a subdural abscess after bacteremia has been reported. The microbiology of these infections reflects the pathophysiology. Infections after a neurosurgical procedure are typically caused by either skin flora such as *Staphylococcus,* or healthcare–associated organisms such as *Pseudomonas* or Enterobacteriaceae. Infections that occur as a complication of upper respiratory tract infections are usually caused by streptococci, pneumococci, *Haemophilus,* anaerobes, and staphylococci. Gram-negative enteric bacilli or *P. aeruginosa* may be associated with middle ear and mastoid infections. As with cranial epidural abscess, surgical drainage is crucial for treatment, followed by prolonged administration of antibiotics.[207]

Spinal Paradural Abscess

The incidence of spinal epidural abscess has increased in the past two decades, which is likely related to improved diagnostics with MRI and increases in comorbidities predisposing to infection. Risk factors for spinal epidural abscess include prior spinal surgery or trauma, injection drug use, diabetes, and end-stage renal dysfunction.[210] Patients typically present with localized spinal pain, with fever present in less than 50% of cases.[211,212] In the absence of treatment, symptoms usually progress through four clinical phases: spinal ache, nerve root pain, radicular weakness, and paralysis. The triad of back pain, fever, and progressive neurologic deficits strongly suggests this syndrome; however, the presence of any of these signs or symptoms should raise concern for the diagnosis.

Diagnosis hinges on visualization of a collection in the epidural space (Fig. 114.3). The diagnostic study of choice is MRI with contrast, which defines cord compression and the presence and extent of abscess, identifies drainable paraspinal fluid collections, and detects concomitant vertebral osteomyelitis. Other procedures such as myelography and CT scan may be used if MRI cannot be performed.

S. aureus accounts for more than two-thirds of cases of epidural abscess.[211,213] Although most cases are community acquired, an increasing number are caused by spinal instrumentation (surgery or nerve block), and nosocomial flora, including *Pseudomonas,* may be causative in this population. Other risk factors for spinal epidural abscess include IV drug use, diabetes mellitus, trauma, and comorbid conditions such as malignancy or alcohol use.[211] *Candida* infections are increasingly reported as causes of spinal epidural abscess.[214] Empiric therapy is directed against the most likely organisms and typically includes vancomycin and an antipseudomonal agent such as cefepime, but when possible, should be delayed until surgical cultures are obtained. Therapy should be refined once cultures confirm a causative pathogen.

Emergency neurosurgical intervention is considered mandatory for a spinal paradural abscess when there is neurologic compromise. A retrospective study found that 41% of patients with a spinal epidural abscess failed medical therapy and that neurologic outcomes were improved for patients with immediate rather than delayed neurosurgical decompression.[215] Progressive weakness mandates the need for immediate MRI and neurosurgical consultation because decompression within 24 hours offers the best chance of neurologic recovery.[213]

SEPSIS SYNDROME WITH CENTRAL NERVOUS SYSTEM INVOLVEMENT

In sepsis syndrome, an acutely ill patient develops CNS dysfunction, often associated with multiorgan system failure. Altered mental status, attributable to hypotension and hypoperfusion, ranges from confusion to obtundation. Seizures may occur as a result of metabolic abnormalities, ischemia, or hemorrhage. In treating such patients, general supportive measures take precedence over CNS concerns. After a brief assessment, general life support measures should correct hypotension, hypoxia, and anuria. After blood culture, broad-spectrum antimicrobials should be administered. A careful history and physical examination may identify a primary source for infection. When findings suggest a focal infection of the CNS, directed evaluation through neuroimaging and lumbar puncture is warranted.

CONCLUSION

Acute infection of the CNS requires rapid therapeutic intervention. The major syndromes of CNS infection (acute meningitis syndrome, subacute CNS infection syndrome that includes brain abscess, viral meningitis and encephalitis, and spinal epidural abscess) differ with respect to signs and symptoms and in the approach to definitive diagnosis and therapy. Moreover, diverse infectious and noninfectious causes may produce similar CNS syndromes. For therapy to be maximally effective, it must be instituted rapidly after the initial evaluation. Thus in the practice of critical care medicine involving CNS disease, the goal remains the rapid institution of empiric therapy for treatable infectious syndromes while efficiently working to identify the specific disease process.

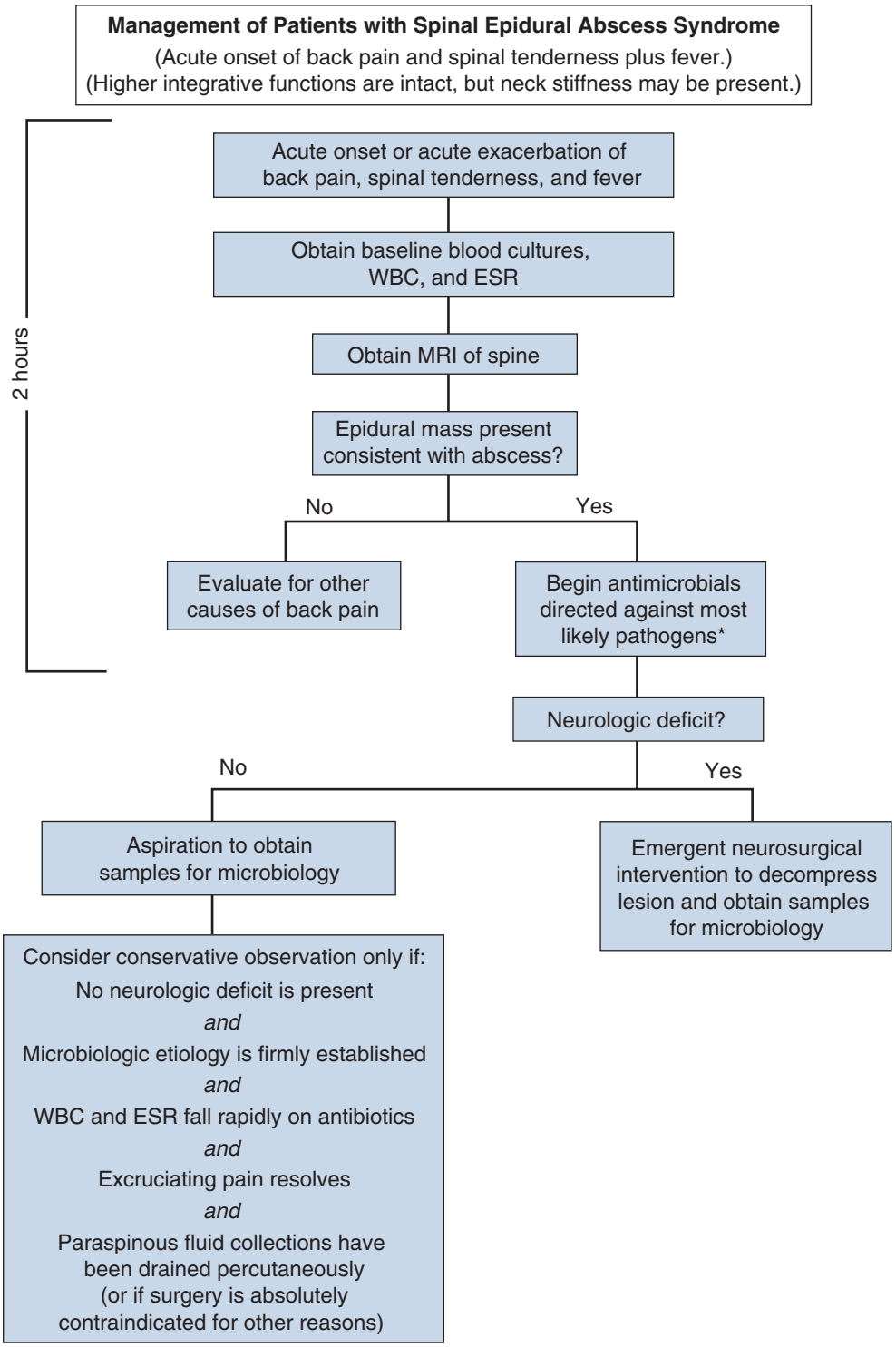

Fig. 114.3 Algorithm for the Management of Patients with Spinal Epidural Abscess Syndrome. If magnetic resonance imaging (*MRI*) cannot be performed, myelography, high-contrast computed tomography (CT), or CT myelography may be an acceptable alternative to localize an epidural abscess. *If abscess drainage can be performed promptly, antimicrobial drugs may be withheld until specimens for microbial analysis are obtained. *ESR,* Erythrocyte sedimentation rate; *WBC,* white blood cell.

KEY POINTS

Bacterial Meningitis

- For patients with bacterial meningitis, neuroimaging before lumbar puncture is associated with treatment delays and decreased yield of cultures and should be limited to patients with focal findings on neurologic examination, immunocompromise (HIV infection, malignancy, or transplant), new-onset seizures in the week prior to presentation, or coma.
- Empiric antibiotic therapy for bacterial meningitis includes vancomycin; a third-generation cephalosporin; and for patients at risk for *Listeria*, ampicillin and should begin as soon as possible after appropriate cultures have been obtained; these can be modified later based on results of CSF Gram stain and culture.
- Patients with negative microbiologic evaluation and limited clinical response after 48 hours of empiric therapy should undergo repeat lumbar puncture MRI scan.
- Adjuvant dexamethasone given within 4 hours of initiating antibiotics should be given to all non-neonatal patients with presumed bacterial meningitis and should be continued for patients with pneumococcal meningitis.

Brain Abscess

- Microbiology of brain abscesses is dependent on the route of infection; abscesses spreading from a contiguous focus (sinusitis, otitis) are frequently polymicrobial, and empiric therapy includes vancomycin, a third- or fourth-generation cephalosporin, and metronidazole.
- Treatment of brain abscesses typically requires neurosurgical drainage and prolonged administration of parenteral antibiotics tailored to culture results.

Encephalitis

- Although an infectious cause of encephalitis is found in less than 50% of cases, diagnostic evaluation to include HSV as either a stand-alone PCR or as part of a molecular diagnostic panel should be performed; other diagnostic testing should be guided by epidemiologic and clinical features.
- Autoimmune syndromes such as NMDAR encephalitis may mimic infectious etiologies but are treated with removal of the antigenic stimulus (i.e., surgical excision of a teratoma) and immunotherapy.

Central Nervous System Infection in HIV-Infected Patients

- HIV-infected patients may develop neurocognitive deficits related to HIV or from secondary infections, with the risk for opportunistic infections increasing inversely with declines in the CD4 count.
- Ring-enhancing lesions seen on neuroimaging are most frequently caused by either toxoplasmosis or lymphoma. In patients with positive *Toxoplasma* serology, empiric therapy for 2 weeks is indicated; brain biopsy should be performed in patients with lack of radiographic improvement.

Epidural Abscess

- Surgical drainage is imperative in patients with spinal epidural abscess and impaired neurologic function; there is little chance of recovery if symptoms have been present for more than 24 hours before decompression.

References for this chapter can be found at expertconsult.com.

ANNOTATED REFERENCES

Brouwer MC, McIntyre P, Prasad K, et al. Corticosteroids for acute bacterial meningitis. *Cochrane Database Syst Rev*. 2013;6:CD004405.
This meta-analysis of 25 studies involving more than 4000 patients examined outcomes in patients with bacterial meningitis treated with corticosteroids in addition to antibiotics. There was no significant difference in mortality, hearing loss, or neurologic sequelae in patients treated with steroids. On subgroup analysis, adjuvant use of corticosteroids reduced mortality associated with S. pneumoniae *meningitis and hearing loss in children with* H. influenzae *meningitis. When the study was stratified by site, coadministration of corticosteroids in high-income (developed) countries was associated with statistically significant reduction in hearing loss and neurologic morbidity. There was no beneficial effect of corticosteroids in patients with bacterial meningitis in low-income countries.*

Brouwer MC, Tunkel AR, McKhann II GM, et al. Brain abscess. *N Engl J Med*. 2014;371(5):447–456.
This comprehensive review provides updated information regarding the pathogenesis, epidemiology, clinical presentation, microbiology, and optimal treatment of brain abscesses. The authors emphasize the role of surgical management and highlight the increasing use of stereotactic biopsy as a less invasive means of identifying the causative organisms and providing therapeutic drainage.

Graus F, Titulaer MJ, Balu R, et al. A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol*. 2016;15(4):391–404.
In the past decade autoimmune disorders have been increasingly recognized as leading causes of encephalitis. These inflammatory etiologies may mimic infectious causes, but the treatment involves immunosuppressive medications rather than antimicrobial agents. This consensus statement by experts in the field of neuroimmunology provides an evidence-based strategy to guide diagnostic testing and identify a subset of patients most likely to benefit from empiric immunotherapy.

Kim SD, Melikian R, Ju KL, et al. Independent predictors of failure of nonoperative management of spinal epidural abscesses. *Spine J*. 2014;14(8):1673–1679.
This retrospective, case-control study compared outcomes among adult patients with nonsurgical spinal epidural abscess treated medically compared with those who underwent surgical decompression in addition to antibiotic therapy. Patients with neurologic compromise, age more than 65 years, diabetes mellitus, or infection caused by methicillin-resistant Staphylococcus aureus *had significantly higher rates of failure with solely medical management, and consideration of early surgical intervention in these populations is warranted.*

Thigpen MC, Whitney CG, Messonnier NE, et al. Bacterial meningitis in the United States, 1998-2007. *N Engl J Med*. 2011;364(21):2016–2025.
This paper summarized the results of a large population-based laboratory surveillance program for bacterial meningitis performed in selected areas in the United States between 1998 and 2007. During this period, there was a 31% overall decrease in the incidence of bacterial meningitis caused by declining rates of pediatric meningitis from S. pneumoniae *and* H. influenzae *as a result of vaccination. The median age of patients increased from 30.3 years to 41.9 years, with an aggregate case fatality rate of 14.8%.* S. pneumoniae *remained the leading cause of bacterial meningitis, accounting for 58% of cases.*

Venkatesan A, Tunkel AR, Bloch KC, et al. Case definitions, diagnostic algorithms, and priorities in encephalitis: Consensus statement of the international encephalitis consortium. *Clin Infect Dis*. 2013;57(8):1114–1128.
The authors provide expert consensus recommendations on a working case definition for encephalitis and outline diagnostic algorithms for both pediatric and adult patients with encephalitis. These protocols were developed to include the most prevalent pathogens and to optimize empiric therapy of treatment etiologies. Clinicians are encouraged to pursue additional diagnostic testing based on local epidemiology, seasonality, specific exposures, or clinical characteristics.

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115

Infections of Skin, Muscle, and Necrotizing Soft Tissue Infections

Rebecca Maine and Eileen M. Bulger

Infections are a leading cause of admission to intensive care units (ICUs). Skin and soft tissue infections (SSTIs) are both the primary cause of admission to the ICU and a complication that develops for patients with other critical illnesses.[1] A large database review in the United Kingdom found that skin infections comprised less than 1% of all ICU admissions.[2] Prompt recognition, diagnosis, and treatment of SSTIs are lifesaving, especially for patients with necrotizing soft tissue infections (NSTIs).[3,4] Appropriate care for SSTIs in the critically ill often requires intensivists to collaborate with surgeons and/or interventional radiologists to achieve source control for the infection. The most common types of SSTIs routinely treated by intensivists include cellulitis, NSTIs, infected wounds including burn wounds and decubitus ulcers, and, more rarely, myositis. Severe infections of the head and neck are also common in critically ill patients but are discussed in greater depth in Chapter 116. This chapter reviews the epidemiology and diagnostic and management recommendations for these infections commonly encountered in the ICU.

CELLULITIS

Cellulitis, a common bacterial infection, occurs at a rate of more than 4 per 100 people per year in the United States.[3] Many episodes of cellulitis are minor, caused by *Staphylococcus* or *Streptococcus* spp., and arise from breakdown of the skin barrier in the interdigit space or after trauma.[5,6] Cellulitis accounts for up to 10% of hospital admissions,[6] but many fewer ICU admissions.[1] Cellulitis was the primary source of sepsis in <1% of patients in a Dutch study of ICU admissions for sepsis, and only 2.5% of all patients hospitalized for cellulitis typically require ICU admission.[1] Skin was the source of approximately 4% of infections that developed 48 hours after ICU admission; however, 0.07% of the patients who remained in the ICU for more than 48 hours developed a skin infection.[7] Predisposing factors for the development of cellulitis include obesity, diabetes mellitus, alcoholism, immunosuppression, and venous insufficiency.[6] Poor hygiene and fragile skin barrier can increase the risk of introducing bacterial pathogens.[6]

Diagnosis

Cellulitis is primarily a clinical diagnosis. Inflammation of the reticular dermis and hypodermis results in the typical findings: heat, pain, swelling, and redness in the affected region.[6] The lower extremities are most commonly affected: 70%–80% of cases.[6] Additional clinical markers include leukocytosis and elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), though the absence of inflammatory markers does not exclude a diagnosis of cellulitis.[6] Cellulitis can be associated with abscesses.[6] When possible, purulent material should be cultured to guide antibiotic therapy, but initiation of antimicrobials targeted at common gram-positive organisms or broad-spectrum antibiotics if the patient is in a high-risk group (see later) need not be delayed for culture results. Imaging is not necessary for all patients with cellulitis. However, ultrasonography, computed tomography (CT), and/or magnetic resonance imaging (MRI) may identify organized collections that require surgical intervention. In 606 episodes of cellulitis, just under half had imaging (46%), and of those 60 (22%) had purulent collection that was not detected on physical examination.[8] Blood cultures are not recommended for all patients with cellulitis, but are indicated for those with signs of systemic inflammation, sepsis, and for neutropenic and immunocompromised patients.[5]

Microbiology

The most common organisms responsible for cellulitis include *Streptococcus pyogenes* and *Staphylococcus aureus,* which cause approximately three-quarters of the infections in which a causative organism is identified.[8] Different causative organisms can be seen, however, in different patient populations (Table 115.1). Purulent cellulitis is most commonly associated with staphylococcal infections, with high rates of rates of methicillin-resistant *S. aureus* (MRSA), even in community-acquired infections in many areas.[6]

Treatment

The cornerstone to cellulitis treatment includes early and appropriate initiation of antibiotic therapy and identification and surgical drainage of any purulent collections. Although some studies suggest that simple cellulitis is cured in over 90% of patients without MRSA coverage, even in areas with high MRSA prevalence,[5] patients with severe cellulitis with associated signs of systemic infection should have empiric antibiotic coverage for MRSA. This is especially true for patients with evidence of prior MRSA colonization or positive nasal swab, purulent drainage, a history of injection drug use, or recent penetrating trauma.[5] If the patient is in a high-risk group, as outlined in Table 115.1, broad-spectrum antibiotic therapy is appropriate while awaiting culture results.[5] Local community and hospital resistance profiles are also important in guiding initial therapy selection. The addition of empiric gram-negative and/or anaerobic therapy is appropriate in certain patient populations, including patients with severe infections, neutropenia, on chemotherapy, cell-mediated immunodeficiency, immersion injuries and/or animal bites, diabetes, and pelvic lymph node dissections, patients who are immunocompromised, or in children.[5,6]

The duration of antibiotics depends on patient factors and the severity of systemic infection. For the patients treated by intensivists, intravenous antibiotic therapy for at least 5 days is appropriate; however, patients whose symptoms fail to resolve should receive a longer duration, with up to 14 days of treatment reported in several studies.[5,8] Failure of initial antibiotic therapy or relapse of cellulitis occurs in up to 8%–20% of lower extremity infections.[5]

TABLE 115.1 Common Infectious Organisms in Specific Patient Populations

Patient Population	Organism
Diabetics with chronic ulcers[1]	Anaerobes; gram negatives
Post–pelvic lymph node dissection[1]	*Streptococcus agalactiae*
Immunocompromised*[1]	Gram negatives, including *Vibrio vulnificus*[2] in endemic areas, *Streptococcus pneumoniae,* and *Cryptococcus neoformans*
Chronic liver disease[1]	
Nephrotic syndrome[1]	
Rheumatologic disease[1]	
After dog/cat bite[1]	*Capnocytophaga canimorsus, Pasteurella multocida*
After human bite[1]	*Eikenella corrodens*
Tropical region with exposure to shellfish[1]	*Vibrio vulnificus*
Fresh water or contact with leeches[1]	*Aeromonas* spp.
Exposure to raw meat or fish[1]	*Erysipelothrix rhusiopathiae*

Surgical incision and drainage of purulent collections and/or aspiration and placement of drains into large fluid collections is necessary for purulent cellulitis.[5] Although the majority of collections are noted on examination (65%), some deeper collections may require imaging. If a patient does not respond to initial therapy, the intensivist should consider the presence of a deeper abscess and proceed with imaging. Aspiration and/or serial evaluation may be appropriate for abscesses that are small (<1.5 cm) or associated with high morbidity with open surgical drainage. However, in a study of cutaneous abscesses without surrounding cellulitis, aspiration alone only resolved 25% of a patient's symptoms, regardless of size.[5,9]

Outcome

Mortality and outcomes after cellulitis vary greatly and are driven by the severity of infection and the patient's comorbidities. In a large series of patients admitted to Spanish hospitals with cellulitis, 3% of patients died, but only 28% of the deaths were related to cellulitis.[8] A recent meta-analysis of hospitalized patients with cellulitis estimated the overall in-hospital mortality rate to be 1%.[10] In patients with severe cellulitis without a necrotizing component, however, mortality rates approach 20%–40%.[1] Recurrence of infections occurs in up to one in five patients with lower extremity cellulitis.[5]

NECROTIZING SOFT TISSUE INFECTIONS

Though rare, the incidence of NSTIs appears to be increasing.[11,12] Previous estimates in the United States suggested the rate to be 4 per 100,000 persons/year; however, a study published in 2020 reported 8.7–10 per 100,000/year.[3,13,14] This is much higher than the rates reported in France at 3.6 per 100,000/year[15] and in New Zealand at 0.3 per 100,000/person/year.[16] Given the lack of consistent data collection, information regarding trends in national incidence rates is not available in most countries. In some studies, the rates of infection and mortality are higher among certain ethnic groups,[16–18] though this has not been extensively evaluated. Whereas historical mortality was as high as 70% in some series, modern mortality approaches 10%–20%, likely because of an emphasis on early surgical débridement, broad-spectrum antibiotic therapy, and advances in critical care.[17,19–21] Especially for patients with systemic symptoms, a high index of suspicion for NSTI is needed to facilitate early surgical consultation and débridement and potential transfer to a tertiary care facility.

NSTIs are most frequently classified by their causative organisms. Type I are polymicrobial, which included anaerobes in up to one-third of patients.[22] Type II infections are monomicrobial, typically caused by group A streptococcus (GAS) (30%),[22] *Clostridia* spp., or MRSA.[4,19,23–25] Different definitions of type III are in the literature. Most commonly, type III infections refer to gram-negative infections associated with aquatic organisms such as *Aeromonas* or *Vibrio* spp.[13,19,26]; however, some authors use this term to include monomicrobial gram-negative infections[11] and clostridial gas-forming infections.[27] Type IV infections are rare and caused by yeast, typically *Candida* spp.[19,27]

Diagnosis

Early diagnosis of NSTI is essential, as initial débridement is required within hours of seeking care to decrease the risk of mortality.[3,25,27–29] Distinguishing severe cellulitis from NSTI is challenging.[13] Misdiagnoses occur in up to 75% of NSTIs,[30] and in some large series diagnoses were delayed in 100% of patients.[31] Patients presenting early in their disease process may have skin findings that are consistent with simple cellulitis because the cutaneous manifestations of the underlying fascial necrosis have not yet manifested or may be very subtle (Fig. 115.1).[27,32] In patients with chronic wounds, distinguishing the progression of NSTI is even more challenging.[27,33] Although NSTI usually presents in one anatomic location, there have been reports of multifocal NSTI.[34,35]

Given the challenge in diagnosis, several studies have tried to determine which clinical features can distinguish severe cellulitis from NSTI. Crepitus from gas-producing organisms is a concerning finding for NSTI, but it will be present in only 10% of NSTI patients.[22] The most common signs of NSTI in a 2014 systematic review of 1463 patients were swelling (81%) and pain (79%).[30] In other studies, however, swelling was only 70% sensitive and 5% specific to distinguish NSTI from cellulitis.[3] Additional skin findings that should raise concern for NSTI include woody induration of the skin, skin sloughing or blistering, and cutaneous gangrene (Fig. 115.2). Pain out of proportion to examination should also be a very concerning sign for necrotizing infection.[3,31,36] Laboratory values have also been evaluated to distinguish patients with a necrotizing component. An ICU-based sepsis study found no difference in admission CRP, white blood cell (WBC) count, creatinine, or lactate between 23 patients with severe cellulitis and 31 NSTI patients, though the NSTI group had higher rates of organ dysfunction and sepsis.[1] Other groups have found erythrocyte counts, fibrinogen levels, pain on examination, and clinical evidence of renal failure helped to distinguish between cellulitis and NSTI.[31]

Several authors have developed scoring systems to distinguish cellulitis from an NSTI by combining different symptoms, signs, and laboratory values. Wong and colleagues' Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score based on WBC, creatinine, sodium, hemoglobin, glucose and CRP,[37] has been the most studied, with the predictive values of scores of ≥6 (high risk) or ≥8 (very high risk) that range in sensitivity (42%–92%) and specificity (63%–78%).[32,37–41] Given this range of performance, other scores have been developed. Cribb and colleagues developed the SIARI score. This score combines six data derived variables: (1) **s**ite other than lower limb (2) **i**mmunosuppression, (3) **a**ge ≤ 60 years, (4) **r**enal impairment and (5/6) **i**nflammatory markers (i.e. WBC, CRP).[39] In their recent 300-patient cohort, their SIARI score outperformed the LRINEC score in both sensitivity (81% vs. 59%) and specificity (73% vs. 64%).[39] Alayed and colleagues considered several factors, including clinical findings (hemorrhagic bullae, pain out of proportion, necrotic skin, progressive erythema, and fluctuance), markers of

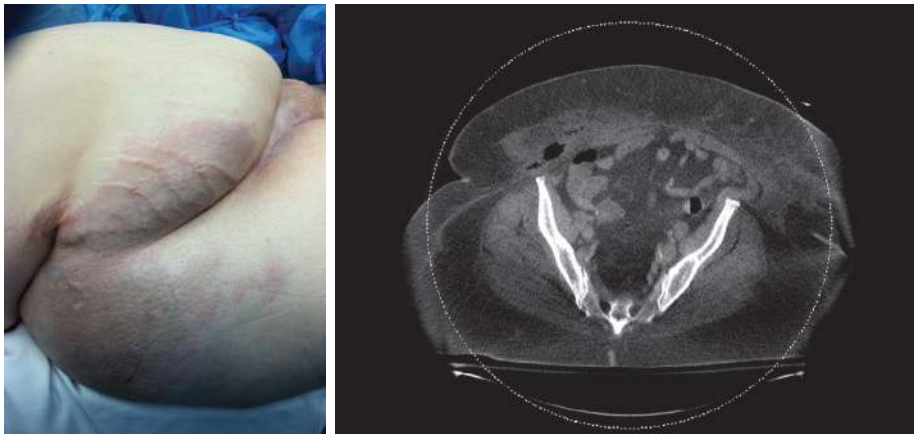

Fig. 115.1 A 45-year-old woman with a history of diabetes presents with diabetic ketoacidosis, pain in the right flank, and mild discoloration of the skin. She developed worsening septic shock over the next 24 hours, and an abdominal computed tomography (CT) scan showed gas in the deep tissues of the abdominal wall. The patient went on to extensive débridement for necrotizing soft tissue infection. This case illustrates the subtle nature of the early skin findings that often result in delays in diagnosis.

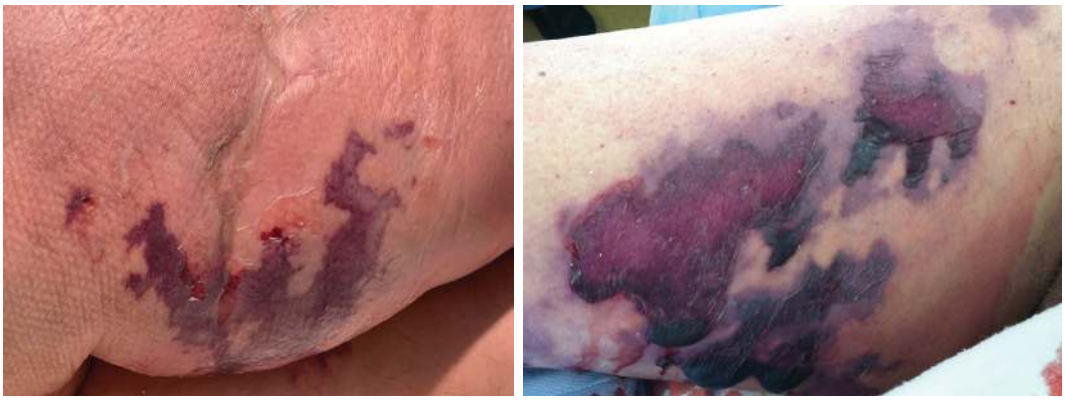

Fig. 115.2 Images from two patients with NSTI showing skin manifestations, including skin sloughing/blistering and cutaneous gangrene.

sepsis (hypotension and altered sensorium), history of surgery in the prior 90 days, and recent diarrhea. They found that patients with at least three of these findings were virtually guaranteed to have an NSTI.[3] Although scoring systems may be helpful to raise the index of suspicion, there should be a low threshold for surgical evaluation of underlying tissue if NSTI is considered possible.

Imaging

The role of imaging (e.g., ultrasound, MRI, CT, and plain x-ray) in diagnosing NSTIs has been evaluated in many studies.[30,42–45] MRI is likely the most precise,[22] and MRI findings combined with LRINEC have improved the ability to predict an NSTI.[41] However, when there is a concern for NSTI, MRI and other imaging modalities should not delay early surgical exploration and débridement, especially for patients with symptoms of sepsis.[3,5,13,46]

Imaging showing gas in the soft tissues (see Fig. 115.1), much like crepitus on examination, conveys a high likelihood of NSTI, but its absence does not rule out NSTI.[3,42] Other CT scan findings associated with NSTI are lack of contrast enhancement of tissue, multiple fluid collections, and subfascial inflammation.[28] Fluid collections deeper than 2–4 mm have had an increased association with NSTI.[43] Other ultrasound findings can include thickening of the fascia and emphysema in the tissues.[43] Imaging may also be considered in truncal NSTI to evaluate for an underlying source of intraabdominal infection presenting as an NSTI.

Operative Exploration

Those evaluating severe SSTIs should maintain a high index of suspicion for NSTI, especially when the severity of illness is not consistent with the physical examination findings, and ensure early surgical consultation. Early surgical consultation facilitates wound exploration to confirm the diagnosis and to debride affected tissue as quickly as possible.[3,4,19,30] At the time of exploration, clinical findings that are associated with an NSTI include thin, foul-smelling dishwasher fluid; fascial sliding; purulence; thrombosed vessels; failure of the muscle to respond to electric stimulation; and necrotic tissue at any layer, including skin, subcutaneous, fascia, or muscle.[13,19,30,47] Tissue cultures and samples of any purulent collections should be sent at the time of initial débridement to guide subsequent narrowing of antimicrobial therapy, but sampling error can lead to false negatives on pathologic evaluation and should not be the only diagnostic consideration.[13]

Bacteriology

Both monomicrobial (type II) and polymicrobial (type I) infections are seen in NSTI. Classically, type II NSTI infections are *Clostridium* and *Streptococcus,* causing gas gangrene and toxic shock syndrome,

respectively.[22] Toxic shock syndrome is reported in up to half of GAS-related NSTIs, but can also be seen in NSTI caused by *S. aureus* infections.[13,19] In certain regions, MRSA and marine organisms, like *Vibrio* spp., *Aeromonas* spp., and *Shewanella* spp., contribute to monomicrobial NSTI as well.[19,30] However, several different organisms have been associated with NSTI, especially in type I infections.[19,30,48] Bacteremia occurs in up to 27% of patients,[48] and in some studies was associated with increased mortality.[23] Failure of cultures to identify an organism is also common in NSTI; in some studies no organisms are identified on cultures in up to one-third of patients.[30,36,49] These negative cultures are likely the result of both initiation of antibiotics before débridement and difficulty in culturing anaerobic organisms.

Treatment

There are two cornerstones to treatment of NSTIs: early, appropriate antibiotic therapy and early complete surgical débridement,[5,13,19,30,48,50] in addition to supportive care for physiologic derangements from shock.[19,29,48] For NSTI, intravenous broad-spectrum antibiotic therapy should be initiated as quickly as possible to cover the range of causative organisms, which includes gram-positive cocci, gram-negative rods, and anaerobes.[19,48] An empiric drug regimen should include penicillin for GAS, clindamycin to cover both GAS and *Clostridium* spp., MRSA coverage, and gram-negative coverage (Table 115.2).[48] In the United States, both clindamycin and penicillin are recommended to address local resistance patterns in GAS and for the beneficial effect of clindamycin on reducing toxin production.[13,31,34] Therapy should be narrowed based on the results of intraoperative cultures once the patient is improving (Table 115.3),[13,31,48] though these may not be positive for up to one-third of patients,[30,48] especially if only culture swab material is processed, rather than tissue samples.[19] Empiric coverage with antifungal agents is not generally indicated, though it should be added if fungal elements are present in tissue or blood cultures.[13] Although erythromycin resistance in GAS has been described for decades, recent clindamycin resistance has emerged as well in up to 35% of isolates in some settings.[25] Clindamycin resistance is also emerging in clostridial species.[25] Studies in mouse models support the use of oxazolidinones (linezolid and tedizolid) as first-line treatment of severe GAS infections in the setting of increased resistance, as they provide similar RNA inhibition to reduce toxin production as clindamycin.[51] The optimal duration of antibiotic therapy has not been defined, and courses of antibiotic therapy in different studies range from 5 to 16 days or more.[19,20,34,48] Antimicrobial therapy should continue until there is no further need for surgical débridement, systemic symptoms have resolved, and infectious markers are improving.[19]

TABLE 115.2 Empiric Antibiotic Regimens for NSTI Before Culture Results

NSTI Type	Antibiotics
Unspecified NSTI	Penicillin, clindamycin*, vancomycin, and levofloxacin
Fournier gangrene or diabetic foot	Piperacillin/tazobactam, clindamycin, and vancomycin
NSTI with penicillin allergy	Aztreonam, clindamycin, ciprofloxacin, and vancomycin
Suspected *Vibrio vulnificus* or *Aeromonas* spp.	Add doxycycline

GAS, Group A streptococcus; *NSTI*, necrotizing soft tissue infection.
*If high rates of clindamycin resistance are observed with GAS, consider linezolid.

TABLE 115.3 Antibiotic Regimen for NSTI Based on Culture Results

Streptococcus pyogenes	Penicillin and clindamycin*
Clostridial species	Penicillin and clindamycin
Vibrio vulnificus	Doxycycline and ceftazidime
Aeromonas hydrophila	Doxycycline and ciprofloxacin
Methicillin-resistant *Staphylococcus aureus*	Vancomycin
Polymicrobial	Vancomycin and piperacillin/tazobactam

NSTI, Necrotizing soft tissue infection.
*If high rates of clindamycin resistance are observed with GAS, consider linezolid.

Operative Débridement and the Skin-Sparing Approach

Early débridement has been recognized as a key factor in the treatment of NSTI and has been associated with decreased rates of mortality from NSTI in modern times.[4,15,20,48] Initial débridement of all necrotic tissue should occur as soon as possible; guidelines recommend within 6–12 hours of presentation.[4,52] Although débridement as quickly as possible is essential, studies conflict about whether or not débridement must occur before transfer from the presenting facility.[53] Study results vary regarding whether débridement before transfer improves survival[15,36] and likely depends on the rapidity of transfer and available resources within the transferring and receiving hospitals. Physicians referring patients to tertiary centers should communicate directly with the receiving surgeon and intensivist to determine the optimal location of débridement, with pretransfer débridement strongly recommended for patients with severe sepsis and/or prolonged transport time.

The initial approach to débridement, wherever it occurs, must remove all infected and necrotic tissue, and the traditional wide débridement included the skin overlying deeper infected tissue, even if the skin was not necrotic.[52,54] This can result in large soft tissue defects. However, for many patients with NSTI, the skin is not as extensively involved as the deeper tissues and does not need to be completely resected to clear infected tissues.[52,54] Recent studies have described success treating patients with skin-sparing approaches that employ perforator-sparing incisions and the elevation of skin flaps, with complete débridement of underlying infected tissues.[54–57] This approach was found to decrease the need for wound grafting without increasing mortality at one high-volume center.[57] Although healthy flaps should be preserved if possible, all necrotic skin should be debrided, and surgeons should also not hesitate to perform amputations as necessary to achieve source control in patients with severe physiologic derangements and/or rapidly progressive extremity infections. Amputation rates range from 10% to 30%.[15,17,20,35,58,59]

Postoperative Care

The complex care needs of patients with NSTIs often involves postoperative critical care, extensive wound care, multiple reoperations, reconstruction, and rehabilitation. Thus transfer to tertiary facilities is frequently appropriate and comprises up to 81% of NSTI patients in some centers.[20,36,60] Treatment at a high-volume center, especially those with capacity for rapid surgical débridement and ongoing complex wound care, has been associated with improved survival in some studies.[15] Given a high frequency of systemic symptoms (76%),[31] sepsis (21.1%–69%),[30,31] and septic shock (32.9%)[49] in patients with NSTI, intensive care is frequently needed.[29,47,49] The percentage of patients who require intensive care varies globally, with rates at some centers as low as 43% and others as high as 98%.[3,12,15,17,49,59,61] Endothelial damage, intravascular hemolysis, and cardiomyopathy can develop as a result of both toxins from infectious bacterial like *Streptococcus* and *Clostridium* and the host inflammatory response to infection.[25]

Comorbidities are common in NSTI patients and occur in up to 92% of patients.[20] Type 1 and 2 diabetes is common in NSTI, with prevalence in studies ranging from 24% to 55%.[12,15,20,22,29,30,32,35,48–50,59,62–65] Alcohol and drug abuse, tobacco use, obesity, cardiovascular disease, liver disease, and respiratory diseases are also common.[12,17,20,22,48–50,65] Intensivists must be aware of the high rates of comorbidities and their increased risk for mortality to adjust management and counsel patients and families.

Most NSTI patients will require wound care, often for extensive soft tissue defects, in addition to critical care, both areas of expertise for burn centers. Regionalization of care, especially for large-area débridement, to burn centers has been associated with successful reconstructions and rehabilitation and reduced costs.[66] An analysis of administrative data regarding NSTI treatment at burn versus nonburn centers demonstrated a higher rate of mortality at burn centers, but likely because sicker patients are transferred to these centers for care.[67] More work is needed to define the optimal definitive treatment location for NSTI patients.

Initial postoperative dressings should facilitate frequent bedside wound assessments to determine if early re-débridement is needed. Gauze soaked in either saline or quarter-strength Dakin's solution is preferred to early wound vac therapy, which can hinder frequent wound assessments and may increase the risk of undetected progression of necrosis. At a minimum, early planned re-exploration after initial débridement within 12–24 hours is recommended.[58] Once no significant débridement is required at serial exploration, wound vac therapy can be initiated to decrease the frequency of dressing changes, and therefore reduced pain for patients, while helping prepare the wound bed for closure by stimulating granulation tissue.

Adjuvant Therapies

Several adjuvant therapies have been evaluated especially for patients with severe systemic illness or a failure to respond to initial therapy. These include hyperbaric oxygen therapy, intravenous immunoglobin G (IVIg), and a novel peptide that mediates CD28 receptor activation by superantigens (Reltecimod, aka AB103).[13,47,64] Few randomized controlled trials have evaluated these therapies, limited in part by the rarity of NSTI.[34]

Hyperbaric oxygen therapy is proposed to be beneficial by increasing tissue oxygen levels to kill anaerobic organisms, which are responsible for 7%–18% of NSTIs.[34] A recent discharge database study found hyperbaric oxygen was used in less than 1% of patients with NSTI.[68] Although in some small case series and retrospective analyses hyperbaric oxygen therapy was associated with decreased mortality,[61,68,69] others have found no difference in mortality.[70,71] Currently, no randomized controlled trials have evaluated the impact of hyperbaric oxygen therapy on NSTI outcomes, and hyperbaric oxygen therapy is not recommended as an essential intervention in current guidelines.[52]

Pooled IVIg infusions have been suggested for patients with severe systemic symptoms or persistent inflammatory response, as they could potentially bind toxins associated with severe GAS and *Staphylococcus* infections.[19,72–74] Although observational trials suggested benefit, randomized controlled trials and propensity-adjusted analysis did not confirm a mortality benefit.[34,72–74] However, for patients with toxic shock syndrome, IVIg infusions for 3 days did shorten the duration of organ failure.[74] Consideration of IVIg for patients with GAS infections causing NSTI is included in recent guidelines, which note that there is no clear mortality benefit.[52]

In 2014 investigators published the results of a phase IIa safety trial of a novel peptide (AB103) that targets the superantigen binding site, CD28, on T cells. They found the drug decreased Modified Sequential Organ Failure Assessment (mSOFA) scores at 2 weeks compared with placebo and was associated with lower levels of most tested cytokines.[64] In the recently completed phase III multicenter randomized controlled trial, the composite outcome (alive at 28 days, no amputation after first operation, <3 débridements by day 14, mSOFA ≤1 at day 14, mSOFA with reduction of ≥3 points) was achieved by 54.3% of patients who received the medication compared with 40.3% of patients in the placebo in the per protocol analysis, and patients receiving reltecimod had significant reductions in prolonged organ dysfunction and a more favorable discharge disposition.[75] This experimental drug is currently under review by the US Food and Drug Administration.

Outcomes

Although historical mortality in a series of patients with NSTI was as high as 70%,[65] in most recent series, the mortality rate for hospitalized patients with NSTI is 10%–20%,[20,23,48,67] though in critically ill patients mortality may be as high as 50%.[15]

Several authors have evaluated predictors of mortality in NSTI patients.[15,48,50,58,62,65,76,77] Although a primary driver of mortality appears to be related to underlying physiology, patient factors, management factors, and infection characteristics have been studied. Several measures of physiologic derangement have been associated with mortality after NSTI, including APACHE scores, SOFA scores, sepsis or septic shock, or need for ICU admission.[15,47,49,61,62,78] Patient factors associated with mortality include older age[15,50,58,65,76,77]; increasing number of comorbidities,[65] including poor renal function or underlying renal disease,[47,58,76,77] liver disease, cardiovascular diseases like heart failure or peripheral vascular disease,[78] cancer or other immunosuppression; and intravenous drug use[21,30,35,58–60] A mortality calculator recently developed using an NSTI cohort in the National Surgical Quality Improvement Program (NSQIP) includes age, prehospital functional status, need for dialysis, high American Society of Anesthesiologists (ASA) class, thrombocytopenia, emergency operation, and septic shock, with an area under the curve (AUC) of 0.83.[21] Infection characteristics associated with NSTI mortality include bacteremia,[48] gram-negative infections including *Vibrio* spp.,[26,49] elevated lactate levels,[48,59] and clostridial infection.[77] Delays in débridement have also been associated with increased mortality. Patients treated for NSTI remain at increased risk of mortality from all causes, including infectious causes, for several years after their NSTI treatment.[65]

Morbidity after NSTI can be quite high.[15] Initial mSOFA scores ≥2 were associated with several worse clinical outcomes in one prospective, multicenter trial, including fewer ventilator-free and ICU-free days and more débridements.[47] Given the need for significant soft tissue débridement, including amputation, these factors can have a significant impact on daily function, including sexual function.[15,78–80] Quality-of-life measures are often decreased after NSTI as well.[78,80–82] When compared with a reference population, German patients after NSTI had significantly decreased physical function and health and high rates of sexual dysfunction (65%), and many required ongoing pain treatment and assistive devices.[80] Studies of long-term outcomes after NSTI are limited, and more work is needed to develop strategies to improve recovery.

PYOMYOSITIS

Pyomyositis can present as a severe progression of cellulitis or as a component of NSTI; however, some patients present with severe chronic infections associated with the muscle without evidence of necrosis and rapid progression.[83,84] Infectious myositis caused by infection with fungus, bacteria, or parasites can be acute, subacute, or chronic.[84] It is a disease more frequently described in the tropics and in children.[84] It can have a multifocal appearance, especially when caused by bacteria.[84] By definition, in pyomyositis, the muscle infection arises from hematogenous spread of the organism. Myositis is rare because

muscles are resistant to infection, with <0.5% of cases of bacteremia developing myositis. Risk factors include trauma, ischemia, or other immunosuppressive condition that increase host susceptibility.[84] Intramuscular hematomas and tissue damage from trauma can create a substrate for the development of bacterial myositis.[84] It is postulated that to develop myositis, muscle injury, whether from trauma or overuse, must be paired with an integumentary break to allow transient bacteremia.[84]

Diagnosis

Infectious myositis typically presents with a leukocytosis and left shift and without an elevation in creatine kinase, except for the approximately one-fifth of patients with pyomyositis who are immunosuppressed from human immunodeficiency virus (HIV).[84] The most common location is in the large muscles of the lower extremities; however, in 10%–20% of cases there is diffuse rather than isolated muscle involvement.[84] Blood cultures are positive in only 5%–35% of patients.[84]

Imaging plays an important role in pyomyositis. Although plain x-rays may suggest muscle edema, CT, ultrasound, and MRI are more sensitive, with MRI being the most precise and thus recommended modality for diagnosis.[5,84] The Infectious Diseases Society of America (IDSA) recommends MRI to establish the diagnosis of pyomyositis.[5] If the muscle infection is diagnosed before developing a purulent collection, antibiotic therapy alone will suffice. Once a collection has developed, open or closed surgical drainage is needed in addition to antimicrobial therapy.[5] Blood and tissue cultures to identify causative organisms should be sent in patients with pyomyositis to narrow antibiotic therapy.[5,84]

Bacteriology

The primary mechanism underlying pyomyositis is the hematogenous spread of bacteria, often from transient bacteremia, to an area at risk in a muscle.[83] Hematogenous spread usually arises from staphylococcal infections, whereas pyomyositis after puncture wounds is typically polymicrobial in nature.[83,84] Typical bacteria in myositis include *S. aureus, Streptococcus* (A, B, C, and G), Enterobacteriaceae, *Yersinia enterocolitica, Pseudomonas, Aeromonas, Clostridium, Peptostreptococcus,* and *Bacteroides* spp.[85] In tropical areas, *S. aureus* causes approximately 95% of pyomyositis infections, whereas it causes about 70% of cases of myositis in high-income countries.[83,84] Immunosuppressed patients are at increased risk of infection with gram-negative organisms and/or polymicrobial infections. In some regions, amoebic infections, with associated eosinophilia, are also common.[83]

Treatment

Intravenous antibiotics are used initially, often for the first week, with a course of 2–6 additional weeks of oral antibiotics after adequate drainage and fever resolution.[5,83,84] Antimicrobial therapy should be accompanied by early surgical evacuation of purulent material.[5] Vancomycin is recommended for empiric coverage, with the addition of gram-negative coverage for patients who are immunocompromised or have had recent trauma that resulted in the pyomyositis.[5] When methicillin-sensitive *S. aureus* (MSSA) infection is confirmed from cultures, cefazolin or anti-staphylococcus penicillins (i.e., oxacillin or nafcillin) are the most appropriate antibiotic choice.[5] For patients with associated muscle necrosis, the addition of clindamycin is appropriate (see earlier for a discussion of NSTIs).

The identification of fluid collections on imaging should prompt surgical consultation to determine whether open or closed drainage of the fluid collections is most appropriate. Loculated fluid collections and deep multifocal collections can pose particular challenges.[84] When there is minimal systemic illness, a conservative and serial approach to drainage may be appropriate.

BURN WOUNDS

Epidemiology and Diagnosis

Given the severity of illness and inflammatory response that can accompany a large body surface area burn, the management of burn patients is frequently led by intensivists. With large areas of disrupted skin and local ischemia, burn patients are at high risk for infections and colonization of their wounds.[86] Distinguishing between active infection and colonization and determining when additional antibiotic therapy may be appropriate is a challenge for the burn physician. Infection and sepsis are the leading causes of mortality (~55%) for patients with burn injuries, with sepsis affecting 3%–30% of patients with a burn that affects ≥20% of their total body surface area (TBSA).[86] In a comparison of guidelines to diagnose sepsis in the background of an inflammatory response, the Sepsis-3 criteria outperformed burn-specific guidelines from the American Burn Association and markers proposed by Mann-Salinas in 2013.[86]

Burn wounds and eschar are frequently colonized with bacteria, making the discrimination between colonization and infection challenging. Wound biopsies, especially in the setting of wound purulence and loss of graft material, with bacterial counts 10^5 are consistent with burn wound infections, and systemic antimicrobial therapy is appropriate.[87] Systemic therapy must be accompanied by aggressive débridement and excision.[87]

Bacteria

Gram-positive bacteria colonize burn wounds early after injury, with gram-negative organisms becoming more common over time.[86]

Treatment

Although wound cultures should be used to guide the ultimate antibiotic selection, coverage of *Streptococcus* and *Staphylococcus* for early infections after burns, with the addition of third-generation cephalosporins for gram-negative coverage, including coverage of resistant *Staphylococcus* and *Pseudomonas,* should start 5 days after injury.[86] Although many topical agents used for initial burn wound care have antimicrobial properties, including silver sulfadine and silver nitrate dressings, there is no role for systemic antibiotics in burn care in the absence of a wound infection.[86] Controversy exists over the role of selective gut decontamination for thermally injured patients.[86] Whereas some studies reported decreased mortality in patients with >20% TBSA, others have shown no benefit in decreasing inflammatory response.[86]

PRESSURE ULCERS

Pressure ulcers are a frequent complication of ICU care, especially for elderly, malnourished patients whose mobility is restricted in the setting of chronic and/or critical illness. Hospital prevalence rates range from 3% to 11%.[88] Although infections and the presence of necrotic tissue in these wounds are not uncommon, severe infections are rare.[89] A large prospective observational study identified only 1.7 episodes of pressure ulcer–associated bacteremia per 10,000 hospital discharges.[88]

As in burn wounds, the diagnosis of serious infection such as sepsis or NSTI is challenging.[89] Studies that have evaluated different signs and symptoms have not identified characteristics with high sensitivity and/or specificity for infections in pressure ulcers. Pain and tenderness in the wound increases the likelihood of active infection.[33] Many

patients who develop NSTI in their pressure ulcers do not have an elevated LRINEC score.[89]

Bacteria

The most common pathogens associated with pressure ulcer infections include mixed gram-positive and gram-negative bacteria.[88,89] Both aerobic and anaerobic species are common. *S. aureus, Enterococcus faecalis, Corynebacterium,* group B streptococcus, *Bacteroides,* and *Peptostreptococcus* were the most commonly recovered organisms from deep tissue cultures in one series.[89] In a series of patients who developed bacteremia associated with pressure ulcers, *S. aureus, Proteus* spp., *Bacteroides, and Escherichia coli* were the most common organisms present in both the blood and wound cultures, with *Pseudomonas* spp. and *Enterococcus* also frequently cultured from wounds.[88] For patients who develop pressure ulcer–associated bacteremia, one-quarter of all blood cultures are positive for multiple organisms,[88] whereas wound cultures are polymicrobial in 73.2% of patients. *S. aureus* grows from 35.7% of wound cultures (30.4% of blood cultures that were positive), and *Proteus* is isolated from 46.4% of wounds.[88]

Treatment

As with other soft tissue infections described, effective therapy combines appropriate antimicrobials with surgical débridement to achieve source control. Broad-spectrum polymicrobial coverage should be initiated, with therapy directed toward organisms isolated on wound cultures, if infection is suspected. Given the depth of many pressure ulcers, treatment for osteomyelitis with longer antibiotic courses may be warranted.[88] In the setting of deep wounds, progressive infections that track along deeper tissue planes that are not visible on the wound surface should be suspected and either visually assessed in operative exploration or at least imaged to look for concerning signs of deep infection.[89] Overall, the diagnosis of severe infection related to pressures ulcers is challenging, but prompt recognition is key to appropriate treatment, especially given that the patients who typically get pressure ulcers have poor physiologic reserve and malnutrition.

CONCLUSION

SSTIs are frequently encountered by the intensivist, but the diagnosis is not always straightforward. Early surgical consultation to facilitate débridement and drainage for source control is essential for many severe SSTIs. Broad-spectrum antibiotics should be initiated and subsequently tailored to cultured organisms. Prompt initiation of treatment can help reduce mortality and improve functional outcomes.

KEY POINTS

- The diagnosis of NSTI is challenging. Any patient for whom the clinician has a high index of suspicion from a combination of physiology, laboratory investigations, and clinical examination should have rapid surgical consultation and operative exploration.
- Severe SSTIs can be complicated by organ dysfunction, requiring rapid resuscitation and initiation of appropriate antibiotics. The intensivist must be aware that growing resistance in common organisms causes SSTI and prescribe initial broad-spectrum antibiotics accordingly,
- The physiologic response to burn injury can mimic signs of sepsis, and burn wounds are frequently colonized with bacteria. Sepsis-3 criteria are the most sensitive to identifying sepsis in burn patients. There is no role for prophylactic systemic antibiotics—only topical—in the burned patient.

References for this chapter can be found at expertconsult.com.

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Head and Neck Infections

Jeremy D. Gradon

Infections of the head and neck range in severity from minor to life threatening. A scoring system reflecting the need for hospitalization of such patients has been proposed.[1] The intensivist is called upon to manage such patients either when they are critically ill or when airway compromise has occurred or is imminent. Besides airway management and control of sepsis, the intensivist must also be aware of the local anatomy and relevant microbiology. This knowledge will help guide the choice of antimicrobial agents and allow the clinician to anticipate the potential for spread of infection to related anatomic spaces and subsequent complications.

NORMAL HEAD AND NECK FLORA

Huge numbers of bacteria reside in the oral cavity in health, with the bacterial load exceeding 10^{11}/mL in the gingival crevices of patients with teeth.[2] The main bacterial species are anaerobes, including *Bacteroides, Fusobacterium, Prevotella,* and *Peptostreptococcus*. Other common oral inhabitants include *Streptococcus mutans, Staphylococcus aureus, Actinomyces* spp., and *Eikenella corrodens*. Pharyngeal colonization and subsequent infection with organisms such as *Streptococcus pneumoniae, Neisseria meningitidis,* and *Streptococcus pyogenes* may also occur.

In acute illness, an additional modifying factor is the decreased production of oral mucosal fibronectin. This is of relevance to the clinician because fibronectin in normal physiologic amounts will preferentially bind gram-positive bacteria (such as *S. mutans*); however, when the production of fibronectin is decreased, there is rapid colonization of the oral cavity with gram-negative organisms, including species such as *Pseudomonas aeruginosa*.[2] These gram-negative organisms may then participate in head and neck infections of oral or odontogenic origin, necessitating broad nosocomial-type, gram-negative antibiotic coverage when the patient has been recently hospitalized or acquired the infection in the intensive care unit (ICU).

SITES OF DEEP HEAD AND NECK INFECTION

Knowledge of the local anatomy is critical to the understanding and management of these infections. This has recently been reviewed.[3] Serious infection of the head and neck can involve the following general anatomic areas:

- Sinus
- Pharynx
- Epiglottis
- Retropharyngeal space
- Submandibular space (Ludwig angina)
- Lateral pharyngeal space (anterior and posterior)
- Internal jugular vein (Lemierre syndrome)

Some of these anatomic areas are connected via actual (e.g., retropharyngeal) or potential (e.g., danger) spaces. Thus infection beginning in one space may spread rapidly to involve others, with potential resultant damage or destruction of vital structures. Such connections are discussed in the following sections, and differentiating features are highlighted in Table 116.1.

Predisposing factors for the development of deep neck infection include uncontrolled dental infection, spread of infection from other local structures (tonsils, vertebrae), local intravenous (IV) catheter placement or injection drug use, diabetes, human immunodeficiency virus (HIV) infection, and local trauma (e.g., the use of laryngeal mask anesthesia).[4,5] The use of cetuximab in combination with either radiation or chemotherapy for locally advanced head and neck cancer is associated with increased risk of local infection, as is the use of rituximab.[6] A poor level of education and living far from a tertiary care center have also been shown to increase the risk of development of severe deep neck space infection.[7]

CLINICAL SYNDROMES

Sinusitis

Acute bacterial sinusitis accounts for a high proportion of physician visits in the primary care setting.[8] In the ICU, patients who are critically ill with nasogastric, endotracheal, or nasotracheal tubes in place, may develop acute sinusitis caused by resistant nosocomial organisms (e.g., methicillin-resistant *S. aureus* [MRSA], *P. aeruginosa*) and anaerobes.[9] Treatment involves the use of broad-spectrum antimicrobial agents (Table 116.2) and close collaboration with an otolaryngologist to determine if drainage is needed. In addition, application of topical vasoconstrictors and inhaled topical steroids to the nasal mucosa is often recommended to help the sinus secretions drain.

Complications of nosocomial sinusitis are related to the local anatomy. Spread via the diploic veins can result in meningitis, brain abscess, contiguous osteomyelitis, or cavernous sinus thrombosis. Spread from the ethmoid sinuses can result in frontal lobe brain abscesses, whereas sphenoid sinus infection can spread to involve the surrounding pituitary gland, optic chiasm, internal carotid artery, cavernous sinus, or temporal lobe of the brain.[3]

In patients with diabetic ketoacidosis, high-dose steroid treatment, severe neutropenia, or history of desferrioxamine treatment, rhinocerebral mucormycosis (most commonly *Rhizopus* spp.) or aspergillosis can develop. This infection can be rapidly fatal if the underlying problem cannot be corrected. The general teaching has been that high-dose antifungal therapy (see Table 116.2) plus extensive surgery are always required for any hope of survival. However, the need for major surgery in all cases has come into question recently.[10] Close collaboration with appropriate surgeons and infectious disease colleagues is required in such cases.

TABLE 116.1 Differentiating Features of Deep Neck Infections

Space	Clinical Features*
Submandibular space (Ludwig angina)	Woody submental induration, protruding swollen/necrotic tongue, no trismus, rotted lower molars commonly present
Lateral pharyngeal space (anterior)	Fever, toxicity, trismus, neck swelling
Lateral pharyngeal space (posterior)	No trismus, no swelling (unless ipsilateral parotid is involved), cranial nerve IX–XII palsies, Horner syndrome, carotid artery erosion
Retropharyngeal space (retropharynx)	Neck stiffness, decreased neck range of motion, soft tissue bulging of posterior pharyngeal wall, sore throat, dysphagia, dyspnea
Retropharyngeal space ("danger space")	Mediastinal or pleural involvement
Retropharyngeal space (prevertebral)	Neck stiffness, decreased neck range of motion, cervical instability, possible spread along length of vertebral column
Jugular vein septic thrombophlebitis (Lemierre syndrome)	Sore throat, swollen tender neck, dyspnea, chest pain, septic arthritis

*Fever and signs of systemic toxicity are common to all.

Pharyngeal Infections

Life-threatening pharyngeal infections include acute anaerobic pharyngitis (Vincent angina) caused by a combination of oral anaerobes and spirochetes. The clinical manifestations of this entity in the critically ill host include acute ulcerations and necrosis of the oral mucosa and gums. Secondary bacteremia with sepsis can complicate matters. Treatment involves adequate oral debridement and administration of antibiotics with both aerobic and anaerobic activity (see Table 116.2).

Quinsy (peritonsillar abscess) can complicate previous tonsillitis and is most common among young adults. In a recent case series from India, quinsy accounted for 12% of deep head and neck infections.[11] Presenting symptoms include fever, pharyngeal pain, and unilateral pharyngeal swelling. If not adequately drained, the infection can spread into the lateral pharyngeal space, which was the most common cause of quinsy-related mortality in preantibiotic days. Infection with anaerobes can result in a higher rate of recurrence of quinsy.[8] *Fusobacterium necrophorum* is currently the most commonly encountered organism in peritonsillar abscesses in Denmark.[12]

Recurrent bouts of tonsillitis (five or more) in patients aged under 30 years have been noted to be a risk factor for the development of peritonsillar abscess.[13]

Diphtheria is now rare thanks to mass vaccination. It presents as a sharply demarcated, adherent, dark gray nasal or pharyngeal membrane. Clinical illness is caused by the release of a bacterial toxin that inhibits translocase (via inhibition of elongation factor 2). Myocardial dysfunction and central nervous system toxin-mediated injury may occur late, but fulminant infections can be complicated by death from acute respiratory obstruction or circulatory failure (bull-neck diphtheria). Culture of the organism *(Corynebacterium diphtheriae)* requires the use of a specific Loeffler medium.

Epiglottitis

Acute epiglottitis is primarily a disease of children who have not received the *Haemophilus influenzae* type b (Hib) vaccine and is thus rare at present.[14] Acute epiglottitis presents as an acute febrile illness usually of less than 12 hours' duration, with the child characteristically sitting forward, drooling saliva, and taking shallow and apprehensive breaths (deeper breathing draws the epiglottis over the airway and produces obstruction). The diagnosis is made clinically, although lateral neck radiography (if the child is stable enough to go for x-ray) characteristically shows enlargement of the epiglottis 30%–57% of the time. Attempts to visualize the classically described edematous cherry-red epiglottis directly may precipitate acute airway obstruction and should not be attempted unless the ability to secure an airway immediately is certain. Blood and epiglottis

TABLE 116.2 Therapeutic Options for Sinusitis, Pharyngitis, and Epiglottitis

Syndrome	Likely Flora	Antibiotic Options*
Sinusitis (community acquired)	*Haemophilus influenzae, Streptococcus pneumoniae, Staphylococcus aureus*	Ampicillin-sulbactam (3 g IV q6h) Ceftriaxone (1–2 g IV q24h)
		Levofloxacin (500 mg IV q24h) *plus* clindamycin (300–900 mg IV q8h) *or* moxifloxacin (400 mg IV q24h)
Sinusitis (ICU acquired)	*Pseudomonas aeruginosa, Escherichia coli* and related coliforms, methicillin-resistant *S. aureus* (MRSA)	Ceftazidime (2 g IV q8h) *or* piperacillin-tazobactam (3.375 g IV q4h) *plus* an aminoglycoside, *plus* vancomycin (1 g IV q12h)
Sinusitis (fungal)	*Aspergillus* spp. *Mucorales* spp.	Amphotericin B (1–1.5 mg/kg/day IV)
		Liposomal amphotericin B (5–10 mg/kg/day IV)
		Voriconazole (6 mg/kg q12h × 2 doses, then 4 mg/kg q12h)
		Itraconazole (200 mg IV q12h × 4 doses, then 200 mg/day IV)
Pharyngitis	*Corynebacterium diphtheriae*	IV penicillin or erythromycin *plus* diphtheria antitoxin
	Epstein-Barr virus (with airway compromise)	No antiviral therapy effective IV steroids
Epiglottitis	*H. influenzae* type b	Ceftriaxone (1–2 g IV q24h)
	Streptococcus pyogenes (group A strep)	Ampicillin-sulbactam (3 g IV q6h)
		Rifampin prophylaxis (600 mg orally q24h) for close contacts for 4 days

*Antibiotic choices listed are examples, because for most infections, multiple different antibiotics are effective; individual choice will be influenced by patient factors (e.g., allergies), local hospital bacterial resistance rates, and microbiologic culture results.

cultures usually grow *H. influenzae* type b. However, since the introduction of mass vaccination against *H. influenzae* type b, the incidence of infection with non–type b strains is increasing.[14]

Antibiotic options for epiglottitis are outlined in Table 116.2. There is no clear consensus on the role of exogenous corticosteroids to decrease epiglottic edema. Rifampin prophylaxis should be administered for 4 days to close household and hospital contacts of patients (especially those younger than 4 years) with invasive *H. influenzae* type b disease.

Retropharyngeal Infections

The area situated between the pharynx anteriorly and the vertebrae posteriorly constitutes the retropharyngeal space, which begins behind the pharynx and ends at the junction of the cervical and T1–T2 thoracic vertebrae (see Table 116.1). The space is subdivided into several distinct anatomic spaces (retropharyngeal, prevertebral, "danger space"), some of which may provide the means of spread of infection from the initial retropharyngeal area to distant sites.[15]

Located between the prevertebral space posteriorly and the retropharyngeal space anteriorly is a potential space called the "danger space," which connects the base of the skull with the posterior mediastinum and diaphragm. Infection may spread unimpeded within this space. In addition, infection occurring between the vertebrae and the prevertebral fascia may spread along the length of the vertebral column.

Infections of the retropharynx occur as:

- Primary infections
- Secondary to extension posteriorly from the pharynx or anteriorly from infected cervical vertebrae
- Via hematogenous spread

Clinically, retropharyngeal infections present with acute fever, systemic toxicity, sore throat, neck stiffness, dysphagia, and dyspnea. Airway obstruction may occur as a consequence of anterior bulging of the pharyngeal wall with supraglottic compression.

Prevertebral infections usually involve the cervical vertebrae and present with neck pain and stiffness and prevertebral soft tissue swelling. Rarely, instability or destruction of the cervical vertebrae may develop, with death the result of acute spinal cord compression.

Danger-space infection is suspected when pleural or mediastinal infection or pain complicates a retropharyngeal infection.[15] Mediastinitis secondary to danger-space infection is generally fulminant, with pleural extension and a high mortality rate. Rarely, mediastinal infections, such as may occur after coronary artery bypass graft surgery, may spread upward through the danger space and present in the retropharynx.

The bacteriology of retropharyngeal infections is that of mixed aerobic/anaerobic oral bacteria. In the critically ill host with nosocomial infection, colonization of the oropharynx with resistant pathogens will necessitate modification of antimicrobial coverage. The imaging techniques needed include plain lateral neck x-rays that will show loss of normal cervical lordosis in addition to thickening of the retrotracheal area (usually <22 mm) or of the prevertebral fascia (usually <7 mm). Bedside ultrasonography may provide information regarding the presence or absence of drainable collections, but if the patient is stable enough to go to the radiology suite, computed tomography (CT) or magnetic resonance imaging (MRI) scans provide the best definition studies.[16] The presence of a hypodense mass with rim irregularity on a contrast-enhanced CT scan is highly suggestive. Close collaboration with appropriate surgical colleagues is necessary for successful management.[15] Therapy is outlined in Table 116.3. On occasion, nonbacterial processes such as Kawasaki disease can mimic retropharyngeal abscesses.

It should be noted that involvement of multiple deep neck spaces can occur simultaneously.[17]

Submandibular Space Infection (Ludwig Angina)

The submandibular space is contained between the mucous membranes of the floor of the mouth superiorly and the muscle and fascia attachments of the hyoid bone inferiorly. The most common route of infection into this space is via infected lower molar teeth, and infection is more common in persons with underlying diabetes, neutropenia, or systemic lupus erythematosus. In a recent case series, 37% of deep infections were caused by submandibular space infection.[11]

Clinical presentation of submandibular space infection is that of an acutely ill patient with mouth pain, dysphagia, drooling of saliva, stiff

TABLE 116.3 Therapeutic Options for Deep Neck Infections

Syndrome	Likely Flora	Therapeutic Options*
Submandibular space infection (community acquired)	Anaerobes, streptococci, *Staphylococcus aureus*	Ampicillin-sulbactam (3 g IV q6h)
		Ceftriaxone (1–2 g IV q24h) *plus* clindamycin (300–900 mg IV q8h) *or* metronidazole (500 mg IV q8h)
		Ertapenem (1 g IV q day)
Submandibular space infection (hospital/ICU acquired)	*Pseudomonas aeruginosa,* methicillin-resistant *S. aureus* (MRSA), anaerobes	Imipenem (500 mg IV q6h) *or* piperacillin-tazobactam (3.375–4.5 g IV q6–8h by continuous infusion) *plus* vancomycin (1 g IV q12h)[18]
Retropharyngeal space infection	Anaerobes, streptococci, *S. aureus*	Ampicillin-sulbactam (3 g IV q6h)
		Ceftriaxone (1–2 g IV q24h) *plus* clindamycin (300–900 mg IV q8h) *or* metronidazole (500 mg IV q8h)
		Ertapenem (1 g IV q day)
Lateral pharyngeal space infection	Anaerobes, streptococci, *S. aureus*	Ampicillin-sulbactam (3 g IV q6h)
		Ceftriaxone (1–2 g IV q24h) *plus* clindamycin (300–900 mg IV q8h) *or* metronidazole (500 mg IV q8h)
		Ertapenem (1 g IV q day)
Internal jugular vein septic thrombophlebitis	*Fusobacterium necrophorum*	Metronidazole (500 mg IV q8h)
		Clindamycin (300–900 mg IV q8h)
		Ampicillin-sulbactam (3 g IV q6h)

*Antibiotic choices listed are examples, because for most infections, multiple different antibiotics are effective; individual choice will be influenced by patient factors (e.g., allergies, concurrent medications), local hospital bacterial resistance rates, and microbiologic culture results.

neck, and fever. The submandibular tissues are "woody," not fluctuant, and true drainable collections are uncommon. The tongue may be swollen and displaced upward against the palate and also protrude out of the mouth. Trismus is not present; however, if the infection spreads to the lateral pharyngeal space, trismus may occur. Unrecognized lateral pharyngeal space involvement may be complicated by subsequent spread to the retropharyngeal space. Late complications of Ludwig angina include death from airway obstruction, aspiration pneumonia, carotid artery erosion, and tongue necrosis.[18]

Lateral neck x-rays will demonstrate edema of the submandibular soft tissues. Pockets of gas may be seen if gas-forming organisms are involved. CT scanning is most helpful diagnostically. However, attention must be paid to having qualified staff accompany the patient to the CT scanner in case acute airway obstruction develops. Should airway protection be needed, tracheotomy or cricothyroidotomy is advocated because of the risk of inducing acute airway obstruction with routine "blind" nasal or oral intubation. The infection is commonly polymicrobial, and appropriate antibiotic therapy options are described in Table 116.3. In approximately 50% of cases, surgical drainage is required. In addition, causative rotted molar teeth (if present) should be removed.[19]

Lateral Pharyngeal Space Infections

Infection of the lateral pharyngeal space is one of the most common deep neck infections encountered. In a review of 110 deep neck infections in adults seen at an academic medical center over a 10-year period, infections of the lateral pharyngeal space accounted for 55%.[19] In contrast, such infections are rare in children, with peritonsillar infection (quinsy) being the most common deep neck infection.

The lateral pharyngeal space is cone shaped, extending from the sphenoid bone down to the hyoid bone. Posteriorly, it is bound by the prevertebral fascia (which separates it from the retropharyngeal space) and anteriorly by the buccinator and superior constrictor muscles. The parotid gland communicates with this space. The styloid process divides the space into an anterior compartment (containing fat, lymph nodes, and muscle) and a posterior compartment (containing the carotid artery, cranial nerves IX–XII, and the cervical sympathetic trunk).

Common precipitating causes of lateral pharyngeal space infection include dental disease (33%), injection drug use (inserting needles directly into the space) (20%), local trauma (9%), and tonsillitis (4%). Patients frequently have underlying diabetes or HIV infection.

Clinically, anterior lateral pharyngeal space infections present with fever, pain, trismus, and systemic toxicity. Turning the head to the opposite side causes increased pain because of stretching of the ipsilateral sternocleidomastoid muscle.

Infection of the posterior lateral pharyngeal space presents differently from infections involving the anterior pharyngeal space. Common symptoms include fever, systemic toxicity, and parotid swelling. Trismus and external swelling do not occur. Involvement of local vital structures can occur, including carotid artery erosion or clot, septic thrombophlebitis of the internal jugular vein, cranial nerve IX–XII palsies, or Horner syndrome.

Therapy involves urgent surgical intervention to drain purulent material and prevent spread of infection to the retropharyngeal space or erosion of the carotid artery. The choice of antibiotics for this frequently polymicrobial infection is shown in Table 116.3.

Descending Necrotizing Mediastinitis

Rapid downward spread of deep neck infections can result in the development of necrotizing soft tissue infections of the chest wall and mediastinum. A recent study of 45 such cases collected over a 12-year period demonstrated that they tended to develop as a complication of dental or deep neck polymicrobial infections, affecting persons aged 40–60 years most commonly. Mixed aerobic/anaerobic flora was the rule, and risk factors included neutropenia, alcoholism, and diabetes mellitus. Mortality was around 15%–20%. Death may be sudden because of medical complications of the infectious process.[20]

Internal Jugular Vein Septic Thrombophlebitis (Lemierre Syndrome)

Septic thrombophlebitis of the internal jugular vein is known as *Lemierre syndrome*. This relatively rare entity is usually caused by infection with the anaerobe *F. necrophorum,* a normal inhabitant of the human gingival crevice. Latest theories on the pathogenesis of this infection indicate that the first stage of infection is pharyngitis in approximately 87% of cases. Recent data suggest that *F. necrophorum* causes pharyngitis in young adults aged 15–24 years as frequently as *S. pyogenes*.[12] This infection is then followed by invasion of the lateral pharyngeal space, with development of septic thrombophlebitis of the internal jugular vein.[21,22] Subsequently, bloodborne infection develops, with the classic findings of septic pulmonary emboli or cavitating pneumonia and septic arthritis. Other precipitating factors include mastoiditis, lateral pharyngeal space infection, and trauma to the internal jugular vein. Lemierre syndrome is the most common identified source of *F. necrophorum* bacteremia.

Clinically, Lemierre syndrome begins with fever and sore throat. When internal jugular vein involvement develops, patients complain of a swollen and/or tender neck, which is thus a warning sign of danger in a patient with recent pharyngitis. Dyspnea and pleuritic chest pain indicate pulmonary involvement.

Early diagnosis is critical to minimize the risk of infectious metastatic complications requiring surgical intervention or drainage. Blood cultures should be promptly obtained and empirical antianaerobic bacterial coverage begun. Radiologic diagnosis is made most reliably by CT scanning, although bedside ultrasound examination of the internal jugular vein can be useful in the critically ill patient who cannot leave the ICU. If the infection occurs secondary to mastoiditis, it is necessary to rule out intracerebral vein thrombosis by MRI scanning. The patient may also develop secondary complications such as carotid artery thrombosis or parotid gland infection with abscess formation.[23]

Antibiotic choices are outlined in Table 116.3. There are no firm data to support or refute the use of anticoagulants in Lemierre syndrome.[22] In addition, surgical ligation or excision of the internal jugular vein for uncontrollable sepsis was necessary in approximately 8% of cases in a recently published series of cases.[23] MRSA has been shown to cause Lemierre syndrome, especially in injection drug users or patients, with the infection developing as a complication of venous cannulation.[24]

CONCLUSION

The intensivist will frequently be asked to assist in the care of patients with serious deep neck infections. Critical issues encountered include protection of the airway, sepsis management, and the potential for erosion of the infection into surrounding vital structures in the neck. Such infections are frequently polymicrobial in nature; thus broad-spectrum antibiotics with both aerobic and anaerobic coverage should be chosen.

Common issues to be decided for each patient individually include the following:

- The safety of performing an intraoral examination, given the risk of precipitating acute airway obstruction.
- The safety of sending a patient out of the ICU for studies such as CT scanning. Although patients may appear stable initially, they are at risk for sudden development of acute airway obstruction and thus should always be accompanied by a team capable of securing an airway when they travel out of the ICU for tests or procedures.

- The need for and timing of possible surgical intervention. Early close collaboration with otolaryngologists, head and neck surgeons, neurosurgeons, or vascular surgeons is critical for successful management of these complex and frequently critically ill patients.

KEY POINTS

- Deep infections of the head and neck are frequently polymicrobial, including both aerobic and anaerobic bacteria.
- Deep infection can threaten the airway, deep vascular structures, and mediastinum by means of local spread along complex deep anatomic planes.
- Intraoral inspection or attempts to palpate the posterior pharynx in such patients can precipitate acute airway occlusion. They should only be undertaken if an emergency airway can be immediately secured.
- Septic internal jugular vein thrombophlebitis is frequently anaerobic in etiology *(F. necrophorum)* and can be associated with metastatic spread of infection to the lungs, joints, and other organs.

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Infectious Endocarditis

Anastasia Antoniadou and Helen Giamarellou

INFECTIOUS ENDOCARDITIS: GENERAL INFORMATION

Infectious endocarditis (IE) is a rare disease with a yearly crude incidence of 1.5–11.6 episodes per 100,000 persons (3–9/100,00 in developed countries), increasing dramatically with advanced age and male sex and with varying epidemiology between high- and low-income countries.[1,2] Despite advances in early diagnosis and treatment, mortality of IE at 1 year has not improved over the last decades, being ≈30%. In low-income countries rheumatic heart disease remains the main risk factor for IE, but in high-income countries the epidemiologic profile has changed. Patients with IE are old, frail, with comorbidities and risk factors including diabetes, cancer, immunosuppression (including human immunodeficiency virus [HIV]), hemodialysis, prosthetic valve replacement, presence of cardiac implantable electronic devices, central venous catheters, intravenous drug use, and degenerative or congenital heart disease.[2–5]

IE is presently classified by the setting and source of infection into healthcare-associated infectious endocarditis (HAIE) and community-acquired infectious endocarditis (CAIE) and as native valve endocarditis (NVE) and prosthetic valve endocarditis (PVE). HAIE includes patients hospitalized for more than 48 hours before the symptoms of IE develop or patients with extensive healthcare contact defined as (1) home-based nursing or intravenous (IV) therapy, hemodialysis, or IV chemotherapy less than 30 days before onset of IE symptoms; (2) hospitalization less than 90 days before onset of IE; (3) residency in a nursing home or a long-term care facility; or (4) history of any interventional procedure during the previous 4–8 weeks.[3,6] The definition of HAIE applies both to NVE and PVE. Early PVE (now defined as presenting <1 year postsurgery) has a portion included in the HAIE definition (those presenting 60 days postsurgery).[2,3] IE in high-income countries is >25% healthcare associated, carrying a significant in-hospital mortality rate of 15%–20%, with a 1-year mortality rate approaching 40%.[7]

Gram-positive cocci (staphylococci, streptococci, and enterococci) comprise 80%–90% of the microbial etiology of IE, whereas rare (<5%) causes include HACEK species (*Haemophilus* spp., *Aggregatibacter* [formerly *Actinobacillus*] spp., *Cardiobacterium* spp., *Eikenella corrodens,* and *Kingella* spp.); aerobic gram-negative bacilli; fungi (*Candida* spp. and *Aspergillus* spp.); *Bartonella* spp.; *Brucella* spp.; *Coxiella burnettii;* and *Tropheryma whipplei*. In 10% of cases, IE is culture negative, and serology or polymerase chain reaction (PCR) assays in blood or on surgically removed heart valves/vegetations may contribute to the diagnosis. *Staphylococcus aureus* is responsible for 35%–40% of NVE and 50% of HAIE, replacing streptococci as the most common pathogen in developed countries, and streptococci are the cause of 30%–40% of CAIE (both NVE and PVE). Group D streptococci (e.g., *Streptococcus gallolyticus,* formerly *Streptococcus bovis*) are isolated in 15% and should be notable for causing IE associated with an underlying colonic tumor (usually undiagnosed). Enterococci (mostly *faecalis*) are implicated in 10% of IE, being more common in HAIE and transcatheter aortic valve replacement (TAVR) IE. Coagulase-negative staphylococci predominate (>60%) in IE in the presence of prosthetic valves, cardiac implanted electronic device (CIED), or venous catheters except for *Staphylococcus lugdunensis,* which can also be the cause of community-acquired NVE.[2–5]

Rapid and accurate diagnosis of IE remains a challenge and affects disease outcome. Fever is present up to 90%, a heart murmur up to 85%, and an embolic event up to 25% at the time of diagnosis. Other signs are less common: hematuria, splenomegaly, splinter hemorrhages, Janeway lesions, Roth spots, conjunctival hemorrhage, sepsis, meningitis, unexplained heart failure, septic pulmonary emboli, stroke, acute peripheral arterial occlusion, and renal failure.[2–5] Cerebral complications are severe and frequent in IE, occurring symptomatically in 15%–30% of patients, and there is evidence that additional clinically silent cerebral embolism may occur in 35%–60%.[2,5] Diagnosis of IE relies on clinical, microbiologic (blood cultures), and imaging findings (the first-line modality is transthoracic echocardiography [TTE] and transesophageal echocardiography [TEE]), incorporated in the modified Duke diagnostic criteria, which have an overall 80% sensitivity and specificity, which decrease in PVE and cardiac device–related IE. A definite diagnosis requires two major, one major with three minor, or five minor criteria[2,3] (Table 117.1 and Fig. 117.1).

Treatment of IE aiming at microbial eradication necessitates the use of bactericidal combination regimens for prolonged periods. In the 2015 guidelines (1) aminoglycosides are no longer indicated in staphylococcal NVE; (2) when used in streptococcal, enterococcal IE, or staphylococcal PVE, they should be given in a single daily dose to reduce nephrotoxicity; (3) rifampin should be used in IE with foreign material in place (PVE) after 3–5 days of effective antibiotic therapy (to prevent an antagonistic effect against planktonic/replicating bacteria) and after bacteremia has been cleared; (4) daptomycin used in methicillin-resistant *S. aureus* (MRSA) IE should be used in high doses (≥10 mg/kg per day) and in combination with a second antibiotic to increase activity and prevent emergence of resistance; (5) in methicillin-sensitive *S. aureus* (MSSA) IE treatment with beta-lactams is preferred (vancomycin is inferior to beta-lactams); and (6) treatment duration is evaluated from day 1 of effective treatment (i.e., negative blood cultures in case of previously positive ones). In the case of new prosthetic valve implantation in the course of IE, if the removed valve is culture positive, a new full treatment course starts postsurgery.[2,3] Indications for cardiac surgery during the course of IE are heart failure (severe regurgitation or obstruction of the affected valve), evidence of uncontrolled infection (persisting bacteremia despite treatment and

TABLE 117.1 Modified Duke Criteria for the Clinical Diagnosis of Infectious Endocarditis

Major Criteria

1. Blood Cultures Positive for IE
   - a. Typical microorganisms consistent with IE from two separate blood cultures:
     - Viridans streptococci, *Streptococcus gallolyticus (Streptococcus bovis),* HACEK group, *Staphylococcus aureus;* or
     - Community-acquired enterococci, in the absence of a primary focus; or
   - b. Microorganisms consistent with IE from persistently positive blood cultures:
     - ≥2 positive blood cultures of blood samples drawn >12 h apart; or
     - All of 3 or a majority of ≥4 separate cultures of blood (with and last samples drawn ≥1 h apart); or
   - c. Single positive blood culture for *Coxiella burnetii* or phase I IgG antibody titer >1:800
2. Imaging Positive for IE
   - a. Echocardiogram positive for IE:
     - Vegetation
     - Abscess, pseudoaneurysm, intracardiac
     - Valvular perforation or aneurysm
     - New partial dehiscence of prosthetic valve
   - b. Abnormal activity around the site of prosthetic valve implantation detected by ^{18}F-FDG-PET/CT (only if the prosthesis was implanted for >3 months) or radiolabeled leukocytes SPECT/CT.
   - c. Definite paravalvular lesions by cardiac CT.

Minor Criteria

1. Predisposition such as predisposing heart condition or injection drug use.
2. Fever as temperature >38°C.
3. Vascular phenomena (including those detected by imaging only): major arterial emboli, septic pulmonary infarcts, infectious (mycotic) aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions.
4. Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, and rheumatoid factor.
5. Microbiologic evidence: positive blood culture but does not meet a major criterion as noted earlier or serologic evidence of active infection with an organism consistent with IE.

Definite IE
- Two major criteria; or
- One major criterion and three minor criteria; or
- Five minor criteria

Possible IE
- One major criterion and one minor criterion; or
- Three minor criteria

Rejected IE
- Firm alternative diagnosis; or
- Resolution of symptoms suggesting IE with antibiotic therapy for ≤4 days; or
- No pathologic evidence of IE at surgery or autopsy, with antibiotic therapy for ≤4 days; or
- Does not meet criteria for possible IE, as noted earlier

CT, Computed tomography; *^{18}F-FDG-PET/CT*, ^{18}F-Fluorodeoxyglucose-positron emission tomography/computed tomography; *IE*, infective endocarditis; *SPECT*, single-photon emission computed tomography.

From Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC): 2015 ESC Guidelines for the management of infective endocarditis. *Eur Heart J.* 2015;36(44):3075–3128.

control of metastatic foci, abscess or fistula formation, infection by fungi or multiresistant organisms), and prevention of embolism (vegetation size, mobility, and embolic events).[2] A summary of antibiotic treatment recommendations is shown in Table 117.2.

HEALTHCARE–ASSOCIATED NATIVE VALVE ENDOCARDITIS

Data emerging from the International Collaboration on Endocarditis Prospective Cohort Study (ICE-PCS) recognize that 34% of NVE is healthcare–associated (HANVE), consistent with the contemporary high incidence of healthcare–associated infection.[8,9] Almost 50% were acquired outside of the hospital, and compared with CAIE, patients with HANVE more often have comorbid conditions (e.g., diabetes mellitus, cancer, or long-term immunosuppressive therapy). Fever is the most common presenting feature, but physical signs of IE present more rarely in HANVE, suggesting a more acute course. Non-nosocomial acquisition of HANVE is most often dependent on hemodialysis or an intravascular catheter (54%), whereas patients with nosocomial acquisition more often have a preexisting valvular disease or undergo a nondental invasive medical procedure. The mitral valve is most frequently involved, followed by the tricuspid and aortic valve.[8] Staphylococci represent the major pathogens in HAIE. *S. aureus* is responsible in >50% of cases, 91% in the presence of an intravascular device.[6] In the ICE-PCS study, *S. aureus* was methicillin-resistant (MRSA) in 47%.[8] The second most common bacteria were enterococci (15%), followed by coagulase-negative strains of staphylococci (13%). MRSA is more prevalent in infections acquired during hospitalization (57% vs. 41%).[8] Among coagulase-negative strains, *S. lugdunensis* deserves attention because it behaves like *S. aureus* with high virulence, has a 50% probability of complicated infection when isolated in blood, and has an aggressive course when it is the cause of IE.[10]

Gram-negative bacilli are rare causes of HANVE despite the fact that they cause lethal bacteremias in hospitals, probably as a result of their decreased ability to adhere to heart valves and susceptibility to bactericidal action of serum.[6,11] Recently, cases of IE caused by multidrug-resistant MDR and extensively drug-resistant (XDR) gram-negatives (e.g., *Pseudomonas, Acinetobacter, Escherichia coli,* and *Burkholderia cepacia*) have been published with poor outcomes despite aggressive management because of a lack of effective treatment options.[12]

Fungal IE is a rare infection, comprising <2% of IE cases, with a mortality rate exceeding 30%. An increasing frequency of fungal endocarditis has been observed in recent years, attributed to the extensive use of vascular lines, noncardiac surgery, and increased numbers of immunocompromised patients.[13,14] Fungi most commonly associated with IE are *Candida* (*albicans* and non-*albicans,* 50%–80%) and *Aspergillus* spp. (20%–25%). In contradistinction to *Candida* spp., in which blood cultures in cases of IE are positive in 83%–95% of cases, blood cultures are positive in only 11% or less of patients with *Aspergillus* spp. In cases of fungal endocarditis, prolonged symptoms before hospitalization and the embolization of major arteries are classic findings. However, the diagnosis is delayed or missed in 82% of patients. For early diagnosis of fungal endocarditis, it should be considered in the differential diagnosis and echocardiography performed, which demonstrates large, bulky vegetations. Peripheral blood cultures should be obtained and accessible embolic specimens subjected to histologic examination.[13,14]

HANVE has higher mortality compared with community-acquired NVIE (25% versus 13%), and factors independently associated with increased risk of death are increased age (>60 years old), diabetes,

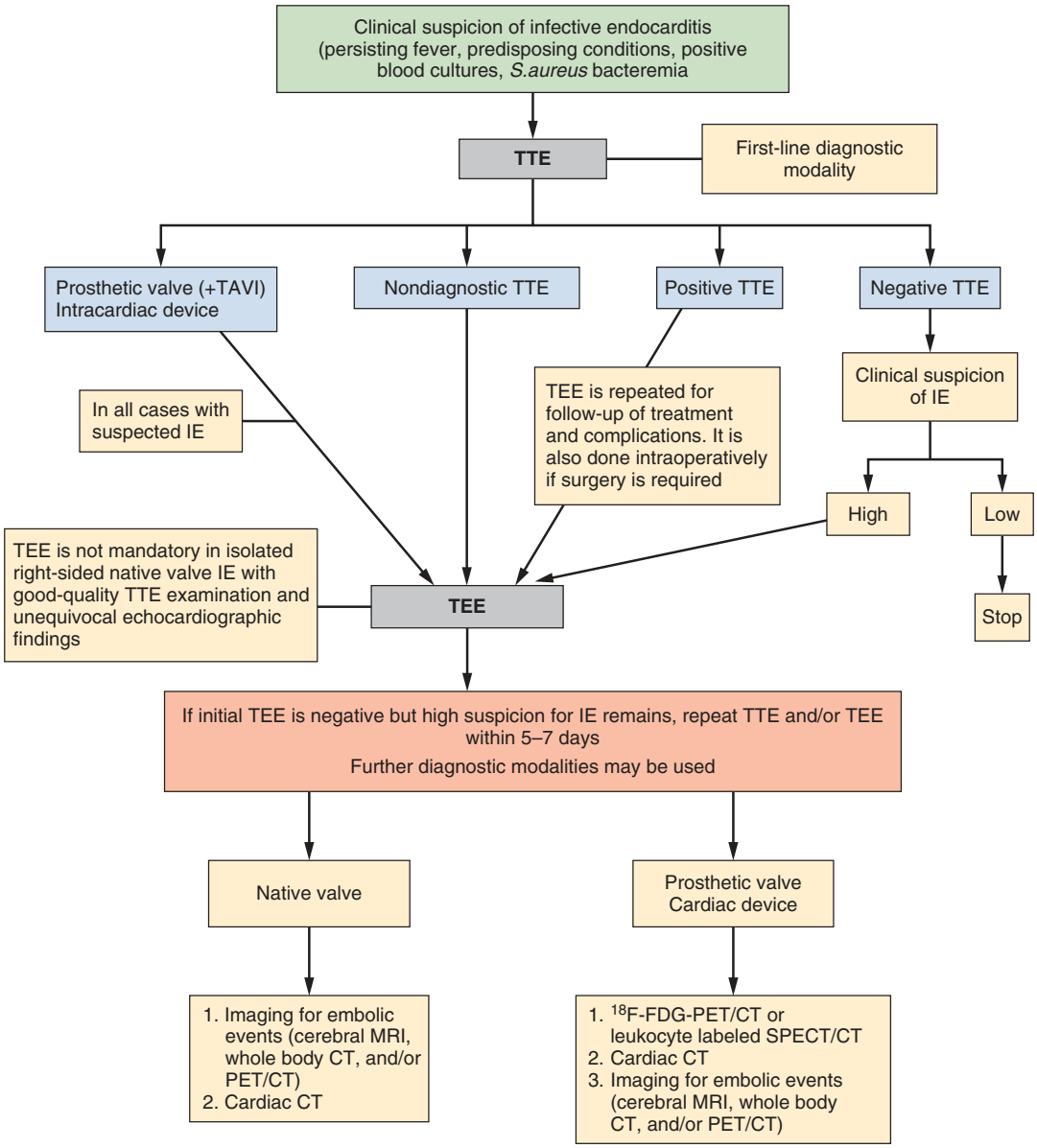

Fig. 117.1 Algorithm of Diagnostic Imaging Modalities in Suspected Infective Endocarditis. *CT,* Computed tomography: ^{18}F-FDG-PET/CT, ^{18}F-Fluorodeoxyglucose-positron emission tomography/computed tomography; *IE,* Infective endocarditis; *MRI,* magnetic resonance imaging; *SPECT,* single photon emission computed tomography; *TAVI,* transcatheter valve implantation. *TEE,* transesophageal echocardiography; *TTE,* transthoracic echocardiography. (Adapted from Habib G, Lancellotti P, Antunes MJ, et al. 2015 ESC Guidelines for the management of infective endocarditis: the Task Force for the Management of Infective Endocarditis of the European Society of Cardiology [ESC]. Endorsed by: European Association for Cardio-Thoracic Surgery [EACTS], the European Association of Nuclear Medicine [EANM]. *Eur Heart J.* 2015;36[44]:3075–3128, Figure 1.)

S. aureus infection, paravalvular abscess, stroke, heart failure, and new conduction abnormality. Cardiac surgery during the IE episode is found to be associated with a lower mortality,[8] and therefore early surgical intervention is often mandatory. In fungal endocarditis, the removal of the infected valve is indicated, and postsurgery suppressive therapy for 2 or more years along with close follow-up are required to detect relapses.[13,14]

Special consideration should be given to chronic hemodialysis (HD) patients, in whom IE is significantly more common (16–18 times) and causes greater morbidity and mortality. In this group of patients, IE is the second leading cause of death after cardiovascular disease, and it has been proposed to be added as a special category in classification by acquisition.[15,16] In the ICE-PCS study, 63% of HANVE cases were HD patients.[8] *S. aureus* was the pathogen in 75%–80% of cases, half of which were MRSA. Fever may not be present, and blood cultures may less often be positive, complicating a diagnosis by the Duke criteria. Mortality remains high: 30% during the first month, about 65% during the first year, and reaching more than 70% if cardiac surgery is indicated. Age older than 65, diabetes as the cause of renal failure, mitral involvement, large vegetations, septic emboli, and infections caused by MRSA or vancomycin-resistant enterococci (VRE) have been identified as risk factors for mortality.[15]

For MSSA, anti-staphylococcal penicillins should be the treatment of choice, whereas in cases of MRSA with minimum inhibitory

TABLE 117.2 Summary of Treatment Recommendations for IE and the Most Common Pathogens

Microorganism	Treatment Regimen	Duration	Comments
Penicillin-susceptible streptococci (MIC ≤0.125 mg/L)	Penicillin G 12–18 million U/day IV in 4–6 doses or continuously or Amoxycillin or ampicillin 100–200 mg/kg/day IV in 4–6 doses or Ceftriaxone 2 g/day IV or IM in 1 dose plus Gentamicin 3 mg/kg/day IV or IM in 1 dose or netilmicin 4–5 mg/kg/day IV in 1 dose	2 weeks	Short-duration treatment only in normal renal function and with monitoring of aminoglycoside levels In PVE 6-week duration is recommended
	Penicillin G 12–18 million U/day IV in 4–6 doses or continuously or Amoxycillin or ampicillin 100–200 mg/kg/day IV in 4–6 doses or Ceftriaxone 2 g/day IV or IM in 1 dose	4 weeks	
	If beta-lactam allergy present: Vancomycin 30 mg/kg/day IV in 2 doses	4 weeks	Vancomycin levels should be monitored
Relatively resistant to penicillin streptococci (MIC 0.250–2.0 mg/L)	Penicillin G 24 million U/day IV in 4–6 doses or continuously or Amoxycillin or ampicillin 200 mg/kg/day IV in 4–6 doses or Ceftriaxone 2 g/day IV or IM in 1 dose Plus Gentamicin 3 mg/kg/day IV or IM in 1 dose	4 weeks 2 weeks	In PVE 6-week duration is recommended If beta-lactam allergy, change beta-lactam to vancomycin
Enterococci and streptococci with penicillin MIC>2 mg/L	Amoxycillin or ampicillin 200 mg/kg/day IV in 4–6 doses Plus Gentamicin 3 mg/kg/day IV or IM in 1 dose	6 weeks 2–6 weeks 6 weeks	
If high-level resistance to gentamicin	Ampicillin 200 mg/kg/day IV in 4–6 doses plus ceftriaxone 4 g/day IV or IM in 2 doses	6 weeks	
If allergy or resistance to beta-lactams (*Enterococcus faecium*)	Vancomycin 30 mg/kg/day IV in 2 doses plus gentamicin 3 mg/kg/day IV or IM in 1 dose	6 weeks	Consultation with ID physician recommended
If resistance to beta-lactams, vancomycin and gentamicin	Daptomycin 10 mg/kg/day IV plus ampicillin 200 mg/kg/day IV in 4–6 doses or ertapenem linezolid 600 mg BID IV	8 weeks	
MSSA NVE PVE	Flucloxacillin or oxacillin 12 g/day IV in 4–6 doses Flucloxacillin or oxacillin 12 g/day IV in 4–6 doses with rifampin 900–1200 mg/day IV or PO in 2–3 doses plus Gentamicin 3 mg/kg/day IV or IM in 1 dose	4–6 weeks ≥6 weeks 2 weeks	Rifampin has been suggested to start 3–5 later
MRSA or beta-lactam allergy NVE PVE	Vancomycin 30–60 mg/kg/day IV in 2–3 doses or Daptomycin 10 mg/kg/day IV once daily Vancomycin 30–60 mg/kg/day IV in 2–3 doses with rifampin 900–1200 mg/day IV or PO in 2–3 doses plus Gentamicin 3 mg/kg/day IV or IM in 1 dose	4–6 weeks 4–6 weeks ≥6 weeks 2 weeks	Daptomycin is superior to vancomycin for MSSA and MRSA bacteremia with vancomycin MIC >1 mg/L. Some experts recommend combination of daptomycin with fosfomycin or cloxacillin.
HACEK	Ceftriaxone 2 g/day IV in 1 dose or ampicillin plus gentamicin if beta-lactamases are not produced	NVE: 4 weeks PVE: 6 weeks	Ciprofloxacin is a not well-validated alternative

[1]For MSSA and MRSA NVE, an alternative regimen is also the combination of sulfamethoxazole 4800 mg/day and trimethoprim 960 mg/day IV in 4–6 doses plus clindamycin 1800 mg/day IV in 3 doses.
[2]For multiresistant or fungal pathogens, ID consultation is recommended.
[3]When vancomycin or aminoglycosides are used, monitoring of drug levels is recommended. Target levels for gentamicin 1 mg/L for trough and 10–12 mg/L 1-hour post-dose levels. For vancomycin trough levels of 15–20 mg/L and 35–40 mg/L 1-hour postinfusion.
IE, Infective endocarditis; *MIC*, minimal inhibitory concentration; *MRSA*, methicillin-resistant *Staphylococcus aureus*; *MSSA*, methicillin-sensitive *S. aureus*; *NVE*, native valve endocarditis; *PVE*, prosthetic valve endocarditis.
Adapted from 2015 ESC Guidelines for the management of infective endocarditis. *Eur Heart J*. 2015;36:3075–3128.

concentration (MIC) >1 mg/L to vancomycin, antimicrobial choices include high-dose daptomycin in combination with another antibiotic.[2] If vancomycin is indicated, drug levels should be followed, with trough levels of 25–30 mg/L required for efficacy.[17]

HEALTHCARE–ASSOCIATED PROSTHETIC VALVE ENDOCARDITIS

PVE accounts for 10%–30% of all cases of IE,[18] with mortality rates ranging between 25% and 60%.[19] It occurs in 3%–4% of patients within 5 years after surgery (0.3–1.2 per patient-year). More than one-third is healthcare acquired. Contamination of prosthetic valves during this early period occurs either directly at the time of implantation by a break in sterile surgical techniques or via transient episodes of bacteremia, emanating mostly from infected intravascular catheters and wound or skin infections during hospitalization, therefore representing a real nosocomial infection.[19] Early PVE (<1 year) presents mostly during the first 2–3 months after surgery.

PVE may manifest as an indolent illness with low-grade fever and immune-mediated manifestations or as a fulminant acute febrile disease with hypotension. When early PVE is caused by *S. aureus,* the clinical picture is accompanied in more than 40% of cases by central nervous system (CNS) and intracardiac complications, with a subsequent mortality ranging from 42% to 85%. Staphylococci prevail in the microbiology of PVE. In the ICE-PCS study, 36.5% of PVE were healthcare associated and 70% were acquired in the hospital.[19] Of PVE cases, 71% were early, the majority diagnosed on day 60 (median on day 84). In 43% of HAPVE, an intravascular device was in place. *S. aureus* was the most common pathogen, with a higher MRSA incidence in cases with healthcare–acquired PVE (HAPVE) (34% and 13.3%), followed by coagulase-negative staphylococci.[19]

Recent progress in TEE, applying a high-resolution biplane or multiplane transducer, has enhanced the diagnostic approach to PVE. Sensitivity and specificity of TEE in the diagnosis of PVE exceeds 90% versus a sensitivity of 40%–70% with transthoracic echocardiography (TTE).[20] New diagnostic modalities are currently used and recommended for the diagnosis of PVE, including multislice cardiac computed tomography (CT), ^{18}F-Fluorodeoxyglucose (FDG) positron emission tomography (PET), and radiolabeled leukocyte single-photon emission computed tomography (SPECT), when suspicion for the presence of PVE is high and the TEE is not diagnostic (see Fig. 117.1). These new methods have been incorporated in the modified Duke criteria (see Table 117.1) in the last update of the European guidelines of IE, which are effectively used to confirm the diagnosis of PVE.[20,21] Mortality in PVE is still substantial, being higher in early PVE (77% vs. 42% in late PVE). Leading causes of death in early PVE are septic shock (36%), congestive heart failure (29%), and renal failure (21%).[6,22,23] In the ICE-PCS study, overall mortality for PVE was 22.8% (for HAPVE it was 30.5%). Other factors related to increased risk of death are older age; diabetes; early PVE; *S. aureus* or fungi as the pathogen; and complications such as heart failure, stroke, intracardiac abscess, and persistent bacteremia.[21] The survival rate with medical therapy alone in cases of moderate to severe chronic cardiac failure caused by prosthesis dysfunction is almost nil. However, valve replacement in this group plus antimicrobial therapy will achieve a survival rate of 44%–64%.[24] It is noteworthy that PVE recurs in only 6%–15% of patients who are operated on with active bacterial invasive infection. Treatment duration for PVE is longer, at least 6 weeks.[2]

Transcatheter valve replacement or implantation (TAVI or TAVR) has transformed the management of severe aortic stenosis in patients with prohibitive or high operative risk and an otherwise grave prognosis. IE after TAVI shares clinical, diagnostic, and management characteristics with PVE and similar incidence (0.3–2.1 per 100 person-years). It occurs early postprocedure, with >75% during the first year, and 18%–60% are healthcare associated. *Enterococcus* is frequently isolated (19%–34%), a pathogen frequently neglected in periprocedural prophylaxis (in 48%, the isolated pathogen was not covered by prophylaxis, which should be tailored according to local epidemiology of resistance). Complications are common (65%–87% rendering indication for surgical care), and mortality is extremely high (in-hospital 11%–64%, 1-year 22%–75%).[25]

CIEDs include permanent pacemakers, implantable cardioverter defibrillators, and cardiac resynchronization therapy devices, and the incidence of infection is overall 1–10/1000 device-years, with staphylococci implicated in the etiology in 60%–80%. CIED-related IE may involve the leads, the endocardium surface, or a valve (most often the tricuspid) and arise either from pocket infection or bacteremia. In CIED-related IE, complete removal of the system is indicated because of increased risk of recurrence and mortality, along with prolonged (4–6 weeks) antibiotic treatment. If a new device is essential, implantation is performed after 72 hours with sterile cultures. If there is evidence for remnant valvular infection, implantation is delayed for 14 days.[2,26]

INFECTIVE ENDOCARDITIS IN THE ICU

Five studies have focused on patients with IE admitted to the intensive care unit (ICU) in the past decade.[27–31] Patients with IE are admitted because of complications (e.g., severe sepsis or septic shock, heart failure with hemodynamic instability, embolic phenomena especially from the CNS, multiorgan failure, or after acute surgery for IE). They usually need prolonged hospitalization, and more than 50% undergo cardiac surgery, which is a protective factor for mortality. A total of 15%–20% of IE patients admitted to the ICU are healthcare associated, 15%–36% involve a prosthetic valve, and one-third are accompanied by embolic phenomena most commonly from the CNS. Pathogens recorded are usually *S. aureus* and streptococci. Mortality rates are 30%–45% among studies for the first 30 days, with risk factors for mortality in recent years being high values of severity scores at admission (SAPS II, SOFA) and multiorgan failure. Long-term mortality has been recently studied by Mirabel and colleagues,[31] and it was found to be 69% for the subsequent 5 years, with risk factors for mortality being a high Sequential Organ Failure Assessment (SOFA) score at admission, the presence of a prosthetic valve, and the size of the vegetation (>15 mm). IE may also be acquired in the ICU, usually as a result of bacteremia related to a medical procedure, and *S. aureus* is the most common pathogen.[32] The expected classic clinical features of IE are often absent in ICU patients. For instance, CNS signs resulting from sedation may be blunted, and manifestations of renal failure are usually attributed to septic multiple organ dysfunction syndrome.

Because the risk of HAIE is proportionally increased with the duration of hospitalization, the diagnosis of IE should always be suspected in the presence of a fever of unknown origin with positive blood cultures after a prolonged stay in the ICU. The latter suspicion is strengthened in patients with prosthetic valves or CIEDs, in those undergoing procedures that may damage the right side of the heart, and whenever bacteremia lasts for more than 72 hours after catheter removal and/or positive blood cultures that persist 3 days after starting appropriate antimicrobials, especially if the microorganism isolated in blood is *S. aureus.*[33]

The diagnostic value of echocardiography in the diagnosis of IE and particularly of the transesophageal view has been established. In a patient with *S. aureus* bacteremia, a TTE should always be performed. If bacteremia persists beyond 48–72 hours and/or the patient has an implantable cardiac device or a prosthetic valve, then a TEE should also be performed because the risk of IE is high.[34,35] In the case of a negative TEE, if clinical suspicion continues to be high, a second examination should be advocated (a multislice CT for native valves and

^{18}F-FDG PET/CT, in addition to radiolabeled leukocyte SPECT/CT for prosthetic valves or CIED).[2] HAIE in the ICU requires the prompt initiation of antimicrobial therapy and cardiosurgical evaluation, keeping in mind that mortality increases sharply with *S. aureus* as a pathogen, with age, and with the origin of the infection (i.e., ICU acquired vs. community acquired). Of note, the treatment duration of catheter-related staphylococcal *(S. aureus)* bacteremia aiming to treat successfully any seeded valve (as occurs in 23% of the cases) should never be shorter than 2 weeks, and echocardiography should be performed before treatment discontinuation. Otherwise, a treatment duration of 4 weeks is recommended.[36]

Prophylaxis of HAIE, especially in ICU patients, mandates (1) intravenous (IV) access and intravascular procedures to be performed with aseptic care; (2) IV and intraarterial catheters to remain in place for as brief a duration as possible; and (3) tunnelization, although a controversial issue, to be considered either as an immediate approach for temporary dialysis catheters or as a systemic procedure if the catheter has been or will be in place for more than 4 days.[37,38] Antimicrobial prophylaxis is not justified before performing TEE.[2]

THE ENDOCARDITIS TEAM[39]

The latest European Society of Cardiology (ESC) guidelines support the management of patients by a multidisciplinary team (incorporating cardiac surgeons, cardiologists, ID specialists, microbiologists, anesthesiologists, and imaging specialists) in reference centers, especially when complications or an indication for cardiac surgery is present. A multidisciplinary approach can substantially reduce the still unacceptably high morbidity and mortality in patients with IE, as it allows early diagnosis and appropriate comprehensive management and follow-up during hospitalization and postdischarge. Decision making within the endocarditis team must follow a standard protocol that is based on current clinical guidelines, and if surgery is indicated, it is best to be performed early.

KEY POINTS

- IE remains a rare disease with high morbidity and mortality and a changing epidemiologic profile in developed countries.
- IE currently is affecting aging populations with comorbidities and is often healthcare associated or related to intracardiac devices or foreign material (prosthetic valves, catheters, CIED).
- Major pathogens (90%) include gram-positive cocci, with *S. aureus* (with increasing rates of MRSA) being the most common pathogen and *Enterococcus* spp. increasing in incidence, both reflecting the extended healthcare–associated profile of IE in the new era.
- Mortality of HAIE is higher in the elderly, in patients with *S. aureus* and fungal endocarditis, and in patients with complications (e.g., heart failure, stroke, intracardiac abscess, persistent bacteremia). Early surgical intervention is mandatory and may improve the in-hospital outcome.
- TEE has enhanced our diagnostic approach in HAIE (NVE or PVE), especially when the Duke diagnostic clinical criteria are effectively used, and it must always be performed in patients with persisting *S. aureus* bacteremia and prosthetic valves or CIED.
- New diagnostic imaging modalities (^{18}FDG-PET/CT, radiolabeled leukocyte SPECT/CT, cardiac CT, MRI) are supporting the still challenging early diagnosis of IE, especially in the presence of cardiac devices or intracardiac foreign material.
- ICU-IE shares overlapping characteristics with HAIE and is either acquired in the ICU or is an emergency necessitating critical care, involving native or prosthetic valves.
- A multidisciplinary approach for the management of IE is recommended by the "endocarditis team" consisting of many specialties in reference centers.

References for this chapter can be found at expertconsult.com.

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Fungal Infections

Philipp Koehler, Paul O. Gubbins, and Oliver A. Cornely

Medical advances continue to improve the prognosis of patients with cancer and other immunodeficiencies. In the past 50 years, the field of transplantation has greatly affected the management of patients with cancer and renal, cardiac, and liver diseases. Moreover, advances in neonatology continue to increase the survival of premature infants. These advances have benefited society greatly, but they have also fueled the emergence of invasive fungal infections. *Candida* species first appeared as significant nosocomial pathogens approximately 40 years ago.[1] For two decades, infections caused by these pathogens increased dramatically.

Fungal infections among critically ill patients are primarily caused by *Candida* spp. However, infections caused by other opportunistic fungal pathogens, including *Aspergillus, Fusarium,* Mucorales, and *Cryptococcus neoformans,* also occur in critically ill populations (e.g., solid-organ transplant [SOT], hematopoietic stem cell recipients, influenza, and acquired immunodeficiency syndrome [AIDS] patients). Moreover, primary or endemic mycosis caused by *Blastomyces dermatitidis, Coccidioides immitis,* and *Histoplasma capsulatum* can cause severe disseminated infection in immunocompetent or compromised hosts.

Fungal infections are generally more prevalent in intensive care units (ICUs) than on the general medical wards.[2] The importance of effective preventive measures against invasive fungal infection is widely appreciated in leukemia or hematopoietic stem cell transplant (HSCT) recipients. As our understanding of these infections continues to improve, so too does the ability to institute appropriate preventive measures. In the past decade, the development of agents possessing either a different mode or broader spectrum of activity, less toxicity, or a reduced propensity to interact with other drugs has increased the number of available systematically active antifungal agents. Consequently, clinicians can now tailor antifungal therapy to specific patients. Moreover, our understanding of antifungal pharmacodynamics is developing, and methods to measure antifungal susceptibility are improving.

FUNGAL INFECTIONS IN THE CRITICALLY ILL

Candida Infections in the ICU

Epidemiology

Candida spp. remain among the 10 most common pathogens of healthcare–associated infections, but are the most common cause of nosocomial bloodstream infections (BSIs).[3] *Candida* spp. have consistently caused a substantial disease burden for more than a decade.[4–7] However, over the past decade, population-based studies have noted a decline in overall incidence, which likely reflects improvements in healthcare delivery.[8] Worldwide, *Candida* spp. are the third most frequent cause of infection in ICUs.[9] Traditionally, ICUs have a higher incidence of *Candida* BSIs than medical and surgical wards, although recent data suggest an increasing prevalence of such infections in non-ICU patients.[2,10–12] Although prior data had suggested the frequency of *Candida* BSIs among ICU patients had declined, estimates from national secondary databases and population-based studies suggest the disease burden may be shifting from the ICU to the general hospital population.[1,11]

Globally, *C. albicans* remains the most common invasive *Candida* spp.[13] However, decreasing trends in the isolation of this species over time have been observed in the ICU and non-ICU setting.[11,13,14] The isolation of *C. albicans* and *C. parapsilosis* among neonatal ICU patients and the prevalence of *C. glabrata* infections among adults have been widely appreciated.[1,13–16] *C. albicans* is responsible for approximately 45% of episodes of candidemia.[11,17] The incidence of infection caused by a particular *Candida* spp. varies considerably by the clinical service on which the patient is hospitalized. However, in general, *C. albicans* is the primary fungal pathogen in the ICU setting and is followed by *C. glabrata, C. parapsilosis, C. tropicalis, C. krusei,* and other *Candida* spp. (i.e., *C. guilliermondii, C. lusitaniae*).[11,17] This rank order varies little across infection site, but it may vary with age, underlying disease, or local epidemiology.[1,13,14,17] Surveillance data have noted that candidemia in neonatal ICUs is predominantly the result of *C. albicans* and *C. parapsilosis* and rarely the result of *C. glabrata* or other *Candida* spp.[1,13,14,17] Surveillance studies have demonstrated that BSI caused by *C. albicans* occurs less frequently with increasing age.[1,13,14,17] In contrast, *C. glabrata* is rarely isolated among infants and children but is more frequently found with increasing patient age.[1,13,14,17]

In 2009 a new multidrug-resistant species, *Candida auris,* first emerged and subsequently, infections caused by this species have spread across the globe.[18–20] Compared with other known non-*albicans* species, the emergence of *C. auris* has fostered significant concern because of its rapid global spread and its multidrug-resistance profile. Genomic sequencing has identified at least four major phylogenetically distinct populations (clades), each of which geographically cluster. Widespread genetic variation exists between each clade, but within each population, there is minimal genetic diversity.[21] Interclade genetic variation leads to differences in pathogenicity, biochemical characteristics, and antifungal susceptibility. For example, strains comprising the East Asian clade are associated with noninvasive infections and appear to be more susceptible to antifungal therapy than isolates of the other three clades.[22] *C. auris* is phenotypically similar to other *Candida* spp., but phylogenetically it is most closely related to *Candida haemulonii*.[23] Historically, *C. auris* has often been misidentified by commercial assays, so prevalence estimates for this pathogen and the frequency with which it causes infections in the ICU are difficult to ascertain.[24] Nonetheless, before its emergence in 2009, it appears the prevalence of *C. auris* was exceedingly rare.[21,25] *C. auris* infections occur in ICUs

among critically ill patients of all ages, those undergoing invasive procedures, or those with serious underlying conditions that affect their host defenses.[26,27]

C. albicans is part of one's microbiota. Infections, including BSIs caused by most *Candida* spp., particularly *C. albicans*, arise endogenously from the gastrointestinal mucosa, skin, and urinary tract.[28] Invasive *Candida* infections occur when alteration of the patient's microbiota leads to overgrowth of yeast which, in the presence compromised skin or gastrointestinal mucosa integrity, translocates from its commensal environment to the bloodstream.[28] *Candida* spp., including *C. albicans,* may also be transmitted exogenously in ICU settings.[29,30] Exogenous transmission of non-*albicans Candida* spp. through indirect contact with the ICU environment occurs commonly.[29] For example, *C. parapsilosis* is known for its ability to form biofilms on catheters and inert devices, which enables it to persist in the nosocomial environment.[31] Moreover, it is spread throughout the hospital through hand carriage by healthcare workers.[31] Infections caused by *C. auris* can arise from colonization, travel to endemic regions, and making contact with the hospital environment. *C. auris* frequently colonizes the axilla and groin, but it can also be isolated from a variety of body sites.[32] Some *C. auris* isolates demonstrate the capacity to form biofilms and can survive on inert surfaces. Estimates suggest that acquisition from a contaminated environment or colonized patient can occur in as little as 4 hours, and invasive infections can reportedly develop within a couple days to weeks of admission to an ICU.[21,33,34]

Detection and Isolation

Candida BSIs are often difficult to detect. Symptomatically, BSIs caused by *Candida* spp. are indistinguishable from BSIs of bacterial etiology. Isolating *Candida* spp. from blood is challenging because they are cleared rapidly from the circulation by several organs, particularly the liver. Blood and deep-seated tissue cultures yield positive results approximately 50% of the time, have slow turnaround, and may not manifest until late in the disease course.[35–37] Deep-seated tissue cultures also must often be collected by invasive techniques, which depending on comorbidities, may not be possible.[37] Despite these limitations, these culture-based methods remain the "gold standard" in the diagnosis of candidemia and other forms of invasive candidiasis. Moreover, the ability of automated blood culture systems to recover *Candida* spp. has continued to improve, and nonculture methods are available that, when used in with culture-based methods, can identify more infected patients earlier.[38]

The biochemical characteristics associated with *C. auris* are difficult to distinguish from other species and can vary across clades. Consequently, routinely used, commercially available identification methods based on phenotypic assimilation/fermentation tests often misidentified *C. auris* as a variety of other *Candida* spp. Much of the problem has been related to the lack of representative isolates, or clade diversity, in the databases of most commercially available biochemical identification systems. This gap should close over time, with system database updates as information and experience with this emerging pathogen continue to grow. Molecular methods have some advantages over biochemical methods, but such systems are still reliant upon accurate and up-to-date databases for comparison to the analyzed sample. Still, molecular diagnostic methods developed to enable accurate and timely diagnosis should be employed as needed to complement biochemical methods.

Mortality

Estimating the mortality caused by *Candida* infections is challenging, particularly in critically ill patients, and is dependent on the underlying conditions and specific patient population. Nonetheless, earlier studies continually demonstrated *Candida* BSIs carry a relatively poor prognosis. *Candida* spp. isolated from the blood have been identified as an independent predictor of mortality.[39–41] Whether expressed as part of all-cause mortality or as crude mortality estimates, *Candida* BSIs are associated with high rates of death. Estimates for mortality rates associated with *Candida* BSIs hospital-wide and in the ICU range from 30% to 40%, with rates as high as 72% in certain countries.[7,41–46] Reported mortality rates associated with the emerging pathogen *C. auris* have varied substantially; whether species-related differences in mortality rates exist is difficult to quantify. With more reporting, it is likely that mortality rates associated with invasive infections caused by *C. auris* will be similar to that reported with other *Candida* spp.

Mortality rates associated with candidemia and other forms of invasive candidiasis hospital-wide and in the ICU, though variable, remain quite high despite the advent of potent and safer anti-*Candida* antifungal therapy.[43,45,47,48] Inadequate treatment may be a reason why mortality has not improved despite the availability of potent and safe antifungal therapy. Inadequate therapy resulting from delays in administration, treatment with an agent to which the organism is resistant, inadequate dosing or treatment duration, or failure to recognize and treat candidemia all contribute to the mortality associated with *Candida* BSI.[49–55] Delaying initiation of adequate antifungal therapy even 12–48 hours is independently associated with mortality in candidemia patients.[50,51,53,56–58]

Candidemia produces significant morbidity and increases the length of hospital stay.[1,28] Given the severity of illness associated with this infection, the added length of stay uses significant healthcare resources.[4–6]

Risk Factors

Among critically ill patients, risk factors for *Candida* infections are well known.[10,59–63] Broad-spectrum antimicrobial use, colonization, indwelling vascular catheters, extremes of age, and hemodialysis have been consistently identified as independent risk factors for *Candida* BSIs.[10,41] Many of these diverse risk factors are commonly present and unavoidable in ICUs. The ICU itself provides an ideal environment for transmission of *Candida* spp., including *C. auris,* among patients; thus it is not surprising that prolonged ICU stay has been identified as an independent risk factor.[33,64] For these reasons, combined with the high mortality rates associated with candidemia and invasive candidiasis, a variety of predictive models to identify patients most at risk for infection have been developed using clinical and/or microbiologic variables. Early efforts using only microbiologic data gained through surveillance cultures focused on the relationship between colonization and infection and sought to quantify it through a so-called "colonization index." The use of resource-intensive surveillance cultures and a lack robust validation studies limit the usefulness of such approaches.[65] Predictive models based solely on clinical variables generally demonstrate poor positive predictive values, and consequently have high negative predictive values (i.e., they are better at identifying those who are unlikely to benefit from antifungal therapy).[65] A model designed using microbiologic data and clinical variables in non-neutropenic patients colonized with *Candida spp.* with a minimum length of ICU stay of 7 days. Performed slightly better at identifying at-risk patients and may be useful for recognizing the need for prompt initiation of antifungal therapy.[66] Although these models may have some utility in curbing inappropriate antifungal therapy, they are somewhat complicated to apply, and certain components of individual prediction rules may be impractical to collect or determine.[60,67] Given the diversity of risks associated with developing infection, caution should be used when employing predictive models for candidemia and invasive candi-

diasis in critically ill patients. Clinicians should also be aware of the patient population and the clinical conditions used to derive a given predictive model and understand it may not be generalizable to their patient.[65]

Opportunistic Fungal Infections in Immunocompromised Critically Ill Patients

Invasive Aspergillosis in Critically Ill Patients With Hematologic Malignancies

In contrast to *Candida* spp., the burden of infection caused by *Aspergillus* spp. is small.[1,28] *Aspergillus* spp. cause infection in critically ill populations immunocompromised by burns, cytotoxic chemotherapy, prolonged corticosteroid therapy, malignancy, leukemia, SOT or HSCT, and other congenital or acquired immunodeficiencies. *Aspergillus* spp. are ubiquitous environmental molds. Although several hundred species of *Aspergillus* have been described, relatively few are known to cause disease in humans. Most *Aspergillus* infections are acquired exogenously via inhalation. In the absence of an effective immune response, airborne conidia invade sinus or lung vasculature. Although the lung is the most common site of invasive aspergillosis, *Aspergillus* spp. also demonstrate tropism for cutaneous, central nervous system (CNS), bone, and cardiac vasculature.[68]

The incidence of invasive aspergillosis in immunocompromised patients varies among specific populations. Among patients with hematologic malignancies, those with acute myelogenous leukemia have the highest incidence of invasive aspergillosis.[69–72] Patients in ICUs are at increased risk, and susceptibility in general depends on the use of immunosuppressants, structural lung damage, and genetic predisposition.[73–80] Like patients with leukemia, patients undergoing HSCT are at high risk for invasive aspergillosis. The incidence of invasive aspergillosis varies depending on transplant type but not the type of conditioning regimen (myeloablative vs. nonmyeloablative). The incidence is higher among allogeneic HSCT recipients than among autologous HSCT recipients. In the HSCT population, whether the incidence of invasive aspergillosis is truly increasing or decreasing is difficult to ascertain, because the rate of autopsy continues to decline. The incidence of invasive aspergillosis among SOT is highest among lung transplant recipients and lowest among renal transplant recipients. Patients receiving HSCT or SOT can develop invasive aspergillosis shortly (within 40 days) after transplantation, but typically it occurs late post-HSCT (>40–100 days) or SOT (>90 days).[81–86]

In patients with acute leukemia or in HSCT recipients, prolonged neutropenia after cytotoxic chemotherapy or HSCT is the primary risk for early invasive aspergillosis. Risk factors associated with invasive aspergillosis in HSCT and SOT recipients vary with time after the transplant. However, in general, risks early in the transplant process are associated with transplant-related factors (underlying disease, neutropenia, type of transplant), biologic factors (hyperglycemia, iron overload), and extrinsic factors (excluding spores from the environment, air filtration). In contrast, risks for invasive aspergillosis occurring later in the transplant process include transplant complications (acute graft-versus-host disease [GVHD] [grade ≥3] and high-dose corticosteroid therapy).[85]

Lesions associated with invasive pulmonary aspergillosis evolve over a period of weeks. Computed tomography (CT) findings, especially nodular infiltrates with "halo sign," are strongly suggestive of invasive aspergillosis and infection from other angioinvasive fungi in immunocompromised patients. Moreover, this finding is associated with significantly improved response and survival if antifungal therapy is initiated shortly upon detection of this sign of infection.[87]

Recent diagnostic efforts have focused on detecting non–culture-based serum markers (e.g., galactomannan test, 1,3-β-D-glucan, polymerase chain reaction [PCR]). Galactomannan is a cell wall constituent of *Aspergillus* spp. that can be detected in the serum during invasive infection. The test is specific for invasive aspergillosis and is commercially available as a sandwich enzyme immunoassay (enzyme-linked immunosorbent assay [ELISA]) that detects circulating galactomannan. The values from this test have been shown to strongly correlate with the clinical outcome of patients with invasive aspergillosis.[88–90] Because 1,3-β-D-glucan is a cell wall component of many fungal pathogens, it can be detected by colorimetric detection assays. Although the test is highly sensitive, the presence of 1,3-β-D-glucan in the serum is not specific for any fungi. Using both of these non–culture-based serum markers may improve the ability to diagnose invasive aspergillosis in high-risk populations and could lead to earlier diagnosis or improved monitoring of the success of antifungal therapy.[91,92] CT-guided biopsy has a high diagnostic yield, and samples should undergo both histopathologic and cultural evaluation.[93] The combination of radiologic, serologic, cultural, histopathologic, and clinical data may ultimately improve the diagnosis of invasive aspergillosis and speed up initiation of appropriate antifungal therapy.[94]

Miscellaneous Pathogens in Critically Ill Patients With Hematologic Malignancies

Candida and *Aspergillus* spp. are the primary fungal pathogens in critically ill patients with hematologic malignancies. However, other pathogens such as Mucorales, *Fusarium, Lomentospora, Scedosporium,* and other orphan but emerging mold diseases are increasing in frequency.[28] Each of these less common organisms has clinical characteristics or tissue tropism. In addition, they are often less susceptible than *Aspergillus* spp. to systemic antifungal agents. Consequently, infections caused by these pathogens are associated with high mortality. Of these, the Mucorales are the most common among critically ill patients. These angioinvasive pathogens are acquired through inhalation and produce a necrotic infection with the highest morbidity and mortality.[95] Rhinocerebral, paranasal, pulmonary with or without transdiaphragmatic extension, cutaneous, and gastrointestinal infections are common manifestations of mucormycosis.[96] Common risks are diabetic ketoacidosis, immunosuppression, organ transplantation, traumatic skin damage, and a prolonged ICU stay.[95,97] Pulmonary and disseminated infection mostly affects patients with hematologic malignancy; rhinocerebral and paranasal mucormycosis is predominant in patients with uncontrolled diabetes.[98,99] The "reversed halo" sign in CT is indicative of pulmonary mucormycosis; however, diagnosis should be enforced by cultural and histopathologic work-up of biopsies.[100–102] Management of mucormycosis, including the important role of surgical debridement, is detailed in the global guideline for the diagnosis and management of mucormycosis.[103]

Influenza-Associated Pulmonary Aspergillosis

Within the last years, increasing numbers of influenza-associated pulmonary aspergillosis (IAPA), especially in critically ill patients, were described. Most importantly is that immunocompetent patients also are at risk to develop invasive aspergillosis after influenza infection.[104–106]

Patients with lower respiratory symptoms and respiratory insufficiency need a thorough clinical work-up in addition to bronchoalveolar lavage with lower respiratory tract samples for galactomannan assay; direct microscopy; culture; and bacterial, fungal, and viral PCR. If *Aspergillus* species are recovered either by culture or via PCR testing, chest CT should be performed.

Cryptococcosis, Histoplasmosis, Blastomycosis, and Coccidioidomycosis in Critically Ill Patients

Cryptococcus neoformans, Cryptococcus deneoformans, Histoplasma capsulatum var. *capsulatum, Blastomyces dermatitidis,* and *Coccidioides immitis* are not common pathogens in the ICU setting. These organisms can cause infection in patients with intact immune function. However, with the exception of *B. dermatitidis,* severe infections caused by these pathogens are more common among critically ill immunocompromised populations, particularly those with AIDS and SOT recipients. Cryptococcosis is the third most common invasive fungal infection among SOT recipients.[28,107]

C. neoformans is a ubiquitous encapsulated yeast isolated from diverse environmental sources (i.e., soil, trees and plant material, and droppings from pigeons). This pathogen is primarily acquired by inhalation.[108] In the lung, the organism elicits a cell-mediated response involving neutrophils, monocytes, and macrophages. The cryptococcal polysaccharide capsule, an important virulence factor, facilitates laboratory identification and recognition by host cell-mediated immune response and possesses immunosuppressive properties. The advent of AIDS significantly altered the incidence of cryptococcosis. Before the AIDS epidemic, cryptococcosis was an uncommon disease in the United States, but since then, the majority of cases have been associated with human immunodeficiency virus (HIV) infection.[109,110] The prevalence of cryptococcosis in HIV in the United States has declined with the widespread use of fluconazole and highly active antiretroviral therapy to treat HIV infection. Cryptococcosis still produces significant acute mortality, but overall long-term outcomes have improved dramatically in the past two decades.[111] Mortality among HIV-infected patients and SOT recipients is similar and is estimated to be approximately 15%–20%.[111–113]

Among critically ill immunosuppressed populations, cryptococcal infections typically involve the CNS.[107] However, HIV-negative patients may have only extra-CNS (i.e., skin, soft tissue, or osteoarticular) manifestations. The onset of this infection may be acute or gradual, and patients often present with nonspecific complaints.[114] When the disease manifests as subacute meningitis or meningoencephalitis, classic meningeal findings such as photophobia or nuchal rigidity may be absent.

In cases of cryptococcal meningitis, characteristic cerebrospinal fluid (CSF) findings may be present; however, CSF leukocyte count can be low, and CSF protein and glucose values may be normal. Therefore CSF analysis for cryptococcal antigen and culture of the organism are required to diagnose cryptococcal meningitis. Detection of the organism by India ink stain is highly specific but associated with low sensitivity. Determination of serum cryptococcal antigen using latex agglutination is a highly sensitive and specific test, and therefore it is an important component of the diagnosis of cryptococcal disease. In patients with cryptococcal meningitis, particularly those with AIDS, the serum cryptococcal antigen is usually positive, and usually titers are very high. Detection of antigen in the CSF strongly suggests infection, but in HIV-infected patients, false-negative results can occur in up to 10%, even in the presence of positive cultures. The definitive diagnosis of cryptococcal infection requires a positive culture for *C. neoformans.*

Histoplasmosis (caused by *H. capsulatum* var. *capsulatum*), blastomycosis *(B. dermatitidis),* and coccidioidomycosis *(C. immitis)* are the major endemic mycoses found in North America. Infections by these pathogens are reported primarily in distinct geographic areas, but owing to population mobility, they can be reported throughout the United States. Diagnosis is established via antigen and antibody detection from urine or serum, respectively.[115,116] *H. capsulatum* is endemically distributed primarily in the Mississippi and Ohio River valleys; *B. dermatitidis* is found primarily in the south central United States, the Mississippi and Ohio River valleys, and in certain regions of Illinois and Wisconsin. *C. immitis* is found primarily in the arid southwest regions of the United States. Infection with all these pathogens is acquired via inhalation. Overall, hospitalization is required in an estimated 4.6 and 28.7 cases per million children and adults, respectively.[117] Nationwide, endemic mycoses require substantial healthcare resources to manage and produce significant crude mortality rates in children and adults (5% and 7%, respectively).[117] The severity of histoplasmosis depends on host immune function and the extent of exposure, particularly in the immunocompetent host. Hematogenous dissemination from the lungs occurs in all infected patients, but in immunocompetent hosts, it is controlled by the reticular endothelial system. However, among elderly hosts or those with cell-mediated immune disorders (e.g., HIV infection), progressive disseminated infection readily occurs. After inhalation, *B. dermatitidis* can disseminate from the lungs to other organs as the yeast form. The primary pneumonia is often undetected and resolves without sequelae. Endogenous reactivation in the lungs, skin, or bones is often the first sign of infection.

C. immitis requires the inhalation of only a few arthroconidia to produce primary coccidioidomycosis. Like the other endemic mycoses, in the majority of patients, primary coccidioidomycosis typically manifests as an asymptomatic pulmonary disease.[118] However, it can also manifest as an acute respiratory illness, chronic progressive pneumonia, pulmonary nodules and cavities, extrapulmonary nonmeningeal disease, and meningitis.[119,120]

Among critically ill patients, histoplasmosis manifests as either chronic pulmonary histoplasmosis or progressive disseminated (extrapulmonary) histoplasmosis. Chronic or cavitary pulmonary histoplasmosis occurs in middle-aged and elderly patients with underlying lung disease that compromises the ability of nonspecific host defenses to effectively clear the organism.

Progressive disseminated histoplasmosis occurs in healthy or critically ill immunocompromised hosts, but it is more common and severe in the latter population (i.e., patients with malignancies or HIV infection). The infection can disseminate to a variety of organs, including the reticuloendothelial system, oropharyngeal and gastrointestinal mucosa, skin, adrenal glands, and kidneys.[118]

Clinical manifestations of blastomycosis can mimic many other diseases, such as tuberculosis (TB) and cancer, but typically occurs as an asymptomatic infection, acute or chronic pneumonia, or disseminated (extrapulmonary) disease.[121] Extrapulmonary blastomycosis typically afflicts the skin, bones, and genitourinary system.[121] Cutaneous lesions are the most common skin manifestations of this disease.[121] Extrapulmonary (disseminated) coccidioidomycosis afflicts 1%–5% of all patients infected with *C. immitis* and is deadly if not treated properly. Even with appropriate treatment, chronic infection is common.[119]

SYSTEMIC ANTIFUNGAL AGENTS

Amphotericin B Formulations

Amphotericin B Deoxycholate

Amphotericin B deoxycholate (AmB-d), a polyene antifungal agent, disrupts biologic membranes, thereby increasing their permeability. AmB-d also stimulates the release of cytokines, which causes arteriolar vasoconstriction in the renal vasculature.[121,122]

Pharmacology and pharmacokinetics. The majority (70%) of an administered AmB-d dose is recovered from the urine and feces over a 7-day period; approximately 30% of the administered dose remains in the body a week after dosing.[123]

Overview of toxicity. AmB-d infusion-related reactions, including hypotension, fever, rigors, and chills, occur in approximately 70% of patients.[124–128] These reactions occur early in therapy and often subside

with time. Pretreatment regimens consisting of diphenhydramine, acetaminophen, meperidine, and hydrocortisone may be used to prevent infusion-related reactions. The efficacy of these regimens is unclear, so their routine use is discouraged until the reactions occur, after which pretreatment regimens should be employed with subsequent dosing.[124] Although common and noxious, infusion-related reactions rarely cause early termination of AmB-d therapy or interfere with the use of other medications.

AmB-d also produces dose-related toxicities, including nephrotoxicity, azotemia, renal tubular acidosis, electrolyte imbalance, cardiac arrhythmias, and anemia.[122,125] AmB-d–induced nephrotoxicity is the most common dose-related toxicity.[129] In the ICU this toxicity often limits the use of AmB-d or interferes with the ability to use other medicines. Saline hydration before dosing can reduce the incidence of AmB-d–induced nephrotoxicity, but in the ICU setting, the utility of saline hydration may be limited by fluid restriction employed to manage the fluid status of critically ill patients. Use of the deoxycholate formulation of amphotericin B is discouraged in most, if not all, indications.[130]

Lipid Amphotericin B Formulations

Amphotericin B lipid complex (ABLC) and liposomal amphotericin B (LAmB) are lipid AmB formulations that in many centers have supplanted the use of AmB-d. They retain the activity of AmB-d but have significantly less associated nephrotoxicity than the parent drug.[129,130]

Pharmacokinetic comparisons of lipid amphotericin B formulations. The lipid AmB formulations differ in physicochemical properties and composition. These differences produce subtle differences in their pharmacokinetic behavior that may ultimately prove to be clinically significant. The disposition and activity of these formulations in human tissue is poorly characterized. However, animal data indicate that high serum concentrations may influence the delivery of lipid AmB formulations to certain infection sites such as the CNS and lungs.[131]

Toxicity comparisons of lipid amphotericin B formulations. Compared with AmB-d, the lipid formulations have significantly less associated nephrotoxicity.[129] The formulations differ in the incidence of infusion-related reactions and other adverse events associated with AmB-d infusion.[127,132] These reactions typically do not result in early termination of therapy.[132,133] Observational safety comparisons between ABLC and LAmB suggest the two formulations have a similar nephrotoxicity profile, but prospective comparative data suggest LAmB is less nephrotoxic than ABLC.[129,134] There are few data comparing the safety of lipid AmB formulations to the triazole antifungal agents in critically ill patients.

Azole Antifungal Agents

Fluconazole, Itraconazole, Isavuconazole, Posaconazole, and Voriconazole

The systemic azoles exert a fungistatic effect by dose-dependent inhibition of cytochrome P-450 (CYP)–dependent 14α-demethylase, the enzyme necessary for the conversion of lanosterol to ergosterol, leading to the depletion of ergosterol, the essential sterol of the fungal cell wall, an event that ultimately compromises cell wall integrity. The degree of inhibition varies among the different azole agents, which accounts for differences in the spectrum of activity.

Pharmacology and pharmacokinetics. The triazoles differ in chemical properties, which form the basis of the pharmacokinetic differences between the agents and the propensity of this class to interact with other medications.

Fluconazole pharmacokinetics in critically ill patients are well established.[135–137] In surgical ICU patients, fluconazole clearance correlates with creatinine clearance (CrCl), and its volume of distribution correlates with body weight.[135] In addition, fluconazole volume of distribution is greater in this population than in healthy volunteers.[135] The fluconazole half-life is markedly prolonged in surgical ICU patients.[135] In patients with severe renal dysfunction (CrCl <30 mL/min), some recommend dosage reductions of 50%, but such reductions should be made cautiously and take into account the infecting pathogen in patients receiving fluconazole via enteral feeding tubes.[135,137] Data suggest that the systemic availability of fluconazole is relatively unaffected by administration via enteral feeding tubes.[137] However, serum concentrations obtained with standard doses administered via an enteral feeding tube may not be adequate to treat *C. glabrata* infections, for example.[136] Moreover, in critically ill abdominal trauma patients with and without abdominal wall closure, intravenous (IV) fluconazole may be warranted because the bioavailability of enterally dosed fluconazole in these patients is highly variable.[135]

Itraconazole is a highly lipophilic weak base and practically insoluble in water. It is available as a capsule and as an oral solution formulated in hydroxypropyl-β-cyclodextrin (HP-βCD). The IV solution was removed from the US market in 2008; however, this dosage form may be available in other countries. Slow and erratic absorption of the capsule formulation precludes its use in critically ill ICU patients. HP-βCD enhances itraconazole solubility and improves its oral systemic availability. HP-βCD is poorly absorbed from the gastrointestinal tract, stimulates gastrointestinal secretion and propulsion, and causes diarrhea.

Under fasting conditions in healthy adults, itraconazole is rapidly absorbed from the oral solution, and compared with the capsule, there is less interpatient and intrapatient variability in serum concentrations.[138] After IV administration, renal elimination of itraconazole is negligible, but HP-βCD is renally eliminated (80%–90%). IV itraconazole was contraindicated in cases of significant renal impairment (CrCl ≤30 mL/min) because of concerns over the renal accumulation of HP-βCD. Itraconazole is extensively metabolized by CYP3A4 to produce several metabolites, including one that is bioactive.[139] Rare cases of congestive heart failure are documented in the literature.[140]

Isavuconazole has been available as an IV formulation and capsules since March 2015. It shows a prolonged half-life of 100–130 hours, long persisting tissue levels enabling once-daily dosing after a 1-day loading dose, and independence of oral food intake.[141–143] Isavuconazole clearance is dependent on hepatic CYP3A4/5 metabolism and subsequently modification by uridine diphosphate glucuronosyltransferase (UGT) to be secreted in the feces and bile.[144,145]

Posaconazole is available as an oral suspension, delayed-release tablet, and IV formulation. It exhibits linear pharmacokinetics with dosages between 50 and 800 mg/day.[146] However, absorption of the oral suspension is saturated at doses exceeding 800 mg/day.[146] Posaconazole oral suspension absorption is influenced by gastric pH and is optimal under acidic conditions. Posaconazole absorption and exposure are maximized by dividing the total daily dose four times daily rather than administering it as a single dose for the liquid solution.[147,148] Posaconazole absorption and exposure are also enhanced by administration with or shortly after a meal.[147] In the ICU, it is often impractical to give posaconazole with or shortly after a meal, but absorption and exposure are also enhanced by administering the drug with a liquid nutritional supplement. With the introduction of posaconazole tablet formulation, the issue of pH- and meal-dependent absorption is overcome.[149] In critically ill patients (e.g., because of severe mucositis or mechanical ventilation), the IV formulation is preferred.[150] Although posaconazole binds extensively (>95%) to plasma proteins, its large estimated volume of distribution suggests that it distributes widely throughout the body, but there are few data describing its penetration into the CSF.

Posaconazole is primarily eliminated in feces and urine as unchanged drug. Less than 20% of a dose is metabolized, most of which occurs by UGT pathways and very little by CYP3A4.[151,152]

Voriconazole is a derivative of fluconazole with limited aqueous solubility and improved antifungal activity. It is available in IV and oral formulations. IV voriconazole contains sulfobutyl ether β-cyclodextrin (SBECD) as a solubilizing agent. There are few data on how critically ill patients handle voriconazole. In healthy volunteers, voriconazole exhibits good oral availability and wide tissue distribution, with hepatic metabolism and renal excretion of metabolites. In patients with moderate to severe renal function, SBECD accumulates, and it is recommended that oral dosing be used in patients with a CrCl less than 50 mL/min.[153] Oral dosing in critically ill patients is often not possible; therefore how SBECD is handled in critically patients on dialysis has been examined. A small study observed accumulation of SBECD in three patients during hemodialysis. No toxicity resulting from accumulation of SBECD was observed, and the accumulated dose values were lower but comparable with those used in previous toxicity studies with animals. Nonetheless, if possible, use of IV voriconazole in patients on hemodialysis should be avoided. Data demonstrate that voriconazole achieves adequate CSF concentrations.[153,154]

For all azoles therapeutic drug monitoring is generally indicated, as pharmacokinetic variability is extensive and levels may be unpredictable.[155]

Overview of toxicity. The azoles are a relatively safe class of drugs and are associated with few serious adverse effects. The advent of fluconazole and subsequent agents greatly improved the safety of this class. All the azoles are associated with gastrointestinal intolerance, transient transaminitis, hepatic toxicity, rashes, and dizziness. Nausea, vomiting, and diarrhea commonly occur with all agents in this class, particularly with oral itraconazole solution. These effects are usually observed with high doses of the azoles, but rarely are they severe enough to warrant discontinuation of therapy. All azoles may produce significant elevations in transaminases. Patients experiencing azole-associated transaminase abnormalities are asymptomatic, but these increases, on rare occasions, can evolve into fatal drug-induced hepatitis. The azoles can also produce allergic skin rashes that are generally mild and subside with discontinuation of the drug.

Fluconazole is perhaps the safest azole, and doses four to five times in excess of the recommended daily dose have been well tolerated. For isavuconazole, reported adverse effects are gastrointestinal disturbances, transaminase abnormalities, and hypersensitivity reactions.[143,145] Whether isavuconazole leads to QTc prolongation or decrease of QTc time is not yet understood.[143,156,157] The common adverse effects associated with posaconazole use have been similar to those observed with the other agents in the class (i.e., gastrointestinal, transient transaminase abnormalities); however, the tolerability in comparison to previous azoles has improved.[158] During the phase II and III clinical trials, a QTc prolongation was described in 4% of patients.[159] In addition to the adverse effects seen with other azoles, voriconazole produces transient visual disturbances in approximately 30% of patients, which rarely lead to discontinuation of therapy. These visual disturbances are acute and include changes in color discrimination, blurred vision, photophobia, and the appearance of bright spots.

Azole drug interactions. Drug interactions occur primarily in the intestine, liver, and kidneys by a variety of mechanisms. In the intestine they can occur as a result of changes in pH, complex formation with ions, or interference with transport and enzymatic processes involved in gut wall (i.e., presystemic) drug metabolism. In the liver, drug interactions can occur because of interference with transport proteins and drug-metabolizing enzymes. Drug interactions in the kidney can occur through interference with glomerular filtration, through active tubular excretion, or by other mechanisms. The azoles are one of the few drug classes that can cause or be involved in drug interactions at all of these anatomic sites by one or more of the mentioned mechanisms. Drug interactions involving the azoles have been extensively reviewed.[160–162] Several of the drug–drug interactions involving the azoles occur class-wide. Therefore when using the azoles, the clinician must be aware of the many drug–drug interactions, both real and potential, associated with this class.

Interactions involving the azoles result because of their physicochemical properties. All azoles are somewhat lipophilic and thus undergo CYP-mediated metabolism.[163] The azoles all inhibit one or more CYP enzymes. Itraconazole, posaconazole, and isavuconazole also inhibit ABC transporters such as P-glycoprotein (P-gp), which is a transport protein involved in drug distribution.[164] Fluconazole is not affected by agents that increase gastric pH, but its potential to cause CYP-mediated interactions is more than that suggested by in vitro studies. CYP-mediated interactions involving fluconazole are often dose dependent and can involve drugs metabolized by CYP3A4 (e.g., midazolam, rifampin, phenytoin) and CYP2C9 (e.g., warfarin).[160–162] Because of its linear and predictable pharmacokinetic properties, these interactions may sometimes be avoided or managed by using the lowest effective fluconazole dose. In patients with SOT or bone marrow transplantation, cyclophosphamide, tacrolimus, and sirolimus levels are increased if fluconazole treatment is concomitantly administered.[165–168]

Itraconazole is subject to pH-based interactions and interactions involving CYP3A4 and P-gp. Drugs that can interact with itraconazole include agents that increase gastric pH (e.g., protonics) and lipophilic CYP3A4 (e.g., HMG-CoA reductase inhibitors, benzodiazepines, immunosuppressive agents), and/or P-gp substrates (e.g., digoxin) with poor oral availability.[160–162] Agents that increase gastric pH do not affect the absorption of voriconazole. However, CYP-mediated interactions involving voriconazole can involve drugs metabolized by CYP3A4/5 (e.g., midazolam, rifampin, phenytoin, tacrolimus), CYP2C9 (e.g., warfarin), or CYP2C19 (e.g., omeprazole).[160–162,169] Significant pharmacogenomics considerations exist for drug–drug interactions with voriconazole because it interacts with several polymorphic CYP enzymes, most notably CYP3A4/5, CYP2C9, and CYP2C19. Such considerations are most relevant in interactions involving tacrolimus, midazolam, and warfarin.[162] Although posaconazole is minimally metabolized by CYP, it inhibits hepatic CYP3A4.[160,161] Like the other azoles, the most clinically significant interactions associated with posaconazole involve benzodiazepines (oral midazolam), calcineurin inhibitors (cyclosporine, tacrolimus), other immunosuppressive agents (sirolimus), and phenytoin.[160,161]

Isavuconazole acts as a CYP3A4 inhibitor, and its clearance is highly dependent on CYP3A4/5 metabolism.[145]

Drug interactions involving the azoles that are relevant to the ICU setting are summarized in Table 118.1.

Emergence of resistance and the selective pressure of azoles. Azole resistance in *Candida* has been widely observed for fluconazole and *C. albicans*; however, resistance to other azoles among other *Candida* spp. has been reported and studied. *Aspergillus fumigatus*–resistant isolates were detected with a substitution of leucine with histidine in the cyp51A gene in combination with a 34 base-pair tandem sequence in the promotor gene (TR/L98H) in patients and environmental isolates.[170–172] Both, resistant *Candida* and *Aspergillus* raised concerns about frequency and clinical relevance for patients at high risk of invasive fungal infection.

Echinocandin Antifungal Agents

Caspofungin, Micafungin, and Anidulafungin

Pharmacology and pharmacokinetics. The echinocandins are generally fungicidal and disrupt cell wall synthesis by inhibiting 1,3-β-D-glucan synthase. The echinocandins are active against *Aspergillus* and *Candida*

TABLE 118.1 Drug Interactions Involving Azoles in the ICU Setting

	Fluconazole	Itraconazole	Voriconazole	Posaconazole	Isavuconazole	Comments
CYP Inducers						
Carbamazepine	X	+	X	X	X	Avoid combination – significantly ↓s azole concentration
Phenobarbital	X	+	X	X	X	Avoid combination – significantly ↓s azole concentration
Phenytoin	+	+	+	+	X	Avoid combination – significantly ↓s azole concentration
Rifampin	+	+	+	+	X	Avoid combination – significantly ↓s azole concentration
CYP Inhibitors						
Amiodarone	X	X	X	X	X	Decreases the metabolism of CYP3A4 substrates
Aprepitant	X	X	X	X	X	Avoid combination
Clarithromycin	X	X	X	X	X	Avoid combination – may ↑ azole concentration
Diltiazem	X	X	X	X	X	Monitor therapy
Dronedarone	X	X	X	X	X	Monitor therapy
HAART	X	X	X	X	X	Avoid combination – may ↑ azole concentration
Idelalisib	X	X	X	X	X	Avoid combination – may ↑ azole concentration
Nilotinib	X	X	X	X	X	Monitor therapy
Verapamil	X	X	X	X	X	Monitor therapy
Benzodiazepines and Anxiolytics						
Diazepam	+	+	+	X	X	Effect of midazolam ↑'d by triazoles
Midazolam	+	+	+	+	X	Effect of midazolam ↑'d by triazoles
Triazolam	+	+	X	X	X	Effect of midazolam ↑'d by triazoles
Immunosuppressants						
Cyclosporine	+	+	+	+	X	Triazoles ↑ calcineurin exposure, troughs
Sirolimus	+	+	+	+	X	Triazoles ↑calcineurin exposure, troughs
Tacrolimus	+	+	+	+	+	Triazoles ↑ calcineurin exposure, troughs
Gastric pH Modifiers						
Antacids	X	+	X	–	X	Significantly ↓s itraconazole concentration
H_2 antagonists	–	+	X	X	X	Significantly ↓s itraconazole concentration
PPIs	X	+	X	+	X	Significantly ↓s itraconazole and posaconazole concentration

+, Interaction documented by clinical study or case series; –, no interaction documented by clinical study; X, no published data. *PPIs*, Proton pump inhibitors.
Updated from http://www.uptodate.com/crlsql/interact/frameset.jsp on January 15, 2020

spp. In addition, their spectrum of activity extends to *Pneumocystis carinii*. These agents have little or no activity against *H. capsulatum, B. dermatitidis,* or *C. neoformans.* The echinocandins are large, poorly absorbed lipopeptide compounds and thus are not formulated for oral dosing. The individual echinocandins all demonstrate linear pharmacokinetic behavior. However, each agent differs slightly in how it distributes throughout the body and how it is metabolized or degraded. These differences, though, are not clinically significant. The echinocandins are not appreciably metabolized by the cytochrome P-450 enzyme system, but their interactions with drug transport proteins remain to be elucidated.

Caspofungin binds extensively to plasma proteins (primarily albumin). Caspofungin distribution is multiphasic; initially it distributes to plasma and extracellular fluid before being actively transported slowly into the liver and other tissues via organic anion transport proteins.[173,174] The prolonged elimination half-life (8–13 hours) of caspofungin is caused in part by this slow multiphasic distribution.[173,174]

Caspofungin is slowly metabolized in the liver via *N*-acetylation and peptide hydrolysis to inactive metabolites, which are then excreted in bile and feces.[175] Compared with healthy subjects, caspofungin average serum concentrations 24 hours after administration vary greatly and are elevated in surgical ICU patients.[176,177] Body weight and hypoalbuminemia were found to be prognostic factors responsible for these increased caspofungin concentrations.[176] The clinical significance of such findings is unclear. Dosage adjustment is not required in patients with impaired renal function, but the dose should be reduced by 50% in patients with significant hepatic impairment.[178,179] Micafungin distribution and metabolism are not fully understood. After IV administration, micafungin binds extensively to albumin and, to a lesser extent, alpha-1-acid glycoprotein.[180,181] In addition, the hepatic uptake of micafungin involves transport proteins.[180,181] Micafungin is hepatically metabolized to several metabolites, and it is predominately eliminated as parent drug and metabolites in feces, and the pharmacokinetics are unaltered in a state of renal dysfunction.[182] Micafungin is a weak CYP 3A4 inhibitor.[183]

Of all the other echinocandins, anidulafungin binds the least to plasma proteins, has a larger volume of distribution, and achieves lower peak (C_{max}) serum concentrations.[184–186] Anidulafungin is not hepatically metabolized, but rather in the plasma, it undergoes slow nonenzymatic chemical degradation to an inactive peptide breakdown product, which likely undergoes further enzymatic degradation and is excreted in feces and bile.[185,186] The majority of an anidulafungin dose is excreted in feces or urine as unchanged drug.[185,186]

Toxicity and drug interactions. In general, echinocandins are well tolerated but are associated with nonspecific (i.e., fever, headache, nausea, phlebitis, rash, elevated hepatic enzymes) adverse effects, which are generally mild and rarely cause early discontinuation of therapy. Similarly, echinocandins have low potential to interact with other drugs.

Pyrimidine Antifungal Agents

5-Fluorocytosine (5-FU; flucytosine)

Pharmacokinetics and toxicity. 5-Fluorocytosine (5-FC) is a fluorinated pyrimidine related to 5-fluorouracil, and it is the only agent in this therapeutic class. This antimycotic possesses a narrow spectrum of activity and is often associated with significant toxicity. Moreover, when used as monotherapy, resistance develops rapidly. Orally, 5-FC is nearly completely absorbed and distributes to total body water. Hepatic metabolism and protein binding of 5-FC are negligible. Nearly all of a dose is renally excreted as unchanged drug, and renal clearance is highly correlated with CrCl. Reductions in CrCl prolong the half-life of 5-FC.

Myelosuppression is the primary toxicity associated with 5-FC. In addition, 5-FC can cause significant rash, nausea, vomiting, diarrhea, and liver dysfunction. Flucytosine toxicity is associated with elevated drug concentrations and often occurs in the presence of renal dysfunction. Because 5-FC is primarily used in combination with AmB, the effects of renal dysfunction on 5-FC pharmacokinetics and the subsequent risk of toxicity cannot be ignored.

Dosing and Therapeutic Drug Monitoring

Therapeutic drug monitoring for 5-FC is beneficial. Ideally, 5-FC serum concentrations should be maintained between 25 and 100 μg/mL to minimize toxicity and avoid the emergence of resistance. There are several nomograms for dosing 5-FC based on CrCl in patients with renal dysfunction. However, the nomograms are based on serum creatinine measurements; thus they should be used only with chronic renal dysfunction. In addition, the nomographs should be used cautiously in elderly patients. During therapy, any necessary dosage adjustments should be made on the basis of plasma concentrations. Use of lower 5-FC doses (75–100 mg/kg/day) to minimize toxicity has been advocated. In vitro data suggest antifungal efficacy would not be compromised by such dosing.

IN VITRO SUSCEPTIBILITY TESTING OF SYSTEMIC ANTIFUNGAL AGENTS

In vitro susceptibility testing of *Candida* spp. is widely accepted. Standardized broth microdilution and disk diffusion methods developed by the Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) for in vitro susceptibility testing of *Candida* spp. are reproducible and accurate. Interpretative breakpoints for *Candida* spp. exist for fluconazole, itraconazole, voriconazole, 5-FC, echinocandins, and posaconazole. For antifungal breakpoints, either CLSI or EUCAST provide data categorizing isolates into susceptible, resistant, and intermediate isolates.[187–193] In contrast to *Candida* spp., in vitro susceptibility testing of *C. neoformans* is not routinely performed because primary resistance to first-line antifungal drugs (5-FC, AmB, fluconazole) is not currently a significant clinical problem, and the susceptibility testing methods and interpretive breakpoints for *Cryptococcus* spp. against any antifungal are not validated.[194] Validated broth microdilution methods for in vitro susceptibility testing methods of *Aspergillus* spp. for the azoles and AmB have been developed, but interpretive breakpoints for these agents have not been established.[195] Validated agar-based disk diffusion methods and commercial kits (Etest) are available and may be reliable methods for determining susceptibilities for *Aspergillus* spp.[195] Although broth microdilution methods for susceptibility testing for *Aspergillus* spp. for the echinocandins exist, the minimum inhibitory concentration (MIC) is not the ideal measure of drug activity for this class of agents.[195] The European Committee on Antimicrobial Susceptibility Testing Subcommittee on Antifungal Susceptibility Testing (EUCAST-AFST) determined breakpoints based on pharmacokinetic and pharmacodynamic data, epidemiologic cutoff values, and clinical experience.[188]

TREATMENT OF FUNGAL INFECTIONS IN THE CRITICALLY ILL

Candidiasis in the ICU

There are many options for empirical therapy of fungal infections in the ICU. For many years, the poor prognosis associated with invasive candidiasis has fueled widespread use of antifungal agents, particularly fluconazole, in ICU patients with or without an established source of fungal infection.

The paradigms of preventive antimycotic therapy are prophylaxis and empirical or "preemptive therapy." Prophylaxis is generally initiated in a population in anticipation of certain risk factors, regardless of whether they ever manifest. There are few data to justify the use of this paradigm in the ICU setting,[196,197] where concerns regarding selection of resistant fungal pathogens with indiscriminate antifungal use persist.[198] Moreover, the risk for invasive candidiasis is not the same for all ICU patients, and some risk factors evolve during an ICU stay. Therefore universal institution of antifungal prophylaxis in the general ICU population is generally discouraged in favor of a more targeted approach selectively directed toward those patients at the highest risk.[196,198] *Empiric treatment,* or fever-driven approach, describes the situation of a patient at risk for invasive candidiasis with persistent fever but no other symptom or microbiologic evidence present.

Preemptive therapy is the administration of antifungal treatment before the occurrence of a septic syndrome in patients with several risk factors for infection and evidence of significant *Candida* colonization.[198]

Historically, AmB-d was the sole option for prevention or treatment of candidiasis in the ICU setting. However, the risk of nephrotoxicity and the advent of safe and effective alternatives such as the echinocandins have diminished its use in the ICU.

Prophylaxis

Most studies of prophylactic antifungal use in the ICU setting have evaluated fluconazole. A placebo-controlled study for the prevention of intraabdominal *Candida* infections in a selected group of high-risk abdominal surgical patients showed that daily fluconazole (400 mg) significantly reduced the incidence of invasive candidiasis.[199] This study included patients who had recurrent gastrointestinal perforations or anastomotic leakages; therefore they were at very high risk of developing intraabdominal candidiasis. The patients in this study had moderate acuity (APACHE II score 13), but prophylactic fluconazole prevented *Candida* colonization and dissemination of *Candida* spp. Similar to experiences with HSCT recipients, this study illustrates that when the prophylactic paradigm is selectively applied, it may benefit specific patient populations. This has also been shown in the HSCT population.[199,200] Similar results were obtained in critically ill surgical patients staying in the ICU longer than 3 days.[136,137] However, these results should be interpreted cautiously. This was a single-center study, and true to the paradigm, patient selection was somewhat subjective and based on an anticipated ICU stay of 3 or more days and the clinician's experience. Therefore the results may not be widely generalizable. Others have also prospectively studied prophylactic fluconazole and shown an advantage for low-dose IV fluconazole (100 mg/day) in reducing *Candida* colonization and candidemia, with no effect on either invasive candidiasis or overall mortality.[201] In this double-blind, randomized, placebo-controlled study, all patients received selective digestive decontamination. The incidence of *Candida* infections, particularly candidemia, was significantly less in the fluconazole-treated patients.

Using these three studies and others that included ketoconazole or nonabsorbable antifungal agents, three meta-analyses have attempted to provide further insight into the role of antifungal prophylaxis in critically ill patients, but with disparate results. One analysis concluded that prophylactic fluconazole administration to prevent mycoses in surgical ICU patients successfully decreased the rate of fungal infections, but it did not improve survival.[202] Conversely, a second analysis demonstrated that antifungal prophylaxis indeed reduced the risk of candidemia and resulted in a reduction of overall mortality and attributable mortality (31% and 79%, respectively).[203] The third and perhaps most rigorous meta-analysis demonstrated that antifungal prophylaxis in non-neutropenic critically ill patients reduces proven invasive fungal infections by approximately half and total mortality by approximately one-quarter.[196] Although the analyses had slightly differing results, all concluded that if antifungal prophylaxis is employed, it should be done selectively and targeted toward those patients at high risk of developing infection.[196,202,203] Thus what the prophylactic studies have highlighted is the need to identify high-risk patients for empiric or preemptive therapy.

Empiric Therapy

Empiric therapy is defined as a fever-driven approach in a persistently febrile patient at risk for invasive candidiasis without microbiologic proof of infection. Early treatment of presumed candidemia is favorable, as it is associated with higher survival rates. However, current clinical trials could not show statistically significant prevention of invasive candidiasis.[36,204,205] The optimal time to start empiric antifungal therapy remains unclear. The choice of the antifungal administered should be based on local epidemiology and currently administered drugs (interactions).

Preemptive Therapy (Diagnosis-Driven Approach)

There are few randomized prospective data addressing preemptive therapy. Nonetheless, in the absence of mechanisms to identify patients who would most benefit by preemptive antifungal therapies, this strategy shares similar drawbacks to the prophylactic strategy. However, a growing body of data clearly demonstrates the importance of early institution of antifungal therapy in the adult ICU.[50,52,53,56,57,206] There are a number of predictive rules of varying complexity described in the literature. All of the studies have produced different predictive algorithms; few have been prospectively validated.[67] Although the methods are improving, published methods have yet to be widely applied in ICU patients as part of routine practice. Moreover, there are few data describing the outcomes associated with preemptive therapy instituted based on a predictive rule. One small study assessed the use of a scoring system to identify high-risk patients and demonstrated that fluconazole significantly decreased the incidence of invasive candidiasis in patients with a corrected colonization index (CCI) of $\geq$0.5.[207] Another prospective study to assess whether preemptive antifungal therapy in high-risk ICU patients (CCI $\geq$0.4) would reduce invasive candidiasis demonstrated a significant decrease in the incidence of surgical ICU–acquired invasive candidiasis with preemptive therapy compared with historical controls.[208] However, to generate the CCI, required weekly surveillance cultures at multiple anatomic sites in all ICU patients is necessary. This method is not practical for most ICUs, and it is doubtful that the CCI could be used with similar success without routine surveillance cultures.[60] The serologic detection of 1,3-β-D-glucan, which is not specific for *Candida* spp., is a useful tool for ruling out invasive fungal infection.[35]

With the exception of fluconazole, there are few prospective data assessing the efficacy of other antifungal agents as preemptive therapy in the ICU. Administering itraconazole capsules through feeding and nasogastric tubes, as used in ICU patients, is difficult. Although the oral solution solves this problem, there are few data assessing its effectiveness in preventing or treating invasive candidiasis. Furthermore, the use of itraconazole in critically ill patients is also limited by a significant drug–drug interaction profile with agents commonly used in the ICU.

In case of invasive candidiasis caused by multiresistant *C. auris,* expert consultation at national or international reference centers with regard to susceptibility testing and tailored treatment should be sought. The newly developed EQUAL Candida Score (a European Confederation of Medical Mycology [ECMM] score derived from current guidelines to measure the QUAlity of Clinical Candidaemia Management) aids in guideline-conforming diagnosis and treatment.[209,210]

The recommended antifungal therapy for candidiasis in the ICU setting is summarized in Table 118.2.

Invasive Aspergillosis, Mucormycosis, and Other Opportunistic Mycoses in Bone Marrow Transplantation

Fever and neutropenia are common among critically ill immunocompromised individuals with hematologic malignancies. Although fever can be the result of many causes, these patients, and particularly leukemia and HSCT recipients, are at risk of developing invasive fungal infections caused by *Candida, Aspergillus* spp., or Mucorales. Owing to the difficulty in diagnosing infections caused by these pathogens, antifungal prophylaxis is standard in HSCT patients. Fluconazole has been shown to decrease the incidence of invasive infections with *Candida* spp. and is widely used in the prophylactic paradigm.[199] As stated previously, invasive aspergillosis occurs relatively late after transplantation. Therefore persistently febrile HSCT recipients should be treated empirically with antifungal agents with activity against molds, particularly *Aspergillus* spp.

TABLE 118.2 Summary of Recommended Antifungal Therapy for Aspergillosis, Candidiasis, and Mucormycosis in the ICU Setting

Infection	Recommended Treatment	Alternative Treatment
Invasive Aspergillosis		
Targeted therapy	VCZ, 6 mg/kg IV q12h for 1 day, followed by 4 mg/kg q12h; oral dose is 200 mg q12h if already administered IV; if not, loading is needed *or* ISA, 200 mg TID IV for 2 days, followed by 200 mg/d IV thereafter. Oral dose is 200 mg/d if already administered IV; if not, loading is needed.	Consider if prior azole exposure, L-AmB, 3 mg/kg/d IV Caspofungin 70 mg IV on day 1 and 50 mg/d IV thereafter. If body weight >80 kg, consider continuation with 70 mg/d IV.
Empirical therapy (fever-driven approach)	Caspofungin 70 mg IV on day 1 and 50 mg/d IV thereafter. If body weight >80 kg, consider continuation with 70 mg/d IV.	
Prophylaxis invasive aspergillosis	PCZ tablet 300 mg BID PO on day 1 and 300 mg/d PO thereafter. PCZ 300 mg BID IV on day 1 and 300 mg/d IV thereafter in patients unable to swallow.	
Invasive Candidiasis (Candidemia)*		
Treatment (non-neutropenic) Alphabetic order	Echinocandin – Anidulafungin 200 mg IV on day 1 and 100 mg/d IV thereafter *or* caspofungin 70 mg IV on day 1 and 50 mg/d IV thereafter (if body weight >80 kg, consider continuation with 70 mg/d IV) *or* micafungin 100 mg/d IV – Consider local epidemiology (*C. parapsilosis*, *C. krusei*) and susceptibility testing – if *C. parapsilosis* switch to FCZ 400 mg/d IV.	L-AmB 3 mg/kg/d *or* VCZ 6 mg/kg IV q12h for 1 day, followed by 4 mg/kg q12h; oral dose is 200 mg q12h.
Treatment (neutropenic)	Caspofungin 70 mg IV on day 1 and 50 mg/d IV thereafter (if body weight >80 kg, consider continuation with 70 mg/d IV) *or* micafungin 100 mg/d IV.	Anidulafungin 200 mg IV on day 1 and 100 mg/d IV thereafter *or* L-AmB 3 mg/kg/d. FCZ 400 mg/d IV should be used as step-down only.
Suspected candidiasis treated with empirical antifungal therapy (non-neutropenic patients)	Early treatment for suspected candidiasis is associated with higher survival. However, because of lack of data, no specific drug can be recommended. Choose according to local epidemiology, administered drugs (interactions) from antifungals recommended for candidemia.	
Suspected candidiasis treated with empiric antifungal therapy (neutropenic patients)	L-AmB 3 mg/kg/d *or* caspofungin 70 mg IV on day 1 and 50 mg/d IV thereafter (if body weight >80 kg, consider continuation with 70 mg/d IV).	Micafungin 100 mg/d IV *or* VCZ 6 mg/kg IV q12h for 1 day, followed by 4 mg/kg q12h; oral dose is 200 mg q12h.
Prophylaxis	FCZ 400 mg/d while patients are at high risk.	Micafungin 50 mg/d IV, caspofungin 70 mg IV on day 1 and 50 mg/d IV thereafter (if body weight >80 kg, consider continuation with 70 mg/d IV).
Mucormycosis		
Targeted therapy	L-AmB 5–10 mg/kg/d IV.	ISA 200 mg TID IV for 2 days, followed by 200 mg/d IV thereafter. PCZ 300 mg BID IV on day 1 and 300 mg/d IV thereafter.
Prophylaxis	PCZ tablet 300 mg BID PO on day 1 and 300 mg/d PO thereafter.	

*In case of invasive candidiasis caused by multiresistant *C. auris,* expert consultation at national or international reference centers with regard to susceptibility testing and tailored treatment should be sought. First-line therapy remains an echinocandin, provided that specific susceptibility testing follows as soon as possible.

BID, Twice daily; *FCZ,* fluconazole; *ISA,* isavuconazole; *ITZ,* itraconazole; *IV,* intravenous; *L-AmB,* liposomal amphotericin B; *PCZ,* posaconazole; *PO,* per os; *TID,* three times a day; *VCZ,* voriconazole.

Adapted from Mora-Duarte J, Betts R, Rotstein C, et al. Comparison of caspofungin and amphotericin B for invasive candidiasis. *N Engl J Med.* 2002;347:2020–2029; Pappas PG, Kaufman CA, Andes D, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2009;48:503–535; Walsh TJ, Anaissie EJ, Denning DW, et al. Treatment of aspergillosis: Clinical practice guidelines of the Infectious Diseases Society of America. *Clin Infect Dis.* 2008;46:327–360; Ullmann AJ, Aguado JM, Arikan-Akdagli S, et al. Diagnosis and management of *Aspergillus* diseases: Executive summary of the 2017 ESCMID-ECMM-ERS guideline. *Clin Microbiol Infect.* 2018;24(Suppl 1):e1–e38; Cornely OA, Alastruey-Izquierdo A, Arenz D, et al. Global guideline for the diagnosis and management of mucormycosis: An initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. *Lancet Infect Dis.* 2019;19(12):PE405–E421; Cornely OA, Bassetti M, Calandra T, et al. ESCMID guideline for the diagnosis and management of *Candida* diseases 2012: Non-neutropenic adult patients. *Clin Microbiol Infect.* 2012;18(Suppl 7):19–37; Ullmann AJ, Akova M, Herbrecht R, et al. ESCMID guideline for the diagnosis and management of *Candida* diseases 2012: Adults with haematological malignancies and after haematopoietic stem cell transplantation (HCT). *Clin Microbiol Infect.* 2012;18(Suppl 7):53–67; and Koehler P, Cornely OA. Contemporary strategies in the prevention and management of fungal infections. *Infect Dis Clin North Am.* 2016;30(1):265–275.

For many years "high-dose" AmB-d was employed as standard empirical therapy of invasive aspergillosis, but within the last decade, based upon data from a randomized trial that compared voriconazole with AmB and suggested superiority with the azole, voriconazole has been considered the gold-standard therapy of documented and suspected aspergillosis.[211] Although voriconazole is considered an initial option for prophylactic therapy, the choice of therapy may vary based upon the individual's organ function. Voriconazole may not be ideal in cases where liver disease is present or if the patient is being treated with concomitant medicines that interact with this azole. Similarly, the presence of reduced renal function may preclude the use of lipid AmB formulations. Fluconazole lacks activity against molds. Itraconazole has activity against *Aspergillus* spp., but as discussed previously, the capsule dosage form is not suitable for many critically ill patients and produces erratic blood levels. The oral solution of itraconazole is not well tolerated and is commonly associated with diarrhea. If available, IV itraconazole solution suffers the same drawback as lipid AmB formulations in patients with diminished renal function. With the new tablet and IV formulations, posaconazole can be administered to critically ill patients independent of food intake or oral application.

The latest development and clinical data on isavuconazole show noninferiority in comparison with voriconazole for the treatment of invasive aspergillosis, but improved tolerability.[156] With their lack of toxicity and low propensity for drug–drug interactions, the echinocandins are promising agents for empirical therapy of invasive aspergillosis in critically ill patients.

For influenza-associated pulmonary aspergillosis pneumonia, neuraminidase inhibitors are first-line therapy. Antifungals are combined as described earlier (mainly voriconazole or isavuconazole). Vaccination is most important to decrease influenza-related illness, especially in patients with comorbidities.[104] The newly developed EQUAL Aspergillosis Score aids in guideline-conforming diagnosis and treatment.[212]

Patients with profound immunosuppression are at risk for mucormycosis, and targeted treatment differs considerably from therapy of Invasive Aspergillosis (IA). With surgery being an integral part of therapy, as it decreases mortality, initiation of high-dosage liposomal amphotericin B or isavuconazole appears warranted.[101,103,156,157,213] A combination of isavuconazole or posaconazole with high-dose L-AmB may be needed in patients with extensive disease.[101,103] The newly developed EQUAL Mucormycosis Score aids in guideline-conforming diagnosis and treatment.[214]

Recommended antifungal therapy for the treatment of invasive aspergillosis and mucormycosis in the ICU setting is summarized in Table 118.2.

Cryptococcosis, Histoplasmosis, and Blastomycosis

Although cryptococcosis, histoplasmosis, blastomycosis, and coccidioidomycosis are not considered nosocomial mycoses, patients with severe infections may require intensive care. The treatment of cryptococcosis, and particularly that in the CNS, evolved from a series of classic clinical trials. Current guidelines base their recommendations on the best data available to address unresolved questions surrounding treatment of this infection.[215] Recommended antifungal therapy for treatment of cryptococcosis in the ICU setting is summarized in Table 118.3.

Management of Increased ICP in CNS Cryptococcosis

Elevations in intracranial pressure (ICP) occur in more than half of patients with cryptococcal meningitis and contribute significantly to the morbidity and mortality associated with this infection.[215] There are much less data on treatment of HIV-negative patients with acute elevated ICP with regard to recommendations of pressure control. Therefore ICP management may be underused in the management of non–HIV-infected patients with CNS cryptococcosis. Persistent elevations in ICP should be managed by sequential lumbar punctures.[215] If necessary, more invasive procedures, including insertion of a lumbar drain or placement of a ventriculoperitoneal shunt, should be performed.[215] The frequency with which sequential lumbar punctures are performed depends on the initial opening pressure and symptoms. For patients with elevated baseline opening pressure, lumbar puncture should be done to reduce the pressure 50% and performed daily to maintain the ICP in the normal range.[215]

Serum and CSF antigen titers are important in establishing the presumptive diagnosis and assessing the prognosis of CNS infection. The test measures cryptococcal polysaccharide capsule antigens but does not differentiate viable from nonviable organisms. Therefore once therapy is started, treatment decisions should not be based on antigen test results.[215] A reduction in antigen titers during therapy is desired, but treatment decisions should be based on culture results. The newly developed EQUAL Cryptococcosis Score aids in guideline-conforming diagnosis and treatment.[216]

Treatment of Histoplasmosis in Critically Ill Patients

Although there are no comparative studies, the efficacy of individual antimycotics for therapy of chronic and disseminated histoplasmosis has been well documented. AmB-d and itraconazole have proven efficacy. The efficacy of 6 weeks to 4 months of AmB-d therapy for chronic infection is approximately 75%; however, relapse is common. The efficacy of itraconazole ranges from 75% to 85%, but, as is the case for AmB-d, relapse may be common. In vitro susceptibility of *H. capsulatum* to fluconazole is poor, and generally it is not used to treat this infection. Voriconazole and posaconazole are likely effective in the treatment of histoplasmosis, but data assessing their safety or efficacy as treatment for this infection are lacking.

The efficacy of AmB-d for therapy for disseminated histoplasmosis among immunocompetent patients is 70% to 90%. Therefore AmB-d is recommended initially in severely ill patients. In a small study, all patients responded to itraconazole 200 to 400 mg daily.[217] Once an adequate response is noted to AmB-d, therapy can be switched to itraconazole.[217] Few data exist concerning the efficacy of the lipid AmB formulations as therapy for disseminated histoplasmosis in immunocompetent patients. Recommended antifungal therapy for treatment of histoplasmosis in the ICU setting is summarized in Table 118.3.

Treatment of Disseminated (Extrapulmonary) Blastomycosis in the Critically Ill

Disseminated blastomycosis and diffuse pulmonary infection are both associated with significant mortality. Treatment of these infections produces cure rates ranging from 85% to 90%, and the effective agents cause little associated toxicity.[119] The optimal duration of therapy for the treatment of blastomycosis with existing antifungal agents is unknown and has been empirically derived from noncomparative studies and clinical experience. In cases of life-threatening infections or extrapulmonary disease and in patients who are severely immunocompromised or have already failed therapy with an azole, the risk of relapse is high.[119] Therefore the duration of therapy is lengthy to prevent relapse. Patients can be switched to safer azole therapy when significant improvement is observed.[119] Pharmacologic treatment of blastomycosis in the ICU setting is summarized in Table 118.3.

TABLE 118.3 Summary of Recommended Antifungal Therapy for Cryptococcosis and Endemic Mycoses in the ICU Setting

Infection	Recommended Treatment(s)	Alternative Treatment
Cryptococcosis		
CNS infection (HIV infected) – Antiretroviral therapy should be delayed to avoid immune reconstitution syndrome	Induction: AmB-d 0.7–1 mg/kg/d IV + 5-FC 100 mg/kg/d PO *or* L-AmB 3–6 mg/kg/d IV *or* ABLC 5 mg/kg/d IV + 5–FC 100 mg/kg/d PO for 4–6 wk, Consolidation: FCZ or ITZ 400 mg/d PO for 8 wk, followed by maintenance with FCZ 200 mg/d PO if disease free and CD4 count >200 μ/L	AmB-d 0.7–1 mg/kg/d IV + FCZ 800 mg/d PO FCZ ≥800–1200 mg/d PO favorable + 5-FC 100 mg/kg/d PO
CNS infection (transplant recipient)	Induction therapy: L-AmB 3–6 mg/kg/d IV *or* ABLC 5 mg/kg/d IV + 5-FC 100 mg/kg/d PO for at least 2 wk Consolidation therapy: FCZ 400–800 mg/d PO for 8 wk Maintenance therapy: FCZ 200–400 mg/d PO for 6 mo to 1 yr	L-AmB 6 mg/kg/d *or* ABLC 5 mg/kg/d for 4–6 wk
CNS infection (non-HIV, nontransplant recipient)	Induction: AmB-d 0.7–1 mg/kg/d IV + 5-FC 100 mg/kg/d PO for at least 4 wk *or* AmB-d 0.7–1 mg/kg/d IV for ≥6 wk *or* L-AmB 3–6 mg/kg/d IV *or* ABLC 5 mg/kg/d IV + 5-FC 100 mg/kg/d PO, if possible ≥4 wk *or* AmB-d 0.7 mg/kg/d IV + 5-FC, 100 mg/kg/d PO for 2 wk Consolidation therapy: FCZ 400–800 mg/d PO for 8 wk Maintenance therapy: FCZ 200 mg/d PO for 6 mo to 1 yr	
Histoplasmosis		
Acute pulmonary (moderately severe to severe)	L-AmB 3–5 mg/kg/d IV; *or* AmB 0.7–1 mg/kg/d IV for 1–2 wk ± corticosteroids, then ITZ 200 mg PO BID for 12 wk	
Progressive disseminated histoplasmosis (moderately severe to severe)	L-AmB 3–5 mg/kg/d IV *or* ABLC 5 mg/kg/d IV; *or* AmB-d 0.7–1 mg/kg/d IV for 1–2 wk; followed by ITZ 200 mg PO BID for at least 1 yr	
Blastomycosis		
Pulmonary (moderately severe to severe)	L-AmB 3–5 mg/kg/d IV; *or* AmB-d 0.7–1 mg/kg/d IV until clinical improvement; followed by ITZ 200 mg PO BID for 6–12 mo	
Extrapulmonary (Disseminated)		
CNS	L-AmB 5 mg/kg/d IV until clinical improvement; followed by an oral azole for at least 1 yr (e.g., FCZ 400–800 mg/d PO *or* ITZ 200 mg PO BID)	
Non-CNS (moderately severe to severe)	L-AmB 3–5 mg/kg/d IV; *or* AmB-d 0.7–1 mg/kg/d IV for 1–2 wk; followed by ITZ 200 mg PO BID for 12 mo	

5-FU, 5-Fluorouracil; *ABLC*, amphotericin B lipid complex; *BID*, Twice daily; *CNS*, central nervous system; *FCZ*, fluconazole; *HIV*, human immunodeficiency virus; *ITZ*, itraconazole; *IV*, intravenous; *L-AmB*, liposomal amphotericin B; *PO*, per os; *VCZ*, voriconazole.
Adapted from Perfect JR, Dismukes WE, Dromer F, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2010;50:291–322; Wheat LJ, Freifield AG, Kleiman MB, et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2007;45:807–825; Limper AH, Knox KS, Sarosi GA, et al. An official American Thoracic Society statement: Treatment of fungal infections in adult pulmonary and critical care patients. *Am J Respir Crit Care Med.* 2011;183(1):96–128; and Chapman SW, Dismukes WE, Proia LA, et al. Clinical practice guidelines for the management of blastomycosis: 2008 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2008;46:1801–1812.

CONCLUSIONS

Invasive fungal infections are widespread in critically ill patients. Specifically in the ICU setting, *Candida* spp. are a common cause of nosocomial BSIs. Many risks are associated with the ICU environment or the patients' underlying disease states that predispose them to infections with these pathogens. In addition, historically, because of the high mortality associated with BSIs caused by *C. albicans*, this species has been the primary fungal pathogen of concern. Although the epidemiology of *Candida* isolates in the ICU continues to shift, whether the changing epidemiology is a consequence of injudicious antifungal use is a matter of speculation and debate. Nonetheless, the steady increase in BSIs caused by *C. glabrata*, a species with reduced susceptibility to antifungal therapy, is concerning. Furthermore, select populations of critically ill patients are at risk of developing life-threatening infections resulting from *Aspergillus* spp., *Fusarium* spp., and the Mucorales. These pathogens are angioinvasive and often respond poorly to antifungal therapy. The endemic mycoses (e.g., histoplasmosis, blastomycosis, and coccidioidomycosis) are not typically a concern in the ICU setting, but patients with severe infections caused by *B. dermatitidis*, *H. capsulatum*, or *C. immitis* will often require intensive care.

Methods to perform antifungal susceptibility tests on a variety of pathogens, particularly *Candida* spp., are becoming routine in clinical practice. There is improved understanding of antifungal resistance and the pharmacodynamic actions of antifungal drugs. This understanding may ultimately lead to more rational use of antifungal agents and improved outcomes in infected patients. The advent of additional safer agents means that the available drugs differ sufficiently in terms of toxicity and potential for drug–drug interactions and that clinicians have the luxury of choice when tailoring antifungal therapy to a specific patient.

KEY POINTS

Overview

- Generally, fungal infections are more prevalent in ICUs than on the general medical wards. Although *Candida* spp. are the most commonly isolated fungi in critically ill patients, infections caused by other opportunistic fungal pathogens (i.e., *Aspergillus, Cryptococcus neoformans, Fusarium,* and Mucorales) are also a concern in selected critically ill populations.
- New antifungal agents differ in mode and spectrum of activity, toxicity, and propensity to interact with other drugs. Antifungal therapy has to be tailored to the specific fungal pathogen and the needs of the patient.

Fungal Infections in the Critically Ill

- *Candida albicans* is the primary fungal pathogen in the ICU setting, but the prevalence of a given species may vary with age. For example, candidemia among neonates is predominantly the result of *C. albicans* and *C. parapsilosis* and rarely because of *C. glabrata* or other *Candida* spp. In adults, *C. glabrata* and *C. albicans* predominate.
- Age differences in the isolation of specific species may have important repercussions for infection control, dosing, and selection of antifungal agents in older critically ill patients.
- BSIs caused by *C. glabrata* have continually become more prevalent.
- In the ICU, *Candida* BSIs are common and difficult to detect, and consequently they carry a relatively poor prognosis. Although isolation techniques have improved, the attributable mortality rate associated with *Candida* BSIs is 35%, and *Candida* spp. are the only BSI pathogens that are an independent predictor of mortality. In surviving patients, candidemia adds approximately 1 month to the length of hospital stay.
- Critically ill patients with hematologic malignancies are at high risk for infections caused by *Candida, Aspergillus* spp., and Mucorales. Infections resulting from these pathogens are associated with high mortality. Influenza-associated pulmonary aspergillosis does not need underlying hematologic malignancy or immunosuppression as a prerequisite and shows high morbidity in critically ill patients.

Systemic Antifungal Agents

- AmB-d possesses a broad spectrum of activity and a long history of use with little acquired resistance, but its toxicity is significant, and it is potentially costly. In low doses for short courses, this agent is tolerable.
- Lipid AmB formulations are safer than AmB-d, but their cost may limit their use.
- Triazoles (azoles) possess a broad spectrum of activity and are relatively safe, but they interact with a vast array of drugs that are commonly used in ICU populations.
- Echinocandins are safe and interact with few drugs, but their spectrum of activity is limited to primarily *Candida* and *Aspergillus* spp.

Treatment of Fungal Infections in the Critically Ill

- The paradigms of preventive antifungal therapy are prophylaxis, empirical, and preemptive therapy. There are few data to support these three approaches. *Empirical therapy* is the administration of antifungals to patients with persistent fever as the only symptom of a potential fungal infection. *Preemptive therapy* is the administration of antifungal treatment before the appearance of sepsis syndrome in patients with risk factors for infection and evidence of significant *Candida* colonization.
- The treatment of CNS cryptococcosis evolved from a series of classic clinical trials. Elevations in ICP occur in more than 50% of patients and contribute significantly to the morbidity and mortality of this infection. Therefore in addition to antifungal therapy, elevations in ICP should be managed by sequential lumbar punctures. Serum and CSF antigen titers aid in the presumptive diagnosis and assessing the prognosis of infection. A reduction in antigen titers during therapy is desired, but treatment decisions should be based on culture results.

References for this chapter can be found at expertconsult.com.

ANNOTATED REFERENCES

Garey KW, Rege M, Pai MP, et al. Time to initiation of fluconazole therapy impacts mortality in patients with candidemia: a multi-institutional study. *Clin Infect Dis.* 2006;43:25–31.
Inadequate antimicrobial treatment is an independent determinant of hospital mortality, and in companion publications, this group demonstrated the most common causes of inappropriate therapy for fungal BSIs are omission of initial empirical therapy and incorrect dosing of fluconazole. In this work, the authors link inadequate therapy to mortality. They demonstrate that delays in initiation of therapy of more than 24 hours were independently associated with mortality in candidemia patients. The rate of development of newer and more potent antifungal agents is tailing off. Thus this work, which has been subsequently corroborated, illustrated that current antifungal agents, if used properly, can perhaps help reduce mortality more than realized to date. In addition, it calls attention to the need to focus on early appropriate therapy as a strategy to reduce the significant mortality associated with candidemia.

Golan Y, Wolf MP, Pauker SG, et al. Empirical anti-*Candida* therapy among selected patients in the intensive care unit: a cost-effectiveness analysis. *Ann Intern Med.* 2005;143:857–869.
*Few studies have prospectively evaluated antifungal prophylaxis, and meta-analyses of these studies all produce slightly different conclusions. However, the meta-analyses all agree that in the ICU, targeted empirical therapy directed at targeted high-risk ICU patients is probably a better strategy than general prophylaxis. However, even fewer studies have prospectively evaluated empirical therapy directed at targeted high-risk ICU patients. This study provides a decision analytic model to evaluate the cost-effectiveness of empirical anti-*Candida *therapy given to high-risk patients in the ICU, defined as those with altered temperature (fever or hypothermia) or unexplained hypotension despite 3 days of antibacterial therapy in the ICU. In doing so, they identify that although empirical caspofungin is the most effective strategy, it does not reduce mortality at an acceptable cost. On the other hand, empirical amphotericin B, regardless of formulation, was the least effective strategy, owing to drug toxicity. Thus the most effective strategy was empirical fluconazole, because it reduced mortality at an acceptable cost.*

Maertens JA, Raad II, Marr KA, et al. Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by *Aspergillus* and other filamentous fungi (SECURE): *a* phase 3, randomised-controlled, non-inferiority trial. *Lancet. 2016;387*(10020):760–769.
This was a phase 3, double-blind, multicenter, comparative-group study. Patients with suspected invasive mold disease were randomized in a 1:1 ratio to receive isavuconazonium sulfate or voriconazole. Isavuconazole was noninferior to voriconazole for the primary treatment of suspected invasive mold disease and was well tolerated, with fewer study drug-related adverse events.

Pittet D, Li N, Woolson RF, et al. Microbiological factors influencing the outcome of nosocomial bloodstream infections: a 6-year validated, population-based model. *Clin Infect Dis.* 1997;24:1068–1078.
This article provides compelling data concerning the importance of Candida *spp. as bloodstream pathogens, in addition to data regarding the crude and attributable mortality rates of* Candida *BSIs in the hospital. The study demonstrates that of all the microbial causes of BSIs, only* Candida *spp. are an independent predictor of mortality resulting from BSI.*

Schauwvlieghe A, Rijnders BJA, Philips N, et al. Invasive aspergillosis in patients admitted to the intensive care unit with severe influenza: *a* retrospective cohort study. *Lancet Respir Med. 2018;*6(10):782–792.
This is the first major study reporting the incidence of invasive pulmonary aspergillosis over several seasons in patients with influenza pneumonia in the ICU. Influenza was identified as an independent risk factor for invasive pulmonary aspergillosis showing high mortality.

Wey SB, Mori M, Pfaller MA, et al. Risk factors for hospital-acquired candidemia: a matched case-control study. *Arch Intern Med.* 1989;149:2349–2353.
This study was one of the first rigorous epidemiologic assessments of the risk factors that predispose patients to candidemia. Established risk factors have been borne out on subsequent analyses.

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Influenza and Acute Viral Syndromes

Sylvain A. Lother, Anand Kumar, and Steven M. Opal

Acute viral infections can produce a variety of clinical manifestations and differing degrees of severity. The vast majority of viral infections range from asymptomatic to mild, occur in the community, and are self-limited. Rarely, acute viral infections cause severe disease, which necessitates critical care management. Common viral upper respiratory tract infections can cause serious acute exacerbations of underlying lung disease. Certain viral agents can become life-threatening when they infect vulnerable hosts or if novel pathogens emerge with an absence of immunologic experience in humans. Systemic viral infections, particularly seasonal and pandemic influenza, will be covered in this chapter. However, the increasing availability of rapid genomic diagnostics, immunotherapies, and antiviral chemotherapies now necessitates that intensive care unit (ICU) clinicians maintain some working familiarity with other viral pathogens that can cause serious illness. A summary of clinical presentations, major pathologies, mechanisms of spread, and treatment strategies for a variety of human viral pathogens will be reviewed.

INFLUENZA

Influenza is an acute febrile respiratory illness of varying severity causing seasonal epidemics during the winter months in temperate climates and year-round endemic infections in tropical climates. This viral zoonosis is indigenous to migratory wild birds, with periodic introduction into domesticated poultry, swine, marine mammals, and humans. The consequences of viral pathogen transfer from the avian reservoir or animal vectors to humans can be devastating, with substantial mortality rates, rapid transmission, and potential for global pandemics. The fate of influenza virus infection in human populations depends on the viral virulence properties, antigenic differences from previous influenza outbreaks, fitness of viral replication, dissemination within humans, and status of the host immune defenses.[1]

For seasonal cases, severe disease may occur in individuals with vulnerabilities in host defenses, including the very young, the very old, and those with immunodeficiency or chronic cardiopulmonary disease. However, healthy and young individuals can be seriously affected, particularly in pandemic years when novel viruses emerge. The incidence rates of epidemics depend on yearly variation in viral transmissibility, infectivity, and host susceptibility. Influenza pandemics typically have much higher incidence rates as the virus circulates throughout the entire susceptible global population. In 2009 the H1N1 pandemic swept through a huge number of patients susceptible to the novel swine influenza A (H1N1)pdm09.[2] Other historic pandemics included the Spanish flu of 1918 (H1N1), the Asian flu of 1957 (H2N2), and the Hong Kong flu of 1968 (H3N2). The Spanish flu was particularly catastrophic, infecting a third of the world's population and killing an estimated 50–100 million people.[3]

Even in a typical nonpandemic year, influenza accounts for hundreds of thousands of deaths worldwide and exacts billions of dollars in terms of morbidity and lost productivity. Estimates from the United States indicate that each year, at least 610,660 life-years are lost, with between 9 and 45 million illnesses, up to 31.4 million outpatient visits, 12,000–61,000 deaths, and ~$10.4 billion in direct medical costs from influenza alone.[4,5] The staggering amount expended for influenza care is $16.3 billion in projected lost earnings and an estimated total cost burden (including lost life-years) amounting to $87.1 billion.[4] The estimated global mortality varies from 291,000 to 645,000 deaths per year,[6] and global costs during a pandemic year such as 2009 have been estimated to be upwards of 374 billion dollars.[7] The costs of intensive care services required for managing the most severely ill influenza victims alone are enormous.[2]

Pathogenicity of Influenza Viruses

Influenza viruses are single-stranded RNA viruses of the family Orthomyxoviridae that are classified by their matrix protein composition.[1,8] Three influenza types can infect humans: influenza A, influenza B, and influenza C. The influenza A virus is divided into specific subtypes based upon two major antigenic proteins on its surface: hemagglutinin (HA) and neuraminidase (NA). Influenza A can replicate in the gastrointestinal (GI) tract of some avian species without causing symptoms, but infection and symptoms may occur in other bird species, mammals, and humans. It is the only subtype with pandemic potential. Influenza B almost exclusively infects humans. The lack of animal reservoir leads to less genetic variability, making pandemics with influenza B not possible. However smaller-scale mutations cause seasonal epidemics with potential serious repercussions. Influenza C affects humans, dogs, and pigs but seldom causes severe illness or epidemics in humans.[9]

Influenza virus has a particular predilection for respiratory epithelial cells. Infected cells undergo abrupt cessation of protein synthesis and subsequent apoptosis. Viral particles are released infecting nearby cells. Local immune cells are also infected, causing measurable deficiencies in immune function, increasing the likelihood of secondary complications. Lung histopathology of fatally infected patients reveals a diffuse alveolar filling process, with early hyaline membrane formation, and occasionally focal areas of hemorrhage.[10] The alveolar lining is thickened, with lymphocytic infiltrates and, occasionally, early fibrosis. A typical lung tissue section is seen in Fig. 119.1.

Influenza A Epidemics and Pandemic Potential

The genome of influenza A viruses consists of eight separate single-stranded RNA segments, each encoding a major viral protein. RNA replication provides a high background mutation rate resulting in antigenic "drift"—point mutations that change the major surface

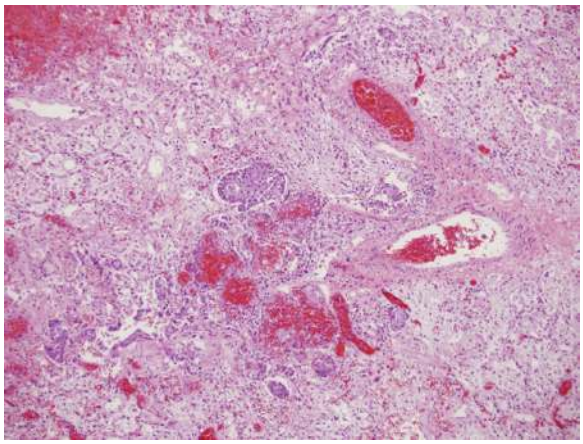

Fig. 119.1 Lung pathology of fatal case of primary influenza pneumonia in a previously healthy 20-year-old woman. Note diffuse alveolar filling, squamous metaplasia, lymphocytic infiltrates, and focal hemorrhage. *(Figure courtesy of David Horn, MD.)*

antigens. The resulting variation is sufficient to evade host immune responses and cause seasonal epidemics. However, influenza pandemics typically occur after an antigenic "shift"—when animal vectors are coinfected simultaneously by more than one influenza A subtype, large-scale reassortment of viral genome segments can occur, resulting in entirely new hybrid viruses with new antigenic constituents. As an example, the swine-origin influenza A/Mexico City/4/2009 (H1N1) pandemic strain was a quadruple-reassorted virus derived from gene segments originating from ducks, Eurasian swine, North American swine, and human-adapted influenza viruses.[11]

Avian-origin influenza viruses can occasionally be transmitted to mammals, causing outbreaks in animals and potentially giving rise to human pandemics. Swine are important "mixing vessels" in shuttling avian influenza viruses to humans.[1] Their mucous membranes express a diversity of sialic acid–coated glycopeptides in a favorable conformation to bind both avian and human viruses via the HA glycoprotein. Avian species primarily express α2,3-linked sialic acids, human upper airways primarily express α2,6-linked sialic acids, and swine express both receptors. This biochemical arrangement in swine facilitates simultaneous dual infections with avian- and human-adapted viruses and the attendant risk of hybrid viruses.[1,11,12]

Seasonal influenza strains in humans bind readily to α2,6 linkages found in the upper airways. This usually leads to high transmission frequency by airborne droplets deposited upon the upper airways, but a relatively low risk of primary influenza pneumonia.[13] However, the lower airways and alveolar pneumocytes of humans express α2,3-linked sialic acids, and avian viruses that bind efficiently to α2,3 linkages can cause severe lower tract disease if deposited into the distal airways. The avian strain of H5N1 preferentially binds to α2,3 linkages in the distal airways, and therefore is poorly transmissible but can cause severe pneumonia. Poultry workers, particularly those in close proximity to infected livestock, can receive large enough inoculums into the distal airways to cause severe pneumonia, with mortality rates ranging from 50%–70%.[13,14]

Notably, the Spanish flu of 1918 (subtype of H1N1) expressed an HA that could bind with high affinity to both α2,6- and α2,3-linked sialic acids.[15,16] This resulted in high transmissibility and spread within the upper airways in addition to severe pneumonia. Disturbingly, the recent 2009 pandemic subtype of H1N1 also bound with high affinity to both α2,6- and α2,3- linkages, resulting in potential for high transmissibility and severe devastation. However, much lower case-fatality rates were seen (<0.1%), likely attributed to fewer viral virulence factors (Table 119.1). Other mitigating factors included infection control strategies, large-scale vaccination, improved supportive care, and effective antivirals. Additionally, populations born before the early 1950s

TABLE 119.1 Pathogenicity Traits and Virulence Factors of Influenza Viruses

Viral Trait	Mechanism of Virulence	Comments
HA and NA – epitope variations	Immune escape from recognition by preexisting antibodies within the population from previous virus exposure	Antigenic drift (point mutations) leads to epidemics; antigenic shift (reassorted genomes) leads to pandemics
HA – cleavability	HA undergoes proteolysis by host-derived proteases before receptor binding	Readily cleaved HA is associated with avid binding and disease severity
HA – binding preference	α2,3-linked sialic acid receptor in alveoli; α2,6 linkage in upper airways	Viruses that bind to the α2,3 linkage or both α2,3 and α2,6 are more virulent; cause lower tract disease and increased transmissibility
HA:NA ratio	NA cleaves sialic acid glycopeptides on host epithelium (binding site for HA)	Optimal ratio of NA and HA activity needed for high replication and viral shedding
NS-1	This viral nonstructural protein inhibits host innate and adaptive immune response; inhibits IFN expression; blocks T-cell activation	Some subtypes have truncated variants of NS-1, associated with lower virulence
PB1-F2	This viral peptide targets host mitochondria, induces apoptosis in CD8 T cells and alveolar macrophages, increases severity of viral pneumonia, increases risk of secondary bacterial infection	Many subtypes do not encode full-length PB1-F2; truncated forms of PB1-F2 are associated with lower virulence; absence of full-length PB1-F2 in 2009 H1N1 pandemic strain led to lower pathogenicity
NA inhibitor resistance	H275Y mutation in the viral NA gene, alters NA inhibitor binding site, leads to oseltamivir resistance	Previously common mutation in seasonal H1N1, but rarely seen in the 2009 H1N1 pandemic strain and in circulating subtypes since then
M2 inhibitor resistance	S31N mutation in viral M2 gene, alters M2 inhibitor binding site, leads to amantadine and rimantadine resistance	Common in both H3N2 and H1N1 circulating subtypes
PB2 temperature range	Viral polymerase preferentially replicates at lower temperatures in mammalian respiratory tract and at higher temperatures in avian GI tract	Mutant polymerases can effectively replicate at broad temperature range, aiding transfer from birds to humans

GI, Gastrointestinal; *H275Y,* histidine substitution for tyrosine at amino acid at position 275; *HA,* hemagglutinin; *IFN,* interferon; *M,* matrix protein; *NA,* neuraminidase; *NS-1,* nonstructural protein; *PB,* polymerase basic; *Pol,* polymerase; *S31N,* serine substitution for asparagine at amino position 31.

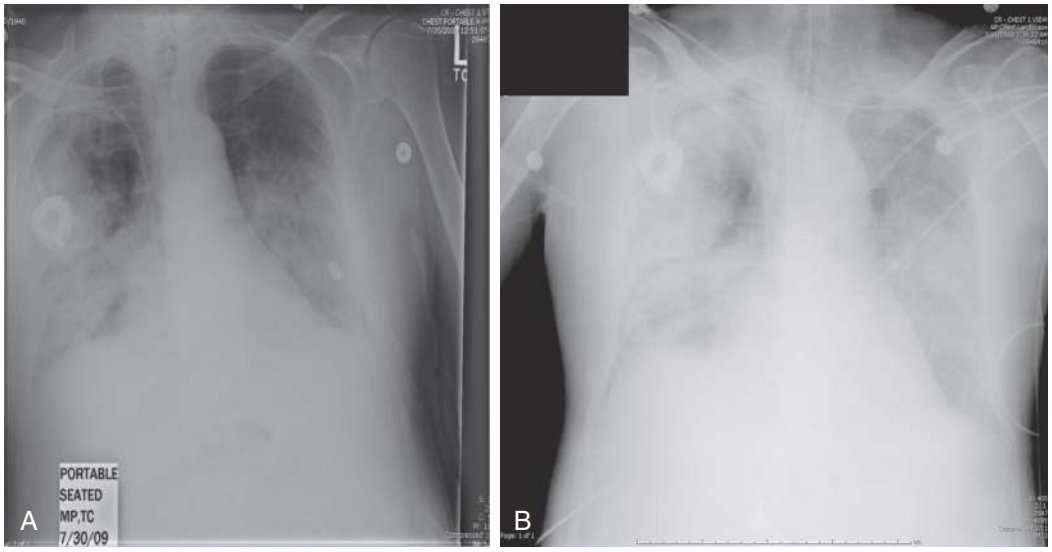

Fig. 119.2 A, Chest radiograph of a 70-year-old male with B-cell lymphoma and hypogammaglobulinemia in the ICU with primary influenza pneumonia. Note Port-a-Cath in right anterior chest wall and diffuse pulmonary infiltrates, most prominently seen in both lower lung fields. **B,** Chest radiograph of same patient 3 days later; note diffuse alveolar filling process associated with profound hypoxemia. The patient expired secondary to severe hypotension and acute kidney injury despite oseltamivir and intensive supportive care.

had a degree of clinical protection from preexisting immunity induced by historical circulation of other H1N1 viruses that evolved from the 1918 H1N1 pandemic virus.[17]

The major subtypes of influenza A currently circulating in humans include several distinct clades of H1N1 and H3N2.[18] The avian flu (H5N1) continues to cause sporadic disease in humans and circulate in birds. Although this is often cited as the most recent pandemic threat, it has yet to demonstrate sustained person-to-person or community-level transmission.[19] Other avian influenza subtypes (H7N2, H7N3, H7N7) cause sporadic outbreaks of mild severity, but more alarming was a novel avian flu (H7N9) that emerged in China in 2013, causing severe pneumonia. Thankfully, inefficient person-to-person transmission has limited spread of this serious subtype.[20] Several other influenza A subtypes are circulating sporadically in humans and animals, but of the 198 possible subtype combinations, only 131 have been detected in nature.[21] The rapid and dramatic evolution of influenza viruses in animals and humans continues to impose a threat to our global population of potential catastrophic proportions. For current updated information on local influenza activity and subtype distribution, the reader is directed to http://www.cdc.gov/flu.

Clinical Manifestations and Pulmonary Complications of Influenza

Classical seasonal influenza in adults is typified by a 4- to 5-day period of sudden-onset fever, chills, upper respiratory tract symptoms, headache, muscle pain, and weakness. High fever is characteristic and correlates with severity of initial symptoms. Fevers typically last for 3 days but may persist for up to 8 days. Diarrhea is more common with influenza than with most other viral upper respiratory tract infections. Other distinguishing features include the predominance of systemic symptoms, often overshadowing the respiratory symptoms (dry cough, pharyngeal pain, nasal discharge and obstruction).

Primary influenza pneumonia is the most common serious complication and occurs in up to 29% of patients hospitalized for influenza.[22] Early symptoms are indistinguishable from typical influenza aside from a rapid and fulminant progression of hypoxemia and widespread bilateral interstitial pneumonitis on chest radiograph (Fig. 119.2). These patients generally present to the hospital within 4 days of symptom onset with shortness of breath and require ICU admission within <1 day of hospital presentation. Influenza pneumonitis frequently progresses to hypoxemic respiratory failure, with over 80% of patients requiring mechanical ventilation. Very few patients can successfully be managed with noninvasive ventilation strategies alone.[22] The mean admission PaO_2/FiO_2 in the ICU is <150 mm Hg, and advanced ventilatory/oxygenation strategies are often needed for refractory cases.[23–27]

Secondary bacterial pneumonia and influenza-bacterial coinfection are frequently severe, and also common, affecting between 11% and 35% of hospitalized cases.[28–30] Secondary bacterial pneumonia is generally attributable to damaged airways and poor mucociliary clearance after severe influenza pneumonia.[31] Patients frequently experience a period of improvement after the classical influenza illness before recrudescence of fever, cough, purulent sputum, and consolidation on chest radiograph. Influenza-bacterial coinfection is more complex, with bacterial and viral synergism. Viral PB1-F2 proteins induce pneumocyte apoptosis, which facilitates *Streptococcus pneumoniae* growth in lung tissue.[32] Sialic acids that have been cleaved by NA allow more efficient *S. pneumoniae* binding to epithelial surfaces and increase lethality in experimental models.[33,34]

The most common pathogens involved in secondary bacterial pneumonia and influenza-bacterial coinfection include *S. pneumoniae* (up to 35%) and *Staphylococcus aureus* (up to 28%),[30] but others may be implicated, including *Streptococcus pyogenes, Haemophilus influenzae, Moraxella catarrhalis,* and gram-negative bacilli.[25,35–37] Given the frequency of secondary bacterial infection, clinicians should have a low threshold for considering antibacterial agents against these commonly observed pathogens.

In children with severe influenza infection, the median age of hospitalized patients is 5.0 years (range 1 month to 17 years).[25,28,29,38] One or more chronic comorbid illnesses are typically observed (70.2%): lung disease (44%), neurologic diseases (19%), immune suppression or immunodeficiency (16%), history of prematurity (9%), and congenital

heart disease (7%). Mechanical ventilation is used in approximately 68% of children admitted to the ICU, and the median duration of ventilation is 6 days (range 0–67).[25]

Extrapulmonary Complications of Influenza

Influenza may cause serious or life-threatening complications in other organ systems, including cardiac, renal, hepatic, and neurologic disease.[8,29] Myocarditis is a common complication of influenza illness and may occur in up to 10% of hospitalized patients.[39] The diagnosis is made on the basis of presenting symptoms, elevated cardiac enzymes, and echocardiographic findings. Importantly, myocarditis may be present with or without serious pulmonary involvement. Occasionally, myocarditis leads to serious complications in the ICU, including atrial and ventricular arrythmias, atrioventricular (AV) conduction block, pericardial effusions with or without tamponade, acute myocardial infarctions, and reduced ejection fraction with heart failure.[39,40] Reduced ejection fraction may occur in up to 80% of patients with influenza myocarditis, leading to serious repercussions in patients with critical illness and shock.[40]

Septic shock may occur in up to 15%–30% of critically ill patients with influenza and is more common in the setting of bacterial coinfection.[41] In addition to the effects of myocarditis, a severe surge of cytokines and capillary leak causes reduced systemic vascular resistance, reduced perfusion pressure, microcirculatory coagulopathy, reduced end-organ perfusion, and cellular toxicity. The presence of shock is associated with approximately 30% mortality, and studies have shown that *S. aureus* coinfection is an independent predictor for mortality.[41] Acute kidney injury (AKI) may ensue as a result of prerenal and tubular injury secondary to sepsis and/or rhabdomyolysis. Many patients also receive nonsteroidal antiinflammatory drugs (NSAIDs) because of myalgias and other systemic symptoms, adding potential nephrotoxicity.

Neurologic complications often accompany severe influenza infection, including encephalitis, encephalopathy, and seizures. Computed tomography (CT) and magnetic resonance imaging (MRI) studies of the brain are often abnormal, but findings are nonspecific. Guillain-Barré syndrome (GBS) incidence increases in the months during and after seasonal influenza. It has been suggested that influenza may trigger this serious neurologic complication.[42]

Risk Factors and Prognosis With Influenza Critical Illness

Patients at highest risk for severe infection and influenza complications requiring ICU care are those with a history of chronic lung disease and/or severe immunosuppression. Underlying lung disease occurs in approximately 20% of patients with influenza in the ICU, most commonly asthma and chronic obstructive pulmonary disease (COPD). Other special populations at increased risk of severe disease and mortality are elderly patients (>65 years of age), women who are pregnant or recently postpartum, residents of long-term care facilities, those with obesity, and Indigenous populations.[25,43] Additional risk factors include patients with other chronic medical conditions, including neurologic diseases (12%), hematologic or oncologic conditions (9.9%), and cardiac conditions (4.6%).[38] However, approximately half of hospitalized patients during pandemic years might otherwise be healthy.[28,29,38]

Whereas most patients with influenza do not develop critical illness, 11%–19% of patients hospitalized with laboratory-confirmed influenza require treatment in the ICU.[29,44] Those who develop critical illness often deteriorate rapidly, and severe illness may be protracted. For patients requiring mechanical ventilation, the mean duration is approximately 5–12 days. Many patients are difficult to oxygenate, and patients often require ancillary therapies such as extracorporeal membrane oxygenation (ECMO) and nitric oxide therapy, leading to increased length of ICU stay and excess mortality.[28,38,45]

Similar to prior pandemics, the primary cause of death remains complications from secondary bacterial infection, including multisystem organ failure and cardiovascular collapse.[31,46] However, mortality rates have significantly improved in recent years (~17%)[47] as a result of better oxygen delivery, supportive ICU care, vaccination, antibacterial agents, and antiviral medications. Unfortunately, sophisticated ICU care remains out of reach for many patients in developing countries, and case-fatality rates remain regrettably high.[48]

Clinical and Laboratory Diagnosis of Influenza

Clinicians should suspect and test for influenza in all patients who present to the hospital during influenza season with an acute respiratory illness, acute decompensation of chronic medical conditions, or any immunocompromised patients.[49] Importantly, a history of current-season influenza vaccination does not exclude the diagnosis of influenza because of variable vaccine effectiveness from year to year. Uncomplicated disease does not typically result in significant respiratory compromise, but shortness of breath should raise concern for severe disease. Other clinical signs indicating severe infection include hemoptysis, frothy pink sputum, and purulent sputum with diffuse lung crackles. Percutaneous oximetric assessment of oxygenation or arterial blood gas evaluation of PO_2 should be performed when assessing a patient with suspected severe influenza. Relative hypoxia should trigger further assessment, including a chest radiograph. Laboratory findings commonly found at presentation with severe disease typically include normal to low leukocyte count and elevated creatine kinase.[25,47,50] A leukocyte shift to immature forms is unusual in the absence of bacterial coinfection. An approach to the diagnosis and treatment of influenza is presented in Fig. 119.3.

Early laboratory diagnosis of influenza infection is greatly facilitated by the use of rapid reverse transcriptase–polymerase chain reaction (RT-PCR) testing.[51] Clinicians should collect nasopharyngeal specimens using flocked swabs.[49] In patients who require mechanical ventilation, endotracheal aspirates should be collected in addition to the nasopharyngeal specimens in order to maximize diagnostic yield.[49,52,53] Virus may only be detected in lower tract samples in patients with severe pneumonitis. For critically ill patients, the use of multiplex nucleic acid amplification tests to detect a panel of other respiratory viruses is recommended. The use of immunofluorescent techniques, enzyme-linked immunoassays, and other rapid diagnostic tests is discouraged because of lack of diagnostic sensitivity.[49,51,54–57] Viral cultures require up to 1 week for processing and should only be considered to provide isolates for further characterization.

Lessons From the 2009 Influenza A H1N1 Pandemic

Starting March 2009, a novel strain of a human-adapted influenza virus, influenza A(H1N1)pdm09, spread from an initial large outbreak in Mexico to virtually all countries of the world. By September 27, 2009, there were over 340,000 cases with 4100 deaths worldwide.[11,58] Over the period of June to September 2009, there were dramatic spikes in Australia, New Zealand, and South America that breached the capacity for ICU care in some regions.[47] Ultimately, 18,500 lab-confirmed influenza deaths occurred worldwide, but modelling data estimate that >300,000 respiratory or cardiovascular deaths attributed to influenza occurred globally, predominantly in patients under 65 years of age and in low- to middle-income countries.[59] This led to lessons that have advanced our current understanding of influenza and control of other emerging global pandemics. Public health officials

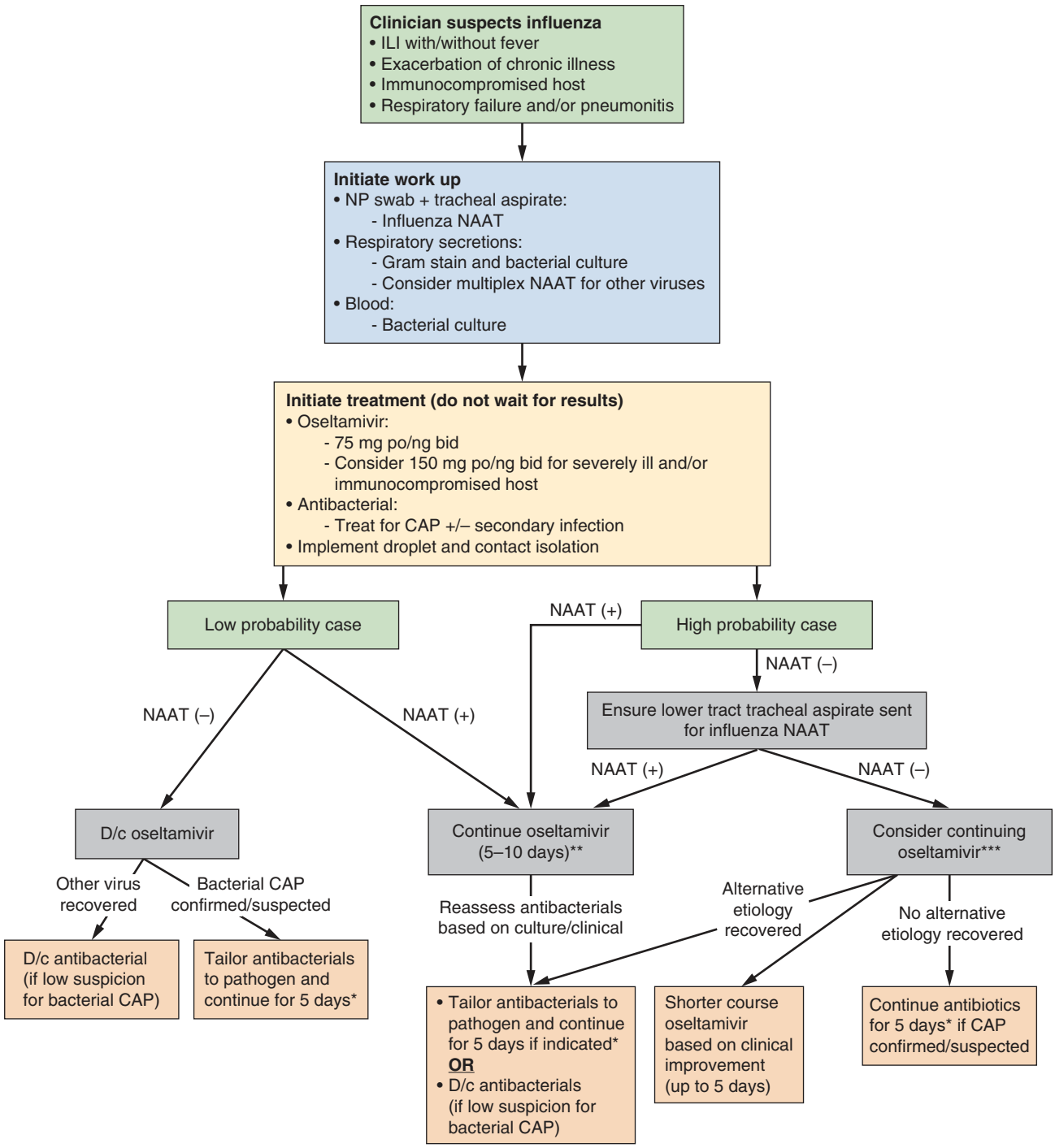

Fig. 119.3 Approach to the workup and management of a patient with suspected influenza pneumonia in the ICU. * A longer course may be needed if CAP) is complicated by meningitis, endocarditis, or other deep-seated infection; suspected or proven *MRSA* or *P. aeruginosa* pneumonia may require a 7-day treatment course; less common specific pneumonia pathogens may require longer courses (e.g., *Mycobacterium tuberculosis, Burkholderia pseudomallei*). ** Because of prolonged viral shedding with primary influenza pneumonia, treatment durations longer than 5 days may be warranted, particularly for ARDS, immunocompromised, and/or severely ill patients, to a maximum of 10 days. *** Results of most NAAT testing are highly sensitive and very highly specific. If influenza is highly suspected clinically during times of high influenza activity and NAAT results are negative, the NPV remains low, and a negative NAAT may reflect a false-negative result. If symptoms present >4 days, diagnostic yield is lower and may also result in a false-negative result. *CAP,* Community-acquired pneumonia; *d/c;* discontinue; *ILI,* influenza-like illness; *NAAT,* nucleic acid amplification test; NP, nasopharyngeal.

were not prepared to quickly assess the transmissibility, severity, and impact of disease. Implementation of risk management plans and global communications were delayed. Despite blunting of the North American spread by widespread deployment of an effective, inactivated, monovalent vaccine program,[60] as many as 61 million Americans were infected, with 274,000 hospitalizations and approximately 12,500 deaths between April 2009 and April 2010.[61]

The events that transpired in Canada were illustrative of the influenza situation in much of the Northern Hemisphere. Among critically ill Canadian patients with influenza A(H1N1)pdm09, the mean age was 32 years, with a possible predilection for more severe disease in women (67% of patients).[25] Pregnant women, obese patients, and Indigenous Canadians were overrepresented and suffered from a disproportionate high level of disease severity, but only 30% suffered from serious comorbid illness.[25,43,62,63] Similar clinical findings were reported in other regions of the world.[47,50,58,64] Nosocomial transmission occurred in approximately 10% of patients. Transmission to healthcare workers occurred early in the outbreak, but this was minimized once the pandemic was recognized and appropriate infection-control safeguards were instituted. A summary of clinical risk factors, comorbidities, and severe complications associated with the latest influenza pandemic is found in Table 119.2.

The most common specific symptoms with influenza A(H1N1) pdm09 included high fever and respiratory symptoms in greater than 90% of patients. Weakness and myalgias were less common. A variety of severe clinical syndromes necessitating ICU care were observed, including:

1. Rapidly progressive, diffuse pneumonitis associated with severe, refractory hypoxemia in relatively healthy teens or adults
2. Secondary bacterial pneumonia, or influenza-bacterial coinfection, frequently with gram-positive pathogens including *S. pneumoniae* and *S. aureus*
3. Acute and prolonged exacerbation of asthma or COPD in those with preexisting disease
4. Life-threatening decompensation of chronic underlying disease in those patients with serious comorbidities, including congestive heart failure, chronic renal failure, end-stage liver disease, poorly controlled diabetes, or immune compromise
5. Bronchiolitis and croup in infants and young children, which frequently required hospitalization, but not ICU care

During pandemic periods, relatively young patients with few serious comorbidities can be affected because of widespread lack of immunity to novel circulating viruses and vigorous intrinsic inflammatory responses.[31] Additionally, vulnerable populations with usual risk factors can be greatly affected, similar to nonpandemic years. The impact on hospital care and costs can be dramatic and necessitates thoughtful critical care resource management in modern ICUs that have limited surge capacity to meet sudden demand for a future pandemic.[25–27,31,47] Establishing a pandemic preparedness plan is imperative to ensure institutions have the capacity to respond to emerging pandemics and mitigate health impact.[65]

Supportive Care Considerations With Influenza

Almost all patients with severe influenza in the ICU will have deficits in oxygenation, leading to acute respiratory distress syndrome (ARDS) and requiring ventilatory support.[25,47] Shock and renal failure are also common, often exacerbated by efforts to optimize oxygenation through diuresis, coupled with high intrathoracic pressures and limited venous return.[25,50,66]

Despite ARDS standard treatment with lung-protective low tidal volume ventilation and open lung strategy with high positive end-expiratory pressure (PEEP),[67] primary influenza pneumonia often results in a relative insensitivity to usual measures of oxygenation and markedly abnormal lung compliance. Control mode ventilation with appropriate sedation and use of neuromuscular blockade to avoid ventilatory dysynchrony and high airway pressures are often needed. Avoidance of volume overload (and judicious diuresis) may also reduce duration of ventilation and length of stay in the ICU for most patients with ARDS.[27,68] Because some patients worsen despite these standard measures, early consideration of transfer to a referral center with experience in rescue therapies should be considered, particularly if severe hypoxemia is encountered.

TABLE 119.2 Prognostic Indicators and Risk Factors for Severe Influenza Complications

Risk Factors and Comorbidities	Comments
**Age <5 years	Especially children <2 years; those with chronic cardiopulmonary disease; <6 months of age associated with higher hospitalization and mortality
Age >65 years	Poor vaccine response; reduced host response to influenza infection
**Chronic cardiopulmonary diseases	Chronic pulmonary disease at highest risk; includes COPD, asthma, cystic fibrosis; cardiac disease includes congestive heart failure, coronary artery disease
Metabolic disease and chronic liver disease	Diabetes mellitus; cirrhosis
Chronic neurologic illness	Includes disorders of the brain, spinal cord, and peripheral nerves; seizures, epilepsy; stroke; developmental delay and institutionalization
Pregnancy	Includes all stages of pregnancy, up to 2 weeks postpartum; women in the third trimester at particular increased risk
Obesity	Particularly with extreme obesity; BMI >35 kg/m^2
Hemoglobinopathy	Sickle cell disease
**Immunosuppression	Glucocorticoids, chemotherapy, malignancy, HIV, organ transplant recipients; lung transplant and advanced HIV at highest risk
Indigenous populations	Increased prevalence of some chronic health conditions; social determinants of health; healthcare access
Access to healthcare services	Nursing home and long-term care residents; hospitalized patients
Secondary bacterial pneumonia	Longer ICU and hospital stays; more nosocomial complications; greater mortality rate

**Comorbidities associated with highest risk of influenza complications, including hospitalization and mortality.

Ancillary strategies may be required to improve refractory hypoxemia, minimize ventilator-induced lung injury, and improve cardiothoracic dynamics. Strategies include prone ventilation, lung recruitment maneuvers, inhaled nitric oxide, and ECMO. These strategies require considerable resources and expertise and offer variable impacts on clinical outcomes.

Early prone ventilation has been demonstrated to be an effective strategy to improve oxygenation and mortality for most causes of ARDS.[69,70] Although little is known about influenza-specific outcomes with prone ventilation, it is recommended for those with severe ARDS in the appropriate experienced facility and in the absence of contraindications. Lung recruitment maneuvers may be used to recruit collapsed alveoli, but because of a lack of convincing benefit, it should not be done routinely.[71] Use of inhaled nitric oxide has demonstrated improvements in oxygenation; however, studies have failed to show improvement in morbidity or mortality, and some studies suggest there may be an increased risk of renal injury.[72–76] Inhaled nitric oxide should not be considered standard therapy. Since the 2009 pandemic, there has been a considerable rise in the use of venovenous ECMO in patients with refractory ARDS from influenza. Although data are limited, pooled analyses suggest that this modality may reduce mortality and should be considered for severe influenza where other options do not exist.[24,27,77–80]

Septic shock is common in critically ill patients with influenza and typically results in refractory hypotension and need for moderate to high doses of vasopressors.[41] Optimal fluid resuscitation strategies remain unknown in this setting and must be balanced with fluid-restrictive strategies that aim to improve oxygenation. It is recommended that all patients with severe influenza, ARDS, and septic shock be treated in accordance with international guidelines and receive at least 30 mL/kg of crystalloid via bolus dosing.[81] The development of AKI often necessitates renal replacement therapy to correct bicarbonate deficiencies to allow for increased tolerability of hypercapnia when poor lung compliance prohibits effective ventilation.

For patients with influenza-associated critical illness, clinical improvement is slow and ICU length of stay is typically prolonged.[82] Clinicians should focus on minimizing the complications of critical illness, including ICU-acquired weakness, delirium, and psychosocial disturbances. Long-term ventilation weaning is often needed, and tracheostomy may be required.

Antiinfluenza Therapy

In severely ill patients with suspected influenza, early initiation of antiviral therapy is predicated on clinical presenting features and epidemiologic data. Therapy must not be delayed pending laboratory confirmation, as initiation within the first 48 hours of illness is most likely to provide benefit.[25,83] For critically ill individuals, early initiation of antiviral therapy may improve survival,[83–88] but antivirals should be administered for all those with severe illness, regardless of the duration of symptoms before hospitalization.[49] The choice of antiviral therapy is dependent on circulating influenza subtypes and local surveillance data examining the risk of oseltamivir resistance.

The NA inhibitor oseltamivir is the preferred agent for severe influenza. Oseltamivir works by selectively binding to the influenza envelope protein NA, inhibiting its enzymatic activity and preventing spread to other uninfected cells. It reduces the duration and severity of symptoms and reduces viral shedding.[83,88–90] It may also reduce the risk of secondary bacterial infection[91–93] and reduce mortality in critically ill patients, though data are limited to pooled analyses of studies that included less severe cases.[44,84–86] The typical dosing for oseltamivir is 75 mg orally twice daily, which must be adjusted for renal dysfunction. Doubling or tripling the dose (150–225 mg orally twice daily) is typically well tolerated, but unnecessary in hospitalized patients without severe illness[94,95]; however, this strategy may benefit severely ill patients, particularly with immunocompromise or patients infected with H5N1 avian influenza.[95–97] In patients with primary influenza pneumonia, viral shedding is often prolonged, with viral clearance occurring after a median of 11 days while on oseltamivir.[52] In these severely ill patients, an extended duration beyond 5 days may be warranted, particularly for those with ARDS or immunocompromise. Current recommendations suggest continued use until adequate clinical response or infection resolution, but formal studies on optimal duration are lacking.[49] Oseltamivir is very well tolerated, but occasionally associated with nausea and vomiting, which rarely requires discontinuation of therapy.

Rare oseltamivir-resistant viruses were isolated during the 2009 H1N1 pandemic but remain very uncommon in current circulating subtypes. The majority of influenza B and influenza A (H3N2) remain susceptible to NA inhibitors. The resistance mutation H275Y, which renders oseltamivir and peramivir ineffective, has rarely been detected (<1.0%) in influenza A (H1N1), but sensitivity to zanamivir is preserved.[98,99] This is in contrast to the seasonal H1N1 subtypes circulating before the 2009 pandemic year, which were often resistant to oseltamivir.[100–102]

Alternative NA inhibitors may be available, including peramivir and zanamivir. These agents are not currently recommended because of limited data in patients with severe lower respiratory tract disease. Peramivir is given by intravenous (IV) route at a typical single adult dose of 600 mg, but duration may be extended to once daily for 5 days in critically ill patients.[103] In studies of ambulatory patients with lab-confirmed influenza, peramivir was shown to reduce time to symptom resolution compared with placebo and to be noninferior to oseltamivir.[104,105] In one study of critically ill patients, similar mortality and ICU length of stay were observed when peramivir was compared with oseltamivir; therefore IV peramivir may be a reasonable alternative to oseltamivir in patients who are unable to tolerate enteral agents.[106,107] Although GI absorption of oseltamivir among critically ill patients had been questioned, comparable blood concentrations have clearly been demonstrated in critically ill influenza patients compared with healthy volunteers.[108,109] Zanamivir by inhalation is not recommended in critically ill patients because of the risk of bronchospasm, lack of efficacy data, and lack of systemic absorption; however, it may be an alternative option for ambulatory patients without asthma or COPD to reduce the duration of symptoms.[110–112]

Baloxavir marboxil is a newer antiviral that selectively inhibits cap-dependent endonuclease, preventing initiation of influenza messenger RNA (mRNA) synthesis and blocking viral proliferation. It is effective in reducing duration of symptoms in acute uncomplicated influenza,[113] but its role in severe infection, in critically ill patients, or in combination therapy with oseltamivir has not been studied. The adamantane family of antivirals, including amantadine and rimantadine, are no longer routinely recommended because of their limited spectrum of activity (only effective against influenza A) and high levels of circulating resistance.[99]

Adjunctive Pharmacologic Therapy for Severe Influenza

The most important adjunctive pharmacologic treatment in critically ill patients with influenza is empiric broad-spectrum antibiotics to cover possible secondary bacterial pneumonia or influenza-bacterial coinfection.[49] Antibiotics should be selected according to local antibiograms to cover the most common pathogens involved, namely *S. pneumoniae, S. aureus* (including methicillin-resistant *S. aureus*

[MRSA]), *S. pyogenes,* and occasionally, gram-negative bacteria. De-escalation of antibiotics is appropriate as lower tract respiratory cultures are finalized. If secondary decompensation occurs after a period of initial clinical improvement, additional antibiotic treatment may be warranted while investigating for newly acquired bacterial or fungal nosocomial infections, examining for empyema, lung abscess, sepsis, or other causes of deterioration.

Many other potential adjunctive therapies for the treatment of severe influenza have been studied. Use of IV immunoglobulins, convalescent serum or plasma, and hyperimmune globulin derived from donors who have recovered from influenza have demonstrated mixed results.[114–116] Meta-analyses suggest that early administration of such products may be associated with improved outcomes, but the effect on survival remains uncertain.[117,118] In addition, case series suggest that similar therapies may be of use in severe influenza A (H5N1) infection,[119,120] but more data are needed before recommending these therapies.

Glucocorticoids have been used to reduce inflammatory responses in influenza, septic shock, and a variety of other infectious conditions.[121–127] Although few randomized trials have been performed, meta-analyses of largely observational studies demonstrated prolonged viral replication, more frequent superinfections with bacterial and fungal pathogens, and increased mortality.[128–133] Because of the very low quality of evidence, potential benefits of glucocorticoid treatment remain uncertain. But extreme caution is needed, and their use in primary influenza pneumonia should be avoided in the absence of a clear alternative indication.

The effect of statins in reducing inflammation and improving illness severity with influenza has been studied in small observational studies. Although there is a suggestion that these may improve outcomes, further trials are needed to assess the risks and benefits before recommending their use.[134] One small open-label trial examined the role of clarithromycin and naproxen in combination with oseltamivir for the treatment of hospitalized patients with influenza. Although this trial demonstrated a reduction in mortality, patients who were already critically ill were not included.[135] This combination merits further investigation.

Infection Control in the ICU to Mitigate the Spread of Influenza

Influenza is transmitted from person-to-person primarily through large-particle respiratory droplets; thus patients with suspected influenza should be instructed to use appropriate hand hygiene, cough etiquette, and be given a face mask to wear upon entry into healthcare facilities. Patients with suspected influenza should be in single-patient rooms, if available, during the initial phase of hospital admission. If clinical demand exceeds the availability of single rooms, cohorting patients with influenza into common rooms may be necessary. Patients who must be transported outside of the room should wear a mask if tolerated, or when necessary, an oxygen delivery system that limits the spread of aerosols. Influenza vaccination is the best way to prevent or mitigate the severity of influenza illness, and in the absence of contraindications, is recommended annually for the entire population, particularly those with risks for severe disease.[49] Vaccination and postexposure chemoprophylaxis are recommended for close contacts who are at very high risk of influenza complications.[49]

Healthcare personnel (HCP) should apply droplet precautions by wearing standard surgical tie masks and use appropriate hand hygiene. Studies have found N95 masks offer no additional protection compared with surgical masks, yet many still advocate their use during cough-inducing procedures.[136] HCPs should also consider contact precautions with gloves when anticipating contact with bodily fluids or touch with contaminated surfaces. Protective eyewear is recommended when providing direct care in close proximity to the patient.[49] The annual influenza vaccine should be mandatory for all HCPs unless specific contraindications exist. Ill HCPs with fever and respiratory symptoms should be instructed not to work until fever has dissipated for >24 hours. For additional information regarding infection prevention strategies in healthcare settings, the reader is directed to updated recommendations from the Centers for Disease Control and Prevention (CDC) at https://www.cdc.gov/flu/professionals/infectioncontrol/healthcaresettings.htm.

OTHER CRITICAL RESPIRATORY VIRAL INFECTIONS

Coronaviruses: SARS, MERS, COVID-19

Coronaviruses are ubiquitous around the world and frequently cause mild to moderate upper respiratory tract infections in humans. These infections seldom cause critical illness; however, three notable severe syndromes were noted with coronaviruses emerging in the twenty-first century: severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and coronavirus disease-19 (COVID-19). SARS is caused by the SARS-associated coronavirus (SARS-CoV), which emerged in November 2002. The first cases were discovered in China, with subsequent clusters occurring in countries around the world. Its somewhat unusual lengthy prodrome of fever and constitutional symptoms typically lasted 3–7 days without respiratory symptoms. Subsequently, dry cough would ensue with potential progression to ARDS and case fatality rates of 9.6%. Ultimately, SARS occurred in localized epidemics in several countries, infecting approximately 8000 people and 774 deaths globally.[137] Because of intensive infection-control strategies, it disappeared as quickly as it emerged by July 2003.[138]

MERS has become an endemic viral pathogen in the Middle East, first appearing in June 2012. Over 2400 lab-confirmed cases have been reported, predominantly from the Arabian Peninsula.[139] Although transmission specifics are not fully understood, person-to-person transmission has occurred, and contact with camels appears to be an important risk factor. MERS predominantly causes a severe, acute, febrile, respiratory syndrome that frequently is accompanied by shock and AKI.[140] The vast majority of patients require ICU care and mechanical ventilation.[141] Hospital mortality appears to be the highest of the coronaviruses, approaching 25% in hospitalized patients and 50% in those who require ICU care.[142]

In December 2019, a novel coronavirus emerged, causing a cluster of pneumonia cases in Wuhan, China. This novel coronavirus, named *severe acute respiratory coronavirus 2* (SARS-CoV-2), is genetically similar to that of SARS-CoV.[143] At the time of this writing, the emerging epidemic is rapidly spreading throughout Southeast Asia, and emerging in many other countries, threatening a global pandemic.[144] Genetic sequencing indicates that the virus probably "jumped" animal species from snakes to bats and then to human hosts. Person-to-person spread of SARS-CoV-2 has been demonstrated from epidemiologic studies, and healthcare workers have been disproportionately affected, similar to prior outbreaks of serious viral respiratory illnesses.

The incubation period of SARS-CoV-2 is thought to last up to 14 days, but most symptoms appear within 5 days of exposure. Clinical manifestations of COVID-19 vary from asymptomatic to severe respiratory compromise. Most patients experience an abrupt onset of fever and respiratory symptoms. Approximately 15% develop severe disease with lower respiratory tract involvement, 5% develop critical illness, and 2.3% of patients die. Mortality rates are much higher in elderly adults and approach 50% for patients in the ICU.[145] Strict isolation precautions and extreme infection control measures have been important in attempts to limit the spread of this outbreak.[146] Work on

vaccines, immunotherapy, and antiviral chemotherapies are underway, but currently treatment is simply supportive.[144]

Paramyxoviruses: Morbillivirus (Measles)

Although a highly effective vaccine has dramatically reduced the incidence of measles in the past decades, recent social and political factors have contributed to low vaccination rates and resurgence of disease in some areas.[147] The World Health Organization (WHO) recently announced a staggering statistic that measles accounted for more than 140,000 deaths worldwide in 2018.[148] The mortality rates are particularly high in children under 5 years of age. Measles typically causes a relatively mild childhood exanthem in otherwise healthy children. This highly contagious virus causes rapid spread of fever, rash, cough, conjunctivitis, and coryza. Regrettably, unvaccinated, malnourished children in developing countries, often with other concomitant respiratory illnesses, fare much worse and can die from measles-induced pneumonia or encephalitis or suffer from permanent blindness and/or deafness.

Pneumonia is the most common life-threatening complication of severe measles infection, often resulting in death, particularly in patients <5 years or >20 years of age. Additionally, measles may cause persistent morbidity and mortality after naturally acquired infection secondary to immunosuppression and risk for secondary infection.[149] Rarely, measles can be complicated by encephalitis, acute demyelinating encephalomyelitis, or, years later, with subacute sclerosing panencephalitis (SSPE). Treatment is largely supportive; however, vitamin A may reduce morbidity and mortality, and ribavirin may be given for life-threatening infection.

CRITICAL VIRAL INFECTIONS CAUSING VESICULAR SKIN LESIONS

Herpesviruses: HSV, VZV, Herpes B Virus

Herpes simplex virus (HSV), varicella-zoster virus (VZV), and herpes B virus are large, enveloped DNA viruses that exhibit lifelong latent infection.[150,151] They all cause vesicular skin lesions but may cause other systemic manifestations. In the ICU, these viruses may be encountered as part of a life-threatening clinical syndrome with primary infection or as a result of secondary reactivation of latent infection, typically causing mild breakouts of skin lesions.

Herpes Simplex Virus

HSV infections are common, with an estimated two-thirds of the world's population latently infected. Characteristically, HSV-1 is associated with orolabial disease, and HSV-2 is associated with genital infection, although this is not a rigid distinction. Primary infections are usually associated with mucosal lesions and systemic signs and symptoms.[152] Localized reactivation of HSV is common in critically ill patients and may require episodic treatment. The diagnosis is usually suspected clinically with clusters of vesicular lesions on an erythematous base, usually in the orolabial or anogenital areas. A precise diagnosis can be established easily by PCR on scrapings from the lesions. Patients with atopic eczema or severe burns may develop extensive infections.

Primary infection with HSV-2 is commonly accompanied by aseptic meningitis and may recur with secondary flares (Mollaret meningitis). Meningeal symptoms usually start 3–12 days after the onset of genital lesions. Transverse myelitis and autonomic nervous system dysfunction may also occur.[153]

Reactivation of latent HSV-1 infection, potentially from the trigeminal or autonomic nerve roots, may cause extension of the virus into the central nervous system (CNS) and cause encephalitis in adults. HSV-1 encephalitis is frequently seen in the ICU. Patients typically present with acute neurologic change and fever, including altered mental status, focal deficits, and/or seizures. There is a notable absence of vesicular lesions or rash. The cerebrospinal fluid (CSF) is typically lymphocytic and can be tested by PCR for HSV-1. MRI of the brain characteristically demonstrates temporal lobe enhancement.[154] Other potential serious complications of primary HSV infection include hepatitis, pneumonia, or thrombocytopenia. In immunocompromised hosts, reactivation of HSV-1 or HSV-2 may be associated with disseminated infection or severe local esophagitis, hepatitis, or pneumonia. Neonatal herpes, occurring in infants of mothers with primary or reactivated infection at the time of delivery, carries a high risk of disseminated fatal infection.

Varicella Zoster Virus

Primary VZV infection causes chickenpox, whereas reactivation of VZV causes shingles (herpes zoster). Chickenpox is typically a mild pediatric disease, but primary infection by VZV in adults or immunocompromised patients may lead to severe, life-threatening infection. The typical primary illness is usually associated with fever, constitutional symptoms, and a vesicular skin rash. Most skin lesions are small vesicular lesions with an erythematous base. Successive crops of lesions occur over 2–4 days, leading to clusters of lesions at all stages of development (from fresh vesicles to crusted lesions).[155] Secondary bacterial infections of vesicular lesions are relatively common, usually involving *S. aureus* and *S. pyogenes*.[156] This should be suspected with recrudescence of fever after an initial period of improvement after the systemic manifestations of chickenpox. Clinicians should monitor for signs of severe infection as a result of toxic shock syndrome.[157]

Chickenpox is associated with pneumonia in 1 in 400 cases of infection.[150] A larger proportion of people may have some pulmonary involvement, but it is typically asymptomatic. Pregnant women and immunocompromised patients are at high risk of severe pneumonia. Chickenpox pneumonia is generally manifested by cough and shortness of breath 3–5 days after the onset of the rash. Chest radiography typically shows a reticulonodular infiltrate, and respiratory failure may occur. Neurologic complications of chickenpox include encephalitis, acute cerebellar ataxia (1 in about 4000 cases), and cerebral angiitis. Encephalitis resulting from VZV is less common than pneumonia. The typical manifestations occur within 2 weeks of the chickenpox rash, and CNS symptoms are indistinguishable from HSV encephalitis. Typical features include small to large vessel vasculopathy, ischemic or hemorrhagic strokes, demyelinating lesions, and/or ventriculitis.[158]

Shingles is caused by reactivation of latent VZV and is characterized by a unilateral vesicular eruption that follows a distinct dermatomal distribution. Rash is frequently accompanied by neuritis, but systemic manifestations are uncommon. Diagnosis is made by clinical assessment and/or confirmation by PCR of vesicular scrapings. Immunocompromised patients with shingles may develop disseminated cutaneous infection resembling chickenpox and spreading to other organ systems.

Herpes B Virus (Cercopithecine Herpesvirus 1)

Herpes B virus (Macacine herpesvirus 1) infection is a relatively benign disease in macaque monkeys that resembles HSV-1 in humans. Rarely, herpes B virus may infect humans, causing a life-threatening encephalitis. Those at risk of herpes B virus are typically immunocompetent laboratory workers in close contact with macaque monkeys that are exposed via monkey bites, scratches, or mucous membrane exposure to monkey secretions. Monkeys of the *Macaca* genus (rhesus and cynomolgus monkeys) are considered to be at the highest risk.[159] An incubation period of 2–14 days is usually observed after the bite or

scratch. Initial symptoms are nonspecific but include fever, malaise, and headache. A cluster of small vesicles may occur at the bite site. Severe encephalomyelitis may ensue, with death occurring in days. In the United States, only one reference laboratory is equipped to identify the virus. Prompt and exhaustive cleaning of wounds, followed by early initiation of postexposure acyclovir or valacyclovir, may prevent the occurrence of severe disease.[160]

Poxviruses: Smallpox and Monkeypox

The global effort to eliminate the scourge of Variola virus (smallpox) from the earth in 1979 remains one of the greatest medical accomplishments of humankind.[161] This double-stranded DNA virus is still relevant today only because of concerns regarding its potential in bioterrorism.[162,163] Jenner's vaccination strategy using a closely related cowpox virus to provide cross-species protective immunity to smallpox eventually eradicated the last human cases of smallpox. A recent added level of protection to smallpox is now available as a novel, oral, antiviral agent called *tecovirimat*. The drug inhibits final cell membrane assembly and release of viral particles.[164]

The classic smallpox eruption starts in the oropharynx and spreads to the face, palms, soles, and centrifugally. Initially macules evolve to papules, and ultimately vesicles and pustules over a 1-week period. All lesions are typically at the same stage of development, and fever and systemic symptoms predate the onset of rash. In contrast, the lesions of chickenpox are present at different stages of development, and fever occurs with the onset of the rash. The rash of smallpox could also be confused with monkeypox, generalized vaccinia, eczema vaccinatum, coxsackievirus infection, HSV infection (especially eczema herpeticum), rickettsialpox, insect bites, drug eruptions, and acne. The poxviruses and their major clinical manifestations are listed in Table 119.3.

Monkeypox

Monkeypox was first recognized in 1958 as a disease of primates and subsequently recognized in rodents. Beginning in 1970, cases in humans were reported in Central Africa. In 2003 cases occurred in the United States in residents of the Midwest who had contact with imported prairie dogs.[165] Patients developed vesicular skin lesions and fever with diaphoresis. Although case fatality rates of 4%–22% have been observed in outbreaks of the infection in Africa, none of the 11 patients in an American outbreak died.[165] There is no clear evidence as yet that tecovirimat is an effective treatment for monkeypox.

TABLE 119.3 Common Clinical Manifestations of Poxviruses

Virus	Clinical Manifestations
Variola (smallpox)	Diffuse vesicular rash; systemic disease; eliminated from the world by vaccination, but still a possible agent of bioterrorism
Monkeypox	Vesicular rash; lymphadenopathy may help differentiate from smallpox; increased risk after African monkey and rodent exposures
Vaccinia (cowpox)	Vesicular, sometimes hemorrhagic rash; may leave black eschar; postinfectious encephalitis may occur; historic use in smallpox vaccination; increased risk after exposure to infected cats
Parapoxvirus	Orf (localized vesicular lesion); increased risk after exposure to infected goats or sheep
Molluscipoxvirus	Molluscum contagiosum; may cause chronic genital lesions and other vesicular skin lesions
Tanapox virus	Vesicular rash; often a presenting as a single pox lesion; endemic to regions in sub-Saharan Africa

CRITICAL NEUROTROPIC VIRUSES

Flaviviruses: WNE, Zika, Japanese Encephalitis, St. Louis Encephalitis, Tickborne Encephalitis

West Nile Encephalitis Virus

West Nile encephalitis (WNE) virus is a neurotropic flavivirus that has circulated for several decades but re-emerged in North America in the 1990s.[166,167] Currently, the virus and its complications are found around the world. The majority of cases are transmitted by mosquitos, particularly in the presence of crows and/or blue jays, but transmission by blood transfusion or organ allograft have been reported.[168,169] Symptoms are nonspecific, but infected patients may experience high fevers, influenza-like illness, retroorbital pain, headaches, and confusion. Conjunctivitis, rash, and lymphadenopathy may be present. Although severe neurologic symptoms occur in <1% of infections, they can be serious, including acute flaccid paralysis (myelitis), a diversity of neuropathies, and meningoencephalitis. Case fatalities are highest in elderly patients.[170]

Zika Virus

Zika virus is a flavivirus first isolated in the 1950s, but it has come to significant attention after epidemics in the Americas, Caribbean, and Pacific in 2015 and 2016. The virus is endemic in tropical climates and transmitted by the *Aedes aegypti* mosquito. The vast majority of symptoms in adults are mild and self-resolving, including fever, maculopapular rash, and arthralgias. Zika virus is neurotropic to the developing fetus, and in utero transmission may result in microcephaly and significant developmental problems. Rarely, adult patients may suffer serious complications necessitating ICU care, including GBS, myelitis, and meningoencephalitis.[171]

Other Flaviviruses

Many other flaviviruses have neurotropic clinical manifestations, predominantly causing encephalitis that might cause serious complications. These viruses are distributed throughout diverse geographic locations around the world. The Japanese encephalitis (JE) virus is endemic in Southeast Asia and transmitted via the *Culex* mosquito, particularly in rural areas near rice paddies and pigs. St. Louis encephalitis (STE) has been found in virtually all U.S. states, Canada, and Mexico. Transmission also occurs via the *Culex* mosquito. Tickborne encephalitis (TBE) virus is found throughout Western Europe, Russia, China, and Japan. Unique to the flavivirus family, this disease is the only one transmitted by ticks *(Ixodes)*. Vaccinations are available for JE and TBE and are only recommended for those with potential for significant exposure and at serious risk of complications. Like WNE, the majority of infections with these agents are subclinical; however, severe systemic and neurologic manifestations can occur, particularly in older patients. Diagnosis is predominantly confirmed by clinical, serologic, and molecular methods. Treatment is supportive without approved specific antiviral therapy.

Paramyxoviruses: Hendra and Nipah Virus

Hendra and Nipah viruses have been associated with high mortality as a result of encephalitis or an acute pulmonary syndrome in Australia (Hendra virus) and Malaysia, Singapore, India, and Bangladesh (Nipah virus). The reservoir for these closely related viruses appears to be fruit bats. Viral transmission appears to occur from bats to horses (Hendra virus) or pigs (Nipah virus). Humans exposed to ill horses or pigs have

developed this potentially fatal infection. In Bangladesh, nosocomial transmission of Nipah virus may have occurred.

VIRAL HEMORRHAGIC FEVERS

Hemorrhagic fevers are caused by Filoviridae, Bunyaviridae, Arenaviridae, or Flaviviridae. Dengue hemorrhagic fever and yellow fever are reviewed in Chapter 123. Other less common, but life-threatening hemorrhagic fevers are reviewed here.

Filoviruses: Marburg and Ebola

Marburg and Ebola viruses are distinct genera in the Filoviridae family and are among the world's most virulent pathogens. Marburg virus appears to have originated in Uganda and Western Kenya, where it infected monkeys and subsequently humans. *Marburg* refers to a town in Germany where monkeys from Uganda infected medical researchers, who subsequently infected hospital staff.

The major subtypes of Ebola virus (Zaire, Sudan, Bundibugyo, Tai Forest) have occurred in Central Africa. Recent large epidemics have occurred and threatened global spread. The West African epidemic with the Zaire species in 2014 infected nearly 29,000 individuals with case-fatality rates of approximately 40%. Cases predominantly occurred in Guinea, Liberia, and Sierra Leone; however, imported cases occurred in the United States, United Kingdom, Italy, Spain, Mali, Nigeria, and Senegal. Additional secondary infections occurred in these countries, mainly nosocomial spread to healthcare workers.[172] The most recent epidemic continues in the North Kivu province of Democratic Republic of the Congo (DRC) (2018), where military conflict has presented significant challenges for treatment and prevention. An additional subtype (Reston) was discovered in Reston, Virginia, among infected monkeys imported from the Philippines but does not cause disease in humans.[173]

Marburg and Ebola virus infections have a typical incubation period of 5–10 days (range 2–21 days) and begin with the abrupt onset of fever, myalgia, and headache. Somnolence and delirium usually follow. Most patients have abdominal pain and diarrhea. Many have a maculopapular rash on the trunk. Hemorrhagic manifestations such as bleeding around needle puncture sites and from the mucous membranes become prominent. Most patients have significant thrombocytopenia, leukopenia, and elevated transaminase levels. Viral culture, serology, and PCR have all been used to establish the diagnosis. At present, management is purely supportive and predominantly geared to fluid replenishment from GI loses and use of broad-spectrum antibiotics in late and severe cases to treat secondary bacterial infection from mucosal translocation. Several investigational therapies are under development, including monoclonal antibodies (mAb114, REGN-EB3, ZMapp), nucleotide analogues (remdesivir), and immunizations. Additionally, strict contact isolation precautions are necessary.

Bunyaviruses: Hantavirus and Nairovirus (Crimean-Congo Hemorrhagic Fever)

Hantavirus and Crimean-Congo hemorrhagic fever (CCHF) virus are from the Bunyaviridae family of viruses. Hantaviruses cause hemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome (HPS). There are over a dozen human pathogenic strains of hantavirus. The subtypes Hantaan, Dobrava, and Seoul cause moderate to severe HFRS in Asia and Europe, whereas Puumala causes a mild form of HFRS.[174] Unlike other Bunyaviridae, hantaviruses do not appear to have an arthropod vector and are usually transmitted via aerosols of virus-contaminated rodent urine or feces. The incubation period is typically 2 weeks. Initially, patients develop fever, headache, dizziness, blurred vision, abdominal pain, and back pain. Petechiae may be evident on the palate and the trunk; most patients have significant thrombocytopenia. After 4–7 days, significant shock can occur. In patients who survive, oliguria and mucosal hemorrhage occur, followed by polyuria. Sin Nombre virus and Andes virus cause HPS in North America and South America, respectively.[174] HPS is characterized by fever and severe vascular permeability with capillary leak, leading to shock and pulmonary edema.

CCHF is a severe hemorrhagic fever with a mortality rate ranging from 3% to 30%; it has been described in parts of Africa, Asia, Eastern Europe, and the Middle East.[175] It has the most extensive geographic distribution of medically important tickborne viral diseases. CCHF occurs through tick bites, by contact with blood or tissues from viremic livestock, and after contact with patients with CCHF during the acute phase of infection.[175] Patients have severe thrombocytopenia, disseminated intravascular coagulation, and extensive bleeding, with hepatitis and rhabdomyolysis. Diagnosis is made by enzyme-linked immunoassay (ELISA) and/or PCR. The clinical course of CCHF includes an incubation period (3–7 days), a pre-hemorrhagic period (3–7 days) with flulike symptoms, a hemorrhagic period (2–3 days), and a convalescence period. Supportive therapy is the most essential part of the management of CCHF. Ribavirin (30 mg/kg as an initial dose, then 15 mg/kg 6-hourly for 4 days, then 7.5 mg/kg 8-hourly for 6 days) is the recommended antiviral agent for severe CCHF, although its mechanism of action is unknown.[175]

Arenaviruses: Lassa Fever and South American Hemorrhagic Fevers

Lassa fever and South American hemorrhagic fevers are caused by Arenaviridae. Lassa fever occurs in West Africa. South American hemorrhagic fevers occur in Argentina, Bolivia, and Venezuela. Lassa fever is transmitted via rodents, but subsequent nosocomial transmission has been extensive. Many cases of Lassa fever are only mildly symptomatic. Some patients develop high fever, pharyngitis, and retrosternal chest pain accompanied by significant mucosal bleeding. Hypotension, renal failure, and pulmonary edema may follow. Serology can be used to establish the diagnosis, but the virus is also easily isolated from blood during the first week of illness, when viremia is often striking. Use of ribavirin has been associated with a decrease in mortality.[176]

South American hemorrhagic fevers (Argentine, Bolivian, and Venezuelan) usually present with unremitting fever accompanied by a variety of nonspecific symptoms. Petechiae are often present on the palate and the skin, especially the axilla; mucosal bleeding may result. Pulmonary edema may occur. Management is extremely difficult owing to the combination of hypotension and refractory pulmonary edema. The diagnosis can be established by serologic tests. No specific therapy is available.

OTHER SYSTEMIC CRITICAL VIRAL INFECTIONS

Herpes Viruses: CMV, EBV, HHV 6, HHV 8

Aside from the vesicular herpes viruses (HSV-1, HSV-2, VZV, and herpes B virus), five other herpes viruses may cause life-threatening infection, by primary or latent reactivation, particularly in immunocompromised hosts. These include cytomegalovirus (CMV); Epstein-Barr virus (EBV); and the human herpesviruses (HHV) types 6, 7, and 8.

Cytomegalovirus

CMV infection is a classic cause of severe infection in immunocompromised hosts, especially transplant recipients and patients with human immunodeficiency virus (HIV) infection.[177–179] Infection can be primary or the result of reactivation. The risk of end-organ CMV

infection depends on the degree of immunosuppression and whether the infection is primary or reactivated. For solid organ transplant recipients, there is a significant risk of primary infection in patients who were seronegative for CMV before transplantation and received an organ from a seropositive donor.[177] The organs commonly affected by CMV infection include the esophagus, colon, retina, and lungs. Virtually any organ can be infected, including the CNS. Some patients present with fever, malaise, and hematologic abnormalities (cytopenias), without specific end-organ abnormalities.

Given the high risk of CMV infections in transplant recipients, strategies should be employed to prevent CMV infections.[177,180,181] Two options are prophylaxis or preemptive therapy. *Prophylaxis* implies the administration of preventive therapy to all persons at risk.[177] In contrast, *preemptive* therapy is the administration of antiviral therapy only to persons at highest risk, as determined by a positive result on a regularly monitored serum PCR to detect CMV viremia.[177] Such therapy is given even if the patient is asymptomatic.

Epstein-Barr Virus

Primary EBV infection may be associated with fever, malaise, and hematologic abnormalities in immunocompromised patients (and also in some immunocompetent individuals). EBV infection may be associated with the development of malignancies such as posttransplant lymphoproliferative disorder.[182–184] In some transplant populations, regular quantitative monitoring of EBV in peripheral blood by PCR is performed to determine the risk of significant EBV infection.[185]

Human Herpes Virus-6

HHV-6 is a ubiquitous viral infection that usually occurs in infancy. Primary HHV-6 infection and possibly reactivation of infection in immunocompromised patients can be associated with serious disease.[186,187] HHV-6 seems to have neurotropism—in addition to fever, HHV-6 infection may be associated with confusion, coma, and seizures.[188,189] Occasionally, CSF examination is normal except for increased protein and the finding of HHV-6 by PCR.

Human Herpes Virus-8

HHV-8 is associated with Kaposi sarcoma, primary effusion lymphoma, and Castleman syndrome.[190,191] It may be transmitted via organ allograft in solid organ transplantation. Primary infection in immunosuppressed patients may be associated with high fever, thrombocytopenia, other severe cytopenias, and mental state abnormalities.[192] Detection of HHV-8 by PCR in whole blood can establish the diagnosis.

Other Systemic Viruses

Adenoviruses

Adenoviruses have a myriad of presentations in immunocompetent and immunocompromised hosts. Adenovirus infection in immunocompetent individuals is rarely associated with severe disease.[193] Although adenovirus infection in immunocompromised hosts may have trivial manifestations, severe diseases may certainly occur. In recipients of hematologic stem cell transplantation, adenoviruses may cause interstitial pneumonitis, hepatitis (including ascending cholangio-hepatitis), hemorrhagic cystitis, nephritis, hemorrhagic colitis, CNS disease, and disseminated infection.[193] In solid organ transplant recipients, the primary site of adenovirus disease is usually related to the transplanted organ. Clinical manifestations of adenovirus infections described in solid organ transplantations include pneumonia, hepatitis, nephritis, hemorrhagic cystitis, enteritis, and disseminated disease.[193] Adenovirus infection in patients with HIV may cause pneumonia, hepatitis, meningoencephalitis, nephritis, and GI and disseminated disease.[193]

Polyomaviruses: JC and BK Virus

The most commonly encountered polyomaviruses are JC virus and BK virus. JC virus may be associated with progressive multifocal leukoencephalopathy, a progressive and ultimately fatal neurologic disease occurring in profoundly immunosuppressed individuals, such as patients with advanced HIV infection. BK virus is associated most commonly with renal infection in renal transplant recipients.[194] This infection is usually not accompanied by systemic manifestations such as fever but is frequently associated with nephropathy and rising serum creatinine. The mainstay of therapy is to reduce immunosuppressive medications. Without resolution of infection, patients are at higher risk of allograft dysfunction and loss.[195] Patients with hematopoietic stem cell transplants and BK virus infection are at risk of hemorrhagic cystitis after engraftment.

Other Acute Viral Syndromes

Many other viruses can cause life-threatening complications such as aseptic meningitis, encephalitis, pneumonia, or hepatitis. Because they are less common than those described in this text, they are not discussed in detail but are summarized in Tables 119.4 and 119.5 and elsewhere in this text. Viruses are continually evolving and because of their genetic plasticity, modified or entirely new pathogens may emerge. In the right setting, viruses may become more contagious and transmissible and/or develop increased virulence with serious health repercussions.

ANTIVIRAL DRUGS

Because of the increasing recognition of viruses in the ICU and the potential for some of the viruses to cause life-threatening infection, it is imperative that ICU clinicians maintain an understanding of antiviral drug regimens and their indications. This section reviews commonly used antivirals in the ICU, with the exception of HIV and viral hepatitis therapies. Antivirals for influenza are reviewed earlier in the text.

Acyclovir

Acyclovir is a deoxyguanosine analog that inhibits viral DNA polymerase. When incorporated into viral DNA, it acts as a chain terminator. Acyclovir has its greatest clinical utility against HSV-1, HSV-2, and VZV. It has only minor activity against CMV; therefore ganciclovir is preferred. There are rare strains of acyclovir-resistant HSV, whereas acyclovir-resistant VZV is very uncommon. Acyclovir is available in oral and IV formulations. It penetrates the CSF reasonably well, and CSF levels are about 50% of plasma levels.[196] Acute mucosal HSV is typically treated with 200 mg orally five times per day; however, valacyclovir may be preferred because of its higher oral absorption and lower dosing intervals. VZV infections can be treated with 800 mg orally five times per day. In HSV encephalitis, acyclovir is usually given by IV at 10 mg/kg every 8 hours. Dose reduction is required in the presence of renal dysfunction. Patients should be monitored for neurotoxicity, usually manifesting as confusion, hallucinations, and tremors. As acyclovir can cause crystalline nephropathy, patients receiving the drug should be well hydrated.

Valacyclovir

Because the bioavailability of orally administered acyclovir is low, valacyclovir (the l-valyl ester prodrug of acyclovir) was developed. It is usually administered twice daily for non–life-threatening HSV infections and three times daily for VZV infections.

Famciclovir

Famciclovir is a prodrug of penciclovir, which is active against HSV and VZV. Similar to acyclovir, penciclovir is an inhibitor of viral DNA synthesis. In general, acyclovir-resistant strains are also resistant to penciclovir. Dose adjustment of famciclovir is needed in renal insufficiency.

TABLE 119.4 Viruses That Cause Aseptic Meningitis or Encephalitis

Virus	Clinical Manifestations
Enteroviruses	Common cause of aseptic meningitis; rapid diagnosis available via PCR of CSF
HSV-1/2	In adults usually the result of reactivation; rapid diagnosis available via PCR of CSF; HSV-1 commonly causes herpes encephalitis; HSV-2 often causes aseptic meningitis
VZV	May cause encephalitis after chickenpox or in immunocompromised hosts; relatively uncommon; diagnosis made via PCR of CSF
HHV-6	Uncommon cause of encephalitis in immunocompromised hosts, particularly in solid organ transplant recipients
JC virus	May cause progressive multifocal leukoencephalopathy in immunocompromised hosts, particularly HIV-infected patients
Japanese encephalitis	Endemic cause of encephalitis in Southeast Asia, particularly after exposure to rural rice paddies, near farms with pigs
St. Louis encephalitis	Outbreaks have occurred throughout the United States; spread by *Culex* mosquito; spectrum of disease including headache, aseptic meningitis, and encephalitis
West Nile virus	Endemic globally, most common cause of encephalitis in United States and Canada; spread by mosquitos; most cases asymptomatic; causes ILI, and some may develop encephalitis
Tickborne encephalitis	Occurs mostly in Europe, Siberia, and the Far East; related North American TBE caused by Powassan virus; causes acute febrile illness, aseptic meningitis, meningoencephalitis, and acute flaccid paralysis
Nipah virus	Occurs in Southeast Asia; severe and often fatal meningoencephalitis; increased risk after zoonotic exposure
Hendra virus	Occurs in Australia; causes ILI leading to fatal respiratory illness or encephalitis; increased risk after zoonotic exposure
Rabies virus	Global zoonosis transmitted after bite from rabid animals (racoons, dogs, bats, etc.); postexposure with active and passive immunotherapy is important
California encephalitis	Caused by La Crosse, Jamestown Canyon, and other related viruses; second most common cause of encephalitis in the United States and Canada
Human immunodeficiency virus	Can cause encephalitis during the early/acute phase of HIV infection

CSF, Cerebrospinal fluid; *HHV-6,* human herpesvirus 6; *HSV,* herpes simplex virus; *ILI,* influenza-like illness; *PCR,* polymerase chain reaction; *TBE,* tickborne encephalitis; *VZV,* varicella-zoster virus.

TABLE 119.5 Viruses That Can Cause Severe Pneumonia

Virus	Clinical Manifestations
Respiratory syncytial virus	Common cause of lower respiratory tract infection in infants; circulates seasonally with influenza; can cause ARDS and other systemic manifestations in adults
Influenza	Well-known cause of endemic and epidemic upper and lower respiratory tract infection
Parainfluenza virus	Among most common URTI globally; causes croup in children; may cause severe pneumonia or exacerbation of chronic pulmonary disease
Measles virus	Common cause of pneumonia in children in developing nations; re-emerging in areas with low vaccine uptake
Coronaviruses	Severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), coronavirus disease 2019 (COVID-19); emerging in epidemics
CMV	Cause of pneumonia only in immunocompromised hosts
VZV	Pneumonia can complicate chickenpox
Adenovirus	Ubiquitous virus; may cause severe pneumonia in immunosuppressed hosts
Hantavirus	Most severe form related to Sin Nombre virus (SNV); febrile illness with severe capillary leak and pulmonary edema; increased risk after exposure to rodents
Hendra virus	Occurs in Australia; may cause fatal pneumonia; increased risk after zoonotic exposure

CMV, Cytomegalovirus; *URTI,* upper respiratory tract infection; *VZV,* varicella-zoster virus.

Ganciclovir

Similar to acyclovir, ganciclovir is a deoxyguanosine analog that inhibits viral DNA polymerases. Its primarily used in the treatment of CMV infections but also has activity against HSV and VZV. Patients with tissue-invasive CMV are treated initially with induction ganciclovir, 5 mg/kg IV every 12 hours. Alterations in dose and frequency are required in patients with renal dysfunction. Typically, maintenance therapy is given at a reduced frequency in patients who have received 2–3 weeks of induction therapy. Myelosuppression is the major toxicity of ganciclovir. Neutropenia typically begins to occur in the second week of ganciclovir therapy. Regular monitoring of hematologic parameters is mandatory for patients receiving ganciclovir. CNS abnormalities such as headaches and confusion have been well described in patients receiving ganciclovir. Ganciclovir also can be administered into the eyes via an ocular implant.[197,198] Resistance of CMV to ganciclovir can occur after mutations in the *UL97* phosphotransferase gene.[199] Risk factors for ganciclovir resistance include prolonged exposure to ganciclovir (usually several months), ongoing active viral replication because of severe immunosuppression, lack of prior CMV immunity, and inadequate antiviral drug delivery with oral ganciclovir.[199]

Valganciclovir

The oral bioavailability of ganciclovir is poor. Valganciclovir, a prodrug of ganciclovir, can be used to enhance bioavailability. Valganciclovir may be used as a prophylaxis against CMV infections in those undergoing solid or hematopoietic transplantation[180] or as a reasonable step-down alternative to ganciclovir in maintenance therapy for CMV disease.

Foscarnet

Foscarnet is an alternative anti-CMV antiviral, typically reserved for CMV-resistant infections (or for those intolerant of ganciclovir). Foscarnet also has activity against HSV and VZV, including acyclovir-resistant and ganciclovir-resistant strains. Although foscarnet and ganciclovir may have synergistic activity against CMV, there is greater toxicity and no proven benefit to using them in combination.[200] Foscarnet is available in an IV formulation only. Toxicity is common with foscarnet. Nephrotoxicity is a major dose-limiting side effect. Electrolyte abnormalities are also common, especially hypocalcemia, hypophosphatemia, hypomagnesemia, and hypokalemia, which may be symptomatic. Foscarnet may produce painful genital ulcerations; saline loading may diminish the likelihood of nephrotoxicity or ulceration.

Cidofovir

Cidofovir is a broad-spectrum nucleotide analog that is active against many DNA viruses, including herpesviruses, polyomaviruses, poxviruses, and adenoviruses. It is active against acyclovir-resistant and ganciclovir-resistant HSV and CMV. Cidofovir is administered via IV once a week or once every 2 weeks. Its use is accompanied by high rates of nephrotoxicity. Neutropenia occurs in 20% of patients receiving this drug.

Ribavirin

Ribavirin was widely used in combination therapy for hepatitis C virus infection before the advent of direct-acting antivirals, but it is discussed here in the context of its use against other viruses. In vitro, ribavirin has activity against a wide range of DNA and RNA viruses. Ribavirin (aerosolized) is approved by the U.S. Food and Drug Administration for the treatment of bronchiolitis and pneumonia caused by respiratory syncytial virus (RSV). It has been used systemically in the treatment of some hemorrhagic fevers. Systemic ribavirin administration is associated with hemolytic anemia and is highly teratogenic. Use of aerosolized ribavirin in patients with mechanical ventilation or aerosolizing procedures is controversial because of potential exposure to healthcare workers; thus use of aerosol containment systems is recommended.

KEY POINTS

- Influenza has exacted an enormous cost to civilization since antiquity and continues to cause annual epidemics and excess deaths to the present day.
- Influenza A is responsible for periodic pandemics when influenza viruses from birds reassort with human-adapted viruses to generate novel, hybrid viruses to which the entire human population is susceptible.
- Secondary bacterial pneumonia is common with or after influenza infection, usually caused by *S. pneumoniae* or *S. aureus.*
- The mainstay of treatment for severe influenza includes supportive ICU care, neuraminidase inhibitors (oseltamivir), and often ancillary treatments for refractory hypoxemia.
- Annual influenza vaccination is the best way to prevent and/or minimize illness severity and is recommended for patients at risk and all healthcare workers.
- Coronaviruses have a propensity to emerge into highly transmissible pathogens causing potentially severe pneumonia, including SARS, MERS, and COVID-19; treatment is supportive, and prevention with appropriate infection control strategies is imperative to limit spread.
- Measles is re-emerging because of lack of herd immunity and low vaccination rates; the typical manifestations include fever, rash, coryza, and conjunctivitis and can be associated with severe pneumonia in otherwise healthy adults.
- Flares of latent herpesvirus infection are common in the ICU, vesicular rashes in the oropharynx or genital region should be swabbed and treated for HSV; dermatomal vesicular rashes should be checked for herpes zoster (VZV).

References for this chapter can be found at expertconsult.com.

ANNOTATED REFERENCES

Davies A, Jones D, Bailey M, et al. Extracorporeal membrane oxygenation for 2009 influenza A(H1N1) acute respiratory distress syndrome. *JAMA.* 2009; 302(17):1888–1895.
Largest observational study of patients with H1N1 influenza–associated ARDS treated with ECMO. Although the duration of ECMO support was long (median 10 days), outcomes were favorable, with >70% survival out of the ICU.

Kumar A, Zarychanski R, Pinto R, et al. Critically ill patients with 2009 influenza A(H1N1) infection in Canada. *JAMA.* 2009;302(17):1872–1879.
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Human Immunodeficiency Virus Infection

Piotr Szychowiak, Élie Azoulay, and François Barbier

INTRODUCTION

The burden of human immunodeficiency virus (HIV) infection remains a global public health issue, with an estimated 1.8 million new infections and almost 800,000 acquired immunodeficiency syndrome (AIDS)–related deaths in 2018.[1] Around 38 million people are currently living with HIV worldwide (including 8 million patients not aware of their seropositive status), corresponding to a ~50% increase over the past two decades that reflects both the continuous dissemination of the virus and a striking improvement of life expectancy in patients with sustained viral replication under combination antiretroviral therapies (cARTs). Indeed, since their advent in 1996, dramatic progresses in the efficacy and safety of cART schemes have converted HIV infection from a rapidly fatal disease to a chronic condition requiring long-term care. Though access to cART remains a major challenge in low-income countries and certain sociologic clusters in middle- and high-income regions,[2] roughly two-thirds of the global seropositive population are now receiving these drugs.[1] This proportion is growing steadily, which translates into a continuous decrease in the incidence of opportunistic infections (OIs) and other AIDS-related events compared with the early years of the HIV pandemic.[3,4] Meanwhile, lifelong residual viral replication and/or cART-related toxicities may result in HIV-associated non-AIDS (HANA) conditions, especially chronic obstructive pulmonary disease (COPD), atherosclerosis, renal dysfunction, certain neoplasms, and liver diseases.[4]

HIV-infected patients are at high risk for critical illness because of the occurrence of severe OI in those with advanced immunosuppression, a marked susceptibility to bacterial sepsis and tuberculosis at every stage of HIV infection, and a rising prevalence of HANA conditions in patients aging under cART. Along with a steady decline in AIDS-related admissions and an opposite trend in those for exacerbated comorbidities, several patterns of intensive care have changed in this population over the late cART era, notably the emergence of new mechanisms of immunosuppression not directly resulting from AIDS (e.g., antineoplastic chemotherapy or solid organ transplantation [SOT]), the management of cART at the acute phase of critical illness, and a dramatic enhancement in short-term survival that mainly ensues from general advances in ICU practices.[5,6]

Here, we seek to provide a comprehensive overview of intensive care in HIV-infected patients, including current epidemiologic features, reasons for intensive care unit (ICU) admission, use of life-sustaining therapies, and determinants of short-term outcome. We also summarize the available evidence regarding the management of cART in the ICU, with a focus on severe adverse events, administration issues, and timing of initiation in patients admitted for AIDS-related OI.

THE CONTINUUM OF HIV INFECTION: IMPACT ON CLINICAL PRESENTATION AT ICU ADMISSION

Acute HIV Infection

Acute HIV infection is characterized by a rapid rise in plasma HIV RNA levels and may trigger a myriad of nonspecific clinical signs such as fever, myalgia, disseminated lymphadenopathy, and rash that mimic mononucleosis syndrome.[7] Yet severe forms with acute encephalitis, myocarditis, or multiple organ failure caused by hemophagocytic lymphohistiocytosis (HLH) have been reported occasionally and may require ICU admission.[8–11]

Progression to AIDS

After 3–4 weeks, the viremia level plateaus because of the appearance of HIV-specific antibodies. The disease then becomes chronic, with a gradual decline in $CD4^+$ T lymphocytes (hereafter referred to as CD4 cells) resulting in the occurrence of AIDS-defining conditions within 2–20 years after seroconversion. Of note, both innate and humoral immune alterations occur upon early HIV infection, explaining the high risk of bacterial infection and tuberculosis at this stage. Without cART, HIV infection nearly always progresses to end-stage AIDS with wasting, recurrent OIs, and other ultimately fatal complications (e.g., HIV encephalitis).

Late-stage HIV infection remains a common reason for ICU admission in settings or sociologic clusters with limited access to diagnosis, cART, and specialized aftercare—migrants, homeless people, and other individuals without adequate health insurance coverage are particularly affected in high-income countries. These patients primarily present with severe AIDS-related OIs against a background of poor nutritional status and advanced immunosuppression, similarly to the early years of the HIV pandemic (1980–1995). *Pneumocystis jirovecii* pneumonia (PCP), cerebral toxoplasmosis, and tuberculosis are the leading diagnoses, especially for inaugural admissions.[5,6] Such patients account for 10%–30% of all ICU admissions of HIV-infected individuals (Table 120.1), though this proportion appears to be dwindling over the past decade.[12–18] Of note, severely immunosuppressed hosts—that is, those with CD4 cells $<100/\mu L$—may have two or more concurrent OIs accounting for clinical presentation at ICU admission.

Severe AIDS-defining conditions may also occur in patients with uncontrolled viral replication despite cART. However, the contemporary therapeutic armamentarium enables achieving viral suppression and immunologic restoration within 6 months in more than 90% of cases—even those involving resistant strains—with maintenance of OI prophylaxis (e.g., sulfamethoxazole plus trimethoprim [SXT] for PCP) until a protective CD4 cell threshold is achieved.[4,28] Beside compliance flaws, virologic failure in 2020 is mainly linked with procurement issues

TABLE 120.1 Critically Ill HIV-Positive Patients in the cART Era: Selected Recent Cohort Studies

Setting and Period (reference)	Patients, Number	Age, y[a]	Prior cART	Inaugural Admission	OI[b]	IMV	RRT	Vasopressors	Mortality
Spain, single ICU, 1997–2003[19]	49	40 (33–47)	31%	31%	81%	NA	NA	NA	54% (hospital)
USA, single ICU, 2000–2004[20]	306	44 (24–72)	33%	NA	21%	68%	NA	NA	21% (hospital)
UK, single ICU, 1999–2005[21]	102	39 (32–44)	37%	30%	67%	62%	19%	NA	24% (ICU) 34% (hospital)
France, single ICU, 1999–2006[14]	284	42 (36–49)	53%	20%	25%	44%	11%	23%	14% (ICU)
Mexico, single ICU, 1996–2006[22]	53	38 ± 10	28%	26%	77%	83%	NA	26%	43% (ICU)
Brazil, single ICU, 1996–2006[23]	278	40 ± 10	45%	38%	81%	55%	NA	NA	55% (ICU) 69% (6 months)
UK, single ICU, 2001–2006[24]	43	44 (40–60)	56%	0 (0%)	44%	62%	27%	56%	32% (ICU)
The Netherlands, single ICU, 1996–2008[25]	80	43 (23–76)	36%	11%	50%	76%	NA	NA	31% (ICU) 45% (hospital) 53% (1 year) 68% (5 years)
France, single ICU, 1997–2008[26]	98	43 ± 11	44%	8%	25%	59%	15%	51%	37% (ICU) 53% (hospital) 55% (1 year)
Brazil, single ICU, 2006–2008[15]	88	40 (31–47)	45%	28%	70%	60%	18%	24%	49% (hospital)
Taiwan, single ICU, 2001–2010[16]	135	39 (31–50)	36%	44%	NA	78%	8%	36%	37% (ICU) 49% (ICU)
USA, 8 ICUs, 2002–2010[13]	539	54 (48–59)	71%	NA	13%	17%	NA	NA	19% (day 30)
France, 41 ICUs, 2005–2010[27]	2884	46 (40–52)	NA	NA	25%	52%	15%	27%	16% (ICU) 25% (H)
China, single ICU, 2009–2013[17]	122	43 (20–76)	39%	64%	48%	80%	8%	30%	64% (ICU) 66% (ICU)
Uganda, single ICU, 2009–2014[18]	101	38 ± 16	55%	10%	72%	57%	NA	27%	57% (ICU)

cART, Combination antiretroviral therapy; *IMV,* invasive mechanical ventilation; *NA,* not available; *OI,* opportunistic infection; *RRT,* renal replacement therapy; *VP,* vasopressors.
[a] Median (interquartile range) or mean ± standard deviation, as reported in the original publications.
[b] Main or secondary reason for ICU admission.

TABLE 120.2 Expected Rise in CD4 Cell Count After cART Initiation

Time Frame	CD4 Cell Count
First month	Increase by 50–75 cells/μL after initiation of cART
Each ensuing year	50–100 cells/μL per year
After several years	>500 cells/μL provided HIV replication remains suppressed (undetectable viral load)

cART, Combination antiretroviral therapy.

(i.e., stock-outs, defective supply, or lack of financial resources) in low- and middle-income countries, as in other environments with restricted access to cART.

Immune Recovery and Aging Under cART

cART initiation is mandatory in patients with acute infection or established AIDS; however, these drugs are beneficial and now recommended upon the early stage of asymptomatic HIV infection.[28] In patients with sustained treatment adherence, cART rapidly controls HIV replication, thereby elevating the CD4 cell count (ideally above 500/μL), although substantial interindividual variations exist regarding the pace and magnitude of recovery. Table 120.2 indicates the expected rise in CD4 cells after treatment introduction in cART-naïve patients.

Importantly, compared with age- and gender-matched seronegative individuals, cART-treated patients aging with sustained viral control are at increased risk for a broad spectrum of chronic HANA conditions that predispose to life-threatening complications,[12] including COPD, atherosclerosis (e.g., coronary heart disease or cerebrovascular disease), non–AIDS-defining cancers (especially lung, liver, and anal carcinoma), and renal or liver impairment.[29–34] Lifetime low-level inflammation caused by silent HIV replication in sanctuary sites, coinfections (e.g., cytomegalovirus [CMV], Epstein-Barr virus [EBV] or hepatitis B and hepatitis C virus [HBV/HCV]), habitus (e.g., tobacco or intravenous drug use), sequelae of past infectious processes, and long-term toxicity of certain antiretroviral medications may be implicated to varying degrees in the pathogenesis of these conditions.[4,35] A role for intestinal dysbiosis has also been suggested by recent metagenomics-based studies in cART-treated patients.[36] Overall, chronic HANA diseases now account for over 75% of deaths in HIV-positive patients living in high-income countries.[37]

Up to 70% of HIV-infected patients nowadays managed in the ICU are receiving long-term cART (see Table 120.1).[13,15,17,18,24–26] This epidemiologic shift translates into a continuous rise in non–AIDS-related ICU admissions—mostly for bacterial sepsis or exacerbated HANA conditions—which broadly exceeded those for severe OIs in the most recent cohorts. Furthermore, on the basis of encouraging outcomes, HIV infection is no longer a definite contraindication for SOT in patients with chronic kidney, liver, or heart failure, thereby enlarging the scope of critical illnesses in this population.[38–41]

CONVERGENCE OF CLINICAL PRESENTATION AND OUTCOMES IN CRITICALLY ILL HIV-INFECTED AND SERONEGATIVE PATIENTS

As a result of easier access to cART and sequential improvements in intensive care practices, critically ill HIV-infected individuals now share several similarities with the general population of ICU

patients. First, the reasons for ICU admission are evenly distributed between seropositive and HIV-uninfected patients, with acute respiratory failure (ARF, 40%–60% of all admissions), bacterial sepsis (10%–20%, mostly resulting from respiratory, intraabdominal, and bloodstream infections), and impaired consciousness (10%–20%) being the main clinical vignettes in both subgroups.[13,14,21,25] Admissions for acute kidney injury (AKI), gastrointestinal bleeding, acute-on-chronic liver failure, or scheduled postoperative management become more regular over time,[27] which merely reflects the increasing prevalence of at-risk comorbidities in HIV-infected individuals—for instance, HIV/HCV-coinfected patients are more prone to developing AKI.[5]

More than two-thirds of current admissions are not directly related to AIDS,[13,27] a proportion that is expected to amplify in the years to come. For a given reason of ICU admission, the etiologic spectrum is increasingly analogous to what is observed in HIV-uninfected subjects. Indeed, bacterial pneumonia, COPD exacerbation, complicated lung cancer, and pulmonary edema caused by congestive heart failure have become major causes of ARF, and stroke or *Streptococcus pneumoniae* meningitis are overtaking classic OIs of the central nervous system (CNS) in patients admitted for life-threatening neurologic disorders.[5,6] Again, chronic HIV infection stands out as an independent risk factor for most of these AIDS-unrelated conditions.

Notwithstanding a manifest propensity to these diseases, the clinical presentation of common community-acquired infections does not differ between HIV-infected patients with mild-to-moderate immunosuppression and their seronegative counterparts. This is notably shown for pneumonia caused by *S. pneumoniae* and *Legionella pneumophila,*[42,43] severe COVID-19,[44,45] or bacterial meningitis.[46] Excepting those with profound immune deficiency,[15,47] HIV-infected patients with sepsis exhibit no discrepancies in terms of plasma levels of host response biomarkers, disease severity, and survival when compared with HIV-uninfected controls.[48,49] Therefore the diagnostic workflow and initial management of HIV-infected patients with a protective CD4 cell count for usual OIs (i.e., above 200–250/μL) has no relevant particularities and should follow standard procedures and guidelines.[50]

The spectacular improvement of life expectancy in cART-treated patients offers long-term perspectives that justify maximizing the level of supportive care when indicated. Invasive mechanical ventilation (MV, 40%–50% of all admissions), vasopressors (15%–30%), and renal replacement therapy for AKI (8%–15%) are now used as frequently in seropositive individuals as in the general ICU population (see Table 120.1),[13,14,16,27,51,52] with comparable prognoses, including in patients at high risk of death, such as those admitted after cardiac arrest or with acute respiratory distress syndrome (ARDS).[53,54] Last-resort venovenous or venoarterial extracorporeal membrane oxygenation can be discussed in selected patients, with promising results in available reports.[55,56]

Strikingly, overall in-hospital mortality rates have fallen from more than 80% in the early 1980s to 20%–40% in the most recent Western cohorts, a shift that likely reflects general improvement in intensive care such as direct admission from the emergency department, prompt antibiotic initiation and hemodynamic interventions in patients with sepsis, or protective MV settings for ARDS.[13,24–27,51] Short-term outcomes of critically ill HIV-infected patients tend to equal those of seronegative subjects with similar demographics, chronic health status, and underlying diseases (e.g., HCV or malignancy), reason for admission, and extent of organ dysfunction.[21] CD4 cell count, HIV viral load, prior cART use, and an admission for an AIDS-related event (versus other diagnoses) are no longer associated with hospital survival.[14,15,57–59]

DIAGNOSTIC WORKFLOW AND THERAPEUTIC APPROACHES IN CRITICALLY ILL HIV-INFECTED PATIENTS

In HIV-positive patients, the CD4 cell count, which is the most readily available surrogate marker of immune deficiency, is essential to guide the etiologic work-up, notably in patients with ARF or neurologic disorders (Fig. 120.1).[5,6,60] Except tuberculosis, severe OIs occur almost exclusively in patients with CD4 cells below 200/μL. Some rare conditions, such as severe CMV infection or invasive aspergillosis, may occur at counts below 50/μL. Because a transient drop in CD4 cells is usual at the acute phase of sepsis, diagnostic algorithms should be based on a recent steady-state count, when available, rather than on the count measured at admission. Other baseline features to consider include a prior history of OI at risk for recurrence (e.g., tuberculosis), a geographic origin that predisposes to specific imported OIs (e.g., histoplasmosis), adherence to cART and anti-PCP prophylaxis when prescribed, and comorbidities.

Admission for Acute Respiratory Failure

In HIV-positive patients, community-acquired bacterial pneumonia (CAP) accounts for 35%–50% of all cases of ARF and is the main reason for ICU admission. The risk of CAP is markedly higher at all stages of HIV infection, but is greatest in patients with profound CD4 cell depletion and decreases with long-term cART use.[61,62] *S. pneumoniae* is the causative agent in 20%–40% of cases.[58,62] As previously mentioned, the clinical presentation and outcomes of *S. pneumoniae* CAP are the same in HIV-positive patients and in their HIV-negative counterparts matched on demographics and comorbidities.[43] Bacteremia is more common in HIV-positive patients, probably because of impaired alveolar macrophage and neutrophil functions.[61] *Haemophilus influenzae, Staphylococcus aureus,* and Enterobacteriaceae are involved in less than 10% of cases.[58,63] *L. pneumophila,* a major pulmonary pathogen in other immunocompromised patients, is uncommonly responsible for severe CAP in HIV-positive individuals.[58] Of note, *Pseudomonas aeruginosa* may cause CAP in patients with very low CD4 cell counts or underlying structural lung damage and should be considered when selecting empirical antibiotics in patients with these predisposing factors.[15,58,64] Lastly, lower respiratory tract infections caused by respiratory viruses (e.g., influenza, rhinovirus, adenovirus, human metapneumovirus, or respiratory syncytial virus) are now commonly diagnosed through multiplex molecular assays in HIV-infected patients, including those admitted to the ICU for ARF, whatever the extent of CD4 cell deficiency.[65,66] The incidence, clinical presentation, and outcomes of severe COVID-19 in cART-treated HIV-infected individuals appear similar to those reported in seronegative patients.[44,45]

PCP continues to decline in frequency but still accounts for 10%–20% of ARF cases and remains the most common AIDS-related OI encountered in the ICU, especially in patients without a previous diagnosis of HIV infection.[13,17,27,67] In HIV-positive patients, PCP manifests as fever, dry cough, and worsening dyspnea culminating in ARF within 2 or 3 weeks. Overall, about a third of all patients with AIDS-related PCP require initial ICU management.[68,69] Extrarespiratory failures (e.g., shock) suggest bacterial coinfection or another concurrent OI. The radiologic presentation evolves from reticular infiltrates to diffuse or patchy bilateral ground-glass opacities with alveolar consolidations (Fig. 120.2). By computed tomography (CT), parenchymal cysts and sparing of subpleural regions are usual at advanced stages of the disease, whereas lymph node enlargement and pleural effusion are not attributable to PCP and should trigger a search for a concurrent OI. The diagnosis of AIDS-related PCP is far easier than in other immunocompromised patients and relies on the visualization of *P. jirovecii* trophozoites or cysts

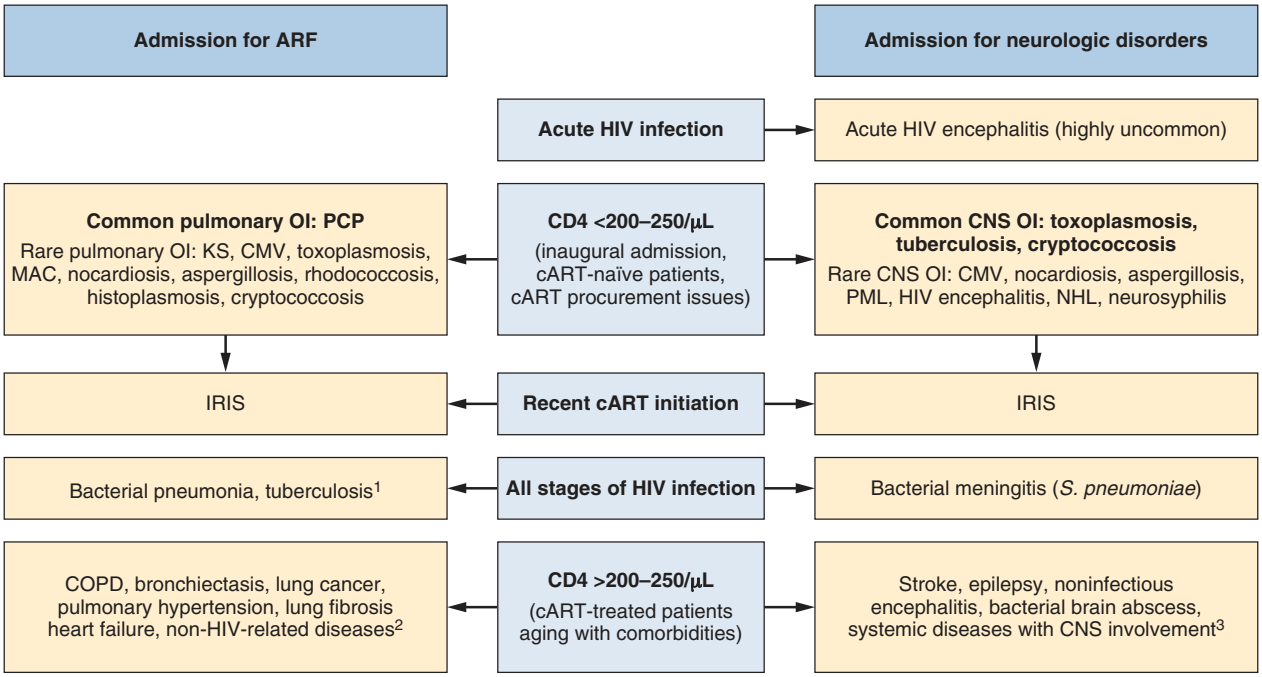

Fig. 120.1 Admission of HIV-Infected Patients for Acute Respiratory Failure or Acute Neurologic Impairment: Etiologic Panel According to Immune Status. *ARF,* Acute respiratory failure; *cART,* combination antiretroviral therapy; *CNS,* central nervous system; *COPD,* chronic obstructive pulmonary disease; *IRIS,* immune reconstitution inflammatory syndrome; *KS,* Kaposi sarcoma; *MAC, Mycobacterium avium* complex; *NHL,* non-Hodgkin lymphoma; *OI,* opportunistic infection; *PJP, Pneumocystis jirovecii* pneumonia; *PML,* progressive multifocal encephalopathy (JC virus encephalitis). [1]Pulmonary tuberculosis is also a major cause of IRIS that may lead to ARF; [2]Interstitial pneumonitis, drug toxicity, asthma, pulmonary embolism, others; [3]Sepsis, endocarditis, anoxia, metabolic disorders, drug toxicity or overdose, malignancies, thrombotic microangiopathy, others. (From Barbier F, Mer M, Szychowiak P, et al. Management of HIV-infected patients in the intensive care unit. *Intensive Care Med.* 2020;46[2]:329–342, Fig. 1.)

in bronchoalveolar lavage (BAL) fluid stained with Gomori-Grocott or Giemsa and immunofluorescence, which has greater than 90% sensitivity.[70] Induced sputum is only 50%–90% sensitive, may be challenging to perform in patients with ARF, and does not allow an exhaustive search for the bacterial or opportunistic coinfections seen in up to 20% of patients with pronounced immunosuppression.[70] The qualitative polymerase chain reaction (PCR) assay is valuable for diagnosing non–AIDS-related PCP,[71] notably in patients on prophylactic therapy, but lacks specificity in HIV-positive patients because of their 14%–69% prevalence of colonization. PCR may, however, be occasionally useful in ruling out PCP, given its greater than 95% negative predictive value.[72] A high fungal load by quantitative PCR supports infection as opposed to colonization,[73,74] but appears to be of limited added value, given the high performance of staining and immunofluorescence. Last, blood 1,3 β-D-glucan elevation (>80 pg/mL) is highly sensitive (92%–95%) but lacks specificity (78%–82%) because this component of the *P. jirovecii* cell wall increases in several other AIDS-related fungal infections (e.g., esophageal candidiasis).[75,76] SXT remains the first-line treatment (Table 120.3). Whether dihydropteroate synthase gene mutations hamper the clinical efficacy of sulfamethoxazole remains controversial,[77] and standard SXT dosages are still recommended in patients with PCP despite prophylaxis.[70] Adjunctive corticosteroid therapy reduces the risk of invasive mechanical ventilation (IMV) and in-hospital death and should be started within 72 hours in all patients with suspected or definite severe PCP (arterial partial pressure of oxygen [PO_2] <70 mm Hg while breathing room air).[70,78,79]

Pulmonary tuberculosis is responsible for up to 10% of ARF cases in Western cohorts of HIV-positive patients and remains a common inaugural AIDS-defining condition, notably in immigrants from endemic areas.[58,80] The presentation is usually typical at the early stages of HIV infection, whereas patients with CD4 cells below 200/μL more often have atypical radiologic patterns (miliary or diffuse alveolar infiltrates without upper lobe cavitation), extrapulmonary localizations, and no acid-fast bacilli (AFB) visible in sputum smears (see Fig. 120.2). Nucleic acid amplification tests (NAATs) should be performed on at least one respiratory sample in all HIV-positive patients with suspected tuberculosis, both to distinguish *Mycobacterium tuberculosis* from other mycobacteria in patients with AFB-positive sputum smears and to allow earlier identification of *M. tuberculosis* in AFB-negative sputum smears—in this last situation, NAATs are positive in 50%–80% of patients with culture-proven tuberculosis.[70] Some NAATs, such as Xpert MTB/RIF, also detect *rpoB* mutations conferring rifampicin resistance several weeks before the availability of conventional susceptibility test results.[81,82] Of note, interferon-gamma release assays may be negative in up to 30% of patients with active tuberculosis and should therefore not be used as a pivotal decision-making tool.[70] The first-line regimen for suspected or definite pulmonary tuberculosis in HIV-positive patients is a four-drug combination of isoniazid, rifampin, ethambutol, and pyrazinamide for 2 months (see Table 120.3). A growing amount of evidence supports benefits from corticosteroids in ARF caused by tuberculosis[83,84]; however, data from HIV-positive patients are lacking, and this adjunctive treatment is currently recommended only in patients with involvement of the CNS or pericardium.

A vast array of other pulmonary AIDS-related diseases may cause ARF in patients with fewer than 50–100/μL CD4 cells, albeit only very rarely. Examples include nontuberculosis mycobacterial diseases (e.g.,

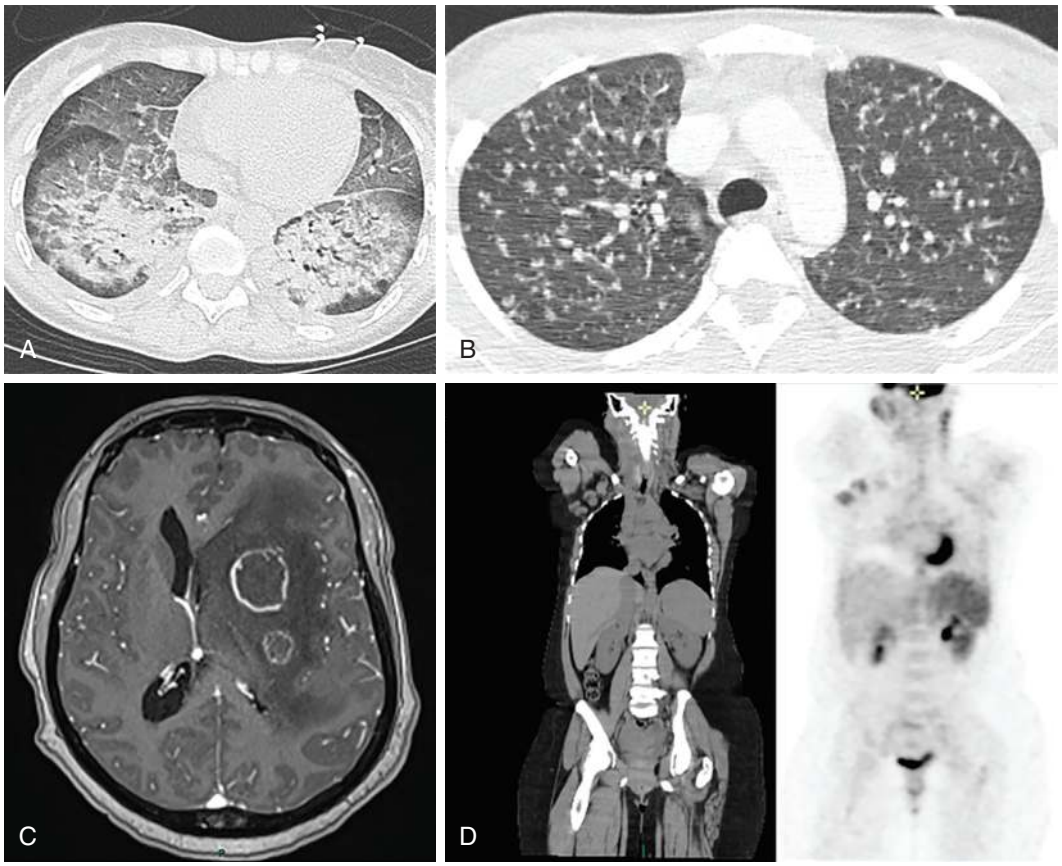

Fig. 120.2 AIDS-related opportunistic infections in the ICU: typical imaging features. **A,** *Pneumocystis jirovecii* pneumonia (chest CT scan showing diffuse ground-glass opacities with focal alveolar consolidations, thickened septal lines, relative sparing of the subpleural regions, and absence of pleural effusion). **B,** Lung involvement secondary to miliary tuberculosis (chest CT scan showing bilateral disseminated nodules without typical excavation in a patient with CD4 cell count <100/μL). **C,** Cerebral toxoplasmosis (T1-weighted cerebral magnetic resonance imaging showing gadolinium-enhanced lesions of the hemispheric grain matter with peripheral edema and mass effect). **D,** Multicentric Castelman disease (positron emission tomography showing enlarged liver, spleen, and axillary/cervical lymph nodes with hypermetabolic patterns). (From Barbier F, Mer M, Szychowiak P, et al. Management of HIV-infected patients in the intensive care unit. *Intensive Care Med.* 2020;46[2]:329–342, Fig. 2.)

Mycobacterium avium complex), pneumonia caused by opportunistic bacteria (e.g., *Rhodococcus equi* or *Nocardia* spp.) or fungi (e.g., *Aspergillus* spp., *Cryptococcus neoformans, Histoplasma capsulatum,* coccidioidomycosis, and mucormycosis), disseminated toxoplasmosis, and Kaposi sarcoma (see Fig. 120.2). Also, CMV has been detected by molecular assays in 5%–10% of patients with PCP or another OI, although CMV pneumonitis appears rare and should be diagnosed only in patients with nuclear inclusions in BAL fluid or lung biopsies or with diffuse interstitial infiltrates or other suggestive patterns by chest CT (e.g., ground-glass opacities, focal consolidation, or parenchymal micronodules).[70]

At last, the prevalence of ARF caused by exacerbated HANA conditions (especially COPD, lung cancer, and, to a lesser extent, pulmonary hypertension) will probably continue to rise in the near future in cART-treated patients aging with sustained viral control. In these patients, the diagnostic work-up does not differ from that in HIV-negative subjects (see Fig. 120.1).[5,6]

Admission for Neurologic Disorders

The incidence of AIDS-related diseases involving the CNS has dropped sharply in high-income countries since the introduction of cART.[70] In a single-ICU study, AIDS-related diseases accounted for only 42% of admissions for altered consciousness, with the most common diagnoses being cerebral toxoplasmosis, tuberculous meningitis, and cryptococcal meningitis.[57] Other OIs such as CMV encephalitis, progressive multifocal leukoencephalitis caused by JC virus, neurosyphilis, cerebral aspergillosis, nocardiosis, and histoplasmosis are exceedingly rare causes of neurologic failure in HIV-positive patients.[27,57] Contrast-enhanced CNS imaging—preferentially magnetic resonance imaging (MRI)—is a key component of the diagnostic work-up in patients with deep CD4-cell depletion and must be performed before lumbar puncture to rule out a mass effect responsible for a high risk of cerebral herniation.

AIDS-related cerebral toxoplasmosis is nearly always the result of reactivation of latent intraparenchymal *Toxoplasma gondii* cysts rather than to primary infection. In a multi-ICU study, altered consciousness, focal deficits, and seizures were observed in 67%, 59%, and 22% of patients, respectively, and fever was absent in almost half the cases.[85] Brain MRI shows multifocal, ring-enhanced, and sometimes hemorrhagic lesions in the cortex and/or basal ganglia region with a mass effect from peripheral edema that may require corticosteroid therapy.[86] Solitary lesions and diffuse encephalitis are far less common. The PCR assay for *T. gondii* in cerebrospinal fluid (CSF) is highly specific (>95%) but is no more than 50% sensitive after a few days of therapy.[86] *T. gondii* PCR in blood is even less sensitive but may provide

TABLE 120.3 Treatments for the Most Common Opportunistic Infections in Critically Ill HIV-Positive Patients

Opportunistic Infection	First-Line Regimen for Severe Cases	Main Alternatives	Adjunctive Therapies	Timing of cART Introduction
PCP pneumonia	TMP (15–20 mg/kg/d) and SMX (75–100 mg/kg/d) IV q6h or q8h Switch to PO after clinical improvement Total treatment duration: 3 weeks (then switch to secondary prophylaxis dosing[a]) No leucovorin supplementation[b]	Pentamidine 4 mg/kg IV once daily (patients with TMP or SMX adverse events such as allergy or hemolysis because of glucose-6-phosphate dehydrogenase deficiency)	Corticosteroids if PaO_2 <70 mm Hg (room air) Prednisone PO: Days 1–5: 40 mg BID Days 6–10: 40 mg daily Days 11–21: 20 mg daily Alternative: methylprednisolone IV (75% of prednisone dose)	Within 2 weeks
Tuberculosis (drug-susceptible *M. tuberculosis*)	• Intensive phase (2 months): isoniazid + rifampin or rifabutin + pyrazinamide + ethambutol • Continuation phase: isoniazid + rifampin or rifabutin • Total treatment duration: Pulmonary TB: 6–9 months Extrapulmonary TB with CNS involvement: 9–12 months Extrapulmonary TB with bone or joint involvement: 6–9 months Extrapulmonary TB at other sites: 6 months	Consult an ID specialist	• CNS disease: dexamethasone 0.3–0.4 mg/kg/d for 2–4 weeks, then taper by 0.1 mg/kg per week until 0.1 mg/kg, then 4 mg/d and taper by 1 mg/wk; total duration of 12 weeks • Pericardial disease: prednisone or prednisolone (e.g., 60 mg PO daily with weekly tapering over 6 weeks)	• Active TB without CNS involvement: • Within 2 weeks for patients with CD4 cells <50/μL • Within 8 weeks for patients with CD4 cells ≥50/μL • Active TB with CNS involvement: deferred initiation (high risk of severe IRIS) • Close collaboration with ID specialists
Toxoplasmosis	• Pyrimethamine 200 mg PO once, then pyrimethamine 50–75 mg PO daily + sulfadiazine 1000–1500 mg PO q6h + leucovorin 10–25 mg PO daily • Total treatment duration: at least 6 weeks (then switch to chronic maintenance therapy[a])	• Pyrimethamine (with leucovorin) plus clindamycin 600 mg IV or PO q6h • TMP 5 mg/kg and SMX 25 mg/kg IV or PO BID	• Corticosteroids if cerebral lesions with mass effect • Anticonvulsants only if seizures (no primary prevention)	• No recommendation, because of insufficient data (usually within 2–3 weeks)
Cryptococcus infections	• Induction therapy (at least 2 weeks): liposomal amphotericin B 3–4 mg/kg IV daily plus flucytosine 25 mg/kg QID • Consolidation therapy (at least 8 weeks) after clinical improvement and sterilization of CSF cultures: fluconazole 400 mg PO or IV once daily • Maintenance therapy (at least 1 year): fluconazole 200 mg PO	Induction therapy: fluconazole (400–800 mg/d) may replace either liposomal amphotericin B or flucytosine	Corticosteroids may be deleterious in patients with CNS disease and are not recommended.	CNS involvement: 2–10 weeks after initiation of specific therapy (longer delay if high intracranial pressure) Other localizations: 2–4 weeks after initiation of specific therapy
Histoplasmosis	Induction therapy (at least 2 weeks): liposomal amphotericin B 3 mg/kg/d IV – *If confirmed meningitis: increase dosage to 5 mg/kg/d and extend induction to 4–6 weeks* Maintenance therapy: itraconazole 200 mg PO TID for 3 days, then BID for at least 12 months	Fluconazole (400 md/d PO) may replace itraconazole for long-term suppressive therapy	–	As soon as possible

TABLE 120.3 Treatments for the Most Common Opportunistic Infections in Critically Ill HIV-Positive Patients—cont'd

Opportunistic Infection	First-Line Regimen for Severe Cases	Main Alternatives	Adjunctive Therapies	Timing of cART Introduction
Disseminated MAC disease	Clarithromycin 500 mg PO twice daily + ethambutol 15 mg/kg PO daily or azithromycin 500–600 mg + ethambutol 15 mg/kg PO daily Addition of a third or fourth drug (rifabutin, amikacin, fluoroquinolone) should be considered for patients with CD4+ T cells <50/μL, high mycobacterial loads (>2 log CFU/mL of blood), or in the absence of effective cART	Consult an infectious disease specialist	–	After completion of the second week of MAC-directed therapy
CMV infection	Ganciclovir 5 mg/kg IV q12h Role of oral valganciclovir: not established Optimal treatment duration: not established	Foscarnet 60 mg/kg IV q8h or 90 mg/kg IV q12h	–	No recommendation, because of insufficient data (usually within 2 weeks)
PML	cART	–	–	As soon as possible

BID, Twice a day; *cART,* Combination antiretroviral therapy; *CFU*, colony-forming unit; *CMV,* cytomegalovirus; *CNS,* central nervous system; *CSF,* cerebrospinal fluid; *HIV*, human immunodeficiency virus; *IRIS,* immune reconstitution inflammatory syndrome; *IV*, intravenous; *IV,* intravenously; *MAC, Mycobacterium avium* complex; PaO_2, arterial partial pressure of oxygen; *PCP*, Pneumocystis jirovecii; *PML,* progressive multifocal encephalopathy (caused by JC virus); *PO,* per os; *SMX,* sulfamethoxazole; *TB,* tuberculosis; *TID*, three times a day; *TMP,* trimethoprim.

[a] Consider discontinuation in patients with CD4 cells >200/μL under cART.

[b] Leucovorin supplementation does not efficiently prevent myelosuppression and may be associated with treatment failure.

Adapted from the guidelines of the Centers for Disease Control and Prevention, the National Institutes of Health, and the Infectious Diseases Society of America for the management of opportunistic infections in adults with HIV.[70]

valuable information if positive in a patient with contraindications to lumbar puncture. The first-line regimen for suspected cerebral toxoplasmosis is combined pyrimethamine, sulfadiazine, and leucovorin (see Table 120.3). The diagnosis must be confirmed by a clinical and radiologic response to empirical toxoplasmosis therapy within 10–14 days. A brain biopsy should be considered promptly in patients who fail to respond, have negative immunoglobulin G (IgG) serology or PCR results, or have imaging study findings suggesting another etiology (notably CNS lymphoma).[70] Of note, disseminated disease with septic shock, multiorgan failure, myocarditis, and HLH appears less common in patients with AIDS compared with other causes of immunodeficiency.[87]

Tuberculous meningitis is present in up to 20% of HIV-positive patients admitted to the ICU with active tuberculosis.[88] The clinical presentation is usually subacute and may include fever, headache, focal abnormalities, consciousness impairments, and seizures. Meningeal inflammation in a predominantly basal location, tuberculomas, hydrocephalus, and vasculitis are common MRI patterns, whereas CSF analysis usually shows lymphocytic pleocytosis with variable cell counts (10–500/μL), low glucose levels, and elevated protein levels (0.5 to >3 g/L).[89] The low mycobacterial inoculum translates into poor sensitivities of CSF staining (10%–20%), cultures (~70%), and NAATs (~50%). However, NAATs are highly specific (>95%) and may remain positive for days after the empirical initiation of tuberculosis treatment, thus documenting the diagnosis in patients without initial CSF sampling.[86,90] A large volume of CSF (i.e., >4–5 mL) should be sampled to improve culture sensitivity.[91] The first-line regimen combines rifampicin, isoniazid, ethambutol, and pyrazinamide. No convincing evidence exists that intensified therapies, including fluoroquinolone or high-dose rifampicin, are clinically beneficial.[92] Adjunctive corticosteroid therapy (dexamethasone 0.3–0.4 mg/kg/day for 2–to 4 weeks, followed by tapering, for a total of 12 weeks) should be considered routinely, given the evidence of lower short-term mortality rates in patients with tuberculous meningitis,[70] with no decrease, however, in the prevalence of residual neurologic impairments in survivors.[93]

Most cases of cryptococcal meningitis and meningoencephalitis are caused by the ubiquitous species *Cryptococcus neoformans,* although *Cryptococcus gattii* infections also occur in subtropical regions. Patients present with fever, headaches, and impaired mental status caused by intracranial hypertension. Moderate lymphocytic pleocytosis, mild protein elevation, low-to-normal glucose levels, and encapsulated yeasts by Gram or Indian ink staining are the most common CSF findings. CSF cultures are positive in over 90% of patients.[86] Cryptococcal antigen testing on CSF and serum is both sensitive and specific and allows earlier confirmation of the diagnosis, including in cases of disseminated disease. An initial combination of amphotericin B and 5-fluorocytosine is recommended for at least 2 weeks,[94] followed by an azole-based consolidation regimen after clinical improvement and CSF culture sterilization (see Table 120.3).[70] Adjunctive corticosteroid therapy does not appear beneficial and may even be deleterious in this indication.[95] CSF depletion by repeated lumbar punctures is an essential component of care in patients with intractable intracranial hypertension caused by severe forms of the disease.

The diagnostic work-up for neurologic failure is similar in cART-treated patients with CD4 cells above 200/μL and in HIV-negative patients (see Fig. 120.1). Nonetheless, intensivists should keep in mind the high risk of bacterial meningitis (notably caused by *S. pneumoniae*) in HIV-positive patients.[46] Also, stroke may become an increasingly common reason for ICU admission, as an independent association has

been reported between long-term HIV infection and stroke resulting from accelerated vascular senescence.[96]

Admission for Sepsis

Sepsis remains a major reason for ICU admission in HIV-positive patients.[14,16,47] HIV infection increases the risk not only of bacterial pneumonia and meningitis but also of skin and soft tissue infections, notably the result of community-acquired methicillin-resistant *S. aureus* in endemic areas (e.g., USA300 strain in North America), because of a combination of both immune impairments and social risk factors.[97] HIV-positive patients are also at increased risk of primary bloodstream infection caused by nontyphi *Salmonella* species, *S. aureus,* and *Escherichia coli,* whose incidence correlates with the depth of immune deficiency.[98] Other severe bacterial infections, such as endocarditis or urinary tract infection, are also more common in patients with advanced HIV infection.[99] Again, the management of sepsis in HIV-positive patients has no specific characteristics and should follow general guidelines.[50] However, the higher risk of infection by multidrug-resistant bacteria caused by repeated antibiotic exposure and frequent contacts with the healthcare system should be considered when selecting empirical antimicrobials. Septic shock and multiorgan failure occur occasionally during the course of disseminated OIs, notably toxoplasmosis, tuberculosis, and histoplasmosis. These infections commonly trigger HLH, which may substantially worsen organ dysfunctions.[100] Lastly, *Clostridioides difficile* (formerly *Clostridium difficile*) infection is the leading cause of bacterial diarrhea in HIV-positive patients.[101] However, it remains unclear whether HIV infection is associated with an increased incidence of severe presentations or adverse outcomes.[102]

Other Clinical Situations

CMV Infection

CMV reactivation, detected by quantitative PCR in peripheral blood, is commonly observed in critically ill HIV-infected patients, especially in those with low CD4 cell counts and/or intercurrent OIs. Careful assessment should be made for identification of rare end-organ diseases (e.g., retinitis, encephalitis, esophagitis, colitis, or pneumonitis) that require treatment with intravenous ganciclovir or foscarnet.[70]

Non–HHV8-Associated Lymphoma

Non-Hodgkin and Hodgkin lymphomas (NHL and HL, respectively) remain a major cause of mortality in the late cART era, with 33%–76% of affected patients having undetectable HIV viral load at diagnosis.[103,104] NHL is almost constantly aggressive and is often EBV-related.[105] Diffuse large B-cell lymphoma (DLBCL) is still the most frequent type, but Burkitt lymphoma (BL) has gained an overgrowing place in recent years and now accounts for 40% of lymphoma-related ICU admissions in seropositive individuals.[104] Primary CNS EBV-induced lymphoma, a hallmark AIDS-defining disease until the early nineties, is now occasional.[106]

The reported prevalence of NHL and HL in HIV-infected patients admitted to the ICU may reach 8% and 1.5% Respectively in recent cohorts, with inaugural admission in up to 75% of cases.[106] Patients may be admitted for lymphoma-induced HLH, tumor lysis syndrome, organ infiltration or compression, or chemotherapy-related complications such as sepsis in neutropenic patients.[106,107] Preserving renal function is crucial to optimize subsequent chemotherapy schemes, notably in BL, that often require high-dose methotrexate. NHL at high risk for tumor lysis syndrome—notably DLBCL with large tumor volume and BL—may require preventive ICU admission at the time of induction chemotherapy for fluid management, rasburicase administration, and prompt renal replacement therapy when necessary.[108]

In addition to supportive care, the cornerstones of management of HIV-associated lymphoma in the ICU include adequate tissue sampling for diagnostic procedures, whole-body imaging (either CT scan or fluorodeoxyglucose [FDG] positron emission tomography) to appraise tumor burden and localizations, biologic evaluation for HLH and tumor lysis syndrome, cardiac evaluation (as most chemotherapy regimens are anthracycline-based), prompt administration of etoposide in case of HLH, and timely chemotherapy induction with prevention of tumor lysis syndrome in high-risk patients.[109,110] Of note, rituximab should not be included in the chemotherapy regimen in patients with CD4 cells $<50/\mu L$ because of excess toxicities without survival benefit.[111] The management of cART in this context requires a close collaboration between ICU, hematology, and infectious diseases physicians.[112] Overall survival rates depend on tumor characteristics rather than on HIV infection, which does not affect the outcome of lymphoma managed in the ICU.[113–115]

HHV8-Related Diseases

The most frequent human herpesvirus-8 (HHV-8)–related disease is Kaposi sarcoma (KS), an endothelial cell–derived tumor that may affect various organs and tissues, especially the skin, mucosa, lymph nodes, lungs, and intestinal tract.[116,117] The severity of KS depends on the presence of life-threatening localizations (e.g., the lower respiratory tract), its extension, and the degree of immune deficiency.[116] The treatment of AIDS-related KS rests on immune restoration through cART and, occasionally, chemotherapy for aggressive presentations. Steroids should be avoided in patients with KS, as they can exacerbate the course of the disease. Multicentric Castleman disease is an HHV-8–induced polyclonal B lymphoproliferative disorder characterized by recurrent bouts of fever with lymphoid hyperplasia and severe systemic inflammatory symptoms linked to inappropriate release of interleukin (IL)-6, IL-10, and other cytokines, ultimately resulting in HLH and transformation to NHL.[118,119] Etoposide is the first-line drug for severe associated HLH, whereas long-term outcomes have markedly improved with the use of rituximab.[120] Primary effusion lymphoma (as diagnosed through positive HHV-8 PCR and presence of large B cells in pleural or peritoneal fluid) and DLBCL may also complicate the course of HHV-8 infection in seropositive patients.

MANAGEMENT OF ANTIRETROVIRAL THERAPY IN THE ICU

Immune Reconstitution Inflammatory Syndrome

Immune recovery may induce paradoxical worsening of an already treated or previously undiagnosed OI within weeks or months after cART initiation. Relevant examples include the occurrence of ARF in patients with an initially mild to moderate pulmonary OI (e.g., PCP with no baseline indication for corticosteroids) or neurologic deterioration caused by the enlargement of cerebral tuberculomas, *Toxoplasma* abscesses, or cryptococcal lesions. Immune reconstitution inflammatory syndrome (IRIS)–induced HLH has also been reported. IRIS has an estimated crude incidence of 16%, and the main risk factors are a high baseline viral load, low baseline CD4 cell count, and rapid CD4 cell count elevation after cART initiation.[121,122]

IRIS drives substantial morbidity and mortality, with a fatality rate of up to 20% in patients with cryptococcal meningitis.[121] IRIS as the main reason for ICU admission was uncommon in recent cohorts of critically ill HIV-positive patients, suggesting better anticipation and management by infectious disease specialists.[14,16,21] Nonsteroidal

antiinflammatory drugs and corticosteroids are the cornerstones of therapy for severe IRIS, without requirement for interrupting cART in most cases.[70]

ICU Admissions for Non-IRIS cART-Related Events

ART-related toxicity accounts for approximately 5% of ICU admissions in this population.[16,26,60] Old antiretrovirals are notably associated with lactic acidosis (e.g., azathioprine [AZT], didanosine) or pancreatitis (e.g., didanosine), whereas proximal tubulopathy with AKI and toxic epidermal necrolysis are well-described adverse events of tenofovir and nevirapine, respectively. New drugs may also cause critical complications such rhabdomyolysis from raltegravir (Table 120.4).

Starting cART in the ICU

Early cART initiation reduces all-cause mortality and the incidence of new AIDS-defining conditions in non–critically ill HIV-positive patients with an active OI, notably those with PCP or pulmonary tuberculosis and less than 50/μL CD4 cells.[123–127] Accordingly, current US and European guidelines recommend cART initiation at 2 weeks after the start of specific OI treatment, except for those with cryptococcosis or CNS tuberculosis because of the risk of severe IRIS that may outweigh potential benefits from rapid immune recovery—in these situations, cART initiation must be deferred until at least 4 weeks and with proven disease control.[28,127]

In contrast, whether antiretroviral drugs should be introduced in cART-naive patients admitted to the ICU for an active OI remains

TABLE 120.4 cART Management in the ICU: Main Toxicities, Drug–Drug Interactions, and Administration Issues

Drug	Most Common Severe Toxicities	Main Drug–Drug Interactions to Consider in the ICU	Alternatives for Administration in the ICU	Dosage Adjustment If Renal Failure
Nucleoside/nucleotide reverse transcriptase inhibitors				
Abacavir	Hypersensitivity syndromes in patients with HLA-B*5701	–	Liquid formulation	No (avoid if end-stage renal failure)
Emtricitabine	Neutropenia	–	Liquid formulation, crushable pills	Yes
Lamivudine	Rash	–	Liquid formulation, crushable pills	Yes
Zidovudine	Lactic acidosis, myopathy, bone marrow toxicity, hepatitis	Rifamycins, valproic acid, fluconazole	Liquid formulation, crushable pills, IV formulation	Yes
Tenofovir	Nephrotoxicity (proximal tubular acidosis with Fanconi-like syndrome, acute renal failure), rash, hepatitis	–	Crushable pills	Yes
Nonnucleoside reverse transcriptase inhibitors				
Efavirenz	Hepatitis, rash	Rifamycins, voriconazole, posaconazole, phenytoin, phenobarbital, carbamazepine, calcium channel blockers, statins, warfarin, midazolam	Crushable pills	No
Etravirine	Bone marrow toxicity, hypersensitivity syndromes, hepatitis	Rifamycins, fluconazole, voriconazole, posaconazole, phenytoin, phenobarbital, carbamazepine, digoxin, amiodarone, warfarin, statins, clopidogrel, dexamethasone	Crushable pills	No
Nevirapine	Neutropenia, hypersensitivity syndromes, hepatitis	Rifampicin (switch to rifabutin), fluconazole, warfarin	Liquid formulation	Yes
Rilpivirine	Bone marrow toxicity, hepatitis, rash	Rifamycins, PPIs, anti-H_2, phenytoin, phenobarbital, carbamazepine, dexamethasone	IV formulation	No
Integrase inhibitors				
Raltegravir	Rash	Rifampicin	Liquid formulation, crushable pills	No
Dolutegravir	Rash, hepatitis	Rifampicin, phenytoin, phenobarbital, carbamazepine, apixaban, metformin	Crushable pills	No
Protease inhibitors (all ritonavir-boosted)				
Atazanavir	Hyperbilirubinemia, renal lithiasis, QT prolongation	Rifamycins, voriconazole, PPIs, phenytoin, phenobarbital, carbamazepine, fentanyl, midazolam, calcium channel blockers, amiodarone, warfarin, statins	–	No

TABLE 120.4 cART Management in the ICU: Main Toxicities, Drug–Drug Interactions, and Administration Issues—cont'd

Drug	Most Common Severe Toxicities	Main Drug–Drug Interactions to Consider in the ICU	Alternatives for Administration in the ICU	Dosage Adjustment If Renal Failure
Darunavir	Rash, peripheral neuropathy	Rifamycins, voriconazole, fluconazole, posaconazole, phenytoin, phenobarbital, fentanyl, midazolam, calcium channel blockers, beta-blockers, amiodarone, digoxin, warfarin, apixaban, rivaroxaban, dabigatran, ticagrelor, metformin, statins, salmeterol	Liquid formulation	No
Fosamprenavir	Rash	Rifamycins, phenytoin, phenobarbital, fentanyl, midazolam, amiodarone, statins, warfarin	Liquid formulation	No
Lopinavir	QT prolongation, bone marrow toxicity, hypersensitivity syndromes, hepatitis	Rifamycins, voriconazole, phenytoin, phenobarbital, valproic acid, fentanyl, midazolam, calcium channel blockers, amiodarone, digoxin, warfarin, rivaroxaban, statins, salmeterol	Liquid formulation	No
Tipranavir	Hepatitis, rash	Rifamycins, voriconazole, phenytoin, phenobarbital, carbamazepine, fentanyl, midazolam, PPIs, amiodarone, digoxin, warfarin, statins	Liquid formulation	No
Fusion inhibitors				
Enfuvirtide	Myalgia, lung toxicity, peripheral neuropathy, pancreatitis, renal lithiasis	-	Subcutaneous formulation	No
CCR5 inhibitors				
Maraviroc	Anemia, rash	Rifamycins, phenytoin, phenobarbital, carbamazepine	Liquid formulation	Yes

CCR5, C-C motif chemokine receptor 5; *HLA*, human leukocyte antigen; *ICU*, intensive care unit; *IV*, intravenous; (HLA) complex; *PPIs*, proton pump inhibitors.
Constructed from FDA approval documents and the French CNS-ANRS guideline documents for the management of cART in HIV-infected patients (available at www.cns.sante.fr).

unsettled. Indeed, there are no prospective evaluations of the safety, efficacy, and timing of cART initiation in the ICU. A few retrospective single-ICU studies suggest that early cART initiation may improve both short-term and long-term survival rates.[23,26,51] A recent meta-analysis found that initiation or maintenance of cART in the ICU was associated with a lower short-term risk of death (random effects odds ratio 0.53, 95% confidence interval 0.31–0.91, $P = .02$); however, heterogeneity was high (I^2 77%), precluding firm conclusions.[128] Given the declining incidence of ICU admissions for inaugural OIs, it is unlikely that a large-scale randomized controlled trial (RCT) could solve this issue in the near future. Therefore the appropriateness of starting cART in the ICU should be discussed on a case-by-case basis in a framework of close collaboration between intensivists and infectious disease specialists.[5,6] Fig. 120.3 shows the algorithm recently proposed by a panel of intensivists and infectious disease physicians for using cART in the ICU.[60]

Continuing cART in Previously Treated Patients

Stopping cART in virally suppressed patients has been shown to increase the hazard of breakthrough OIs and all-cause death.[129] The possible emergence of resistant HIV mutants (requiring new genotyping before cART reintroduction) should also be considered, although the risk is presumably limited after a short interruption. Hence, in patients treated before admission, cART should be continued in the ICU whenever possible (see Fig. 120.3). Factors that may complicate the continuation of cART in critically ill patients include adverse drug reactions; drug–drug interactions; impaired enteral absorption; the need to deliver drugs via a nasogastric tube; avoidance of proton pump inhibitors, H_2 antagonists, and other antacids if cART contains components such as atazanavir or rilpivirine (which require gastric acidity for absorption); avoidance of enteral nutrition products containing iron, calcium, magnesium, or aluminum to prevent malabsorption of integrase inhibitors; and dose adjustment because of renal and/or hepatic impairment (see Table 120.4). Several solutions exist, such as switching to liquid drug formulations, dosing adjustment based on plasma-level monitoring, and occasionally, parenteral administration. Again, close cooperation with infectious disease specialists is fundamental when deciding to continue, modify, or interrupt cART during the ICU stay.[60]

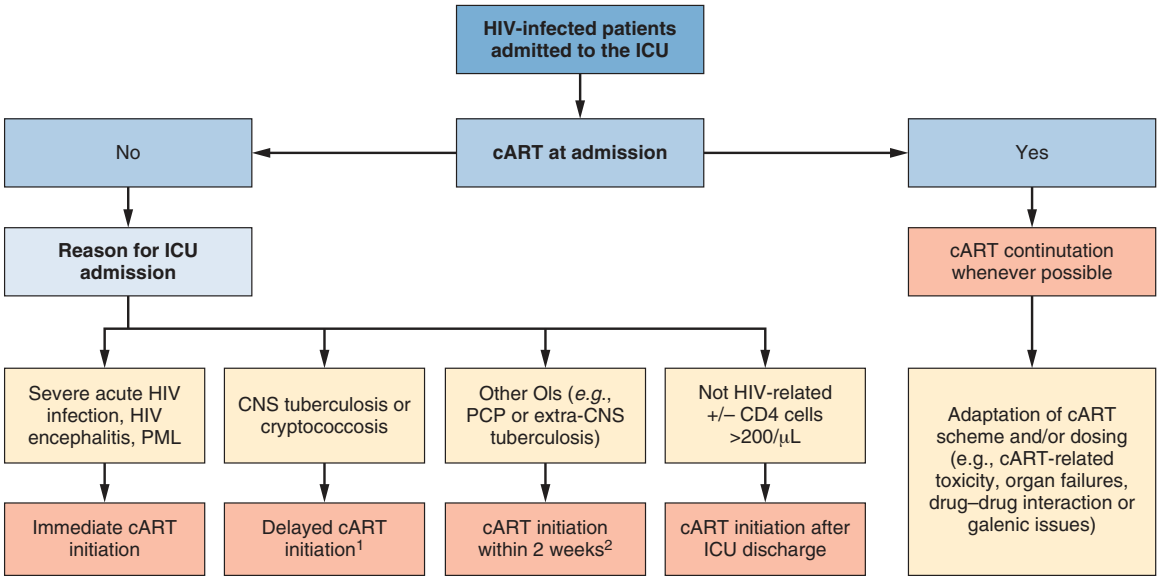

Fig. 120.3 Proposed Algorithm for use of Combination Antiretroviral Therapy in the ICU. *cART,* Combination antiretroviral therapy; *CNS,* central nervous system; *HIV,* human immunodeficiency virus; *ICU,* intensive care unit; *OI,* opportunistic infection; PCP *Pneumocystis jirovecii* pneumonia; *PML,* progressive multifocal encephalopathy. [1] Delayed cART initiation because of the substantial risk of severe immune reconstitution inflammatory syndrome (e.g., up to 10 weeks in cryptococcal meningoencephalitis with elevated intracranial pressure and delayed clinical improvement or cerebrospinal fluid [CSF] culture sterilization); [2] cART initiation may be deferred for up to 8 weeks in patients with pulmonary tuberculosis and CD4 cells >50/μL. (From Barbier F, Mer M, Szychowiak P, et al. Management of HIV-infected patients in the intensive care unit. *Intensive Care Med.* 2020;46[2]:329–342, Fig. 3 and based on the guidelines of the Centers for Disease Control and Prevention, the National Institutes of Health, and the Infectious Diseases Society of America for the use of antiretroviral agents in adults and adolescents with HIV. Note than no academic dedicated guidelines exist for the management of antiretroviral drugs in the specific context of critical illnesses. Close collaboration with an infectious disease physician is mandatory in every case.

CONCLUDING REMARKS AND POTENTIAL RESEARCH AXES

ICU admission for life-threatening OIs continues to occur in patients with previously undiagnosed HIV infection or with failure to respond to cART because of viral resistance or poor adherence. Yet HIV-positive patients with controlled viral replication and CD4 cell count above 200/μL under cART account for a growing proportion of ICU admissions, of which the main reasons are bacterial pneumonia and exacerbation of chronic HANA conditions. Regardless of the depth of immune deficiency, HIV-positive patients now tend to have similar hospital survival rates, as do HIV-negative ICU patients with the same comorbidities, reasons for admission, and severity of organ failures. Hence, the HIV status should no longer be viewed as a pivotal criterion for ICU admission decisions, which should instead be based on frailty, performance status, comorbidities, and other clinical features associated with mid- and long-term outcomes, as with all critically ill patients.

Several domains should be explored to further improve the management of critically ill HIV-positive patients. First, there is a crucial need for longitudinal studies of the long-term impact of critical illness on HIV-specific care, progression of HANA conditions, cognitive decline, functional status, and quality of life. Second, the conversion of HIV infection to a chronic manageable disease has ethical implications. Although major interventions such as IMV, vasopressor therapy, and renal replacement therapy are now equally used in HIV-positive and HIV-negative ICU patients, the determinants of end-of-life decisions in the specific setting of critical illness have not been reappraised in detail. Third, solid and hematologic malignancies act as new immunosuppression vectors in patients with controlled HIV replication. How the coexistence of malignancy may influence the management and post-ICU outcomes of HIV-positive patients deserves to be addressed specifically. Along this line, SOT is increasingly performed in selected HIV-positive patients with end-stage renal or heart failure: the reasons for and prognosis of ICU admission have not yet been investigated in this emerging subpopulation.

KEY POINTS

- In recent Western cohorts, up to 70% of HIV-infected patients admitted to the ICU were receiving long-term cART.
- Bacterial sepsis and exacerbated comorbidities such as COPD, non–AIDS-defining neoplasms, atherosclerosis, and chronic renal diseases have become the leading reasons for ICU admission.
- Admissions for severe AIDS-defining OIs continue to occur in patients with previously unknown HIV infection or restricted access to cART.
- PCP, tuberculosis, and cerebral toxoplasmosis are the most common OIs in the ICU.
- The management of cART in the ICU requires a close collaboration between intensivists and HIV specialists.
- In-hospital mortality mostly depends on age, underlying comorbidities, and extent of organ dysfunction rather than on HIV-related characteristics (i.e., CD4 cell count, viral load, admission for AIDS-related diagnoses, and prior cART use).
- Lymphomas, solid neoplasms, and SOT are emerging drivers of immunosuppression in cART-treated patients with otherwise controlled HIV replication.
- Ethical issues and long-term outcomes warrant dedicated investigations in this patient population.

References for this chapter can be found at expertconsult.com.

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Infections in the Immunocompromised Patient

Steven A. McGloughlin and David L. Paterson

Many immunocompromised patients are managed in intensive care units (ICUs) every year, with infection being a leading cause of ICU admission. Common examples of such infections include community-acquired pneumonia, bacteremia, and central nervous system (CNS) infections. The incidence of infections acquired by immunocompromised patients during ICU admissions is also significant.[1] Mortality from certain infections in immunocompromised patients exceeds 50%.[2] Early diagnosis, initiation of appropriate antimicrobial and supportive therapy, and reduction in immunosuppression where possible can improve outcomes significantly.

COMMONLY ENCOUNTERED IMMUNOCOMPROMISING CONDITIONS

Immunocompromise can be broadly defined as a state in which the response of the host to a foreign antigen is subnormal. It can be congenital (primary) or acquired. Congenital immunodeficiencies are now much less common than acquired immunodeficiencies. In general, congenital immunodeficiency is observed more frequently in patients in pediatric ICUs than in those in adult ICUs. Patients with congenital immunodeficiencies usually have repeated infections, especially infections affecting the sinuses and lower respiratory tract. Congenital immunodeficiencies are usually "pure," in that the defects in the host response to foreign antigens are usually specific and well defined. For example, Bruton X-linked agammaglobulinemia is associated with a defect in the normal maturation process of immunoglobulin-producing B cells. As a result, mature circulating B cells, plasma cells, and serum immunoglobulin are absent. The patient is susceptible to organisms, such as *Streptococcus pneumoniae* and *Haemophilus influenzae,* normally dealt with by immunoglobulins. Other congenital immunodeficiency syndromes are listed in Table 121.1.

Most immunocompromised patients managed in adult ICUs have acquired immunocompromise. Although the response of host defenses in the elderly, people with diabetes, and people with alcohol use disorder is compromised, this chapter deals primarily with four categories of immunocompromised patients: (1) patients receiving therapy for hematologic malignancies and solid tumors; (2) patients receiving immunosuppressive therapy in the context of solid organ transplantation; (3) patients receiving corticosteroids, methotrexate, monoclonal antibodies to tumor necrosis factor, and other disease-modifying agents for rheumatoid arthritis, Crohn disease, and autoimmune disorders; and (4) patients with human immunodeficiency virus (HIV) infection.

Hematologic Malignancies and Solid Tumors

Prolonged neutropenia from chemotherapy carries a significant risk of bacterial and fungal infection. Classically, gram-negative organisms such as *Pseudomonas aeruginosa* and fungal organisms such as *Aspergillus* species have been associated with severe neutropenia. It has long been known that the severity and duration of neutropenia influence the risk of infection.[3] It has also been well established that aggressive chemotherapy and radiotherapy for Hodgkin disease coupled with splenectomy significantly impair humoral defense against encapsulated organisms such as *S. pneumoniae, H. influenzae,* and *Neisseria meningitidis*.[4] Stem cell transplantation (particularly allograft transplantation) is associated with a substantial risk of graft-versus-host disease (GVHD). Prophylaxis and treatment for GVHD may involve use of drugs such as cyclosporine or tacrolimus plus corticosteroids. Cyclosporine and tacrolimus inhibit calcineurin, an enzyme important in the lymphocyte activation cascade. Corticosteroids also affect lymphocyte function and depress functions of activated macrophages. As a result, patients receiving therapy for GVHD may be prone to fungal, viral, and mycobacterial infections, in addition to bacterial infections associated with prolonged neutropenia. Chimeric antigen receptor (CAR) T-cell therapy is an additional treatment modality used to treat some blood cancers.[5] Patient lymphocytes are engineered to produce CARs, which are directed towards tumor cells. Patients receiving CAR T-cell therapy experience multifactorial immune suppression related to their cancer and its prior treatment, pretreatment chemotherapy, depletion of B cells, and the effects of cytokine release syndrome. Additionally, management of severe cytokine release syndrome often involves administration of interleukin (IL)-6 inhibitors (e.g., tocilizumab) and high-dose corticosteroids, both of which themselves carry an additional risk of infection.[6]

Solid Organ Transplantation

Solid organ transplant recipients are uniquely susceptible to infection.[7] They undergo significant surgery, breaching the defenses provided by the skin. Furthermore, they can remain in ICUs for prolonged periods, requiring intravenous access and mechanical ventilation—here, cutaneous and pulmonary barriers to infection are breached. Finally, solid organ transplant recipients receive immunosuppressive therapy to prevent graft rejection. The commonly used immunosuppressive medications are listed in Table 121.2. Immunosuppressive regimens are in a constant state of flux—more recent trends have been toward aggressive "pretreatment" immediately before transplantation, coupled with decreased immunosuppression in the posttransplant period.[8]

In the early posttransplant period, transplant recipients are susceptible to nosocomially acquired bacterial infections such as pneumonia, catheter-related bloodstream infection associated with usual ICU care, and wound and intraabdominal infections associated with surgical procedures. Opportunistic infections may be acquired from the organ graft; cytomegalovirus (CMV) is the most pertinent example,[9] but a wide variety of infections (e.g., rabies, histoplasmosis, tuberculosis, and West

TABLE 121.1 Congenital (Primary) Causes of Immunodeficiency

Condition (Immunodeficiency)	Organisms With Increased Tendency to Cause Infection in This Condition
T-Lymphocyte Deficiencies	
DiGeorge syndrome (thymic aplasia with reduced CD4 and CD3 cells)	Viruses (especially HSV and measles), sometimes *Pneumocystis jirovecii,* fungi, or gram-negative bacteria
Purine nucleoside phosphorylase deficiency (marked T-cell depletion)	*P. jirovecii* and viruses
B-Lymphocyte Deficiencies	
Bruton X-linked agammaglobulinemia (absence of B cells, plasma cells, and antibody)	*Haemophilus influenzae, Streptococcus pneumoniae, Staphylococcus aureus, Pseudomonas aeruginosa, P. jirovecii* (after the first 4–6 months of life when maternal antibody has been consumed)
Selective IgG subclass deficiencies	Variable
Selective IgA deficiency	*S. pneumoniae, H. influenzae*
Hyper-IgM immunodeficiency (elevated IgM but reduced IgG and IgA)	*S. pneumoniae, H. influenzae, P. jirovecii* (rarely)
Mixed T- and B-Lymphocyte Deficiencies	
Common variable immunodeficiency (leads to various B-cell activation or differentiation defects and gradual deterioration of T-cell number and function)	*S. pneumoniae, H. influenzae,* CMV, VZV, *P. jirovecii*
Severe combined immunodeficiency (severe reduction in IgG and absence of T cells)	*P. jirovecii,* viruses, *Legionella*
Wiskott-Aldrich syndrome (decreased T-cell number and function, low IgM, occasionally low IgG)	*S. pneumoniae, H. influenzae,* HSV, *P. jirovecii*
Ataxia-telangiectasia (decreased T-cell number and function; IgA, IgE, IgG_2, and IgG_4 deficiency)	*S. aureus, S. pneumoniae, H. influenzae*
Disorders of Complement	
C3 deficiency (congenital absence of C3 or consumption of C3 caused by deficiency of C3b inactivator)	*S. pneumoniae, H. influenzae,* enteric gram-negative bacilli
Phagocyte Defects	
Chronic granulomatous disease (defect in NADPH oxidase in phagocytic cells)	*S. aureus, Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, S. marcescens, P. aeruginosa, Aspergillus*
Chédiak-Higashi syndrome (impaired microbicidal activity of phagocytes)	*S. aureus, H. influenzae, Aspergillus*
Kostmann syndrome, Shwachman-Diamond syndrome, cyclic neutropenia (low neutrophil count)	*S. aureus,* enteric gram-negative bacilli, *P. aeruginosa*

CMV, Cytomegalovirus; *HSV,* herpes simplex virus; *Ig,* immunoglobulin; *NADPH,* nicotinamide adenine dinucleotide phosphate; *VZV,* varicella-zoster virus.

TABLE 121.2 Immunosuppressive Drugs Used in Solid Organ Transplantation and Their Mechanisms of Activity

Immunosuppressive	Mode of Action
Corticosteroids	Negative regulation of cytokine gene expression
Azathioprine	Inhibits DNA and RNA synthesis; inhibits T- and B-cell function
Cyclosporine	Calcineurin inhibitor; inhibits cytokine expression
Tacrolimus	Calcineurin inhibitor; inhibits cytokine expression
Sirolimus (rapamycin)	Prevents translation of mRNAs encoding cell cycle regulators
Mycophenolate mofetil	Blocks purine biosynthesis; inhibits T- and B-cell proliferation
Polyclonal antilymphocyte	Lymphocyte depletion antibodies (e.g., Atgam, Thymoglobulin)
Muromonab-CD3 (OKT3)	Anti-CD3 monoclonal antibody
Alemtuzumab (Campath)	Anti-CD52 monoclonal antibody
Daclizumab, basiliximab	Anti-CD25 monoclonal antibody

Nile virus) have also been rarely acquired from grafts. Solid organ transplant recipients, by virtue of their iatrogenic immunosuppression, are also susceptible to reactivation of latent infection (e.g., CMV infection, tuberculosis, or histoplasmosis) or to infections acquired through the hospital environment (e.g., aspergillosis, legionellosis, or tuberculosis).

Rheumatoid Arthritis and Autoimmune Disorders

Therapy for rheumatoid arthritis and other autoimmune disorders may be with simple analgesics or nonsteroidal antiinflammatory drugs. Drugs with the potential to cause significant immunocompromise are also frequently used. Classically, therapy has been with corticosteroids or disease-modifying antirheumatic drugs such as azathioprine, cyclosporine, penicillamine, gold salts, hydroxychloroquine, leflunomide, methotrexate, or sulfasalazine. The effects of corticosteroids, azathioprine, and cyclosporine on host defenses have been noted previously (see Table 121.2). Methotrexate reversibly inhibits dihydrofolate reductase and interferes with DNA synthesis and repair and cellular replication. In addition to its use in rheumatoid arthritis, it can be used as an antineoplastic agent. Methotrexate, however, can cause significant neutropenia, and low-dose methotrexate is generally less likely to increase the infection risk in patients with rheumatoid arthritis.[10,11]

A variety of "biologic" agents are now widely used for rheumatoid arthritis. These include tumor necrosis factor (TNF)-alpha inhibitors (for example, etanercept, infliximab, adalimumab, certolizumab, and golimumab), IL-6 inhibitors (for example, tocilizumab and sarilumab), IL-1 beta inhibitors (anakinra), CD80/86 inhibitors (abatacept), and an antibody against the CD20 protein (rituximab) (Table 121.3). The indications for the use of these biologic agents are also increasing—for example, they may also be used in treatment of Behçet disease, Crohn disease, GVHD, hairy cell leukemia, psoriasis, pyoderma gangrenosum, sarcoidosis, and ulcerative colitis. Considerable attention has been paid to the possibility of tuberculosis developing after treatment with such agents.[12] The risk is sufficiently high that it is recommended that tuberculin skin testing or interferon gamma (IFN-γ) release assays be performed to detect latent tuberculosis before the initiation of anticytokine agents. Invasive infections with *Histoplasma, Candida, Pneumocystis jirovecii, Aspergillus, Cryptococcus, Nocardia, Salmonella, Listeria, Brucella, Bartonella,* nontuberculous mycobacteria, *Leishmania,* and *Toxoplasma* have also been reported to be associated with the use of "biologics."[13–16] As is the case with transplant-associated immunocompromise, these infections may represent reactivation of latent infection or new acquisition of organisms through environmental exposure.

Human Immunodeficiency Virus Infection

HIV infection remains a relatively common infection, but acquired immunodeficiency syndrome (AIDS) has become less frequently encountered in ICUs since the advent of highly active antiretroviral therapy. A decline in CD4 counts creates a predisposition to *P. jirovecii* pneumonia, mycobacterial infection, fungal infection (e.g., cryptococcal meningitis), and viral infection (e.g., CMV infection). Many patients with HIV infection are coinfected with hepatitis C virus, and as a result, liver failure is now a relatively common reason for ICU admission in HIV-infected patients. In some centers, liver transplantation is performed in HIV-infected patients with hepatitis virus–induced liver diseases.[17,18]

TABLE 121.3 Commonly Used Anticytokines for Management of Rheumatoid Arthritis

Drug	Mechanism of Action	FDA-Approved Indications
Adalimumab (Humira)	Recombinant, fully human anti-TNF monoclonal antibody	Ankylosing spondylitis Crohn disease Psoriatic arthritis Rheumatoid arthritis
Anakinra (Kineret)	Recombinant human interleukin-1 receptor antagonist	Rheumatoid arthritis
Etanercept (Enbrel)	TNF receptor p75 Fc fusion protein	Ankylosing spondylitis Juvenile rheumatoid arthritis Plaque psoriasis Psoriatic arthritis Rheumatoid arthritis
Infliximab (Remicade)	Chimeric monoclonal antibody to TNF	Ankylosing spondylitis Crohn disease Psoriatic arthritis Plaque psoriasis Rheumatoid arthritis Ulcerative colitis
Tocilizumab (Actemra)	IL-6 receptor–inhibiting monoclonal antibody	Rheumatoid arthritis

FDA, US Food and Drug Administration; *IL-6,* interleukin-6; *TNF,* tumor necrosis factor.

GENERAL DIAGNOSTIC APPROACH TO IMMUNOCOMPROMISED PATIENTS WITH SEVERE INFECTIONS

Immunocompromised patients are a heterogeneous group. The infections commonly encountered by a patient with neutropenia as a consequence of chemotherapy may be different from infections observed in a patient with rheumatoid arthritis who is receiving infliximab. Even within a particular category, different renal transplantation recipients, for example, may have a different degree of immunocompromise and a different susceptibility to infection. In solid organ transplant recipients, the "net state of immunosuppression" (i.e., the cumulative burden of immunosuppression with a special weighting toward recent T-cell ablative therapy) influences the risk of infection. A renal transplant recipient who is receiving tacrolimus monotherapy twice per week would be less susceptible to opportunistic infection than a patient with recent acute cellular rejection who is receiving OKT3 or alemtuzumab. There have been attempts to quantify immune function in solid organ transplant recipients,[19] although it has not yet been definitively proved that such tests predict infection risk. In contrast, with HIV infection, CD4 lymphocyte count and HIV RNA quantification ("viral load") predict risk of infection.[20] Patients with CD4 counts greater than 500 cells/mm^3 are unlikely to be infected with an opportunistic pathogen, whereas those with CD4 counts of 200–500 cells/mm^3 may be infected with organisms such as *Mycobacterium tuberculosis,* but they are unlikely to be infected with opportunistic pathogens such as CMV or *Mycobacterium avium* complex. Patients with CD4 counts less than 200 cells/mm^3 have an increased risk of a wide variety of opportunistic infections.

Specific environmental exposures may be potentially important for immunocompromised patients. A travel history to the deserts of the southwestern United States and northern Mexico, for example, may increase the likelihood that an immunocompromised patient has coccidioidomycosis[21]; histoplasmosis is endemic in the Ohio River Valley.[22] Alternatively, there may be environmental risks within the ICU. Outbreaks of invasive pulmonary aspergillosis have been linked to construction activity within the hospital. Outbreaks of legionellosis may be waterborne via air conditioning cooling units, drinking water, or aerosolization from showers.[23] Furthermore, it is possible that many fungal and bacterial infections are waterborne.[24,25] Tuberculosis transmission has been well described in ICUs caring for transplant recipients or HIV-infected patients.[26] In summary, the net state of immunosuppression must be considered in the context of recent environmental exposures.

Although elements of history taking and physical examination may narrow the differential diagnosis of the causative agent of infection in immunocompromised patients, some of the "rules" applied to diagnosis in immunocompetent patients do not apply. Caution must be exercised in use of the diagnostic principle that follows Occam's razor: "entities are not to be multiplied without necessity." In an immunocompetent patient, given all the patient's symptoms, signs, and noninvasive laboratory test results, one unifying diagnosis usually explains all. Importantly, in contrast, immunocompromised patients may have more than one infection at any given time. A neutropenic patient may have bacterial pneumonia and invasive pulmonary aspergillosis simultaneously, whereas an immunocompromised patient with HIV infection may have *P. jirovecii* pneumonia and pulmonary infiltrates because of human herpesvirus (HHV)-8 infection (Kaposi sarcoma).

BOX 121.1 Diagnostic Approach for Severe Infections in Immunocompromised Patients

History Taking and Review of Prior Records

Likely degree of immunocompromise
- Recent CD4 lymphocyte count and HIV viral load
- Time since transplantation
- Recent acute cellular rejection or GVHD and treatment thereof
- Current or recent receipt of immunosuppressive medications
- Current or recent receipt of antiretroviral medications

Prophylaxis against opportunistic infections
- Receipt of antimicrobial prophylaxis against *Pneumocystic jirovecii,* HSV, or CMV
- Vaccination status (pneumococcus, influenza, *Neisseria meningitidis*)

Family history
- Personal or family history of tuberculosis or chickenpox

Potential environmental exposures
- Travel history to southwestern United States
- Exposure to hospital construction activity (aspergillosis)
- Exposure to hospital water supply (legionellosis, aspergillosis)
- Exposure to patients with tuberculosis or chickenpox
- Donor and recipient serostatus for CMV or *Toxoplasma gondii*

Physical Examination

Skin
- Presence of cutaneous nodules consistent with cryptococcosis or nocardiosis
- Presence of cutaneous manifestations of GVHD
- Kaposi sarcoma
- Line insertion site erythema or pus
- Peripheral embolic phenomena
- Scars consistent with prior surgery

Mouth and other mucous membranes
- Presence of candidiasis

Respiratory system
- Presence of signs of focal versus multilobar pneumonia

Cardiovascular system
- Murmurs, prosthetic heart sounds

Abdominal examination
- Signs of peritonitis
- Hepatomegaly or splenomegaly
- Tenderness of renal allograft

Neurologic examination
- Nuchal rigidity
- Cranial nerve signs

Noninvasive Laboratory Tests

White blood cell count and differential
Blood and urine cultures
Serum cryptococcal antigen
Serum galactomannan antigen (aspergillosis)
Serum and urine *Histoplasma* antigen
Urinary *Legionella* antigen

Invasive Laboratory Tests

Bronchoalveolar lavage
Pleural fluid aspiration
Upper gastrointestinal endoscopy
Colonoscopy
Biopsy of liver, kidney, bone marrow

CMV, Cytomegalovirus; *GVHD,* graft-versus-host disease; *HIV,* human immunodeficiency virus; *HSV,* herpes simplex virus.

The potential for multiple diagnoses underscores the need for early invasive testing in immunocompromised patients with severe infection. Patients with unexplained severe community-acquired pneumonia may be best managed by early bronchoalveolar lavage performed before antimicrobial therapy has commenced. Bronchoalveolar lavage could be sent for Gram stain, Ziehl-Neelsen stain, modified acid-fast stain, calcofluor stain, direct fluorescent antibody tests, polymerase chain reaction (PCR), and cytologic analysis to enable rapid diagnosis of infection with bacteria, mycobacteria, *Nocardia*, fungi, *Legionella,* CMV, community-acquired respiratory viruses, and *P. jirovecii*. Close liaison with the microbiologic laboratory is vital to ensure that appropriate attempts are made to identify the causative pathogens as rapidly as possible. For example, newer microbiologic techniques such as mass spectrometry, matrix-assisted laser desorption/ionization (MALDI-TOF) and DNA sequencing have been demonstrated to be useful in identifying fungal isolates rapidly.[27] The bronchoalveolar lavage should be inoculated onto solid media, and molecular diagnostic testing should be used as appropriate. An outline of the diagnostic approach in immunocompromised patients is given in Box 121.1.

MAJOR MANIFESTATIONS OF INFECTION IN IMMUNOCOMPROMISED PATIENTS

The organism causing infection in an immunocompromised patient sometimes can be inferred by the specific host defect in the immunologic defense or the specific clinical manifestation. In most circumstances, the differential diagnosis is too broad, however, to make a definitive clinical diagnosis.

Pulmonary Infection

Pneumonia is a significant cause of morbidity and mortality in immunocompromised patients. In contrast to a normal host, the impaired responsiveness of the immune system means that the disease presents in unusual ways, which may lead to challenges in establishing a diagnosis.

Infectious microorganisms usually gain access to the respiratory tract through inhalation, although hematogenous spread sometimes may occur. Mechanical defenses remove the bulk of potentially harmful agents from the lungs (Table 121.4); inhaled particles greater than 10 μm in diameter usually become trapped in the upper airways or are removed by coughing or mucociliary clearance. Most bacteria range from 0.5 to 2 μm in size and are able to reach the terminal airways/alveoli and potentially cause infection. In the alveoli, the alveolar macrophages are the first line of defense. Subsequently, an inflammatory response consisting of polymorphonuclear neutrophils is important. Finally, specific T-cell and B-cell immune responses are essential for successful defense against many pathogens.

As noted earlier, although it may be possible to pinpoint a major immunologic deficiency, most immunocompromised individuals have an assortment of deficiencies in host defenses working together. An organ transplant recipient may be intubated, have multiple intravenous lines, be diabetic, and be on corticosteroids and tacrolimus. All

TABLE 121.4 Host Defenses Against Respiratory Infections and How They Are Affected in Immunocompromised Patients

Location	Host Defense	Defect
Upper airway	Filtration	Endotracheal intubation
	Mucociliary apparatus	CF, cigarette smoking
	Cough	Impaired consciousness
Lower airway (nonspecific)	Alveolar macrophages	Immunosuppressive medication, corticosteroids
	Polymorphonuclear leukocytes	Corticosteroids, malnutrition, chemotherapy, malignancies
Lower airway (specific)	B lymphocytes	Hypogammaglobulinemia, CLL, MM
	T lymphocytes	AIDS, malignancies, immunosuppressants

AIDS, Acquired immunodeficiency syndrome; *CF,* cystic fibrosis; *CLL,* chronic lymphocytic leukemia; *MM,* multiple myeloma.

these factors contribute to the overall degree of immunity, each paving the way for its own peculiar array of susceptibilities to pulmonary infection. In solid organ transplant recipients, specific causes of pulmonary infection are most frequent at certain times posttransplantation (Table 121.5). In a similar manner, specific causes of pulmonary infection are more frequent at different CD4 lymphocyte counts for patients with HIV infection (Table 121.6).

A normal chest radiograph does not rule out pulmonary infection in immunocompromised patients. Additionally, although some diseases have suggestive radiologic findings (e.g., apical cavitations in tuberculosis), most radiographic findings have to be interpreted in light of all other data available. Frequently, computed tomography (CT) is required (e.g., evaluation of pulmonary nodules). Pulmonary nodules have a broad differential diagnosis in immunocompromised patients, including infections caused by fungi (especially *Cryptococcus neoformans, Coccidioides immitis,* and *Aspergillus fumigatus*), *Nocardia,* mycobacteria, *Rhodococcus equi,* and *Bartonella*. Additionally, carcinomas and posttransplant lymphoproliferative disorders may present with pulmonary nodules. The differential diagnosis of cavitary lesions includes mycobacteria, invasive pulmonary aspergillosis, legionellosis, and infection with *R. equi*. As noted earlier, the broad differential diagnosis of pulmonary infection in immunocompromised patients mandates early and aggressive diagnostic strategies such as bronchoscopy, with the bronchoalveolar lavage sent for a comprehensive battery of microbiologic investigations.

Central Nervous System Infections

Most infectious agents reach the CNS via hematogenous dissemination from an extraneural site. Exceptions include retrograde propagation of infected thrombi within emissary veins, spread along olfactory nerves, and spread from a contiguous focus of infection. The blood-brain barrier presents a natural and an efficient barrier to hematogenous infection. The function of the blood-brain barrier in immunocompromised patients has not been well studied. It is well known, however, that when a CNS infection is established, immune defenses (even in immunologically competent hosts) are inadequate to control the infection.[28] Local opsonization is deficient within the brain. In animal models of bacterial brain abscess, corticosteroid administration led to a reduction in macrophage and glial response, with an increased number of viable bacteria in the abscess.[29]

TABLE 121.5 Occurrence of Pulmonary Infection After Solid Organ Transplantation Stratified by Time From Transplantation

Time After Transplant (mo)	Organism
<1	Nosocomial bacteria (e.g., MRSA, ESBL-producing Enterobacteriaceae, *Pseudomonas aeruginosa, Acinetobacter baumannii*)
	Legionella spp.
	Respiratory viruses (e.g., influenza virus, parainfluenza virus, RSV, adenovirus, rhinovirus, human metapneumovirus)
	Aspergillus spp.
1–6	Nosocomial bacteria (if still mechanically ventilated)
	Legionella spp.
	Nocardia spp.†
	Mycobacterium tuberculosis
	Herpesviruses (e.g., HSV, VZV, CMV)‡
	Respiratory viruses (e.g., influenza virus, parainfluenza virus, RSV, adenovirus, rhinovirus, human metapneumovirus)
	Pneumocystis jirovecii†
	Cryptococcus neoformans
	Aspergillus spp.
	Coccidioides spp.
	Histoplasma spp.
>6	Bacteria associated with community-acquired pneumonia (e.g., *Streptococcus pneumoniae, Haemophilus influenzae, Legionella* spp., *Mycoplasma pneumoniae*)
	Nocardia spp.*†
	*Rhodococcus equi**
	Mycobacterium tuberculosis
	Atypical mycobacterium
	Aspergillus spp.*
	Zygomycetes*
	*Cryptococcus neoformans**

*These organisms should be considered when immune suppression is still substantial.
†These organisms are less likely in patients on prophylactic cotrimoxazole.
‡These viruses are less likely in patients on prophylactic ganciclovir or valganciclovir.
CMV, Cytomegalovirus; *ESBL,* extended-spectrum beta-lactamase; *HSV,* herpes simplex virus; *MRSA,* methicillin-resistant *Staphylococcus aureus; RSV,* respiratory syncytial virus; *VZV,* varicella-zoster virus.

Bacterial meningitis caused by *N. meningitidis* is relatively uncommon in immunocompromised patients, except if they have undergone splenectomy. In contrast, pneumococcal meningitis seems to occur with increased frequency in patients who have undergone stem cell transplantation[30–32] and in those with HIV infection.[33,34] Meningitis caused by *Listeria monocytogenes* is classically associated with immunocompromise, reflecting the need for adequate T-cell function and IFN-γ production to kill this intercellular pathogen.[35] In addition to meningitis, *Listeria* infection may be associated with a brain abscess, particularly that occurring in the brainstem.[36,37] Enteric bacteria (e.g.,

TABLE 121.6 Etiology of Pulmonary Infections in Patients Infected With Human Immunodeficiency Virus Stratified by CD4 Lymphocyte Count

	CD4 COUNT (cells/mm³)			
	>500	200–500	50–200	<50
Organism	*Streptococcus pneumoniae* *Haemophilus influenzae*	*S. pneumoniae* *H. influenzae* *M. tuberculosis*	*Pneumocystis jirovecii* *Mycobacterium tuberculosis* *Cryptococcus*	*P. jirovecii* *Cryptococcus* CMV MAC *Aspergillus*

CMV, Cytomegalovirus; *MAC, Mycobacterium avium* complex.

Escherichia coli) are rare causes of bacterial meningitis in immunocompromised patients. A classic association exists, however, between meningitis with such organisms and disseminated infection with *Strongyloides stercoralis.*[38,39] In the presence of immunosuppression (e.g., large doses of corticosteroids), *Strongyloides* can migrate from the gastrointestinal (GI) tract to the CNS, carrying enteric bacterial flora into the CNS. Mortality is high without prompt recognition and treatment. *Nocardia* and mycobacteria must also be considered in the differential diagnosis of CNS infections in immunocompromised patients; diagnostic samples should be sent for inoculation onto appropriate media for isolation of these organisms.[40–42]

Fungal infection of the CNS may cause meningitis or space-occupying lesions. Cryptococcal meningitis is associated with advanced HIV infection (CD4 lymphocyte count <100 cells/mm³) but can also occur in transplanted patients.[43] The presentation is usually subacute, although dangerous elevations in intracranial pressure are sometimes observed. Space-occupying lesions in the brain may occur with disseminated mold infections; these infections usually arise in the lung, but dissemination to the brain is part of multiorgan spread. Mortality is extremely high in these cases. Any of the pathogenic molds[44,45] such as *Aspergillus,* zygomycetes,[46,47] *Scedosporium,*[48] or *Fusarium*[49] can undergo dissemination to the brain. The dimorphic fungi (e.g., *Histoplasma, Coccidioides*) may also disseminate from the lung, causing infection of the CNS. Zygomycetes may also be associated with frequently fatal infection arising within the nose or sinuses (rhinocerebral mucormycosis).[46,47]

The most common protozoal pathogen to affect the CNS is *Toxoplasma gondii.* The classic association is between *T. gondii* infection and advanced HIV infection, although cases have shown associations with other forms of immunocompromise.[50–52] Amebic encephalitis has been reported occasionally in conjunction with advanced HIV infection or organ transplantation.[53]

Additionally, a variety of viruses can cause CNS infections in immunocompromised patients. Perhaps as a result of the widespread use of anti-herpesvirus prophylaxis in many immunocompromised populations, herpes simplex virus (HSV) encephalitis is rare.[54] Some of the newer herpesviruses, such as HHV-6, have been associated with neurologic infection in transplant recipients.[55–57] Lack of diagnostic capabilities for these viruses may partially explain their apparent infrequency. CMV meningoencephalitis is well described in patients with advanced HIV infection[58] and occasionally has been reported in transplant recipients.[59] Further, disseminated infections with varicella-zoster virus (VZV) in immunocompromised patients may result in CNS infection; West Nile virus may also be acquired from transplanted organs or blood transfusions and is associated with a significant meningoencephalitis in transplant recipients.[60,61] Table 121.7 summarizes the agents capable of causing CNS infections in an immunocompromised host.

The wide variety of organisms that could be responsible for CNS infection presents a need for a broadly based diagnostic work-up before empiric therapy is begun. If the cerebrospinal fluid (CSF) is collected, it should be sent for Gram stain and Ziehl-Neelsen stain for rapid diagnosis of bacterial and mycobacterial infections. PCR can be performed for the diagnosis of most viral infections such as HSV, CMV, and VZV. Cryptococcal antigens can be detected rapidly in the CSF, enabling a quick diagnosis of this form of meningitis, but for patients with space-occupying lesions of the brain, collection of the CSF may not be possible. Aspiration may be performed in some circumstances. Before invasive diagnostic testing of the brain is performed, however, the patient's skin is examined for lesions (such as that which may occur with cryptococcosis or nocardiosis) and the

TABLE 121.7 Central Nervous System Infections in the Immunocompromised Host

Etiologic Agent	Special Considerations
Meningitis	
Streptococcus pneumoniae	Especially in HIV-infected individuals
Listeria monocytogenes	Predilection for brainstem
Enteric bacteria	Associated with disseminated *Strongyloides* infection
Cryptococcus neoformans	Rapid diagnosis by cryptococcal antigen or India ink stain
Mycobacterium tuberculosis	Consider PCR for rapid diagnosis
Meningoencephalitis	
HSV	Rare in immunocompromised patients
HHV-6	May be associated with lack of CSF pleocytosis
VZV	Skin lesions yield diagnosis
West Nile virus	Transmitted via transplanted organ or blood
Space-Occupying Lesions	
Nocardia	Pulmonary lesions usually also present
Toxoplasma gondii	Especially in HIV-infected individuals
Fungi	Pulmonary lesions usually also present

CSF, Cerebrospinal fluid; *HHV-6,* human herpesvirus-6; *HIV,* human immunodeficiency virus; *HSV,* herpes simplex virus; *PCR,* polymerase chain reaction; *VZV,* varicella-zoster virus.

lungs are carefully reviewed by CT. Because most CNS lesions arise from infection in other parts of the body, a diagnosis may often be made more easily by microbiologic sampling of these body sites.

Gastrointestinal Infections

Severe GI infections in immunocompromised patients may occasionally warrant ICU admission because of dehydration or visceral perforation. As with respiratory and CNS infections, the differential diagnosis is usually broad, and a precise diagnosis rarely can be made based on clinical suspicion alone. Immunocompromised patients have an increased predisposition to GI infections, depending on the type and degree of immunocompromise and exposure to certain pathogens.

The most commonly involved organisms in the etiology of infective esophagitis or gastritis are *Candida,* CMV, and HSV, although a variety of other organisms (e.g., mycobacteria and zygomycetes) occasionally are implicated. Candidal esophagitis is a common opportunistic infection in patients with AIDS. Approximately 13.3 events of candidal esophagitis per 100 person-years occur in HIV-infected patients with CD4 counts less than 300 cells/mm^3.[62] A study of renal transplant patients in the United States showed that esophageal candidiasis is the most common fungal infection in these patients, making up 22% of all fungal infections.[63] Other predisposing factors for severe esophageal candidiasis include broad-spectrum antibiotic therapy, steroid therapy, cancer chemotherapy, diabetes mellitus, cutaneous burns, radiotherapy, and hematologic stem cell transplant. Although *C. albicans* is the most frequently diagnosed organism, there is an increase of other species, including *C. krusei* and *C. glabrata*—this is notable because of the increase in resistance to fluconazole in these species. Finally, as noted previously, immunocompromised patients may have a combination of pathogens causing infection at any one time. Upper GI endoscopy with biopsy is the gold standard for making the diagnosis.

Diarrhea is a common problem in immunocompromised patients with multifactorial etiologies. It may lead to the diagnosis of immunosuppression in a previously undiagnosed patient when an opportunistic pathogen is found and appropriately investigated. Severe complications such as malabsorption leading to malnutrition, dehydration, and wasting can occur. Occasionally, intestinal perforation may result from a GI infection. In an immunosuppressed patient, it is important to differentiate diarrhea caused by opportunistic infections from diarrhea caused by neoplasms, GVHD, drugs, and other therapeutic agents. GVHD accounts for more diarrhea in blood and bone marrow transplant patients than infective organisms.[64] In these patients, organisms that cause mild self-limiting disease in the normal host may cause severe and life-threatening infections.[64]

Prolonged use of multiple antibiotics in high doses predisposes patients to colonization with *Clostridium difficile* and development of pseudomembranous colitis. Antibiotic prophylaxis to prevent *P. jirovecii* pneumonia or spontaneous bacterial peritonitis has been associated with *C. difficile.* In addition to the classic antibiotic risk factors of clindamycin or cephalosporin use, fluoroquinolones may predispose to epidemic strains of *C. difficile* (BI/NAP1/027 strain).[65] Enteric bacterial pathogens such as *Salmonella* occur at increased frequency in immunocompromised patients, especially HIV-infected individuals. In some regions of Africa, nontyphoidal *Salmonella* infections are among the most common causes of bacteremia.[66] Severe *Salmonella* infections may be associated with intestinal perforation. *Shigella, Campylobacter jejuni, E. coli* (enterotoxigenic, enteroadherent, and enteroaggregative), and *Yersinia* species are other bacterial causes of diarrhea, although they are less commonly associated with bacteremia.

Protozoal infections are seen more commonly in HIV-infected patients than in other immunocompromised groups. At CD4 counts less than 200 cells/mm^3, patients with HIV infection may present with unusual protozoa (e.g., *Cryptosporidium* and *Microsporidium*). Occasionally, these pathogens are also seen in transplant recipients.[67,68] Such pathogens are not detected on routine microscopic examination for ova, cysts, and parasites. Special stains and microbiologic techniques are needed. A routine examination usually detects *Giardia lamblia, Entamoeba histolytica,* and other more common pathogenic protozoa.

CMV can cause significant colitis in all immunocompromised populations. CMV colitis may occur in the absence of systemic evidence of infection (i.e., PCR finding on peripheral blood may be negative[69,70]). An intestinal biopsy may be required to make the diagnosis. A CMV intestinal infection may present with diarrhea, but may have more profound presentations such as intestinal perforation.[71,72]

Finally, mycobacterial infections such as tuberculosis occasionally can be associated with colitis.[73] *M. avium* complex can be grown readily from the feces of patients with HIV infection and CD4 counts less than 50 cells/mm^3, but it is not always the cause of diarrhea in such patients.

SEPSIS WITHOUT A DEFINED SITE OF INFECTION

Immunocompromised patients may be referred for ICU admission because of signs of sepsis despite no localizing source of infection being found. Classically such patients have gram-negative bacteremia (including with *Pseudomonas aeruginosa*), and antipseudomonal therapy needs to be commenced empirically. However, gram-positive cocci (for example, *Staphylococcus aureus*), gram-positive bacilli (for example, *Listeria monocytogenes*), and gram-negative cocci (for example, *N. meningitidis* after splenectomy or use of eculizumab) may sometimes be responsible for presentations with sepsis.

CAR T-cell therapy may be associated with a syndrome resembling sepsis called *cytokine release syndrome (CRS).* CRS is caused by the production of inflammatory cytokines by the CAR T cells themselves and by other activated immune cells.[74] It presents with high-grade fever, hypotension, hypoxia, and reduced cardiac function and usually manifests within 7 days after CAR T-cell infusion.[75] CRS has been reported in up to 93% of patients receiving CAR T-cell therapy and causes significant morbidity and poor outcomes and can be extremely difficult to distinguish from sepsis.

THERAPEUTIC DIFFICULTIES IN IMMUNOCOMPROMISED PATIENTS

Empiric Therapy

The choice of empiric antimicrobial therapy is often difficult in immunocompromised patients because of the broad differential diagnosis involved and the substantial risk of antimicrobial resistance (stemming from prolonged hospitalization and frequent prior use of antibiotics). As emphasized earlier, management of infection in an immunocompromised patient can be simplified by narrowing the differential diagnosis by thorough history taking, review of prior medical records, and careful physical examination. Aggressive early diagnostic maneuvers before beginning empiric antimicrobial therapy can enable a definitive diagnosis to be made. Failure to collect specimens before beginning empiric therapy can lead to prolonged, expensive, and unnecessary therapy.

Empiric antibiotic therapy in suspected bacterial infections should be tailored to the individual to maximize the chance that the therapy is microbiologically adequate. There is a clear link between microbiologically adequate empiric therapy and successful outcomes from infections in the ICU.[76] In settings such as severe pneumonia in an immunocompromised patient, empiric regimens comprising vancomycin, ciprofloxacin,

meropenem, amphotericin (or voriconazole), ganciclovir, and trimethoprim/sulfamethoxazole may be necessary to cover potentially lethal infections with methicillin-resistant *S. aureus, P. aeruginosa, Legionella,* fungi, CMV, and *P. jirovecii*. However, increasing resistance to carbapenems may necessitate consideration of newer antibiotics such as ceftazidime-avibactam, cefiderocol, and ceftolozane-tazobactam. Nephrotoxic antibiotics such as colistin, polymyxin B, or amikacin may be problematic in immunocompromised patients with baseline renal impairment, despite the activity of these antibiotics against many carbapenem-resistant organisms.

There is no established role of combination empiric therapy with antifungal agents. The decision to start empiric mycobacterial therapy is never an easy one. In general, it is only advised when there is a substantial risk of tuberculosis. Empiric therapy for disseminated *Strongyloides* infection may have a role in immunocompromised patients coming from an endemic area and with the classic presentation of disseminated infection.

Immunocompromised patients presenting with acute meningitis should receive treatment that covers *S. pneumoniae* and *L. monocytogenes*. The combination of vancomycin, ampicillin, and ceftriaxone may be necessary (vancomycin and ceftriaxone for multidrug-resistant *S. pneumoniae* and ampicillin for *Listeria*). The combination of liposomal amphotericin and 5-flucytosine is recommended empirically for meningitis in which antigen testing or India ink stain of the CSF reveals encapsulated fungi consistent with *C. neoformans*. Immunocompromised patients with space-occupying lesions of the brain can be treated empirically with an antifungal drug (amphotericin or voriconazole) if the suspicion of disseminated fungal infection is high, although nocardiosis, toxoplasmosis, or mycobacterial infection would not be covered without specific therapy.

For immunocompromised patients with severe diarrhea requiring ICU admission, empiric therapy with metronidazole or oral vancomycin (for *C. difficile)* and ganciclovir (for CMV) may be given after fecal samples have been collected. Colonic biopsy may be necessary if it can be safely performed. For immunocompromised patients with intestinal perforation, antibiotic coverage against gut flora (i.e., treatment of peritonitis) plus treatment of the most likely causes of perforation (e.g., ganciclovir for CMV) may be chosen.

Pathogen-Directed Therapy

The importance of appropriate specimen collection is that empiric therapy can be streamlined (de-escalated) if cultures or other diagnostic tests reveal positive findings. With immunocompromised patients, antimicrobial therapy is often complicated by drug interactions or adverse reactions. Transplant recipients taking calcineurin inhibitors (e.g., cyclosporine or tacrolimus) or HIV-infected patients taking protease inhibitors are most at risk because these drugs may be metabolized by the cytochrome P-450 system.[77] Significant interactions may occur between rifampin, macrolide antibiotics, azole antifungal drugs, and calcineurin inhibitors.[78] Aggressive treatment of infections in immunocompromised hosts (e.g., with amphotericin, pentamidine, or foscarnet) may be associated with renal dysfunction, compounding the nephrotoxic effects of calcineurin inhibitors. Antimicrobial agents such as linezolid or ganciclovir frequently cause neutropenia, potentially adding further host defense defects.

COVID in the Immunocompromised

The COVID-19 pandemic has had a disproportionate effect on immunocompromised patients. Recent studies suggest that immunocompromised patients have typical manifestations of COVID-19; however, they are at an increased risk of poor outcomes and prolonged viral replication. Hematopoietic cell transplant (HCT) recipients diagnosed with COVID-19 at a median time from transplant of 17 months had increased rates of mechanical ventilation and a 30-day postdiagnosis survival of only 68% for recipients of allogeneic transplants and 67% for autologous recipients.[79] A review in Sweden of solid organ transplant recipients demonstrated a 30-day all-cause mortality of 9.6% in patients with COVID-19, which was higher than the general Swedish population over the same period (3.1%). Worse outcomes were demonstrated in those with older age, male, and a high body mass index (BMI).[80] COVID-19 has also been demonstrated to lead to a poorer prognosis in patients living with a diagnosis of HIV, with increased mortality and an increased rate of hospitalization, particularly among those without viral suppression and lower CD4 counts.[81] Importantly, prolonged COVID-19 symptoms and viral shedding have also been demonstrated in immunocompromised patients. Studies have demonstrated this in patients with HCT, CAR T-cell therapy, and hematologic neoplasms and solid tumors. However, the risk of transmitting infection despite persistent viral shedding remains uncertain, and decisions to remove infection control precautions should be made in consultation with infection prevention experts and local guidelines.[82]

CONCLUSION

Infection is likely to be one of the most significant problems an immunocompromised patient faces. These patients may present with severe infection or acquire infection while critically ill resulting from other causes. Prevention of infection in the ICU is of primary importance. Pneumonia can be readily prevented by many strategies. Ventilator-associated pneumonia may be prevented by a bundle of interventions.[83] Aspiration of subglottic secretions and selective digestive tract decontamination, although supported by some trials, are still controversial. Opportunistic pneumonia with *P. jirovecii* can be prevented by use of prophylaxis with trimethoprim/sulfamethoxazole, dapsone, or nebulized pentamidine. Environmental exposure to *Legionella* and *Aspergillus* spp. can be prevented by ensuring water purification techniques (e.g., copper-silver ionization) and by preventing exposure of patients to construction activity. Infections caused by pathogens transmitted human to human, such as *M. tuberculosis,* can be prevented by isolation precautions.

Many extrapulmonary infections can also be prevented. CMV infection can be prevented by universal prophylaxis with ganciclovir, valganciclovir, valacyclovir, or a preemptive approach using serial PCR of peripheral blood.[84,85] A similar preemptive approach may be useful in preventing aspergillosis by monitoring peripheral blood for the galactomannan antigen, although this remains controversial.[86,87] *C. difficile* infection is difficult to prevent because there is a clear need for antibiotic therapy for immunocompromised patients with infection. The increasing incidence, severity, and high rate of recurrence of *C. difficile* infection have become significant problems.[88] A randomized controlled study demonstrated that the addition of monoclonal antibodies against *C. difficile* toxins to antibiotic agents significantly reduced the recurrence of *C. difficile* infection, even among patients with the epidemic BI/NAP1/027 strain.[89] Finally, attention to classic infection control practices such as appropriate immunizations,[90–92] hand hygiene, and contact isolation is paramount in immunocompromised patients.

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KEY POINTS

- The degree of immunocompromise in a patient is a guide to the likelihood of particular opportunistic infections and may be indicated by the type and timing of immunosuppressive therapy and, in HIV-infected patients, by the CD4 lymphocyte count and viral load.
- Environmental exposures can be important predictors of infection type. Travel history and exposure to *M. tuberculosis, Aspergillus,* or *Legionella* are important considerations.
- The differential diagnosis of opportunistic lung infection in immunocompromised hosts is so broad that bronchoscopy with bronchoalveolar lavage, before antimicrobial therapy, is highly desirable.
- CNS lesions in immunocompromised hosts are often the result of disseminated infection. Careful examination of the skin, with biopsy of suspicious lesions, and CT of the lungs may obviate the need for brain biopsy.
- Antimicrobial therapy in immunocompromised hosts is beset by difficulties with antimicrobial resistance (especially carbapenem resistance), drug interactions, and adverse effects. Increased frequency of monitoring of immunosuppressive drug levels is essential.

References for this chapter can be found at expertconsult.com.

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Tuberculosis

Melissa L. New and Edward D. Chan

EPIDEMIOLOGY

The World Health Organization (WHO) estimates that 1.7 billion people are latently infected with *Mycobacterium tuberculosis* worldwide.[1] Approximately 10 million active tuberculosis (TB) cases emerge annually, resulting in 1.2 million deaths and making TB the leading cause of death by an infectious agent worldwide.[1–3] The majority of TB cases occurs in the developing world, with nearly 90% of cases emerging from 30 countries with a high TB burden.[1] The global incidence rate is 132 cases per 100,000 persons; however, this rate is much higher in much of sub-Saharan Africa and South Asia, with many countries having rates of over 300 cases per 100,000 persons, with some areas such as certain townships in South Africa with much higher incidences.[2,4] Countries with the most cases per year include India (2.7 million cases per year), China (866,000 cases per year), and Indonesia (845,000 cases per year). Over the past two decades, global incidence and mortality from TB have declined, thanks to efforts for screening and prevention in countries with a high TB burden; however, because of the growing global population, the number of active TB cases has not gone down.

In the United States, the TB rate continues to decline, with 2.8 new cases per 100,000 reported in 2018, the lowest rate recorded since national reporting began in 1953.[5] Foreign-born persons and racial/ethnic minorities bear a disproportionate burden of TB in the United States. In 2018 more than 70% of new TB cases were in foreign-born persons, with non-Hispanic Asians and Hispanics representing most of this group.[5,6]

Four states (California, Florida, New York, and Texas) account for around half of all TB cases in the United States. Among US-born racial and ethnic groups, TB disproportionately affects racial and ethnic minorities, with blacks/African Americans, Native Americans/Alaska Natives, and Native Hawaiians/Pacific Islanders having TB incidence rates 6.5 times, 10 times, and 14 times higher than US-born whites, respectively.[5] Other groups at increased risk of active TB include prisoners, homeless persons, residents of long-term care facilities, and human immunodeficiency virus (HIV)–positive individuals.[5]

The acquired immunodeficiency virus syndrome (AIDS) epidemic has contributed significantly to the rise in TB cases worldwide, with approximately 9% of new cases developing in people living with HIV, mostly in Africa.[1] HIV increases the risk of developing TB by 21-fold in countries where the prevalence is more than 1% in the general population.[7]

The bacille Calmette-Guérin (BCG) vaccine has been widely used in TB-endemic areas for decades. Its efficacy against TB resides mainly in its excellent protection against disseminated and meningeal TB in children.[8] Although its efficacy against pulmonary TB has an overall rate ratio of ~0.50—translating to an efficacy of 0%–80% in different trials—its effectiveness varies widely depending on age at vaccination (better protection when given at school age and to neonates), tuberculin skin test (TST) status (better protection when TST is negative), and distance from the equator (better protection the farther away the recipient lives from the equator).[8,9] BCG is given subcutaneously, but a recent report indicated that in macaques, BCG given intravenously provides much greater protection.[10] Results from the trial of a TB vaccine ($M72/AS01_E$) are promising and raise the hope for a reduction in the global incidence of active TB.[11]

DRUG-RESISTANT TUBERCULOSIS IS A FOREBODING PROBLEM

Drug-susceptible TB is readily curable, provided adherence to medications is followed. However, TB caused by *M. tuberculosis* strains with resistance to one or more first-line agents often requires a significantly longer course of antibiotics; second-line agents have more difficult-to-tolerate side effects, and the treatment of drug-resistant TB is significantly more challenging. More important, multidrug-resistant TB (MDR-TB)—defined as resistance to at least both isoniazid (INH) and rifampin (RIF), two of the most powerful first-line anti-TB drugs—is associated with significant increase in morbidity and mortality.[12–14]

It is estimated that of the 10 million new cases of TB per year worldwide, approximately 500,000 are caused by MDR-TB.[1] Most cases of drug-resistant TB are in India, China, and Russia.[1,15] Although cases of MDR-TB are well known to spawn from inappropriate treatment of drug-susceptible TB, the Baltic countries of the former Soviet Union have very high rates of MDR-TB among new, not previously treated TB cases. Additionally, new molecular epidemiologic techniques have demonstrated direct transmission as a significant contributor to new cases of drug-resistant TB.[16] Fortunately, the percentage of MDR-TB cases in the United States decreased between 1991 and 2006 from 3.5% to 1.1%.[17,18] MDR-TB disproportionately affects foreign-born individuals, with 86% of cases coming from non–US-born persons.[6]

Extensively drug-resistant tuberculosis (XDR-TB) is defined as resistance to INH, RIF, any fluoroquinolone, and a second-line injectable (amikacin, kanamycin, or capreomycin). XDR-TB has emerged with a wide geographic distribution, including the United States, and is associated with poorer treatment outcomes than MDR-TB, especially in those coinfected with HIV.[15,19–25] There are strains of TB with resistance beyond XDR; however, it is debated how to define and treat these strains.[16,26] Fortunately, new drugs and treatment regimens for MDR-TB and XDR-TB have emerged in the past decade, including a change in the recommended treatment strategy put forth by the World Health Organization (WHO). New regimens raise the hope for shorter courses of treatment, better adherence, fewer adverse effects, and improved outcomes in treating drug-resistant TB.[27–33]

TUBERCULOSIS IN THE INTENSIVE CARE UNIT

Tuberculosis patients requiring intensive care unit (ICU) care represent 1%–3% of all patients hospitalized with active TB. Most studies of TB patients requiring ICU admission are retrospective and frequently include a disproportionate number of HIV-positive individuals. TB should be considered in the differential diagnosis of critically ill patients, particularly in foreign-born individuals who emigrated from countries with a high prevalence of TB. With the increased use of tumor necrosis factor-alpha (TNF-α) antagonists and other immunosuppressive agents, ICU physicians are more likely to encounter patients with nonclassical features of TB. In this chapter, selected critical care issues in TB are discussed. Some disease forms, such as renal and peritoneal TB, are omitted because they are less likely to be seen in the ICU.

PULMONARY TUBERCULOSIS

Pulmonary disease is by far the most common manifestation of active TB and of TB requiring ICU admission. Lung disease from TB may be the result of progression of a primary infection or of reactivation disease.

Primary infection occurs after airborne implantation of tubercle bacilli into the lungs. *M. tuberculosis* is transported by infected dendritic cells from the lungs to hilar lymph nodes and then throughout the bloodstream, resulting in secondary occult infections at extrapulmonary sites (Fig. 122.1). Although primary infection is usually asymptomatic in adults, it can present with fever, hilar adenopathy, lung opacifications, pleural effusion, and even severe pulmonary disease that can mimic viral or bacterial pneumonia, potentially delaying the diagnosis of TB. In severely immunocompromised patients, primary TB may be aggressive and become disseminated. Pleural TB, which can present as pleuritis or empyema, is usually a manifestation of primary TB, although it may also occur with reactivation disease. Pleural biopsy specimens are more likely to yield positive cultures than pleural fluid.

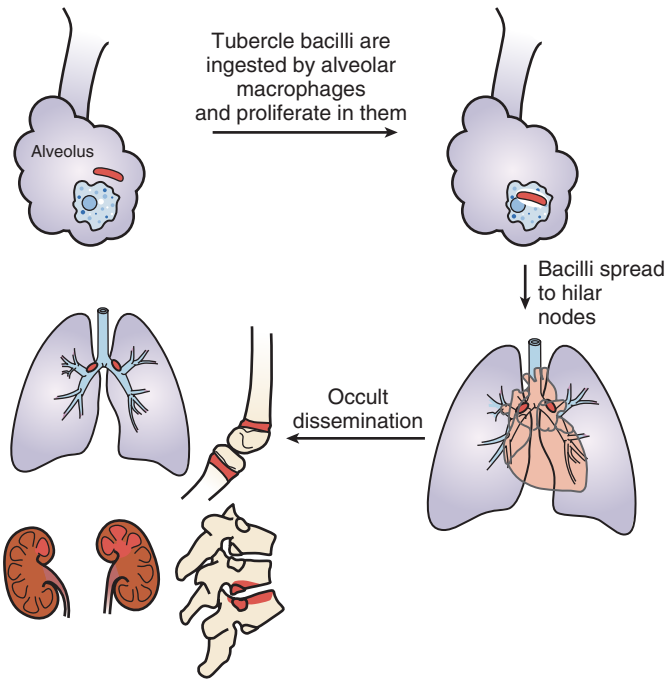

Fig. 122.1 Cartoon representation of a primary infection of TB and occult dissemination. Largely asymptomatic, dissemination of *M. tuberculosis* after primary infection occurs when infected mononuclear cells migrate throughout the body, particularly to the lung apices, kidneys, bone growth plates, and vertebrae, resulting in latent infection.

In non–TB-endemic countries, most cases of active TB are caused by reactivation of latent TB infection (LTBI). Risk of reactivation from LTBI is about 5% within the first 18 months of the initial infection and about 5% for the remaining lifetime for immunocompetent individuals.[34] Typically, reactivation TB is a subacute fibrocavitary pneumonia involving the upper lobes and/or superior segments of the lower lobes. However, reactivation TB can involve any organ system and can present in a fulminant fashion with respiratory failure.[35]

Both primary and reactivation TB can cause bilateral alveolar infiltrates, hypoxic respiratory failure, and acute respiratory distress syndrome (ARDS).[35,36] Consolidation is the most frequent radiographic pattern of patients with pulmonary TB who are admitted to the ICU.[37,38]

Because this radiographic pattern is highly nonspecific, chest x-rays are often not helpful in raising suspicion for TB. Nevertheless, in patients with active TB, consolidation on initial chest radiographs was found to be a stronger, independent predictor for in-hospital mortality than the presence of nodules, interstitial infiltrates, or cavities.[38,39] One possible reason for this is a delay in diagnosis, as clinicians may be more prone to favor nontuberculous bacterial pneumonia in the absence of cavitation or a miliary pattern. Another reason is that consolidation may be an indication of a suboptimal immune response to the infection. Pulmonary gangrene, which carries a mortality of up to 75%, can ensue when rapid progression of infiltrates causes vascular damage and death of lung tissue.[40] Other life-threatening complications of pulmonary TB include hemoptysis, spontaneous pneumothorax, bronchopleural fistula, and empyema. Not unexpectedly, delayed recognition and treatment of nosocomial pneumonia complicating TB patients requiring mechanical ventilation have significant adverse effects on survival.[41,42]

Perhaps the best safeguard to prevent missing a diagnosis of pulmonary or disseminated TB in critically ill patients is to maintain a high index of suspicion for it in at-risk individuals—for example, the foreign-born, immunosuppressed, and/or those known to have a history of untreated LTBI. Studies have shown that the presence of diffuse infiltrates consistent with ARDS and/or acute respiratory failure may cause physicians to inappropriately dismiss the diagnosis of TB, especially as TB remains a rare cause of ARDS.[43–46] Older individuals (≥65 years old) or patients with AIDS may also have a delayed diagnosis of TB resulting, in part, from atypical presentations.[47,48]

In-hospital mortality among TB patients who require ICU admission is high, at 26%–73%, and may be higher among those requiring mechanical ventilation, at 48%–81%.[39,41,42,49–56]

Delayed initiation of anti-TB treatment has been shown to increase mortality.[53] Other risk factors for death among TB patients in the ICU are less specific to TB, such as severity of illness; hypoalbuminemia; anemia; lymphopenia; alcoholism; advanced age; and organ failure requiring life support, including mechanical ventilation, renal replacement therapy, and use of vasopressors.[39,41,42,49,50,57,58] Despite being a relatively rare cause of respiratory failure, pulmonary TB requiring ICU care carries a poor prognosis. Early recognition of the infection is essential in reducing mortality and preventing the nosocomial spread of *M. tuberculosis*.[45]

DISSEMINATED TUBERCULOSIS

Disseminated, or "miliary," TB is more likely to occur in the very young, the very old, and patients with underlying diseases such as AIDS. It may result from either primary or reactivation TB. Disseminated TB typically presents subacutely with symptoms present for days to months, but it can manifest fulminantly with ARDS, septic shock, and multiorgan failure.[59,60] Typical presenting signs and symptoms include fever, malaise, weight loss, dyspnea, and hypoxia.

The chest radiograph (Fig. 122.2A) and computed tomography (CT) scan (see Fig. 122.2B) may show a typical miliary pattern manifested by

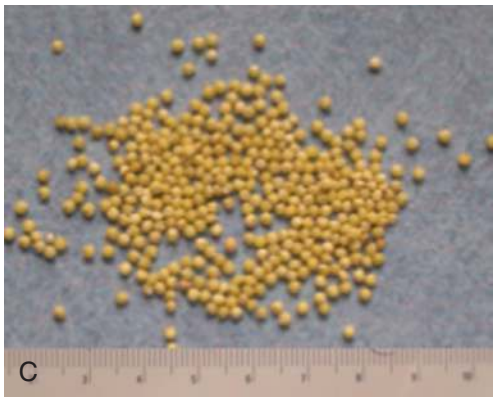

Fig. 122.2 Miliary TB. **A**, Chest radiograph of a patient with miliary TB. **B**, The chest CT scan of the same patient. Both show the characteristically small nodules (less than 2 mm) that are supposed to resemble **(C)** millet seeds.

a profusion of diffuse small (<2 mm) nodules that resemble the size and uniformity of millet seeds (see Fig. 122.2C). In some cases of disseminated disease, the chest x-ray may appear normal. Virtually any organ may be involved, including the adrenals, brain, meninges, spleen, liver, gallbladder, pancreas, eyes, kidneys, and skin. Bone marrow involvement by TB commonly manifests with anemia, leukemoid reaction, and thrombocytosis. The diagnosis of miliary TB can be difficult. If disseminated TB is suspected, sputum acid-fast smear and culture should be obtained even if lung disease is not apparent. Biopsy and culture of affected tissues such as the bone marrow are often required. Culture of blood, urine, and/or stool may be positive, especially in AIDS patients.[60,61]

NEUROLOGIC TUBERCULOSIS

Tuberculous Meningitis

TB meningitis is rare, accounting for more than 1% of global TB cases and with only 107 cases reported in the United States in 2013.[62] It occurs via rupture of a subependymal tubercle that seeded and formed during primary infection or disseminated disease. Individuals at high risk of TB meningitis include very young children with primary TB and older patients with immunodeficiency disorders such as HIV. Most will have no known history of TB, but evidence of extrameningeal disease (e.g., pulmonary, urinary) can be found in about half of the patients.[63,64]

TB meningitis is typically a subacute disease. Symptoms can be present for 1 day to 9 months, with a median of 10–14 days before diagnosis.[63,65] A prodromal phase of low-grade fever, malaise, headache, dizziness, vomiting, and/or personality changes may be present for 2–3 weeks before patients seek medical care. Typical findings at presentation include worsening headache, altered mental status, stroke, hydrocephalus, and cranial neuropathies. These clinical features are the result of basilar meningeal fibrosis and vascular inflammation.[66] Classic manifestations of bacterial meningitis, such as stiff neck and fever, may be absent. When allowed to progress, seizures and coma may ensue.[67]

The diagnosis of TB meningitis can be difficult and may be based only on clinical findings without definitive microbiologic proof. The TST is positive in only about 50% of patients with TB meningitis. Certain clinical characteristics such as longer duration of symptoms (>6 days), moderate cerebrospinal fluid (CSF) pleocytosis, and the presence of focal deficits increase the probability of TB meningitis.[68,69] Characteristic CSF findings of TB meningitis include the following:

- Leukocytosis with predominance of lymphocytes. White blood cell counts are usually between 100 and 500 cells/μL. Lower white blood cell counts and neutrophil predominance may be seen very early in the course of the disease.
- Elevated protein levels, usually between 100 and 500 mg/dL.
- Low glucose levels, typically less than 45 mg/dL.

CSF samples should be sent for acid-fast smears, but this has low sensitivity. Because TB meningitis is a paucibacillary disease, centrifuging larger quantities of CSF (10–15 mL) from several lumbar punctures can increase the sensitivity. Culture is also associated with low sensitivity and can take weeks to become positive. A stereotactic biopsy can be performed if tissue samples are needed. Mycobacterial antigens by enzyme-linked immunosorbent assay (ELISA) or radioimmunoassay have been detected in the CSF of patients with TB meningitis.[70] A large study cited sensitivities of 90% for interferon-gamma (IFN-γ) release assay performed on whole blood, 82% for CSF in automated culture systems, 73% for CSF in Lowenstein-Jensen medium, 30% for CSF adenosine deaminase, and 27% for Ehrlich-Ziehl-Neelsen acid-fast staining of the CSF.[71]

In recent years, the use of nucleic acid amplification assays (NAAs) has been shown to aid in the diagnosis of TB meningitis. These tests can detect *M. tuberculosis* in a few hours with a sensitivity of 56%–80% and a specificity of 95%–98%.[72–75] The sensitivity of CSF microscopy and culture falls rapidly after the start of treatment, whereas mycobacterial DNA may remain detectable within the CSF up to a month after the start of treatment.[76] Given the high morbidity and mortality associated with TB meningitis, the WHO recommends use of Xpert MTB/RIF, an NAA, to test CSF in preference to conventional microscopy and culture as the initial diagnostic test in patients with suspected TB meningitis.[1] The novel loop-mediated isothermal amplification (TB-LAMP) assay, which is an NAA technique, has some advantages over polymerase chain reaction (PCR) in that it is performed at a constant temperature and produces a high amount of DNA amplification. This technology has been used on CSF in some settings to diagnose TB meningitis.[77] Regardless of which diagnostic test is used, a negative test neither excludes the diagnosis nor obviates the need for continued empiric treatment if the clinical suspicion is high.[78]

Magnetic resonance imaging (MRI) often reveals a basilar meningeal enhancement (Fig. 122.3) and/or hydrocephalus.[64] Hypodensities indicating cerebral infarcts and ring- or nodular-enhancing lesions can also be seen. MRI is superior to CT for evaluating the brainstem and the extent of lesions.

The outcome of TB meningitis is improved by timely treatment. Thus empiric treatment is warranted when risk factors and clinical features are suggestive of TB meningitis, even before microbiologic confirmation. Chemotherapy for TB meningitis follows the model of short-course chemotherapy for pulmonary TB—an induction phase, followed by a continuation phase. However, unlike pulmonary TB, the optimal drug regimen and duration of each phase of treatment are not

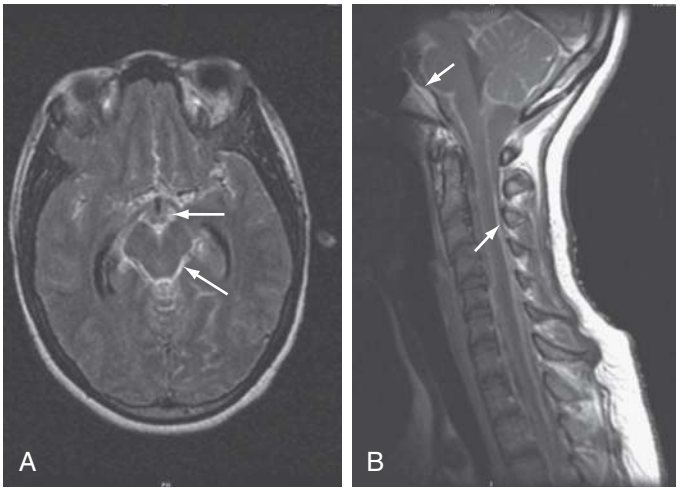

Fig. 122.3 Tuberculous meningitis. T1-weighted **(A)** transverse MRI of the brain and **(B)** sagittal MRI of the base of the brain and the spinal cord in a patient with tuberculous meningitis. Note the enhanced meninges (*arrows*) in the basilar regions of the brain, brainstem, and spinal cord.

clearly established. INH and RIF remain the most essential drugs. INH penetrates the CSF freely and has potent early bactericidal activity.[79–81] RIF penetrates the CSF less well (maximum concentrations around 30% of plasma), but the high mortality from RIF-resistant TB meningitis has confirmed its central role in the treatment of central nervous system (CNS) disease.[82] One study compared standard oral doses of RIF (450 mg) with higher doses of RIF (600 mg) administered intravenously. The higher-dose RIF group had three times higher CSF concentrations than the standard oral dose group and improved mortality (35% vs. 65%).[83] Increased CSF concentrations of RIF have also been achieved with high oral doses (1350 mg, approximately 30 mg/kg) of RIF.[84] INH, RIF, and pyrazinamide are considered mandatory at the beginning of TB meningitis treatment, and some centers use all three drugs for the duration of therapy.[85] There are no data from controlled trials to guide the choice of the fourth drug. Most authorities recommend either streptomycin or ethambutol, although neither penetrates the CSF well in the absence of inflammation, and both can produce significant adverse reactions. Although fluoroquinolones have good CNS penetration, their addition to a standard regimen did not improve outcomes in treatment of drug-susceptible TB meningitis; fluoroquinolones are recommended for treatment of RIF-resistant and MDR-TB strains.[86] Linezolid, which also has good CNS penetration, may be beneficial for severe TB meningitis, though data are few.[86,87] Therapy should be continued for 9–12 months.

Adjunctive glucocorticoid treatment of TB meningitis has been recommended for more than 50 years. There has been long-standing concern that glucocorticoids may reduce the penetration of anti-TB drugs into the CNS; however, data increasingly point toward their benefit in TB meningitis.[66] A Cochrane systematic review and meta-analysis of seven randomized controlled trials involving 1337 participants concluded that glucocorticoids improved survival from TB meningitis by 25%; however, this analysis included few HIV-infected individuals.[88] Currently, the WHO recommends initial adjuvant glucocorticoid therapy in patients with TB meningitis.[89]

Because there are no controlled trials comparing different glucocorticoid regimens, the choice of regimen should be based on those found to be effective in published trials. One recommended regimen for adults is dexamethasone 12 mg a day for 3 weeks, followed by a gradual taper over the next 3 weeks.[90] In a large study from Vietnam, patients with mild disease received intravenous dexamethasone 0.3 mg/kg/day × 1 week, 0.2 mg/kg/day × 1 week, and then 4 weeks of tapering oral therapy.[91] For patients with severe TB meningitis, intravenous dexamethasone was given for 4 weeks (1 week each of 0.4 mg/kg/day, 0.3 mg/kg/day, 0.2 mg/kg/day, and 0.1 mg/kg/day), followed by 4 weeks of tapering oral dexamethasone therapy.[91]

The prognosis of TB meningitis largely depends on the neurologic status at the time of presentation and time to treatment initiation. Various case series indicate a mortality rate between 7% and 65% in developed countries and up to 69% in underdeveloped areas.[63,64,92] Most patients will die in 5–8 weeks if not treated. Mortality risk is the highest in those who are elderly and with comorbidities, severe neurologic involvement on admission, and rapid progression of disease. Neurologic sequelae occur in up to 50% of survivors.[92]

Other Central Nervous System Manifestations of Tuberculosis

Other CNS manifestations of TB include brain abscesses, intracranial tuberculomas, vasculitis, radiculomyelitis, and spinal arachnoiditis. These can occur in conjunction with TB meningitis but are less likely to be seen in the ICU when isolated. Intracranial tuberculomas are more common among pediatric patients, especially infants, and can occur in any region of the brain. They result from hematogenous spread of TB. Tuberculous radiculomyelitis is a paradoxical reaction to the treatment of TB meningitis and may respond to glucocorticoids. Signs and symptoms include subacute paraparesis, radicular pain, bladder disturbance, and paralysis.[93]

CARDIOVASCULAR TUBERCULOSIS

Tuberculous Pericarditis

Pericarditis is an uncommon, but important, manifestation of TB. In countries with a low incidence of TB, it is primarily a disease among the elderly and those with HIV, but it should be considered as a differential diagnosis of any patient with pericarditis and/or pericardial effusion. Tuberculous pericarditis can result from local spread from the lungs, tracheobronchial tree, lymph nodes, or adjacent bones or by disseminated infection. The onset is usually insidious. Presenting signs and symptoms can be nonspecific (fever, dyspnea, and weight loss) and/or more specific to the pericardium, such as characteristic chest pain that is relieved with sitting up and leaning forward. Large hemorrhagic effusions may develop, resulting in cardiac tamponade. Pericardial inflammation and thickening may eventually cause constrictive pericarditis. The presence of both pericardial effusion and constrictive pericarditis is physiologically characterized by the continued elevation of diastolic pressure after pericardiocentesis. Such a finding should raise suspicion for tuberculous pericarditis.

The diagnosis of tuberculous pericarditis can be difficult to prove. Culture of pericardial fluid is positive in only 30% of cases, and pericardial biopsy has a yield of approximately 60%. Biopsy of the pericardium may reveal granulomatous changes consistent with TB or stain positive for acid-fast bacteria. The presence of elevated adenosine deaminase levels in the pericardial fluid has been shown to indicate tuberculous pericarditis, but confirmation is needed.[94] PCR holds promise as a more sensitive test in the diagnosis of tuberculous pericarditis.[95,96] Many individuals are treated empirically for tuberculous pericarditis based on clinical suspicion, positive TST results, imaging studies, and exudative pericardial fluid with high protein and mononuclear white count. Treatment involves standard four-drug regimens as for other manifestations of TB. Glucocorticoids have been used as adjunctive treatment for TB pericarditis to reduce the need for operative intervention.[97] However, a more recent study of 1400 adults with TB pericarditis did not have a lower mortality or frequency of cardiac tamponade with corticosteroid treatment. Additionally, the steroid-treated group had a

higher frequency of AIDS-related malignancy.[98] Thus there is no consensus on whether to administer adjunctive glucocorticoids for TB pericarditis patients with corticosteroids.[89,99]

Other Cardiovascular Manifestations of Tuberculosis

In addition to the pericardium, TB may affect the endocardium, myocardium, and epicardium (coronary arteries). These disorders are very rare. Endocardial involvement may manifest as endocarditis or as mural thrombi with entrapped *M. tuberculosis*. Tuberculous myocarditis occurs via direct spread from pericardial or mediastinal lymph nodes or from disseminated disease.[100] TB may also affect the coronary arteries, resulting in coronary arteritis with granulomatous inflammation of the arterial wall and obliterative intimal fibrosis.[101]

The aorta can be affected by TB, causing aortitis, aortointestinal fistula formation, or rupture.[102,103] The pathogenesis of aortitis includes septic embolization from endocarditis, seeding of a preexisting aneurysm from bacteremia, or extension from a contiguous site of infection. Signs and symptoms include fever, abdominal or back pain, and a palpable abdominal mass. Blood cultures are positive for *M. tuberculosis* in approximately 15% of cases. CT findings include air in the aortic wall, a periaortic nodularity, a saccular aneurysm in a noncalcified aorta, and a rapidly increasing aortic diameter. A primary mycotic aneurysm of the aorta may be a sequela of chronic tuberculous aortitis.[104,105]

TUBERCULOSIS IN HUMAN IMMUNODEFICIENCY VIRUS–POSITIVE PATIENTS

HIV is the most important host risk factor for active TB.[106] In many developing countries, TB is the most common opportunistic infection associated with HIV. The estimated annual risk of active TB among persons with LTBI in the general population is 12.9 per 1000 person-years. In contrast, rates of progression to active TB among HIV-infected persons with LTBI range from 35 to 162 per 1000 person-years. More recent estimates for reactivation TB in HIV-positive individuals shows a rate ratio of 57 (95% confidence interval [CI], 27–120) compared with HIV-negative individuals with LTBI.[107] Because TB may be an initial manifestation of HIV infection, all patients with TB should be tested for HIV. The WHO estimates that globally, 8.6% of TB patients in 2018 were coinfected with HIV and that HIV coinfected patients accounted for over 20% of deaths from TB.[1]

The mechanism of increased TB susceptibility in HIV-positive persons is incompletely understood. Unlike other AIDS-related opportunistic infections, the $CD4^+$ count is not always a reliable predictor of increased risk of TB disease, although $CD4^+$ lymphopenia does reduce IFN-γ production, impairing macrophage and dendritic cell activation. Alveolar macrophages (AMs) are important components of an effective immune response to TB,[108] and AM apoptosis represents a critical host defense mechanism that promotes *M. tuberculosis* elimination. In this context, another possible mechanism by which HIV increases susceptibility to TB is that HIV-infected AMs have a reduced apoptotic response to *M. tuberculosis* compared with AMs from healthy individuals.[109,110]

When the $CD4^+$ count is above 350 cells/μL, pulmonary TB in AIDS patients is more likely to present with typical chest radiographic findings of upper lobe fibrocavitary disease.[111] However, as the $CD4^+$ count decreases, pulmonary TB tends to manifest with more atypical radiographic manifestations, such as mediastinal adenopathy, diffuse miliary or nodular infiltrates, focal lower zone opacifications, and lack of cavitation.[111] Among HIV-positive persons, death from TB was significantly associated with low $CD4^+$ counts.[41,112]

Although coinfection with HIV is considered to contribute significantly to TB-related mortality, a study showed no difference in mortality in TB patients requiring ICU care between those who were HIV negative and those with advanced AIDS in a low-burden, resource-rich country where state-of-the-art intensive care is available, suggesting that the severity of illness has a greater influence on mortality than the HIV status per se.[41] Extrapulmonary TB is more common among HIV-positive patients, occurring in up to 70%. Disease involving the lymph nodes is especially common. Other extrapulmonary manifestations include miliary disease, sepsis, and CNS disease.[47,113] Empiric treatment may be necessary before the diagnosis is confirmed. If rapid diagnosis is needed, NAAs can be used, although they are more accurate in smear-positive cases.

After initiating antiretroviral therapy (ART) in severely immunosuppressed patients, those with subclinical or recently diagnosed TB may display a paradoxical reaction, where there is an apparent clinical worsening of TB while on appropriate anti-TB treatment.[114–116] This phenomenon, also known by the more descriptive name of *immune reconstitution inflammatory syndrome* (IRIS), can manifest as early as 7 days after starting ART. Signs and symptoms include fever, weight loss, and evidence of local inflammatory reactions such as lymphadenitis and worsening pulmonary disease such as increased pulmonary consolidation, nodules, and effusions. Histologically, a vigorous suppurative and necrotizing granulomatous reaction occurs, with or without caseation; cultures of infected material are almost invariably positive.

TUBERCULOSIS AND IMMUNOMODULATORY THERAPIES

TNF-α plays a central role in the pathogenesis of various inflammatory disorders and in the pathophysiologic response to many infections. TNF-α is produced predominantly by macrophages and lymphocytes and is active both as a membrane-bound and soluble protein.[117,118] In several animal models, TNF-α plays an essential part in the host response to TB.[119] One mechanism by which it potentiates the host defense is by its ability to induce apoptosis of *M. tuberculosis*–infected cells. Macrophage apoptosis helps contain *M. tuberculosis* by maintaining granuloma integrity, increasing the efficiency of antigen presentation, and promoting the killing of intracellular *M. tuberculosis*.[120] Administration of antibodies neutralizing TNF-α resulted in the reactivation of TB in a mouse model.[121] Interruption of the normal TNF-α–controlled response to TB reduces apoptosis, disrupts granuloma integrity, and predisposes to disseminated infection.

TNF-α antagonists are increasingly used for the treatment of various chronic inflammatory disorders. Currently licensed TNF-α antagonists fall into two main types: monoclonal neutralizing anti–TNF-α antibodies and the soluble p75 subunit of the TNF-α receptor (TNF-α–R). The soluble TNF-α–R antagonizes TNF-α function by acting as decoys to bind TNF-α. Four monoclonal anti–TNF-α antibodies (infliximab, adalimumab, certolizumab pegol, and golimumab) and one soluble TNF-α–R (etanercept) are in clinical use. Patients treated with TNF-α blockers have a TB incidence rate of 1.17 per 1000 patient-years—12.2 times that of the general population[122]; almost all these cases are caused by reactivation of LTBI. A consensus statement reported that the relative risk for reactivation TB is increased 25-fold in individuals who use TNF-α antagonists compared with nonusers.[123]

Important differences have emerged among the TNF-α antagonists in regard to the risks of reactivation TB. Consistently, the excess risk is associated with infliximab and adalimumab rather than with etanercept. For example, compared with etanercept, infliximab is associated with a twofold to sevenfold greater risk of TB, shorter time to TB onset (17 vs. 48 weeks), and higher proportion of TB cases with disseminated or extrapulmonary disease (25% vs. 10%).[124,125] It is not entirely clear why the neutralizing antibodies to TNF-α put people at greater

risk of reactivation TB than soluble TNF-α receptors. Possible reasons include a longer duration of action of infliximab and adalimumab and their ability to bind to membrane-bound TNF-α with greater affinity than etanercept.[117] As a result, infliximab can induce death in T cells that express the membrane-bound TNF-α, whereas etanercept cannot. In addition, anti–TNF-α antibodies can inhibit T-cell activation and IFN-γ production, whereas etanercept cannot. Thus the pharmacokinetic and biologic differences between the two main types of TNF-α antagonists may account for the greater susceptibility to intracellular pathogens with the use of the anti–TNF-α antibodies.[117,126] As might be anticipated, when anti–TNF-α antibodies are used in combination with other immunosuppressive medications such as methotrexate or azathioprine, the risk of TB reactivation is higher than that with the use of anti–TNF-α antibodies alone.[127]

DIAGNOSIS OF TUBERCULOSIS

When TB is suspected, the first diagnostic test should be a microscopic examination and culture for mycobacteria of relevant body fluids or tissues. Several specimens are often required, especially for CNS disease.

Patients with suspected pulmonary TB should be placed in respiratory isolation until two to three sputa, collected with at least 8 hours between samples, are negative for acid-fast bacteria. Because patients with extrapulmonary disease may also have occult pulmonary disease, it is generally recommended that sputum smears be sent for these patients regardless of chest radiographic findings.

Acid-fast smear does not differentiate between *M. tuberculosis* and nontuberculous mycobacteria, so culture is used to confirm species and determine drug susceptibility. Simultaneous culture on both liquid and solid media is recommended. Liquid medium such as the BACTEC systems allow growth of the organism in about 14 days, whereas growth takes 3–6 weeks on solid media (Lowenstein-Jensen or Middlebrook 7H11). Once sufficient growth is obtained, species identification can be obtained via conventional biochemical tests or more rapid tests such as nucleic acid probes, high-performance liquid chromatography, the NAP test (*p*-nitro-α-acetylamino-β-hydroxypropiophenone), or molecular tests. Only experienced laboratories should complete susceptibility testing on culture-positive specimens. Molecular fingerprinting by restriction fragment-length polymorphism can be used to distinguish strain types when laboratory contamination is suspected.

Although rapid and inexpensive, acid-fast smear microscopy is limited by its poor sensitivity (approximately 50% sensitivity in culture-confirmed pulmonary TB cases) and suboptimal specificity (50%–80%) in settings where nontuberculous mycobacteria are commonly isolated.[128–130] NAAs have become a routine procedure in many settings because they can reliably detect *M. tuberculosis* in specimens 1 or more weeks earlier than culture and can report the presence of genes that confer rifampin resistance.[129] Because of the increasing use of NAAs and the potential impact on patient care and public health, the Centers for Disease Control and Prevention (CDC) and the Association of Public Health Laboratories made recommendations for using NAAs for laboratory confirmation of TB. The CDC recommends that NAAs be performed on at least one respiratory specimen from each patient in whom a diagnosis of TB is being considered but has not yet been established and for whom the test result would alter case management or TB control activities.[131,132] A newly available assay, TB-LAMP, has a sensitivity of 98% in smear-positive and 53% in smear-negative/culture-positive patients. TB-LAMP can be used instead of or in addition to microscopy for the diagnosis of pulmonary TB, which can reduce the time to diagnosis to several hours. The sensitivity of TB-LAMP is close to that of NAAs, and the amount of laboratory infrastructure is much less, making it an appealing technology for more remote and resource-limited settings.[133]

TREATMENT OF TUBERCULOSIS

Standard treatment of adults with drug-susceptible TB is a three- or four-drug regimen for at least 6 months.[134,135] The typical course of therapy for drug-susceptible disease is 2 months of INH, RIF, pyrazinamide (PZA), and ethambutol (EMB) (initial phase), followed by 4 months of INH and RIF (continuation phase) (Tables 122.1 and 122.2). A 9- to 12-month regimen is suggested for TB meningitis; for pulmonary TB that is slow to respond to therapy, such as those with cavitary lesions and persistent sputum culture positivity even after 2 months of an appropriate four-drug regimen; or when PZA is not used in the induction regimen. EMB can be discontinued when drug susceptibility studies show sensitivity to INH and RIF. Streptomycin can be used instead of EMB if resistance is unlikely or susceptibility is shown. The continuation phase can be daily therapy, twice-weekly therapy, or thrice-weekly therapy for drug-susceptible TB (see Table 122.1). Specific guidelines, including information on first- and second-line agents, have been published by the CDC.[136]

Treatment of TB in patients with HIV is similar to that in HIV-negative patients but is often complicated by drug interactions between TB medications and antiretrovirals.[139] Protease inhibitors and nonnucleoside reverse transcriptase inhibitors can either induce or inhibit activity of the P-450-3A (CYP3A) system. RIF can increase the activity of CYP3A, leading to decreased levels of several antiretrovirals. Rifabutin is a less potent inducer of the CYP3A system and is associated with fewer drug–drug interactions, but dose adjustments may be needed. Despite these potential drug interactions, a RIF-based regimen should be used whenever possible. Patients with liver disease caused by hepatitis C virus may be at increased risk of drug-induced hepatotoxicity. Another treatment issue in HIV-TB coinfection is that patients may fail to properly absorb the anti-TB drugs, which may increase the risk of treatment failure, relapses, and acquired drug resistance.[140]

Because of the increased risk of RIF resistance, patients with HIV should *not* receive once-weekly INH-rifapentine in the continuation phase of treatment. Twice-weekly INH-RIF or INH-rifabutin should be avoided when the $CD4^+$ cell count is less than 100 cells/μL. Treating drug-susceptible pulmonary TB in HIV-positive individuals for 9 months

TABLE 122.1 Current Regimens for Treatment of Drug-Susceptible TB

Regimen	Initial Phase	Continuation Phase
Daily or 5 days per week	8 weeks of INH, RIF, PZA, ± EMB	18 weeks of INH and RIF
Intermittent	(a) 2 weeks of daily INH, RIF, PZA, and EMB (or SM), then 6 weeks of INH, RIF, PZA, EMB BIW or TIW	18 weeks of INH and RIF BIW
	(b) 8 weeks of thrice-weekly INH, RIF, PZA, and EMB (or SM)	18 weeks of INH and RIF TIW

BIW, Twice weekly; *EMB,* ethambutol; *INH,* isoniazid; *PZA,* pyrazinamide; *RIF,* rifampin; *SM,* streptomycin; *TIW,* thrice weekly.
The daily regimen is employed when patients self-administer their drugs. There is enough redundancy that if patients miss some of their doses, the outcome will remain acceptable.
The intermittent regimens are intended for directly-observed therapy (DOT) Regimen (a) entails a total of 62 doses and has yielded over 95% success rates.[137] Regimen (b) involves 78 doses and has also resulted in success rates of approximately 95% in Hong Kong, where it is the standard regimen.[138]

TABLE 122.2 Dosages of First-Line Antituberculosis Drugs in Adults and Major Adverse Effects

Drug	Daily Dosage	Twice- or Thrice-Weekly Dosage	Adverse Effects
Isoniazid	5 mg/kg oral (max: 300 mg)	900 mg BIW 600 mg TIW	Hepatitis, peripheral neuritis, drug-induced lupus, seizures, and hypersensitivity with rash and fever. Drug interactions with Dilantin and disulfiram. Pyridoxine can decrease neurotoxicity.
Rifampin	5 mg/kg oral (max: 300 mg)	10 mg/kg 600 mg BIW 600 mg TIW	Orange body secretions, flulike syndrome, hepatitis, pruritus, thrombocytopenia, nausea, anorexia, diarrhea, renal failure, and **multiple drug interactions**.
Rifabutin*	10 mg/kg oral (max: 300 mg)	5 mg/kg	Neutropenia, uveitis, hepatotoxicity, orange discoloration of body fluids
Rifapentine**	10 mg/kg ***once weekly*** (max: 600 mg)		Similar to rifampin
Pyrazinamide	15–30 mg/kg oral (max: 2.0 g)	30–35 mg/kg	Hyperuricemia, hepatitis, rash, nausea, and anorexia
Ethambutol	25 mg/kg initial 2 months, then 15 mg/kg oral	50 mg/kg BIW 30 mg/kg TIW	Optic neuritis and gastrointestinal discomfort

BIW, Twice weekly; *TIW,* thrice weekly.
*Rifabutin and rifapentine are considered first-line agents when intolerance to rifampin precludes its use or concerning drug interactions exist.
**Rifapentine is only used in a once-weekly dose in HIV-negative patients with noncavitary and uncomplicated disease. It is not approved for use in children.

rather than the standard 6 months is associated with lower relapse rates and is recommended for patients who are not receiving ART treatment or who have delayed response to therapy.[141,142] Recommendations regarding the treatment of TB in HIV patients are frequently revised as new drugs and information become available. The following websites can assist with treatment decisions and information on drug–drug interactions:
http://www.cdc.gov/tb/publications/guidelines/TB_HIV_Drugs/default.htm
http://www.medscape.com/updates/quickguide
https://www.currytbcenter.ucsf.edu/

If a patient develops IRIS while on ART, it is generally recommended that HIV therapy be continued during TB treatment whenever possible because IRIS is usually self-limited. However, more severe IRIS may require the addition of corticosteroids and/or temporary discontinuation of ART. Patients with the lowest $CD4^+$ counts, less than 50 cells/μL, are at highest risk of severe IRIS with the initiation of ART, though they also have the greatest mortality benefit with early ART initiation.[143–145] Although there has been debate as to the safest time for the initiation of ART relative to starting TB treatment, mounting evidence demonstrates that early initiation is associated with improved survival.[143,146,147] The WHO currently recommends the initiation of ART, for those not already on it, within 8 weeks of TB treatment initiation, and within 2 weeks for those with $CD4^+$ count[89] <50 cells/μL.

When MDR-TB is suspected or confirmed, a specialized treatment regimen should be used. Whenever possible, treatment for an MDR-TB strain should be guided by drug susceptibility testing to EMB, PZA, and the second-line anti-TB drugs.[148] New drugs have been developed over the past few years that can now be used for the treatment of drug-resistant TB. Typical regimens for MDR-TB will include a fluoroquinolone (levofloxacin or moxifloxacin), bedaquiline, and linezolid, in addition to other medications, including clofazimine and cycloserine or terizidone. Other medications that may be used, depending on a resistance profile, may include EMB, delamanid, PZA, imipenem-cilastatin, meropenem, amikacin, streptomycin, ethionamide, prothionamide, or para-aminosalicylic acid.[16,27,30] Local public health departments should be contacted to meet reporting requirements and will usually be responsible for treatment monitoring, including for medication adverse events. Directly observed therapy should be implemented. Patients with MDR-TB require longer therapy (generally 18 months of treatment after the last negative sputum culture). Surgical resection after 2–3 months of treatment may improve outcome.[136]

There is increasing evidence that regimens that contain some of the newer agents is highly efficacious against drug-resistant TB. A 6 month of treatment with bedaquiline, pretomanid, and linezolid resulted in a 90% favorable clinical outcome in 109 South Africans with highly-drug resistant TB, comprised of both multi-drug resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB).[149a] A multi-drug regimen that included bedaquiline (63%), delamanid (27%), or both (10%) resulted in an 85% sputum conversion rate within 6 months in a multi-national study of over 1,000 individuals with rifampin-resistant TB or MDR-TB.[149b]

Parenteral therapy may be required in ICU patients and is recommended for patients with fulminant disease (Table 122.3). When delivered

TABLE 122.3 Selected Parenteral Medications Used in Treating Tuberculosis[136]

Medication	Preparation	Initial Dosage in Adults (maximum dosage)
Isoniazid	PO, IV, IM	5 mg/kg/day (300 mg)
Rifampin	PO, IV	10 mg/kg/day (600 mg)
Streptomycin	IV, IM	10–15 mg/kg/day or 750–1000 mg/day
Amikacin	IV, IM	10–15 mg/kg/day or 750–1000 mg/day
Kanamycin	IV, IM	10–15 mg/kg/day or 750–1000 mg/day
Capreomycin	IV, IM	10–15 mg/kg/day or 750–1000 mg/day
p-Aminosalicylic acid	PO, IV	8–12 g/day in 2 or 3 doses
Levofloxacin	PO, IV	500–1000 mg/day
Moxifloxacin	PO, IV	400 mg/day
Linezolid	PO, IV	600 mg/day

IM, Intramuscular; *IV,* intravenous; *PO,* oral.
Table shows routine daily dosing (taken from https://www.currytbcenter.ucsf.edu/sites/default/files/tb_sg3_chap5_medications.pdf). Dosages may differ in children and in patients in intermittent therapy. Persons over age 59 should receive the lower dose for aminoglycosides (750 mg).

enterally, half of the ICU patients have subtherapeutic levels of RIF.[149] INH and RIF are available in parenteral forms; EMB and PZA are not. Other active medications available for intravenous use include aminoglycosides, fluoroquinolones, capreomycin, and linezolid. In patients with renal failure, dose adjustments are required for those taking EMB, PZA, cycloserine, an aminoglycoside, capreomycin, or a fluoroquinolone. INH and PZA should probably be withheld in the setting of severe liver failure. An expert in the treatment of TB should be consulted when treating complicated ICU patients or those with MDR-TB.

Glucocorticoids are generally recommended in the adjunctive treatment of TB meningitis and possibly pericarditis, as discussed earlier.[150] There is some evidence that use of glucocorticoids in patients with acute respiratory failure from pulmonary TB may be beneficial; however, data regarding HIV-infected patients are lacking.[151,152] Typical therapy includes prednisone at 40–80 mg per day, tapered over a few weeks.

RISK TO HEALTHCARE WORKERS

The awareness that caring for TB patients poses a risk to healthcare workers (HCWs) did not emerge until the 1950s and 1960s, when studies established that *M. tuberculosis* infection was transmitted by the airborne route.[153] However, occupational transmission received little attention until numerous outbreaks of TB and MDR-TB occurred in US and European hospitals in the late 1980s and early 1990s.[154] At that time, more than 20 HCWs became ill with MDR-TB and at least 10 died.[155] Hundreds of HCWs may be latently infected with MDR-TB and thus represent a relatively large reservoir of individuals at risk of future reactivation MDR-TB.

Pulmonologists are at higher risk of occupational exposure to TB than other medical specialists. Atypical presentations of TB can put providers at increased risk when TB is not suspected and proper precautions are not taken.[156] Bronchoscopy requires close contact with patients and provokes coughing, which likely contributes to the TST conversion rate of 11% among pulmonary fellows.[156] DMF-HEPA respirators should be used when performing bronchoscopy on patients with known or suspected TB.[156]

In HCWs with negative TST reactions who undergo repeat testing, an increase in reaction size of more than 10 mm within a period of 2 years should be considered a skin-test conversion indicative of recent infection with *M. tuberculosis*. Because TST conversion typically occurs 3–8 weeks after primary infection, skin testing should be performed at 3 weeks after exposure.

HCWs with potential exposure should be monitored for symptoms, and unless they are known to have a positive TST at baseline, skin testing or an IFN-γ release assay should be performed as soon as possible after the exposure to establish a baseline. If initial screening is negative, testing should be repeated 8–10 weeks after exposure, and if found to be positive, treatment for LTBI is recommended.

KEY POINTS

- Although pulmonary TB classically develops cavitary lung disease, it can present in many ways, including ARDS and respiratory failure.
- Tuberculous meningitis typically has a subacute presentation and has a high mortality rate, which is improved with prompt treatment.
- Tuberculous pericarditis is rare but can result in constrictive pericarditis or cardiac tamponade from a hemorrhagic effusion.
- Disseminated TB can affect nearly any organ and is most common in very young or old patients and those who are immunocompromised.
- Patients with HIV and those on anti-TNF therapies are at increased risk of developing active TB.
- Culture remains the cornerstone of diagnosis of TB and is important for drug resistance testing. However, NAA assays can provide a much more rapid diagnosis and are especially recommended for use with CSF and other fluids where culture positivity is classically low, such as pericardial and pleural fluid.
- Treatment of TB requires several drugs given over many months, though the exact regimen will vary depending on the site of disease and the susceptibility of the cultured organism.
- Treating with a course of glucocorticoids is recommended to reduce morbidity and mortality from TB meningitis and possibly TB pericarditis.

References for this chapter can be found at expertconsult.com.

ANNOTATED REFERENCES

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This study compared the outcomes of MDR-TB vs. XDR-TB patients at a referral hospital in the United States. Odds ratios for long-term treatment success was 21.1 (MDR-TB vs. XDR-TB). The hazard ratio of death from TB was 7.9 (XDR-TB vs. MDR-TB). Despite aggressive treatment, XDR-TB was associated with significantly poorer long-term outcome and survival than MDR-TB.

Erbes R, Oettel K, Raffenberg M, et al. Characteristics and outcome of patients with active pulmonary tuberculosis requiring intensive care. *Eur Respir J.* 2006;27:1223–1228.
Retrospective study from Germany looking at 58 TB patients admitted to the ICU. The in-hospital mortality was 15 of 58 (25.9%); 13 (22.4%) patients died in the ICU. The factors independently associated with mortality were acute renal failure, need for mechanical ventilation, chronic pancreatitis, sepsis, acute respiratory distress syndrome, and nosocomial pneumonia.

Nahid P, Gonzalez LC, Rudoy I, et al. Treatment outcomes of patients with HIV and tuberculosis. *Am J Respir Crit Care Med.* 2007;175:1199–1206.
The optimal length of tuberculosis treatment in patients coinfected with HIV is unknown. HIV-infected patients who received a 6-month rifamycin-based course of tuberculosis treatment or who received intermittent therapy had a higher relapse rate than HIV-infected subjects who received longer therapy or daily therapy, respectively. Standard 6-month therapy may be insufficient to prevent relapse in patients with HIV.

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Malaria and Other Tropical Infections in the Intensive Care Unit

Taylor Kain, Andrea K. Boggild, Frederique A. Jacquerioz, and Daniel G. Bausch

Malaria infections are classified broadly into three clinical categories: (1) *asymptomatic parasitemia,* which generally does not require treatment for those living in endemic areas; (2) *uncomplicated malaria,* defined as parasitemia (typically low, though perhaps elevated in those who are semi-immune or immune) and fever without evidence of end-organ damage or other signs of severe disease (these patients may often be treated as outpatients with oral antimalarials); and (3) *severe and complicated malaria,* defined as parasitemia of any value in conjunction with vital organ damage or other signs of severe disease. Patients with severe and complicated malaria require hospitalization, often in an intensive care unit (ICU), and parenteral antimalarials. This third category is the focus of this chapter.

Although the spectrum of possible "tropical" infections (i.e., infections that are prevalent in tropical and subtropical regions, especially those that are resource-poor) in a patient with exposures in tropical areas may initially seem daunting, a detailed history of the travel itinerary, activities, and exposures can often significantly narrow the differential diagnosis (Table 123.1). This must include more than simply recording the countries to which the patient traveled; exposures of a traveler staying at upscale hotels and dining in fine restaurants may differ drastically from those of someone backpacking through rural areas of the same country. General knowledge of the diseases endemic to a given area and their incubation periods and drug resistance patterns is vital (Fig. 123.1 and Table 123.2). In addition, most routine "nontropical" infections common in industrialized countries are also common in low-resource settings, and thus must be considered in the differential diagnosis.

Of all tropical diseases potentially manifesting as acute, life-threatening illness, malaria is the most prevalent globally and should be considered in any patient reporting travel in malaria-endemic areas or with exposure to unscreened blood products ("transfusion malaria") or blood-contaminated needles. Increased travel and migration over the past several decades have resulted in increases in imported malaria in most industrialized countries.[18–23]

Patients at risk of malaria can be divided into three groups: (1) nonimmune persons, either because they have no history of exposure to malaria—primarily nonexpatriate travelers—or because immunity has waned, such as in young children, regardless of geographic origin, after the waning of maternal antibodies (around age 6 months). Pregnant women, who are transiently relatively immune-suppressed, are also included in this category. (2) Immune or semi-immune persons residing in malarious areas who are repeatedly exposed. (3) Those originally from malaria-endemic countries but now residing elsewhere who, in the absence of continued exposure, have waning immunity. The degree of immunity may exert profound effects on the clinical presentation and severity of illness. For example, a returning traveler may develop severe malaria at a relatively low parasitemia, whereas a resident of an endemic area in sub-Saharan Africa who has had repeated infection may have the same degree of parasitemia but be asymptomatic. Various human genetic traits relate to mutations in red blood cells (RBCs) and confer resistance to malaria, such as reduced susceptibility to *Plasmodium vivax* in populations across Africa because of genetic absence of the Duffy antigen, which serves as a key *P. vivax* receptor, or the relative protection from severe malaria of any species afforded to those carrying the sickle cell trait or with thalassemia.[24–29] Parasite strain differences may also play a role in the ultimate course of any given malaria infection.

In returning travelers, knowledge of pretravel vaccinations and both prescribed and taken chemoprophylaxis (which often turn out not to be the same) is imperative. Both physicians and patients frequently err in the prescribing of and adherence to appropriate prophylactic regimens.[30,31] Furthermore, these preventive measures do not confer 100% protection and should not be used to discard a given entity from the differential diagnosis. There is also increasing evidence that failure of prophylaxis may occur because of malabsorption of oral medications rather than resistance.[32] Chemotherapy, complete or partial, may prolong the incubation period or alter the presentation of the illness. Those initially from tropical countries are often less likely to seek pretravel medical advice before making a visit home and also often have considerably more exposures to tropical pathogens during their visit than do short-term travelers from industrialized countries.[33–35]

People living in resource-constrained tropical countries may be more likely to have complicating health problems but less likely to have them previously diagnosed or controlled. Underlying diabetes, hypertension, malnutrition, chronic anemia, intestinal parasites, tuberculosis, human immunodeficiency virus (HIV), or hepatitis virus infection may be discovered at the time of the acute illness.[36,37] Infection with multiple tropical pathogens is common in those living in endemic areas. Thus the finding of a given pathogen cannot automatically be assumed to be causally related to the patient's current illness.

EPIDEMIOLOGY

Malaria parasites are spread to humans by the bite of anopheline mosquitoes. Five species of *Plasmodia* commonly cause malaria in humans: *Plasmodium falciparum*, *P. vivax*, *P. ovale*, *P. malariae,* and *P. knowlesi* (see Table 123.2).[38–41] Furthermore, recent evidence suggests that there may be distinct species of *P. ovale. vivax.* Simultaneous infections with multiple strains of *P. falciparum* are common in some areas of sub-Saharan Africa and also occur with *P. vivax* in Southeast Asia and Latin America.[42–44]

The most prevalent and dangerous form of malaria is that due to *P. falciparum*. The risk of acquiring *P. falciparum* is highest in sub-Saharan

TABLE 123.1 Selected Tropical Diseases That May Merit Management in an Intensive Care Unit*

Disease and Organism	Distinguishing Clinical Features	Incubation Period	Geographic Distribution	Mode of Transmission and Typical Risk Factors
Nonspecific Febrile Syndromes				
African trypanosomiasis, hemolymphatic stage (*Trypanosoma brucei gambiense* and *T. b. rhodesiense*)	Lymphadenopathy, HSM, edema, rash, 30% have history of chancre, rarely DIC and thrombocytopenia	3–21 days	Sub-Saharan Africa	Tsetse fly bite; camping, safari
Babesiosis (*Babesia* spp.)	Hemolytic anemia, HSM	3–28 days	North America, Europe, sporadic cases worldwide	Tick bite, blood transfusion (rare); especially severe in asplenic persons
Brucellosis (*Brucella* spp.)	Subacute presentation over weeks/months, HSM, weight loss, may involve large bones, joints, spine	2–8 weeks	Worldwide, especially Mediterranean, Middle East, and Latin America	Ingestion of contaminated dairy products; respiratory, skin, or conjunctival inoculation from contact with farm animals; abattoir workers, butchers, farmers
Candidiasis, disseminated (*Candida* spp.)	May involved any organ; skin or mucosal lesions not always present	1–4 weeks	Worldwide	Usually in IH or after administration of long-term antibiotics or maintenance of indwelling catheters
Cat scratch disease *(Bartonella henselae)*	Papule or eschar at site of inoculation, regional lymphadenopathy, fever may be mild, may progress to CNS involvement or endocarditis	1–2 weeks	Worldwide	Cat scratch or bite, severe disease most often seen in IH
Coccidioidomycosis *(Coccidioides immitis)*	May see pneumonia with cavities, meningeal, skin, and bone involvement, eosinophilia	1–4 weeks, often RD† in IH	Desert areas of the Americas	Inhalation of spores from soil; disseminated disease more common in black persons and those of Filipino or Hispanic descent, IH, and in pregnancy
Echinococcal cyst, leak, or rupture *(Echinococcus granulosus)*	Allergic symptoms: urticaria, pruritus, anaphylaxis	Years	Worldwide	Ingestion of eggs in feces of infected carnivores such as dogs and wolves; raising of domestic livestock
Ehrlichiosis (*Ehrlichia* spp.)	Rash (<50%), leukopenia, thrombocytopenia, HSM; may progress to GI, renal, pulmonary, or CNS involvement	7–21 days	Sporadic foci worldwide	Tick bite; camping, safari
Histoplasmosis, disseminated *(Histoplasma capsulatum)*	Mucocutaneous lesions, lymphadenopathy, HSM, DIC; any organ may be involved	1–4 weeks, usually RD	Tropics worldwide	Inhalation of spores from soil; severe disease usually IH
Leptospirosis (*Leptospira* spp.)	Icterus, jaundice, conjunctival suffusion, rash, HSM; may be biphasic; may develop hepatorenal syndrome ("Weil disease"), CNS involvement, or pulmonary disease with hemorrhage	2–20 days	Worldwide	Contaminated urine of many types of small mammals, either directly or through soil or standing water; hunting, military exercises
Malaria (*Plasmodium falciparum, P. vivax, P. ovale, P. malariae*, and *P. knowlesi*)	See text	Table 123.2	See Fig. 123.1 and Table 123.2	Mosquito bite, transfusion
Measles	Conjunctivitis, coryza, cough, rash, Koplik spots	5–14 days	Worldwide	Person-to-person via aerosol
Melioidosis *(Burkholderia pseudomallei)*	May develop pneumonia or local suppurative infection, shock (especially if IH)	2–21 days	Southeast Asia (especially Thailand), Australia, sporadic foci in tropics worldwide	Exposure to contaminated soil or infected animals, person-to-person (rare), often IH
Monkeypox (monkeypox virus)	Diffuse vesicular rash resembling chickenpox but involving palms and soles, lymphadenopathy	3–21 days	Central and West Africa	Person-to-person and from exposure to infected small mammals and monkeys; exotic pets; rule out smallpox/bioterrorism

Continued

TABLE 123.1 Selected Tropical Diseases That May Merit Management in an Intensive Care Unit—cont'd

Disease and Organism	Distinguishing Clinical Features	Incubation Period	Geographic Distribution	Mode of Transmission and Typical Risk Factors
Mycobacterium avium-intracellulare, disseminated	Usually subacute, HSM, weight loss	Months to years	Worldwide	Environmental organism causing opportunistic infection in IH
Oroya fever *(Bartonella bacilliformis)*	Acute anemia, jaundice, HSM, lymphadenopathy	2–3 weeks	Peru, Ecuador, and Colombia	Sandfly bite; hiking, camping
Paracoccidioidomycosis *(Paracoccidioides brasiliensis)*	May involve lungs, bones, skin, lymph nodes, adrenal glands, or mucous membranes	1–4 weeks, often RD	Tropical America	Inhalation of spores from soil; more severe in IH
Talaromycosis *(Talaromyces marneffei)*	Mucocutaneous lesions, HSM, lymphadenopathy, may have skeletal or pulmonary involvement	Unknown, probably >1 week	Southeast Asia	Reservoir unknown, most often IH
Plague *(Yersinia pestis)*	Localized tender lymphadenitis ("bubo"), pneumonia, shock	2–8 days	Worldwide	Flea bite or person-to-person; areas of heavy rat infestations, R/O bioterrorism
Q fever (*Coxiella burnetii*)	HSM; may develop pneumonia, endocarditis, hepatitis, osteomyelitis, or neurologic abnormalities	2–29 days	Worldwide	Inhalation of organism from products of infected livestock or pets, especially birth products but also milk, urine, and feces; farmers, ranchers
Rat bite fever (*Spirillum minor* or *Streptobacillus moniliformis*)	Peripheral rash, sometimes with desquamation, polyarthritis in *S. moniliformis*, eschar or ulcer at site of bite in *S. minor*	2–28 days	Worldwide, especially Asia and North America	Bite of rat or other animal that preys on rats; ingestion of food contaminated by rat
Relapsing fever (*Borrelia* spp.)	Recrudescent fever pattern, HSM, petechiae, epistaxis, neurologic abnormalities	4–18 days	Worldwide (especially East Africa)	Body louse (*B. recurrentis*) or tick bite (various *Borrelia* species); conditions of poor hygiene, outdoor exposures, refugee camps, camping, safari
Rickettsiosis, spotted fever group (*Rickettsia rickettsii, R. conorii, R. africae, R. australis, R. sibirica, R. japonica, R. honei, and R. akari*)	Peripheral skin rash, eschar at site of tick bite may be seen ("tache noire"), may progress to GI, renal, pulmonary, or CNS involvement	7–14 days	Worldwide (with circumscribed distributions of each specific organism)	Tick bite (mite for *R. akari*); camping, safari
Rickettsiosis, typhus group (*Rickettsia prowazekii, R. typhi, and R. felis*)	Centripetal rash (~50%), no eschar	7–14 days	Worldwide, especially cold climates	Feces from infected louse (*R. prowazekii*) or flea (*R. typhi* and *R. felis*) rubbed into broken skin; crowding, poor hygiene, abundant rodents, refugee camps, flea-infested cats
Scarlet fever (group A *Streptococcus pyogenes*)	Pharyngitis, "sandpaper" rash, cervical adenopathy	1–4 days	Worldwide	Person-to-person via aerosolization/droplets
Schistosomiasis, Katayama fever (*Schistosoma* spp., especially *S. japonicum*)	Lymphadenopathy, HSM, eosinophilia	1–2 months	Africa, Asia, Caribbean, Middle East, South America, Caribbean	Skin penetration of cercaria; swimming or bathing in contaminated water
Scrub typhus *(Orientia tsutsugamushi)*	Centripetal rash, conjunctival suffusion, lymphadenopathy, eschar at site of chigger bite (~50%), hearing loss in one-third of cases	6–18 days	Asia, Australia, Pacific Islands	Chigger bite; outdoor rural or suburban exposures
Strongyloidiasis, disseminated *(Strongyloides stercoralis)*	Abdominal pain and distension, shock, pulmonary and CNS involvement common	2–3 weeks; may be maintained via autoinfection for decades	Tropics worldwide	Skin contact with contaminated soil; miliary exercises; dissemination may occur in IH (AIDS, steroid treatment)
Toxic shock syndrome (*Staphylococcus aureus*, group A *S. pyogenes*)	Rash, extremity or abdominal pain, skin desquamation, soft tissue infection (70%)	2–10 days	Worldwide	Wound or vaginal colonization with toxin-producing bacteria; history of minor trauma (often without break in skin), previous surgery, or varicella infection; staphylococcal syndrome often associated with menses

TABLE 123.1 Selected Tropical Diseases That May Merit Management in an Intensive Care Unit—cont'd

Disease and Organism	Distinguishing Clinical Features	Incubation Period	Geographic Distribution	Mode of Transmission and Typical Risk Factors
Trench fever *(Bartonella quintana)*	Rash, HSM, shin pain, may develop endocarditis and angioma-like lesions	1–2 weeks	Worldwide	Body louse bite; areas of crowding or poor sanitation, more severe in IH
Trichinellosis (*Trichinella* spp.)	Diarrhea followed by myalgias, periorbital edema, eosinophilia, may involve heart or CNS	7–30 days	Worldwide	Ingestion of contaminated meat, including pork (*T. spiralis*), wild boar, horse, bear, and walrus
Tularemia, typhoidal form *(Francisella tularensis)*	Pulse-temperature dissociation, diarrhea (~40%); may develop pneumonia	1–21 days	Sporadic foci worldwide, mostly Northern Hemisphere	Tick or fly bite or direct exposure to small mammals; hunting, camping, military exercises; R/O bioterrorism
Typhoid/paratyphoid fever (*Salmonella enterica* serotypes typhi or paratyphi)	Pulse-temperature dissociation, abdominal pain, rash, intestinal perforation and bleeding, HSM, 10% with extraintestinal manifestations	8–28 days	Worldwide	Fecal-oral
Vibrio infection, nonepidemic type (*Vibrio vulnificus*)	Bullous skin lesions, DIC, thrombocytopenia, GI bleeding, shock	1–2 days	Worldwide	Contaminated saltwater or seafood; severe disease mostly in IH, history of alcoholism, liver disease
Viral hemorrhagic fever (dengue, yellow fever, Ebola, Marburg, Lassa, Junin, Machupo, and Rift Valley fever viruses, many others)	Capillary leak syndrome; may or may not exhibit frank hemorrhage, GI hemorrhage, shock	3–21 days, depending on specific virus	Select areas worldwide	Depending on specific virus: exposure to rodent excreta, infected nonhuman primates, person-to-person, tick or mosquito bite, some unknown; R/O bioterrorism
Viral hepatitis (hepatitis A, B, C, D, and E; Epstein-Barr virus; cytomegalovirus; others)	HSM, light-colored stools, dark urine, jaundice	2 weeks to 5 months, depending on specific organism	Worldwide	Fecal-oral or ingestion of seafood from contaminated sea beds (hepatitis A, E); percutaneous (blood exposure), sexual, or mother-to-child transmission (hepatitis B, C, D); hepatitis D requires coinfection with hepatitis B virus
Visceral leishmaniasis (*Leishmania* spp.)	Weight loss, HSM, neutropenia	Months to years	Tropics worldwide, especially Indian subcontinent, Middle East, and North Africa	Sandfly bite; military exercises, outdoor exposures
Gastrointestinal Syndromes				
Amebic dysentery (Entamoeba histolytica)	Abdominal pain and diarrhea, sometimes bloody, minority may develop ameboma, toxic megacolon, peritonitis, or abscesses in solid organs (usually liver)	2–4 weeks (usually longer for solid organ involvement)	Worldwide	Fecal-oral; may be transmitted through anal sex
Anthrax, gastrointestinal or oropharyngeal *(Bacillus anthracis)*	Abdominal pain and bloody diarrhea, neck swelling, pharyngitis, mucosal lesions, shock	2–10 days	Worldwide	Ingestion of spores; exposure to domestic animals or animal by-products; R/O bioterrorism
Ascending cholangitis (*Clonorchis sinensis* and *Opisthorchis* spp.)	May be recurrent and accompanied by pancreatitis	Months to years	Asia, former USSR	Ingestion of raw infected freshwater fish; sushi consumption
Bacterial dysentery (*Shigella* spp., *Campylobacter* spp., invasive and hemorrhagic *Escherichia coli,* non-typhi *Salmonella* spp., *Vibrio parahaemolyticus,* others)	Abdominal pain and diarrhea, sometimes bloody	10 hours to 7 days, depending on specific organism	Worldwide	Fecal-oral
Cholera (*Vibrio cholerae*)	Copious "rice water" diarrhea, abdominal pain, severe hypovolemia, fever minimal or absent	1–3 days	Tropics worldwide	Contaminated water or food, especially seafood; ceviche consumption

Continued

TABLE 123.1 Selected Tropical Diseases That May Merit Management in an Intensive Care Unit—cont'd

Disease and Organism	Distinguishing Clinical Features	Incubation Period	Geographic Distribution	Mode of Transmission and Typical Risk Factors
Clostridial gastroenteritis *(Clostridium difficile)*	Abdominal pain and diarrhea, sometimes with mucus or blood, toxic megacolon	≈ 1 week to months	Worldwide	Alteration of GI flora through previous antibiotic administration and/or GI manipulation
Eosinophilic gastroenteritis *(Angiostrongylus costaricensis)*	Mimics appendicitis or inflamed Meckel diverticulum, right lower quadrant abdominal pain and mass, eosinophilia	Estimated 3–4 weeks	Latin America	Ingestion of larvae in undercooked mollusks, crustaceans, or frogs
Hemolytic uremic syndrome (*Escherichia coli* O157:H7)	Bloody diarrhea followed by hemolysis and renal failure	2–5 days	Worldwide	Ingestion of poorly cooked meat, fecal-oral
Neurologic Syndromes				
African trypanosomiasis, meningoencephalitic stage (*Trypanosoma brucei gambiense* and *T. b. rhodesiense*)	Headache, HSM, cervical lymphadenopathy, somnolence, change in mental status, extrapyramidal and cerebellar signs	Months to years	Sub-Saharan Africa	Tsetse fly bite; camping, safari
Antiretroviral syndrome (human immunodeficiency virus-1)	Usually asymptomatic or mild flu-like illness, meningoencephalitis occurs rarely	2–4 weeks	Worldwide	Sexual transmission or percutaneous blood exposure; unprotected sex, IV drug use
Arboviral encephalitides (eastern equine, Japanese encephalitis, West Nile, Murray Valley encephalitis, St. Louis encephalitis, and Venezuelan equine encephalitis viruses, many others)	Encephalitis, focal neurologic deficits, seizures, change in mental status	3–21 days	Sporadic foci worldwide	Mosquito bite, seasonal
Bacterial meningitis (*Neisseria meningitides, Streptococcus pneumoniae, Haemophilus influenza* type B, *Listeria monocytogenes*, others)	Petechiae, ecchymoses, and bleeding suggest *N. meningitides*	2–10 days, depending on specific organism	Worldwide; *N. meningitides* more frequent in African "meningitis belt"	Person-to-person, asymptomatic carrier states, seasonal fluctuations
Botulism (*Clostridium botulinum*)	Bilateral cranial nerve deficits with symmetric descending weakness, fever absent	1–3 days	Worldwide	Toxin ingestion or wound contamination; home-canned foods, soil contamination
Brain abscess (various bacteria, fungi, and parasites)	Focal neurologic signs	Days to months, depending on specific organism	Worldwide	Varies with infecting organism
Cryptococcosis *(Cryptococcus neoformans)*	Mild meningitis with low-grade fever, nonfocal neurologic examination, sometimes seizures or pulmonary involvement	1–4 weeks	Worldwide	Inhalation of spores from soil and bird and bat excreta; usually IH
Eosinophilic meningitis *(Angiostrongylus cantonensis)*	Headache, meningitis, sometimes cranial nerve involvement, fever minimal	1–7 days	Southeast Asia, South Pacific, sporadic foci worldwide	Ingestion of larvae in undercooked mollusks, crustaceans, or frogs
Gnathostomiasis (*Gnathostoma* spp.)	Migratory skin and subcutaneous swellings, epigastric pain and vomiting, eosinophilia, may invade any organ, especially CNS	Weeks to years	Southeast Asia, with sporadic cases from Central and South America	Consumption of raw freshwater fish, frogs, snakes, crustaceans, or poultry; sushi consumption
Herpes encephalitis (various herpesviruses)	Encephalitis, focal neurologic deficits, seizures, change in mental status, may show vesicular eruption	2–20 days, depending on specific virus	Worldwide; herpes B virus via monkey exposure in Asia and North Africa (wild monkeys) or captive monkeys worldwide	Person-to-person, often more severe in IH; herpes B virus via bite or other exposure to monkeys of the genus *Macaca*; person-to-person transmission reported; researchers, animal handlers

TABLE 123.1 Selected Tropical Diseases That May Merit Management in an Intensive Care Unit—cont'd

Disease and Organism	Distinguishing Clinical Features	Incubation Period	Geographic Distribution	Mode of Transmission and Typical Risk Factors
Mucormycosis (various fungi from the order Mucorales)	CNS infiltration with loss of consciousness, black exudate around mucous membranes of face, pulmonary infiltrates	1–7 days	Worldwide	Inhalation of spores from soil, traumatic inoculation of wound; usually IH (diabetes mellitus or steroid use)
Neurocysticercosis *(Taenia solium)*	Seizures, headache, change in mental status, muscle pain	Years	Worldwide, especially Latin America and India	Ingestion of cysticerci in contaminated pork; areas where pigs roam freely
Paragonimiasis, cerebral (*Paragonimus* spp.)	Meningoencephalitis, often accompanied by pulmonary disease	Years	Sporadic foci worldwide, especially East Asia, Peru, Ecuador, West Africa	Ingestion of raw infected crustaceans; sushi consumption
Poliomyelitis (poliovirus)	Acute flaccid paralysis, meningeal signs, muscle pain	9–12 days	Sporadic foci in Africa, Asia, and eastern Mediterranean	Fecal-oral
Primary amebic meningoencephalitis *(Naegleria fowleri)*	Fulminant meningoencephalitis	3–7 days	Sporadic foci worldwide	Entry of trophozoite through the nose; swimming in contaminated fresh warm water; hot springs
Rabies (rabies virus)	Change in mental status, autonomic instability, photophobia, aerophobia, paralysis	20–90 days	Worldwide	Animal bite or bat exposure; spelunking, caring for injured animals
Schistosomiasis, CNS (*Schistosoma* spp.)	Encephalopathy, meningoencephalitis, transverse myelitis, seizures	Weeks to months	Africa, Asia, Caribbean, Middle East, South America, Caribbean	Skin penetration of cercaria; swimming or bathing in contaminated water
Tetanus (*Clostridium tetani*)	Diffuse muscle spasms, opisthotonos, trismus, autonomic dysfunction	3–21 days	Worldwide	Soil contamination of wound, commonly involves umbilical stump in neonates
Tickborne encephalitis (tickborne encephalitis virus)	Encephalitis, focal neurologic deficits, seizures	7–14 days	Central and East Asia, Europe, North Africa, North America	Tick bite
Toxoplasmosis, cerebral *(Toxoplasma gondii)*	Meningoencephalitis, HSM, focal neurologic deficits, seizures, change in mental status	Usually RD	Worldwide	Ingestion of cysts in undercooked meat or oocysts from exposure to cat feces; usually IH
Variant Creutzfeldt-Jacob disease (prion)	Change in mental status, myoclonus, spasticity, rigidity, extrapyramidal and cerebellar signs and symptoms, occasionally seizures	Months to years	United Kingdom, with sporadic cases elsewhere in Europe, Canada, and United States	Recipients of cadaveric transplants or injections of biomedical products derived from infected patients, contaminated surgical apparatuses, person-to-person(?), ingestion of contaminated beef or lamb(?)
Visceral larva migrans *(Toxocara canis)*	Cough, wheezing, HSM, eosinophilia; may develop CNS or other solid organ involvement	Weeks to years	Worldwide	Ingestion of eggs in puppy feces
Pulmonary Syndromes				
Anthrax, inhalation *(Bacillus anthracis)*	Pulmonary infiltrates with widened mediastinum, shock, CNS involvement	2–60 days	Worldwide	Inhalation of spores, exposure to domestic animals or animal by-products; R/O bioterrorism
Aspergillosis (*Aspergillus* spp.)	Pulmonary "fungus ball," (aspergilloma), transient infiltrates and allergic symptoms in allergic bronchopulmonary aspergillosis	1–4 weeks	Worldwide	Inhalation of spores from soil
Bacterial pneumonia (*Streptococcus pneumoniae, Legionella pneumophila, Mycoplasma pneumoniae, Haemophilus influenza, Chlamydophila* spp., others)	Extrapulmonary findings frequent in Legionnaires' disease and psittacosis	2–21 days, depending on specific organism	Worldwide	Person-to-person spread; Legionnaires' disease associated with colonized air/water systems; psittacosis associated with bird exposure
Blastomycosis *(Blastomyces dermatitidis)*	Subacute pneumonia; bone, skin, and GU tract involvement	1–4 weeks, usually RD	Sporadic foci worldwide	Inhalation of spores from soil

Continued

TABLE 123.1 Selected Tropical Diseases That May Merit Management in an Intensive Care Unit—cont'd

Disease and Organism	Distinguishing Clinical Features	Incubation Period	Geographic Distribution	Mode of Transmission and Typical Risk Factors
Diphtheria *(Corynebacterium diphtheriae)*	Low-grade fever, cough, pharyngitis, oropharyngeal membrane, neck swelling, mucosal bleeding, myocarditis, polyneuritis	3–7 days	Worldwide, especially temperate areas	Person-to-person through respiratory route and breaks in the skin
Eosinophilic pneumonia (various parasites, helminthes and filaria)	Eosinophilia, asthma-like condition, elevated IgE	Days to weeks, depending on specific organism	Worldwide, depending on specific organism	Lung passage of larvae or adult helminthes, mosquito bite (filaria), filarial disease occurs primarily in those living in endemic areas with continued exposure
Hantavirus pulmonary syndrome (various hantaviruses)	ARDS, thrombocytopenia, leukocytosis, hemoconcentration, circulating immunoblasts	1–5 weeks	Americas	Contaminated rodent urine or feces; outdoor exposures
Pertussis *(Bordetella pertussis)*	Low-grade fever, coryza, rhinorrhea, paroxysmal dry cough	5–21 days	Worldwide	Person-to-person; adults vaccinated as children are susceptible to milder disease
Pneumocystosis *(Pneumocystis jiroveci)*	Dyspnea, dry cough, hypoxemia, often only mild findings on pulmonary auscultation and CXR	Usually RD	Worldwide	Inhalation; usually IH
Tuberculosis *(Mycobacterium tuberculosis)*	Upper lobes infiltrates and cavities; miliary TB, meningitis, and GU involvement all also common	Usually RD	Worldwide	Person-to-person via aerosol/droplet; increased frequency and likelihood of extrapulmonary involvement in IH
Tularemia, pneumonic form *(Francisella tularensis)*	Pulse-temperature dissociation, diarrhea (~40%)	1–21 days	Sporadic foci worldwide, mostly Northern Hemisphere	Tick or fly bite, or direct exposure to small mammals; hunting, camping, military exercises, R/O bioterrorism
Viral pneumonia (influenza, parainfluenza, respiratory syncytial, and SARS coronavirus, many others)	May be complicated by bacterial suprainfection	Days to weeks, depending on specific organism	Worldwide, depending on specific organism	Person-to-person spread and zoonotic, depending on specific virus; contact with farms or live animal markets, birds, or pigs (zoonotic influenzas); civet cats suspected to be a reservoir of SARS coronavirus
Localized Infections				
Mycetoma (various fungi and bacteria)	Chronic swollen limb with nodules, sinus tracts, drainage of pus and "grains"	Weeks to months	Tropics worldwide	Traumatic implantation of organism into skin; soil exposure
Necrotizing fasciitis (group A strep *S. pyogenes, Clostridia* spp., *S. aureus*)	Rapid progression of edema, erythema, tenderness, bullae, necrosis, and gangrene	~24 hours	Worldwide	Posttraumatic or surgical

ARDS, Acute respiratory distress syndrome; *CNS,* central nervous system; *CXR,* chest x-ray; *DIC,* disseminated intravascular coagulopathy; *GI,* gastrointestinal; *GU,* genitourinary; *HSM,* hepatosplenomegaly; *IH,* immunocompromised host; *IV,* intravenous; *RD,* reactivation disease; *R/O,* rule out; *TB,* tuberculosis.

*Only diseases that typically have acute or subacute presentations and may cause severe disease are included. Diseases are classified by the most typical associated severe syndrome. In practice, significant variation may exist.

†Initial infection is usually asymptomatic or mild. Reactivation with severe disease may occur years later, usually in immunocompromised hosts.

Africa, in particular West Africa,[45] and in New Guinea; moderate in India; and comparatively low in Southeast Asia and Latin America.[46–48] There is increasing recognition that *P. vivax,* the second most common cause of malaria and previously considered to be benign, can also cause severe disease and death.[49,50] *P. vivax* malaria is especially frequent in travelers returning from Oceania, although the parasite exists in all malaria-endemic regions except Haiti and the Dominican Republic.[51,52] The dormant liver stage parasites (hypnozoites) that characterize *P. vivax* sometimes result in primary disease or relapse even years after infection. *P. knowlesi* is found in rainforests of Southeast Asia, including parts of Cambodia, China, Indonesia, Laos, Malaysia, Myanmar, the Philippines, Singapore, Thailand, and Viet Nam.[53,54] *P. knowlesi* is now the most common cause of malaria in Malaysia and parts of Indonesia. Although quite rare, deaths resulting from *P. ovale* or *P. malariae* infection have been reported.[55,56]

Although rare, malaria has been reported in persons without documented travel, usually resulting from the carriage of malaria-infected passengers (who may be asymptomatic) or anopheline mosquitoes on aircraft arriving from endemic areas.[57–59] The parasite may then be

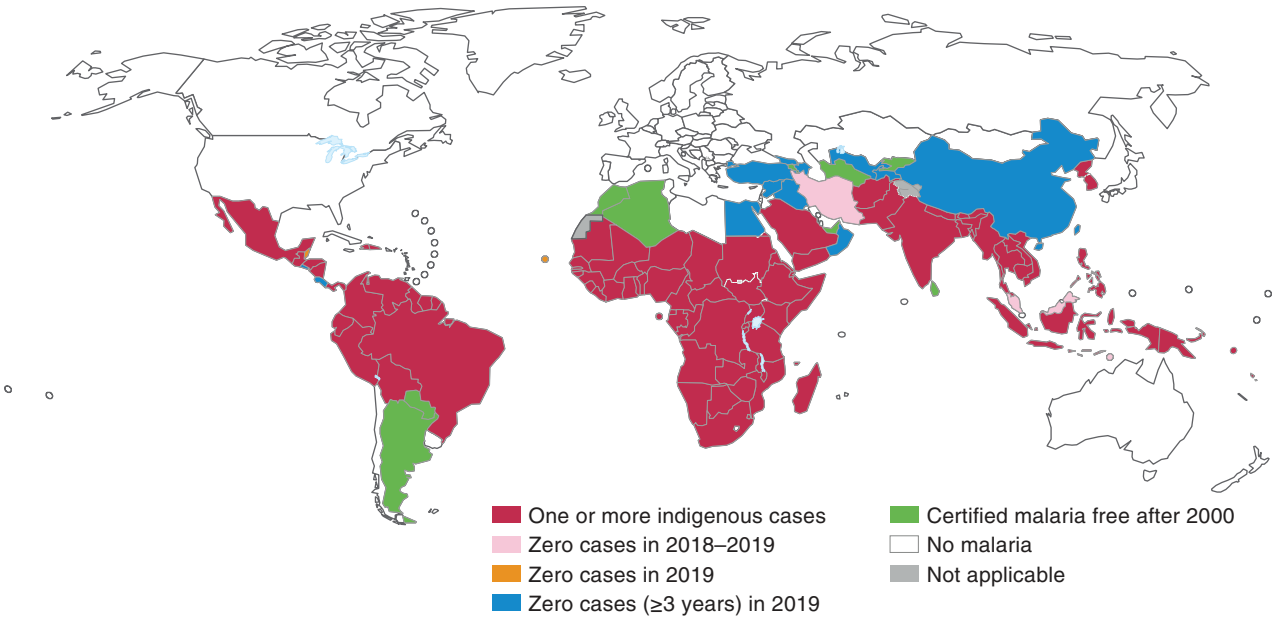

Fig. 123.1 Population at risk in malaria-endemic countries in the Western and Eastern Hemispheres. The risk of malaria may vary within specific regions of each country. (From the World Health Organization [2020]. Available at https://www.who.int/teams/global-malaria-programme.)

TABLE 123.2 Features of the Five Species of Malaria Known to Cause Disease in Humans

	Plasmodium falciparum	Plasmodium vivax	Plasmodium ovale	Plasmodium malariae	Plasmodium knowlesi
Incubation period (days)	6–25	8–27	8–27	16–40	12–13
Asexual cycle (hours)	48 (tertian)	48 (tertian)	48 (tertian)	72 (quartan)	24 (tertian)
Relapse	No	Yes*	Yes*	No†	No
Chloroquine resistance	Yes‡	Rare§	No	No¶	No
Characteristic on thin blood film	Rings predominate, multiply infected RBCs, high parasitemia, rings with threadlike cytoplasm, double nuclei, banana-shaped gametocytes	Enlarged RBCs, Schüffner dots, trophozoite cytoplasm ameboid, 12–24 merozoites in mature schizont	Oval RBCs with fringed edges, Schüffner dots, trophozoites cytoplasm compact, 6–16 merozoites in mature schizont	Trophozoite cytoplasm compact (band forms), 6–12 merozoites in mature schizont, RBC unchanged	Similar to *P. malariae*, 8–10 merozoites in mature schizont, often in rosette pattern with central clump of pigment

*Relapses may appear months to years after initial infection because of dormant hypnozoites in the liver.
†Although relapse does not occur, *P. malariae* can produce persistent infections that remain below detectable limits in the blood for 20–30 years or more.
‡*P. falciparum* resistance to sulfadoxine/pyrimethamine, mefloquine, halofantrine, and artemisinin has also been reported in some areas, along with partial resistance to quinine and quinidine.[1–3]
§*P. vivax* resistance to chloroquine now reported in some areas of Southeast Asia, Oceania (Ethiopia, Madagascar), and South America.[4–16]
¶Chloroquine-resistant *P. malariae* has also been reported in south Sumatra, Indonesia.[17]

secondarily transmitted by anopheline mosquitoes endemic in some industrialized countries, including the United States, Canada, and Southern Europe.

PATHOPHYSIOLOGY

P. falciparum accounts for the vast majority of severe malaria because of (1) its ability to infect RBCs of all ages, resulting in overwhelming parasitemia (up to 70% of RBCs); (2) its induction of adherence of parasitized RBCs to the microvascular wall, with consequent obstruction; (3) its induction of severe metabolic derangements, both directly through glucose consumption and lactate production and indirectly through the induction of cytokines; and (4) the high prevalence of chloroquine and multidrug resistance to *P. falciparum* in many parts of the world (see Table 123.2). Unlike the other species of malaria, *P. falciparum* causes decreased RBC deformability and the production of small protrusions, or "knobs," on parasitized RBC membranes that mediate their adhesion to the venular endothelium (Fig. 123.2). These knobs are high-molecular-weight (>200 kD), strain-specific molecules displayed on the surface of infected RBCs. The best described of these is *P. falciparum* erythrocyte membrane protein 1 that plays a critical role in malaria pathogenesis, including in evasion of the host immune system.[60,61]

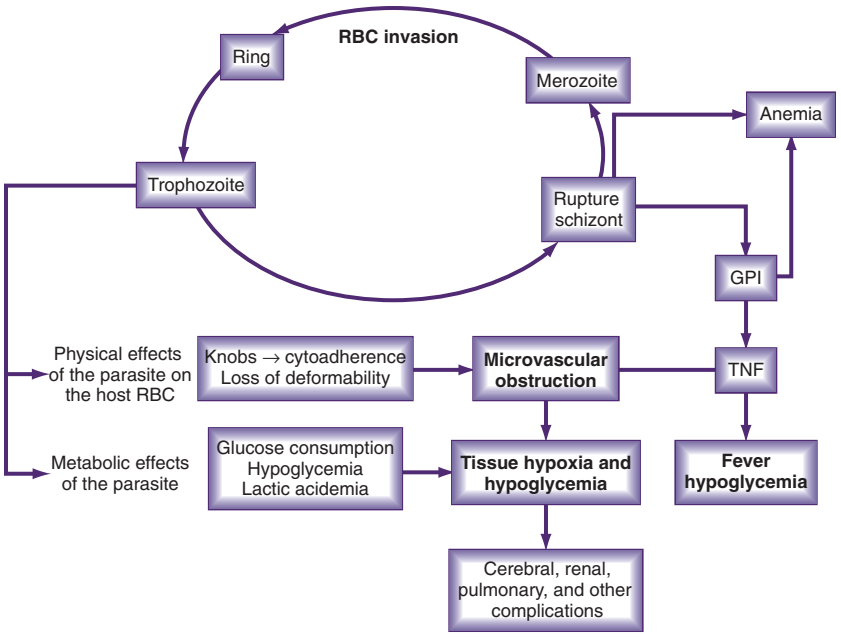

Fig. 123.2 Pathogenesis of severe and complicated *Plasmodium falciparum* malaria. *GPI,* Glycosylphosphatidylinositol; *RBC,* red blood cell; *TNF,* tumor necrosis factor. (Modified from Krogstad D. Plasmodium species (malaria). In Mandell GL, Bennett JE, Dolin R, eds. *Principles and Practice of Infectious Diseases,* 5th ed. Philadelphia, PA: Churchill Livingstone; 2000.)

The rupture of schizont-stage parasites exposes glycosylphosphatidylinositol anchors on the parasite and RBC surface that induce macrophages and other inflammatory cells to release a host of inflammatory mediators, including tumor necrosis factors, interleukin-1, and various kinins and reactive nitrogen intermediates.[62–65] These cytokines play a role in up-regulation and activation of endothelial adhesion molecules such as ICAM-1 and E-selectin, enhancing cytoadherence of parasitized cells and mediating pathologic processes such as hypoglycemia, lactic acidemia, shock, gut mucosal damage, and increased permeability and neutrophil aggregation in the lung.

The sum total of this cascade is sequestration of parasitized RBCs in the microvasculature, where they are not only sheltered from removal but cause sluggish flow and obstruction, resulting in impaired oxygen delivery and organ dysfunction.[62,65–67] The most profound effects are usually on the cerebral capillaries, although a host of tissues may be affected, including the kidney, liver, spleen, placenta, intestine, lung, bone marrow, heart, and retina. Histopathologic changes are usually minimal, but ring hemorrhages and perivascular infiltrates sometimes develop at the sites of obstructed vessels, perhaps facilitated by thrombocytopenia because of splenic sequestration of platelets. Although subendocardial and epicardial hemorrhages have been noted at autopsy, myocarditis does not occur, and primary cardiac events are relatively rare in malaria.

In *P. falciparum* infection, acute pulmonary hypertension can be precipitated by nitric oxide consumption by free plasma hemoglobin released from intravascular hemolysis.[68] Endothelial injury leading to increased alveolar permeability and noncardiogenic pulmonary edema also contributes. Autopsy studies have shown increased markers of endothelial activation (vWF and ANG-2) in patients with acute malaria-associated respiratory distress syndrome (MA-ARDS) compared with infected and uninfected controls.[69] Interstitial edema and inflammatory cell infiltrates are seen at autopsy, but sequestration of parasitized RBCs in the lung is not common.[70] There is evidence, however, that *P. falciparum* erythrocyte membrane protein 1 interaction with host endothelial cell receptors (e.g., ICAM-1 and endothelial protein C receptor) plays a role in cytoadherence and pathogenesis of MA-ARDS.[71]

Parasitemia usually reaches a lower level in *P. vivax* infection because of a strong predilection for reticulocytes. Chronic exposure to *P. vivax* parasites may be sufficient to destroy the new reticulocytes and, over time, to reduce the population of mature RBCs, thereby contributing to severe anemia. This, combined with a lack of cytoadhesive properties of the infected cells, results in reduced microvascular obstruction and suggests different pathogenetic mechanisms to severe infection.[72,73] The main pathogenesis of *P. vivax* is the result of higher cytokine production and endothelial activation caused by an increased guanine-cytosine DNA content in its genome and a higher associated content of Toll-like receptor 9-stimulating GpG motifs.[74–76]

The returned traveler exposed to *P. vivax* for a short period will rarely present with a severe or fatal infection unless there is an underlying condition. However, in endemic regions, children with prolonged *P. vivax* infection resulting from frequent exposures and relapsing infections from the liver hypnozoites can present with profound anemia with subsequent high morbidity and mortality, particularly in the presence of malnutrition and other causes of anemia.[77] *P. vivax* anemia is exacerbated by splenic removal of uninfected RBCs, which occurs at a higher proportion compared with *P. falciparum,* although the removal mechanism is not well understood.[50,78,79]

In *P. vivax* infection, a cytokine-mediated inflammatory response in the pulmonary microvessels leads to increased alveolar permeability and fluid buildup. Because of a lower parasitic biomass, the effect of the hemolysis-associated nitric oxide depletion on pulmonary pressures is minimal.[72,76] There is greater inflammatory and endothelial activation per parasite in *P. vivax* compared with *P. falciparum* infections, and this likely contributes to MA-ARDS in the absence of other

risk factors specific to *P. falciparum*.[80] In addition to the acute hemolytic destruction of parasitized RBCs, the more chronic processes of removal of parasitized cells from circulation by the spleen and cytokine inhibition of erythropoiesis may contribute.[81]

CLINICAL PRESENTATION

Malaria classically produces three stages of symptoms that progress over an 8- to 12-hour period, comprising a "paroxysm." These correspond and are attributable to the period of schizont rupture and appearance of ring forms (merozoites) in the blood, accompanied by the release of numerous host inflammatory mediators. The paroxysm classically begins suddenly with a "cold stage" in which the patient experiences rigors and chills, often accompanied by headache, nausea, and vomiting. Intense peripheral vasoconstriction may result in pale, goosepimpled skin and cyanosis of the lips and nail beds. Within a few hours, the "hot stage" ensues, with high fever, flushed skin, throbbing headache, and palpitations. The paroxysm concludes with the "defervescent stage," consisting of a drenching sweat and resolution of the fever. The exhausted patient often then sleeps. Clinical deterioration with *P. falciparum* usually appears 3–7 days after onset of fever.

Although a classic periodicity is described for the different malaria species (see Table 123.2), this occurs only when the infection has persisted untreated long enough to allow for synchronization of schizont rupture. Furthermore, schizont rupture tends to be asynchronous in *P. falciparum* and in most primary infections of any *Plasmodium* species. Therefore malaria may often result in persistently spiking fevers difficult to distinguish from fever produced by many other infections, and the absence of a classic paroxysm and periodicity should not be used to exclude the diagnosis. Paroxysms may be accompanied by cough, sore throat, myalgias, back pain, postural hypotension, abdominal pain, nausea, vomiting, diarrhea, and weakness. These flulike symptoms are more common in children and may lead to misdiagnoses. Rash and lymphadenopathy are not typical of malaria and suggest another diagnosis.

Severe and Complicated Malaria

Although all species of malaria may produce severe consequences in a debilitated patient, potentially fatal malarian which merits attention in an ICUn can be grouped into three categories: (1) severe complications of *P. falciparum* and, less commonly, *P. vivax* and *P. knowlesi* in nonimmune children and adults; (2) splenic rupture, which occurs most frequently with *P. vivax;* and (3) chronic nephrotic syndrome caused by immune-complex nephritis associated with *P. malariae,* usually seen in children and often complicated by overwhelming bacterial infection. The first category is responsible for the vast majority of severe disease worldwide (Box 123.1). There is emerging evidence that *P. knowlesi* can also cause severe fatal malaria and should be treated in an ICU setting.[33]

Cerebral Malaria

Cerebral malaria is the most frequent severe complication of plasmodium infection, accounting for most fatalities and chronic sequelae. It is most frequent in children of 3–5 years of age. Strictly defined, cerebral malaria implies unarousable coma caused by *P. falciparum.* Hyperpyrexia and febrile convulsions in young children may produce transiently altered mental status without true involvement of the cerebral microvasculature and do not constitute cerebral malaria. However, in clinical practice, seizures or persistent changes in sensorium that cannot be attributed to other disease processes should be considered cerebral malaria until proven otherwise. Although cerebral malaria is classically attributed to cytoadhesion and microvascular obstruction in the brain, other ongoing processes, including hypoglycemia, metabolic acidosis, and impaired oxygenation caused by anemia and pulmonary edema, also contribute.

Box 123.1 Clinical and Laboratory Features That Classify a Patient as Suffering From Severe *Plasmodium falciparum* Malaria* According to the World Health Organization

Clinical Features

Impaired consciousness (including unarousable coma); Glasgow Coma Score <11 in adults or a Blantyre coma score <3 in children
Prostration: generalized weakness so that the patient is unable walk or sit up without assistance
Multiple convulsions (more than two episodes in 24 hours
Pulmonary edema: radiologic evidence or oxygen saturation <92% on room air with a respiratory rate >30/min
Respiratory distress (severe acidosis): rapid, deep, labored breathing
Circulatory collapse or shock, systolic blood pressure <80 mm Hg in adults and <70 mm Hg in children, with evidence of impaired perfusion (cool peripheries or prolonged capillary refill)
Clinical jaundice plus evidence of other vital organ dysfunction
Abnormal spontaneous and significant bleeding

Laboratory Findings

Hypoglycemia (blood glucose <2.2 mmol/L or <40 mg/dL)
Metabolic acidosis; base deficit of >8 mEq/L, plasma bicarbonate <15 mmol/L, or venous plasma lactate >5 mmol/L.
Severe normocytic anemia (hemoglobin ≤5 g/dL, hematocrit ≤15% in children <12 years of age (<7 g/dL and <20%, respectively, in adults) with a parasite count >10,000/μL;
Jaundice: plasma or serum bilirubin >50 μmol/L (3mg/dL) with a parasite count >100,000/μL
Hyperparasitemia: >10%
Renal impairment: serum creatinine >265 μmol/L (3mg/dL) or blood urea >20 mmol/L)

(From World Health Organization. (2012). Management of severe malaria: a practical handbook, 3rd ed.. World Health Organization. https://apps.who.int/iris/handle/10665/79317

* For severe *P. vivax* malaria, the same criteria are used as for *P. falciparum* malaria but with no parasite density thresholds. Likewise, severe *P. knowlesi* malaria is defined as for falciparum malaria but with two differences: (1) P. *knowlesi* hyperparasitemia: parasite count >100,000/μL and (2) jaundice and parasite count >20,000/μL.

The altered sensorium of cerebral malaria may develop gradually within a few days of onset of illness or manifest as persistent coma after a generalized convulsion. Compared with adults, children with cerebral malaria have a shorter history of fever before progressing to coma (average about 2 days). The most common neurologic picture is of a diffuse symmetric encephalopathy with hypertonia and hyperreflexia. Pupils are usually symmetric with intact pupillary, corneal, oculocephalic, and oculovestibular reflexes. Gag reflex is usually intact. In severe cases, clonus, opisthotonos, disconjugate gaze, nystagmus, sixth nerve palsy extensor Babinski responses, occasional signs of frontal lobe release such as a pout reflex or bruxism, and decorticate or decerebrate posturing can occur.[82,83] Mild neck stiffness may occur, but meningismus, severe neck rigidity, photophobia, and papilledema are almost never seen.[83]

Seizures may occur in up to 50% of cases of cerebral malaria. Among children ages above 3–4 years, seizures are increasingly likely to represent cerebral malaria rather than febrile convulsions.[84] Although generalized seizures are typical, partial motor seizures, with or without secondary generalization, may occur.[85] Electroencephalogram (EEG) studies may sometimes reveal underlying status epilepticus even when it is not clinically evident.[82]

Pulmonary Edema and Malaraia-Associated Acute Respiratory Distress Syndrome

Pulmonary complications occur in up to 30% of patients with severe malaria, especially pregnant women, nonimmune persons, and patients already suffering from other complications.[70] The onset may be any time during the course of illness, even if the patient appears to be improving and parasitemia has decreased. Symptoms include dyspnea and cough, with rapid progression to hypoxia and respiratory distress. Pulmonary edema, which may progress to MA-ARDS, is frequent and typically the most lethal of the complications of malaria globally. MA-ARDS is most commonly associated with *P. falciparum, P. vivax,* and *P. knowlesi*, but has been seen with all malaria species.[84,86] Pulmonary complications are seen in about 5% of hospitalized patients with *P. vivax* infection.[87]

Anemia and Hematologic Perturbations

Although some degree of anemia is common in all types of malaria, severe anemia (hemoglobin less than 5 g/100 mL) occurs mostly with *P. falciparum* and *P. vivax*. In *P. falciparum* infection, it is most common and often severe in pregnant women and young children (<1 year), in whom it may be the presenting sign.[88,89] In addition to the acute hemolytic destruction of parasitized RBCs, the more chronic processes of removal of parasitized cells from circulation by the spleen and cytokine inhibition of erythropoiesis may contribute.[81] Nonimmune subjects may develop anemia within days after infection, but usually more slowly in those who are semi-immune.

In *P. vivax* infection, profound anemia is seen in young children from high-endemic areas and results from several pathogenic processes, including frequent hemolysis because of relapsing infection, increased fragility of infected and uninfected reticulocytes, high splenic removal rate of uninfected RBCs (four times higher than in *P. falciparum*), and recrudescence of chloroquine-resistant parasites.[78]

The degree of anemia generally correlates with bilirubin level and level of parasitemia. It may be exacerbated by underlying glucose-6-phosphate dehydrogenase deficiency in the setting of administration of oxidant antimalarial drugs (e.g., quinine, sulfadoxine) and iron-deficiency anemia resulting from malnutrition or soil-transmitted helminthiases. Delayed hemolytic anemia can also occur in patients treated with parenteral artesunate.[89] Significant jaundice and hemoglobinuria may result. Thrombocytopenia, although frequent, is not usually associated with bleeding or correlated with disease severity. Disseminated intravascular coagulation (DIC) has been reported, but in less than 10% of severe cases.

Acute Kidney Injury

Acute kidney injury (AKI) is seen in about 30% of nonimmune adult patients with cerebral malaria and may result in electrolyte abnormalities such as hyponatremia, hypocalcemia (usually related to albumin loss), hypophosphatemia, and metabolic acidemia, in addition to fluid overload with pulmonary edema. For unclear reasons, AKI is rare in semi-immune persons. It is usually the result of acute tubular necrosis, is oliguric in nature (<400 mL urine/24 hr for adults), and is most often reversible. Renal ischemia caused by hypovolemia, renal vasoconstriction, microvascular obstruction, and pigment nephropathy from hemolysis may all contribute. AKI occurs mainly with *P. falciparum,* but it is also described with *P. vivax* and *P. malariae*. It was previously thought to be uncommon in children, but this idea has been challenged by more recent studies showing almost two-thirds of children to have AKI on presentation or to develop AKI while hospitalized with severe malaria.[90] Classically, AKI has been a sign of poor prognosis,[84,91,92] but this may be the result of underrecognition and limited resources, because smaller studies have shown good renal recovery with limited excess mortality.[93]

Blackwater fever refers to a severe syndrome characterized by low or absent parasitemia, intravascular hemolysis, hemoglobinuria, and AKI. It is classically seen in people of Northern European descent chronically exposed to *P. falciparum* and irregularly taking the quinoline antimalarial drugs quinine or quinidine (see later), which together are known as the *cinchona alkaloids*. The syndrome virtually disappeared after 1950 when chloroquine superseded quinine. However, it is now said to be resurgent, albeit with lower mortality, in relation to mounting chloroquine resistance and consequent increased use of quinine, and other newer antimalarials.[94]

Hypoglycemia, Lactic Acidosis, and Other Metabolic Perturbations

Severe metabolic derangements are frequent, especially in pregnant women and young children. Although sometimes asymptomatic in pregnancy, malaria-induced hypoglycemia (blood or plasma glucose <2.2 mmol/L) often causes convulsions and impaired consciousness and may be confused with cerebral malaria. The pathogenesis is not completely known and likely multifactorial, but direct glucose consumption by the malaria parasite and cytokine inhibition of gluconeogenesis seem to be the main mechanisms. Decreased oral intake, depletion of liver glycogen, and insulin release stimulated by quinine or quinidine may also contribute.[95,96] Hypoglycemia has been found to be less frequent with artesunate treatment compared with quinine.[97] Serum insulin levels are low, and lactate, alanine, and counterregulatory hormones are appropriately elevated. Although rarely clinically significant, mild hepatocellular damage may occur and be manifested by elevated hepatic transaminases and jaundice. At least theoretically, such hepatic dysfunction could result in impaired metabolic clearance of antimalarial medications and lactate and deficits in the production of coagulation factors and albumin.

Shock and Bacterial and Other Suprainfection

So-called *algid malaria,* referring to hypotension and shock, may resemble and indeed sometimes be the result of gram-negative sepsis from impaired flow in intestinal capillaries, with resultant mucosal erosion. Algid malaria is often seen in the setting of hyperparasitemia, with concomitant hypoglycemia and lactic acidemia, and may progress to multiorgan system failure and death. As with most malaria complications,

severe hemodynamic derangements are most often seen in nonimmune persons.[98] Whether bacteria are isolated or not, a classic septic shock picture is typical, with elevated cardiac index and decreased systemic vascular resistance.[99] Hypovolemic shock resulting from splenic rupture may mimic algid malaria.

A host of infectious complications, including sepsis, aspiration pneumonia, and parvovirus infection, may be related to *P. falciparum* malaria. Nontyphoidal *Salmonella* septicemia, exacerbated by the iron-rich intravascular environment of hemolysis, is specifically associated with *P. falciparum*.[100] Malaria occurs with increasing frequency and severity in those who are HIV-infected, especially during pregnancy, and can also transiently up-regulate HIV replication.[101–107] An association between severe malaria infection and hepatitis B virus carriage has also been noted.[108] Other infections, such as dengue virus and bacteremia, or noninfectious processes may trigger relapses of *P. vivax and P. malariae* infections.

Tropical Splenomegaly and Splenic Rupture

Splenomegaly is common in infection with all species of malaria. The *tropical splenomegaly syndrome,* also sometimes termed *hyperreactive malarial syndrome,* refers to a condition of massive splenomegaly, high titers of total serum immunoglobulin M (IgM) and malaria-specific antibodies, and scant or absent parasitemia. It is seen in individuals with a history of residence in an endemic area and can be associated with any malaria species. Host genetic factors appear to play a role.[109–111]

Unlike virtually all the other complications of malaria that are most often associated with *P. falciparum,* acute splenic complications occur most commonly in *P. vivax,* especially with the first infection. Although the term *spontaneous splenic rupture* has traditionally been used, in reality a range of hematomas or tears of varying severity may occur. The rupture or tear usually occurs 2–3 months after infection, presumably because of increased intrasplenic tension, often precipitated by varying degrees of trauma or mechanical ventilation.[112] Fever, tachycardia, vomiting, prostration, abdominal pain or guarding, tender splenomegaly, hypovolemia, and rapidly worsening anemia are common presenting features. Abdominal pain may be localized or diffuse, mild or severe. Shock may ensue. Diaphragmatic irritation after rupture may cause referred pain to the left shoulder, supraclavicular, or scapular regions, known as the *Kehr sign.* This is present in about one-half of cases and is said to have good specificity for rupture.

Malaria in Pregnancy and Neonates

In addition to being more susceptible to infection, malaria is particularly dangerous in pregnant women and their fetuses, with increased risk of pulmonary edema, hypoglycemia, severe anemia, premature delivery, low birth weight, and maternal and fetal death. Malaria parasites can often be found in the placenta and may impair oxygen and nutrient transport to the fetus. Placental thickening and decreased transplacental nutrient and hormone production occur, which can result in uterine and placental blood flow reduction and intrauterine growth restriction.[113] Disease is most severe in primiparae, especially if nonimmune. In contrast, women from endemic areas are often asymptomatic, with the exception of the effects of anemia, which are more severe in primiparae.

Congenital malaria is vertically transmitted when malaria parasites cross the placenta, or via direct contact at the time of delivery. Congenital malaria is not as rare as previously thought in endemic areas, with a recent meta-analysis showing a rate of 6.8%, but with significantly higher prevalence in areas of unstable malaria prevalence.[114] Malaria may be symptomatic or asymptomatic in newborns with nonspecific signs requiring a high index of suspicion and appropriate testing.[115]

DIAGNOSIS

Clinical

Malaria often presents with nonspecific signs and symptoms, so making a clinical diagnosis may be difficult. Furthermore, although almost all patients have a history of fever, they may be afebrile at the time of examination.[116–118] Physicians in industrialized countries who are unfamiliar with the disease may initially neglect to include malaria in the differential diagnosis, resulting in delayed diagnosis, which is associated with a poor outcome.[33,119] Only slightly more than half of severe malaria cases in the United States receive appropriate treatment.[120] Most patients with *P. falciparum* malaria present within 1 month of exposure (see Table 123.2). Longer incubation periods may be seen in semi-immune persons or in those who have taken partial chemoprophylaxis. *P. vivax* and *P. ovale* infections can manifest later, months or even years after initial infection, because of reactivation of liver hypnozoites.[121–124]

The differential diagnosis includes most febrile illnesses found in the tropics (see Table 123.1). Babesiosis may present both clinically and microscopically similar to malaria in patients with travel to Lyme-endemic areas. Cerebral malaria must be distinguished from bacterial meningitis, viral meningoencephalitides, metabolic coma, and intoxications, usually necessitating a lumbar puncture.[125,126] Lumbar puncture has been shown to be generally safe in comatose patients with suspected cerebral malaria, even if there are signs of raised intracranial pressure.[127] In cerebral malaria, the cerebrospinal fluid (CSF) opening pressure is usually normal, although a few lymphocytes and moderate elevation of protein may be seen. High CSF lactate and low glucose indicate a poor prognosis.

Conventional Microscopy

Laboratory diagnosis has traditionally been via light microscopy of thick and thin Giemsa-stained smears. Thick smears are more sensitive, whereas thin smears allow identification of the specific parasite and accurate staging of visible forms. Either smear can be used to quantify the level of parasitemia, but thick smears are theoretically more sensitive for this purpose.[128,129] In addition to diagnosis, parasite quantification, and species identification, microscopy allows the clinician to monitor the response to treatment via decreased parasitemia and evaluate parasitic markers of disease severity, such as the presence of schizonts in *P. falciparum* infection.[130,131]

Smears should be taken as soon as the diagnosis of malaria is considered, without waiting for manifestation of a classic paroxysm. Blood obtained by pricking a fingertip or earlobe is preferred because parasite densities are higher in these capillary-rich areas, although blood obtained by venipuncture collected in heparin or ethylenediaminetetraacetic acid (EDTA) anticoagulant-coated tubes is acceptable if used shortly after being drawn before possible alteration in the morphology of white blood cells and malaria parasites.[132,133]

Parasitemia may be undetectable in the early stages of the illness in those with partial immunity and/or who have already taken antimalarials, a common practice in malaria-endemic areas.[134] Levels of parasitemia may fluctuate over time, necessitating repeated smears for diagnosis. Furthermore, *P. falciparum*–parasitized RBCs may be sequestered in the deep capillaries of the spleen, liver, and bone marrow and thus not visible in peripheral blood. In these cases, a positive antigen test (see later) may yield the diagnosis.

Although a blood film is unlikely to be falsely negative in a patient with severe disease, negative smears should not prevent prompt administration of antimalarial therapy if the diagnosis is strongly suspected.[48] Nonimmune individuals may be symptomatic at low parasitemia, and so blood smears should be repeated every 12–24 hours for a total of

three sets before malaria can be excluded.[135] Conversely, asymptomatic parasitemia is common in children from endemic areas, and thus a positive smear does not necessarily signify malaria as the cause of disease under these circumstances.

Considerable expertise at reading malaria smears may be necessary to detect and distinguish the parasites (see Table 123.2). An experienced technician can detect parasitemia as low as 4–20 parasites/μL of blood (0.0001%–0.0005% parasitemia).[136,137] *P. knowlesi* may often be misdiagnosed as *P. falciparum* or *P. malariae* because of similar morphology.[138] Superimposed platelets, particles of stain, pits in the slide, RBC inclusions such as Howell-Jolly bodies and those seen in siderocytes, and other intracellular pathogens such as *Bartonella* and *Babesia* must also be distinguished from malaria parasites. Alterations in parasite morphology may occur related to strain variation, drug pressure, and blood collection methods.

Rapid Diagnostic Tests and Other Newer Laboratory Methods

Various new diagnostic techniques for malaria have been developed in recent years, including dipstick antigen detection (i.e., rapid diagnostic test [RDT]), microscopy with fluorescent stains, DNA probes, polymerase chain reaction (PCR) assays, and automated blood cell analysis.[128,129,139–144] Use of one of these new diagnostic modalities should be considered when a high suspicion of malaria remains despite repeatedly negative blood smears, especially if the microscopist has limited experience with reading malaria smears. Each technique has unique advantages and disadvantages, but the sensitivity and specificity for *P. falciparum* are generally similar or better than conventional microscopy. Because of its greater sensitivity (as low as 5 parasites/μL), PCR may be a particularly valuable tool in nonimmune persons. PCR also allows evaluation for possible infection with multiple malaria strains and determination of drug resistance.

Although they have not completely replaced microscopy in low-resource settings, RDT use is increasingly common in many areas of the world.[145] RDTs are fast (usually have a result in less than 30 minutes) and easy to perform, with sensitivities and specificities comparable to microscopy for *P. falciparum,* depending on the specific product and level of parasitemia. Sensitivity and specificity are lower for *P. vivax* and when the parasitemia is less than 100 parasites/μL, regardless of the species.

RDTs generally detect one or more of three malaria antigens: *P. falciparum* histidine-rich protein 2 (*Pf*HRP2), *Plasmodium* lactate dehydrogenase (pLDH), and aldolase. *Pf*HRP2 is specific for *P. falciparum,* whereas pLDH and aldolase are common to all *Plasmodium* species. RDTs that rely on lactate dehydrogenase or aldolase are not sufficiently sensitive for detecting *P. vivax* and may miss infections because of lower parasitemia.[146] No RDT reliably detects *P. knowlesi.* RDT sensitivity for any *Plasmodium* parasite is diminished when parasitemia is less than 100 parasites/μL. RDTs based on pLDH detection can be used to determine the efficacy of drug therapy because this antigen disappears rapidly after parasite clearance relative to other antigens detected by RDTs. However, most licensed and available RDTs should not be used for patient monitoring, given the longevity of serum antigenemia even with adequate treatment.[147] False-negative malaria RDT results may occur because of a prozone-like effect in high parasitemia, or because of PFHRP2 mutations or deletions leading to reduced or absent production of this antigen by *P. falciparum,* the incidence of which is rising and worrisome. There is currently no RDT specific for *P. knowlesi* detection, and cross-reaction with *P. falciparum* and *P. vivax* pLDH antibodies has been described. No RDT has sufficient negative predictive value to justify withholding treatment in severe illness.[148–150]

In the United States, both microscopy and RDTs are recommended. Although a large number of malaria RDTs have been approved for use globally in recent years, only one is currently approved in the United States: BinaxNOW Malaria (Inverness Medical, Princeton, NJ), which detects both PFHRP2 and aldolase, with a reported sensitivity of 94% for *P. falciparum* and 84% for non–*P. falciparum* malaria.[151,152]

Molecular testing (e.g., PCR) is generally limited to research and epidemiologic purposes, but it does have a role in select clinical situations.[153] The U.S. Centers for Disease Control and Prevention offers PCR testing for species confirmation and identification of drug-resistance mutations. It should be requested if *P. knowlesi* is suspected, given the challenges with diagnosis outlined earlier, in the case of microscopy-RDT discordance, and in situations where aberrant morphologies are noted microscopically. PCR has a theoretical limit of detection of 0.02–1 parasite/μL, far better than conventional microscopy.[154] It therefore can serve an important role in nonimmune patients with low parasitemia or in placental malaria, in which there is significant sequestration and sensitivity of light microscopy is low.[155,156] Research continues on a number of biomarkers that could help distinguish malaria from bacterial and viral diseases.

Imaging

Computed tomography (CT) or magnetic resonance imaging (MRI) scanning of the abdomen is the usual diagnostic modality when splenic rupture is considered, although ultrasonography, angiography, or exploratory laparotomy sometimes may be needed. Findings such as increased brain volume and occasionally brain swelling have been noted in CT and MRI studies in cerebral malaria, but these tests are generally unhelpful clinically and are indicated only to rule out suspected mass lesions when the diagnosis of cerebral malaria is uncertain.[157] Chest imaging may be helpful for identification of MA-ARDS, but there are generally no specific features on imaging to help narrow the diagnosis.

CLINICAL MANAGEMENT

Indications for Admission to the Intensive Care Unit and General Management

Features that indicate severe disease meriting admission to an ICU and urgent intravenous (IV) therapy are noted in Box 123.1. Treatment should follow current septic shock guidelines in terms of fluid resuscitation and vasopressor use.[158] For patients in profound shock, blood cultures should be drawn and broad-spectrum antibiotics begun unless the diagnosis of severe malaria has already been confirmed and bacterial coinfection ruled out.

Careful attention to fluid balance is imperative, especially considering the very poor prognosis once pulmonary edema or MA-ARDS develops. Monitoring of central venous pressure should be considered in critically ill patients. In patients with stable blood pressure and cardiac output, careful fluid maintenance with regular assessment of tissue perfusion as a therapeutic endpoint seems to be more beneficial than liberal fluid resuscitation to minimize the risk of acute pulmonary edema.[159,160]

Hemofiltration or hemodialysis or peritoneal dialysis are indicated for severe AKI and may aid not only through improved fluid and electrolyte balance and control of acidemia but also via removal of circulating cytokine mediators of inflammation.[161,162] Increasing evidence suggests peritoneal dialysis may be a safe and effective alternative to hemodialysis in resource-limited settings.[163–165] Cautious transfusion of packed cells is usually indicated when the hematocrit falls below 20% or Hb <7 g/dL, as extrapolated from other large trials around the topic.[166] In addition to improved oxygen transport, blood transfusion

may reduce the parasite load and cytokine mediators of inflammation.[116,167] Concurrent administration of diuretics with blood products may be warranted to avoid fluid overload. Use of low-dose dopamine and epinephrine have not been associated with significant improvement in renal oxygen metabolism or function, but these or other intravascular vasoactive medications may be needed to support patients with hypotension and/or signs of shock.[168]

Increasing respiratory distress may indicate the onset of MARDS. Arterial blood gas or pulse oximetry measurements may reveal hypoxemia, and chest imaging (x-ray, ultrasound, CT) may reveal bilateral infiltrates. Evidence of cardiogenic pulmonary edema suggests an alternative diagnosis. Supplemental oxygen and mechanical ventilation may be required. Lung-protective ventilation, with tidal volume of 6 mL/kg predicted body weight and plateau pressures less than 30 cm H_2O, are indicated for improved survival.[70,169] Extracorporeal oxygenation has also been employed.[170–173] Metabolic acidosis should be treated by improving pulmonary gas exchange, correcting hypovolemia and hypoglycemia, and treating associated septicemia. Careful monitoring of serum potassium with appropriate supplementation is warranted, especially when correcting acidosis. Blood glucose should be checked at least every 6 hours, especially in pregnant patients, and 50% dextrose administered when needed. Results of studies on the efficacy of continuous IV infusion of 5% dextrose have been mixed.[174,175] If a quinoline is the selected antimalarial, it should be administered with dextrose to avoid quinine-induced hypoglycemia.[176] Once hypoglycemia is ruled out as the etiology, acute seizures should be treated with IV benzodiazepines as preferred first-line therapy. Phenobarbital is an alternative if benzodiazepines are unavailable but has a slower administration time and potentially longer duration of action. Prolonged seizures can be treated with phenytoin, fosphenytoin, valproic acid, or levetiracetam, with phenobarbital as an alternative second-line agent if none of the other agents are available.[82,177,178] Prophylactic anticonvulsants are not recommended and may be harmful.[158] Although the risk of bleeding is low, aspirin and nonsteroidal antiinflammatory drugs should be avoided in the presence of thrombocytopenia. Many patients with splenic rupture can be managed conservatively with supportive therapy, although splenectomy may be necessary.[109,179]

When malaria occurs during pregnancy, an ultrasound should be performed to assess amniotic fluid volume, fetal size, and fetal well-being (i.e., biophysical profile). In late pregnancy, fetal monitoring should be initiated before treating with quinoline therapy so that the effects of the disease can be distinguished from those of drug toxicity.[180] Early obstetric intervention may be considered for the benefit of both mother and fetus at the discretion of the obstetrician. Although fetal distress is usually the result of placental insufficiency, it may sometimes be related to high maternal temperature and hypoglycemia. Thus these parameters should be carefully monitored and treated accordingly. Fluid balance is particularly crucial in pregnant patients because the sudden increase in peripheral vascular resistance postpartum may precipitate pulmonary edema. In young children prone to febrile convulsions, extra efforts should be made to control fever by the use of acetaminophen, cooling blankets, and baths.

Antimalarial Chemotherapy

Because delay of therapy is associated with increased mortality, empirical parental treatment should be implemented immediately in all suspected cases of severe malaria after obtaining appropriate blood specimens. Infection with chloroquine-resistant *P. falciparum* should be assumed unless specifically ruled out. Treatment regimens for severe *P. falciparum* are also effective for the more infrequent cases of severe malaria caused by other species.

Two classes of medicines are indicated for parenteral treatment: the artemisinin derivatives (artesunate, artemether) and the cinchona alkaloids (quinine, quinidine) (Table 123.3). Large randomized trials and a Cochrane systematic review have shown that artesunate is superior to quinine for severe malaria in both adults and children.[181,182] IV or intramuscular (IM) artesunate is the World Health Organization (WHO) first-line recommended drug for severe malaria and should be administered for at least 24 hours even if there is early improvement. If IV or IM artesunate is not available, IM artemether should be considered in preference to quinine for both adults and children with severe malaria. After 24 hours, and if patients are able to tolerate oral therapy, they may be transitioned to one of three recommended oral artemisinin-based combination therapies (ACTs) to complete a total of 3 days (see Box 123.1). If not possible to treat with one of the three recommended ACT regimens, oral artesunate can be combined with either clindamycin or doxycycline, or oral quinine plus either clindamycin or doxycycline can be used for a total of 7 days for both drugs. Doxycycline is preferred to other tetracyclines because it can be given once daily and does not accumulate in renal failure. Doxycycline is contraindicated, and thus clindamycin preferred, in children and pregnant women (see Box 123.1). The dosage of artemisinin compounds does not need to be adjusted for patients with AKI or hepatic dysfunction, and artemisinin compounds do not need dose adjustment with hemodialysis or hemofiltration. This is not true of quinine, which accumulates in renal failure and must be dose adjusted.

Despite its use throughout much of the world, artesunate has not been licensed in many industrialized countries. In the United States, artesunate was approved for use in 2020 but is not widely available.[183] The drug can be procured through the U.S. Centers for Disease Control and Prevention (770-488-7788).[184,185] If artemisinin is unavailable, parenteral quinine or quinidine gluconate can be used as an alternative, although these drugs are no longer widely available in the United States.[183,185,186]

There is increasing artesunate resistance in the Greater Mekong area after first being described in Western Cambodia in 2008.[187–190] Cinchona alkaloids may also be considered in patients infected from countries where resistance to artemisinin compounds has been documented. Currently, guidance is to administer both IV artesunate and IV quinine for severe malaria from the Greater Mekong region, although this is based on expert opinion rather than evidence.[191] Combination therapy with dihydroartemisinin and piperaquine for resistant malaria has been used, with mixed results.[192,193] Chloroquine and sulfadoxine/pyrimethamine are not recommended for treatment of severe malaria.

Adverse Effects of Therapy

Artemisinin compounds are generally well tolerated. Infrequent adverse effects include mild abdominal pain, diarrhea, contact dermatitis, decreases in reticulocyte and neutrophil counts, and elevated hepatic transaminases.[194,195] Severe allergic reactions and cerebellar dysfunction have been rarely reported.[196] In nonimmune adult travelers with high parasitemia, delayed hemolysis has been described after administration of parenteral artesunate, and thus patients treated with this compound should be monitored for anemia for 1 month post-treatment.[88,197–199]

Adverse effects of quinine and quinidine, known as *cinchonism,* are common and typically include nausea, vomiting, headache, dysphoria, vasodilation, tinnitus, and changes in auditory and visual acuity. These alterations are dose related and reversible. Less common side effects include rash, urticaria, angioedema of the face, pruritus, agranulocytosis, hepatitis, blackwater fever, and psychiatric disorders.[200] Overdoses are associated with depressed respiration, circulatory collapse, and

TABLE 123.3 Treatment Guidelines for Severe *Plasmodium falciparum* Malaria

Drug	Dose	Comments
Artemisinin Compounds		
Artesunate Artemether	2.4 mg/kg IV bolus at 0, 12, 24 hr, then daily until patient is able to transition to the following oral regimen: 1. Artemether + lumefantrine: tablets containing 20 + 120 mg, or 40 + 240 mg of artemether and lumefantrine, respectively • Adults: ≥35 kg: 80 + 480 mg twice daily for 3 days • Children: 5 to <15 kg: 20 + 120 mg twice daily for 3 days 15 to <25 kg: 40 + 240 mg twice daily for 3 days 25 to <35 kg: 60 + 360 mg twice daily for 3 days 2. Artesunate + amodiaquine: A fixed dose of combination tablets containing 25 + 67.5 mg, 50 + 135 mg, or 100 + 270 mg of artesunate and amodiaquine, respectively • Adults ≥36 kg, 200 1 540 mg daily for 3 days • Children: 4.5 to <9 kg: 25 + 67.5 mg daily for 3 days 9 to <18 kg: 50 + 135 mg daily for 3 days 18 to <36 kg: 100 + 270 mg daily for 3 days 3. Dihydroartemisinin (DHA) + piperaquine (PPQ): tablets containing 20 + 160 mg, or 40 + 320 mg of DHA and PPQ, respectively • Adults: 36 to <75 kg: 120 + 960 mg daily for 3 days ≥75 kg: 160 + 1280 mg daily for 3 days (no data on dose recommendation above 100 kg) • Children: 5 to <7 kg:10 + 80 mg daily for 3 days 7 to <13 kg: 20 + 160 mg daily for 3 days 13 to <24 kg: 40 + 320 mg daily for 3 days 24 to <36 kg: 80 + 640 mg daily for 3 days 4. Artesunate or quinine PO to complete 7 days PLUS doxycycline, 100 mg PO BID × 7 days 5. Artesunate or quinine PO to complete 7 days PLUS clindamycin, 20 mg base/kg/d PO, TID × 7 days Initial dose: 3.2 mg/kg intramuscularly (IM) (anterior tight); maintenance dose: 1.6 mg/kg IM daily until patient is able to transition to oral regimen as describe earlier for artesunate	Artesunate has recently been approved by the FDA in the United States, but until widely stocked, it remains available from the CDC (770-488-7788) via expanded use investigational new drug protocol. Eligibility requirements include inability to take oral medications, high levels of parasitemia, clinical evidence of severe malaria, intolerance of or contraindication to quinidine, failure of quinidine therapy, and lack of rapid access to quinidine.[86] Where available, artesunate rectal suppositories (10 mg/kg) may be used in children <5 years of age if IV or IM administration is not possible. Doxycycline is contraindicated in children <8 years of age and in pregnancy. Atovaquone/proguanil is packaged in the United States in fixed-dose combination tablets of 250 mg atovaquone/100 mg proguanil for adults and 62.5 mg atovaquone/25 mg proguanil for children. Safety of atovaquone/proguanil in pregnancy has not been established.
Cinchona Alkaloid Regimens		
Quinine dihydrochloride	20 mg salt/kg IV or IM on admission, then 10 mg/kg q8h. Can be given IM if IV administration is not possible. One of the following drugs should also be given concurrently: 1. Artemisinin combination therapy as noted earlier 2. Doxycycline as noted earlier. If patient unable to take PO, give 100 mg IV q12h and switch to PO when possible. Avoid rapid IV administration. 3. Clindamycin as noted earlier. If patient unable to take PO, give 10 mg base/kg loading dose IV followed by 5 mg base/kg IV q8h and switch to PO when possible. Avoid rapid IV administration.	The infusion rate of IV quinine should be rate controlled and not exceed 5 mg salt/kg/hr. The drug is usually diluted in 5% dextrose and infused over 4 hours. IV quinine is not available in the United States. When administering IM, the dose should be split and diluted to a concentration of 60–100 mg/kg delivered to each thigh. Reduce the quinine dose by one-third (to 10 mg salt/kg every 12 hours) after 48 hours in patients with severe renal and/or hepatic dysfunction. Doxycycline is contraindicated in children <8 years old and in pregnancy.
Quinidine gluconate	6.25 mg base/kg (=10 mg salt/kg) IV on admission over 1–2 hours, then 0.0125 mg base/kg/min (=0.02 mg salt/kg/min) continuous infusion. An alternative regimen is 15 mg base/kg (=24 mg salt/kg) loading dose IV infused over 4 hours, followed by 7.5 mg base/kg (=12 mg salt/kg) infused over 4 hours q8h, starting 8 hours after the loading dose. A second drug should be given concurrently as listed earlier for quinine.	The loading dose should be omitted if the patient received >40 mg/kg quinine in the preceding 48 hours or mefloquine in the previous 12 hours. Reduce the dose by one-third after 48 hours in patients with severe renal and/or hepatic dysfunction.

central nervous system (CNS) alterations, including seizures and coma, which may be difficult to distinguish from cerebral malaria.[201] Simultaneous use of two quinolines or retreatment with the same quinoline within a short period may predispose to severe side effects.[202] The cinchona alkaloids are metabolized in the liver and excreted in the urine. Monitoring blood levels is recommended for persons with impaired renal or hepatic function, and dose reduction is necessary in those with severe renal impairment. Quinine metabolism appears to be decreased in children with kwashiorkor but increased in those with marasmus.[203]

Although often not clinically significant, prolongation of the electrocardiographic QT interval with IV quinoline therapy is common.[204] Severe conduction abnormalities may occur along with hypotension, blindness, and deafness.[204] Dysrhythmias and hypotension may also result from overly rapid infusion and can be fatal. Coma may result when serum quinoline levels exceed 20 mg/L. Cardiac monitoring should be performed with IV quinoline use, especially with quinidine, which although more potent against the malaria parasite is also generally more toxic.[204] Infusion rates of quinidine should be decreased if the QT interval increases by more than 25% of its baseline level.

Quinoline-induced stimulation of insulin release may elicit significant hypoglycemia, especially in pregnancy.[175,205] Hypophosphatemia may also be precipitated by both quinoline and IV dextrose, causing CNS dysfunction.[116] Levels of digoxin, mefloquine, neuromuscular blocking agents, and oral anticoagulants may all be increased with quinoline administration. Quinine can cause hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency. Because of their curarelike effect on skeletal muscle, quinolines are contraindicated in patients with myasthenia gravis. An extensive list of drug interactions reported for recommended antimalarial drugs is available in the WHO guidelines for the treatment of malaria.[158]

Ancillary Therapies

Various ancillary therapies have been proposed for severe malaria, but in most cases controlled data are not available to determine their efficacy. Exchange transfusion and erythrocytapheresis have been employed in cases of severe malaria with high parasitemia with anecdotal benefit.[206–211] However, multiple studies reviewing case series and controlling for confounding have shown no benefit of exchange transfusions on mortality, parasitemia, and ICU or hospital length of stay.[212–214] In an era of artemisinin-based therapy, which is characterized by rapid clearance of parasitemia, the biologic plausibility of benefit from conventional exchange transfusion is becoming less relevant. However, there is ongoing research studying the role of exchanging malaria-resistant RBCs (T-REX) in cases of severe artesunate-resistant malaria.[215,216] Treatments such as heparin, prostacyclin, deferoxamine, pentoxifylline, low-molecular-mass dextran, urea, high-dose corticosteroids, aspirin, antitumor necrosis factor antibody, cyclosporine A, dichloroacetate, adrenaline, hyperimmune serum, N-acetylcysteine, inhaled nitric oxide, and bolus administration of albumin are not recommended because their effectiveness is not proven or they have shown to be detrimental in severe malaria.[158,217]

Laboratory Monitoring

Findings in severe malaria may include profound hemolytic anemia and thrombocytopenia, leukocytosis with a left shift (although milder cases may show leukopenia), prolonged coagulation times with increased fibrin degradation products and low fibrinogen reflecting DIC, hyponatremia, hypoalbuminemia, hypophosphatemia, hypoglycemia, lactic acidemia, and elevated hepatic enzymes, LDH, bilirubin, blood urea nitrogen (BUN), and creatinine. Urinalysis may reveal proteinuria, RBCs and RBC casts, and hemoglobinuria. Coagulation defects and thrombocytopenia often correlate with the degree of parasitemia. The level of parasitemia should be monitored via blood smear every 12 hours after initiation of therapy. A decrease of 75% should be noted within 48 hours of starting artemisinin therapy. If this does not occur, drug resistance should be suspected, and the regimen should be changed accordingly (see Table 123.3).

PROGNOSIS AND SEQUELAE

Case fatality rates of severe malaria vary by geographic context and quality of care from 2% to 50%.[82,85,218–220] Factors that correlate with a poor prognosis include the infecting species and resistance profile, choice of parenteral therapy, CNS involvement, pulmonary edema, shock, hypoglycemia, lactic acidosis, renal failure, severe anemia, younger age, pregnancy, and treatment in a rural health facility as opposed to an ICU.[91,116,221–230] There is a semi-quantitative relationship between level of parasitemia and risk of death, especially in nonimmune patients.

Although less than 10% of adults with cerebral malaria have persistent neurologic sequelae, this number may be as high as 40% in children, especially if associated with hypoglycemia.[174,218,231] Commonly seen sequelae include psychosis, hemiparesis, cerebellar ataxia, blindness, and extrapyramidal rigidity.[82,85,231] Children who survive without obvious neurologic sequelae often still have behavioural or cognitive impairments, in some studies in over 50%.[232] A postmalarial neurologic syndrome, usually associated with mefloquine use, of an acute confusional state, psychosis, convulsions, and tremors, has been described but is usually self-limited.[82]

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KEY POINTS

- A detailed history of the patient's travel itinerary, activities and exposures, and any pretravel prophylaxis, in addition to general knowledge of the prevalent diseases and their incubation periods and drug-resistance patterns in the region of travel, are imperative when evaluating patients with exposures overseas.
- Most "nontropical" infections are also common in low- and middle-income countries and thus need to be considered.
- Assessing the patient's immune status based on history of exposure to malaria is essential in directing the diagnostic workup and management.
- Infection with multiple tropical pathogens is common in those living in endemic areas, and malaria may not be the primary causative pathogen even if identified.

Risk of Infection and Uncomplicated Malaria

- Malaria is the most common serious infection in the majority of tropical countries and in returning travelers and therefore should be considered in any patient reporting travel in malaria-endemic areas or exposure to unscreened blood products ("transfusion malaria") or blood-contaminated needles.
- Malaria classically produces a three-stage "paroxysm" progressing over an 8- to 12-hour period, consisting of rigors and chills ("cold stage"), followed by fever ("hot stage"), followed by sweating with resolution of all symptoms

("defervescent stage"). In practice, neither the classic paroxysm nor the periodicity is invariably seen.

Severe and Complicated Malaria

- The overwhelming majority of severe and complicated malaria is caused by *P. falciparum* in nonimmune children, adults, and pregnant women, but *P. vivax* and *P. knowlesi* can also cause severe disease.
- The risk of acquiring *P. falciparum* is highest for those traveling to sub-Saharan Africa (especially West Africa) and New Guinea; the risk is moderate in India and comparatively low in Southeast Asia and Latin America. *P. vivax* is widely distributed, with the highest risk in Oceania. *P. knowlesi* is only found in Southeast Asia.
- The most frequent severe complication is cerebral malaria, mostly seen in children. It manifests as coma, convulsions, changes in sensorium, or focal neurologic signs. Other severe complications include severe anemia (especially in young children and pregnant women), hypoglycemia, lactic acidosis, AKI, pulmonary edema and ARDS, shock, and bacterial suprainfection.
- Other potentially severe complications caused by non–*P. falciparum* malaria include splenic rupture and severe anemia *(P. vivax)* and chronic nephrotic syndrome *(P. malariae).*

Diagnosis

- Malaria often presents with nonspecific signs and symptoms, and the differential diagnosis is broad, so making a clinical diagnosis may be difficult.
- The vast majority of malaria cases will present within 1 month of exposure. *P. vivax* and *P. ovale* infections can present months or even years after infection because of the possibility of dormant forms (hypnozoites) in the liver.
- Laboratory diagnosis is traditionally made through microscopy of thick and thin Giemsa-stained smears. Low or fluctuating parasitemia or altered parasite morphology may complicate diagnosis, especially with an inexperienced microscopist. Asymptomatic parasitemia is common in children from endemic areas.
- Various new diagnostic techniques for malaria (e.g., dipstick antigen detection, PCR) have been developed in recent years, with sensitivities and specificities for *P. falciparum* generally superior to conventional microscopy. Use of one of these new modalities can be considered when the diagnosis of malaria is unclear if local resources are available.
- Radiographic imaging of the abdomen is indicated when splenic rupture is suspected.

Clinical Management

- Patients with evidence of severe or complicated malaria should be assumed to have chloroquine-resistant *P. falciparum* and admitted to the ICU for aggressive supportive care and urgent antimalarial drug therapy. Therapy should consist of IV artesunate followed by oral ACT for 3 days. Parenteral artesunate should be given for at least 24 hours and until the patient is able to tolerate oral medication. Acceptable alternatives when parenteral artesunate is unavailable include IM artemether, IV quinidine gluconate, or IV quinine (transitioned to oral artesunate or quinine according to the same criteria as noted earlier), given simultaneously with oral/IV doxycycline or clindamycin for 7 days.
- Artemisinin compounds are usually well tolerated. Side effects with cinchona alkaloid therapy are frequent, but are usually mild, dose related, and reversible. Cardiac toxicity and arrhythmias are common in the case of overadministration of cinchona alkaloids.
- Many patients with splenic rupture can be managed conservatively with supportive therapy, although splenectomy may be necessary.
- The hemoglobin/hematocrit, electrolytes, platelet count, glucose, lactate, arterial blood gas, BUN/creatinine, liver function and coagulation enzymes, and the level of parasitemia in response to therapy should be monitored closely.
- The case fatality rates of severe malaria treated in an ICU vary by geographic context and quality of care and may be up to 50%.

References for this chapter can be found at expertconsult.com.

ANNOTATED REFERENCES

Balikagala B, Fukuda N, Ikeda M, et al. Evidence of Artemisinin-resistant malaria in Africa. *New Engl J Med.* 2021;385(13):1163–1171.
This is a longitudinal study in Uganda looking at in vivo and ex vivo susceptibility of malaria strains to artemisinins. The authors found that from 2017 to 2019, 14/240 (5.8%) of patients treated with IV artesunate had in vivo evidence of artemisinin resistance (parasite clearance half-life >5 hours); 13/14 (93.6%) of these malaria parasites had mutations in the kelch13 *gene. This is evidence of independent emergence of clinical artemisinin-resistant* P. falciparum *in Africa.*

Blanshard A, Hine P. Atovaquone-proguanil for treating uncomplicated *Plasmodium falciparum* malaria. *Cochrane Database Syst Rev.* 2021;1(1):CD004529.
This is a Cochrane review to assess the safety and efficacy of atovaquone-proguanil compared with other antimalarials for treatment of uncomplicated P. falciparum *malaria in both adults and children. The review showed that atovaquone-proguanil was effective for uncomplicate malaria, although failure rates were 5%–10% and could be decreased with the addition of artesunate to the regimen.*

Conroy AL, Hawkes M, Elphinstone RE, et al. Acute kidney injury is common in pediatric severe malaria and is associated with increased mortality. *Open Forum Infect Dis.* 2016;3(2):ofw046.
This study looked at 180 children in rural Uganda with malaria. The investigators found that 81 (45.5%) had AKI. There were higher rates of AKI than anticipated in children, and AKI was associated with increased rates of mortality and neurodisability.

Khuu D, Eberhard ML, Bristow BN, et al. Malaria-related hospitalizations in the United States, 2000-2014. *Am J Trop Med Hyg.* 2017;97(1):213–221.
This review identifies all U.S. malaria cases from 2000 to 2014 from hospital discharge records. There were an estimated 22,029 malaria-related hospitalizations (4.88 per 1 million population) in the United States, with 4823 severe cases and 182 in-hospital deaths. The rate of malaria-related hospitalizations did not change significantly over the study period. On average, malaria patients were hospitalized for 4.36 days with charges of $25,789. Enhanced primary and secondary prevention measures, including strategies to increase the use of pretravel consultations and prompt diagnosis and treatment, are needed.

van der Pluijm RW, Tripura R, Hoglund RM, et al. Triple Artemisinin-based combination therapies versus Artemisinin-based combination therapies for uncomplicated *Plasmodium falciparum* malaria: A multicentre, open-label, randomised clinical trial. *Lancet.* 2020;395(10233):1345–1360.
Investigators compared treatment of uncomplicated P. falciparum *malaria in 18 hospitals across eight countries. They found that dihydroartemisinin-piperaquine plus mefloquine and artemether-lumefantrine plus amodiaquine triple artemisinin-based combination therapies are efficacious, safe, and well-tolerated treatments for uncomplicated* P. falciparum *malaria even in areas with developing artemisinin resistance.*

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Clostridioides difficile Infection

Massimo Sartelli

INTRODUCTION

Clostridioides difficile is an anaerobic, spore-forming, gram-positive bacillus that may be part of the normal intestinal microbiota in healthy babies.[1–4] It was officially renamed in 2016 to *Clostridioides difficile*. The new name reflects the taxonomic differences between this species and other members of the *Clostridium* genus.[5] It is spread via the oral-fecal route, and in hospitalized patients may be acquired through the ingestion of spores from other patients, healthcare personnel's hands, or environmental surfaces.[6,7] *C. difficile* is the main pathogen associated with nosocomial infections and is the most common cause of diarrhea in hospitalized patients.[8] *C. difficile* infection (CDI) can present as a spectrum of symptoms ranging from an asymptomatic carriage to fulminant disease with toxic megacolon. Extracolonic manifestations of CDI are rare and most commonly involve small intestine infiltration, reactive arthritis, and bacteremia.[9] The mortality rate directly attributable to CDI is estimated at 5%, whereas mortality associated with CDI complications reaches 15%–25%, and up to 34% in intensive care units (ICUs). Mortality doubles in ICU patients with CDI as compared with ICU patients without CDI.[9,10]

PATHOGENESIS

CDI occurs via the fecal-oral route as a result of ingestion of spores that are resistant to their environment. During gastrointestinal passage, bile acids and other substances stimulate the germination of vegetative growth forms; these produce toxins, depending on the surrounding microflora (microbiota) The primary toxins produced by this bacterium are toxins A and B.[11] Toxins A and B act as glucosyltransferases, promoting the activation of Rho GTPases and leading to disorganization of the cytoskeleton of the colonocyte and eventual cell death.[12] Because CDI is a toxin-mediated infection, nontoxigenic *C. difficile* strains are nonpathogenic. The increased incidence, severity, and mortality of CDI have been largely attributed to the epidemic strain ribotype 027 (formerly referred to as *NAP1/BI/027*). The *C. difficile* BI/NAP1/027 epidemic strain is characterized by two mutations in the toxin regulatory gene *tcdC*, an 18–base-pair (bp) deletion, and deletion at position 117, which leads to increased production of toxins A and B.[9,13]

RISK FACTORS

Risk factors for CDI may be divided into three general categories: host factors (immune status, comorbidities), exposure to *C. difficile* spores (hospitalizations, community sources, long-term care facilities), and factors that disrupt normal colonic microbiome (antibiotics, other medications, surgery).[14]

PATIENT FACTORS

Risk factors identified to date include age >65 years, comorbidity or underlying conditions, inflammatory bowel diseases, immunodeficiency (including human immunodeficiency virus (HIV) infection), malnutrition, obesity, female sex, and low serum albumin level.[14]

Exposure to *Clostridium difficile* Spores

Factors that increase risk of exposure to *C. difficile* spores, such as increased duration of hospital stay, increase the risk of CDI. A length of stay >2 weeks has been shown to be a risk factor for CDI.[14] During the first days of hospitalization, the incidence of *C. difficile* colonization ranges from 2% to 20%[15–19] and increases with longer hospital stays.[20–21] It must be noted that colonization does not necessarily mean symptomatic infection; it is suggested that only 25%–30% of asymptomatic colonized patients develop diarrhea. *C. difficile* spores survive in the environment for several months.[22]

Normal Flora Disruption

The indigenous gut microbiota is a complex community of microorganisms that populates the gastrointestinal tract in a healthy person. This micro-ecosystem plays a crucial role in protecting the gut by providing resistance to colonization and infection by pathogenic organisms.[23] Gut microbiota also has immeasurable effects on homeostasis of the host.[24] Under normal conditions, the human gut microbiota impedes pathogen colonization through general mechanisms such as direct inhibition through bacteriocins, nutrient depletion (consuming growth-limiting nutrients), or stimulation of host immune defenses. However, the exact mechanism by which the microbiota protects against CDI is unknown.[25] Disruption of the normal balance of colonic microbiota as a consequence of antibiotic use or other stressors is of major importance.[26]

In 1974 Tedesco and colleagues published a prospective study of clindamycin-associated colitis, which had become endemic in many hospitals.[27] In 200 consecutive patients, administration of clindamycin resulted in diarrhea in 21% and the incidence of endoscopy-diagnosed pseudomembranous colitis was 10%. The study led to a search for an infectious cause of colitis, and it identified *C. difficile* as the main causative agent.[28] Nearly every antibiotic has been associated with the development of CDI, including the antibiotics used for treatment of CDI such as metronidazole and vancomycin. Broad-spectrum penicillins and cephalosporins, clindamycin, and fluoroquinolones possess a higher risk for CDI induction than other antibiotics.[14] The risk for development of CDI is eightfold to tenfold higher during antibiotic therapy and 4 weeks thereafter and threefold higher in the next 2 months.[29]

DIAGNOSIS

CDI should be considered in patients who have diarrhea (≥3 loose stools in 24 hours) with or without abdominal pain, especially if they have a recognized risk factor (including recent antibiotic use, hospitalization, or advanced age) with no obvious alternative diagnosis (including laxative use in the past 48 hours). Nausea, vomiting, and fever are often, but not always, present.

Several diagnostic options are available; however, no single test is considered to be the best laboratory testing method. The most common diagnostic option for CDI is based on detection of *C. difficile* toxins directly in a stool sample, most commonly with an enzyme immunoassay (EIA), which provides rapid turnaround time (about 1–2 hours), in addition to sensitivity of 75%–85% and specificity of 95%–100%.[9] Because of its low cost and ease of use, this is the most popular test in all laboratories. Tests detecting *C. difficile* antigens are based on the detection of glutamate dehydrogenase (GDH) and are characterized by ease of use and rapid turnaround time in addition to a specificity of almost 100%. However, they do not distinguish whether the strain is toxigenic (specificity of 59%).[9] In 2009, nucleic acid amplification tests (NAATs) were introduced. NAAT has higher sensitivity (80%–100%) and specificity (87%–99%) compared with an EIA test. The specificity is especially high, reaching 95%, when a negative result is obtained. In this situation, another cause of diarrhea should be considered.[9] The NAAT has also limitations: namely, high cost and some interpretation difficulties. NAAT detects the presence of a toxin-encoding gene and thus confirms the presence of a *C. difficile* toxin–producing strain, but it does not necessarily mean that the strain produces any toxins at the moment. A multistep algorithm to diagnose CDI (GDH plus toxin EIA, GDH plus toxin EIA with NAAT confirmation if results are discordant, or NAAT plus toxin EIA) is generally suggested in clinical practice.

In certain clinical settings, adjunct testing methods such as radiologic diagnostic imaging may be useful for diagnosing CDI. Diagnostic computed tomography (CT) imaging can assist with an early diagnosis and may help determine the severity of disease in patients with CDI.[14] Typical CT findings of CDI include colonic wall thickening, dilation, pericolonic stranding, "accordion sign" (high-attenuation oral contrast in the colonic lumen alternating with low-attenuation inflamed mucosa), "double-halo sign, target sign" (intravenous contrast displaying varying degrees of attenuation caused by submucosal inflammation and hyperemia), and ascites.[14] However, the most common finding, colonic wall thickening, is nonspecific and can be found in other forms of colitis, although it may be more pronounced with CDI.

TREATMENT

Treatment should only be started in patients with CDI symptoms; presence of the *C. difficile* toxin without symptoms of the infection is not an indication for treatment. When antibiotic therapy is indicated for symptomatic cases with a positive *C. difficile* toxin result, options include metronidazole, oral or intraluminal vancomycin, and oral fidaxomicin. Although metronidazole may be associated with more frequent side effects and there has been a significant increase in treatment failures (especially in patients infected with the emergent 027/BI/NAP1 strain), oral metronidazole 500 mg three times per day for 10 days has been used for treating mild to moderate cases of CDI.[30] Repeated or prolonged courses of metronidazole should be avoided because of the risk of cumulative and potentially irreversible neurotoxicity.[31]

In 2017 the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) updated their guidelines, pointing out that vancomycin and fidaxomicin are the cornerstone of CDI treatment, suggesting metronidazole only for patients with an initial episode of nonsevere CDI in settings where access to vancomycin or fidaxomicin is limited.[32] Vancomycin orally 125 mg four times daily for 10 days is considered superior to metronidazole in severe *C. difficile* disease.[33–36] This may reflect the superior pharmacokinetic properties of vancomycin, which is concentrated in the gut lumen. Doses of up to 500 mg have been used in some patients with severe or fulminant disease, defined as hypotension or shock, ileus or megacolon,[14] although there is little evidence for this in the literature. Unlike vancomycin delivered enterally, intravenous vancomycin has no effect on CDI because the antibiotic is not excreted into the colon. Vancomycin enemas may be an effective therapy for patients who cannot tolerate the oral preparation or patients with ileus who have delayed passage of oral antibiotics from the stomach to the colon.[37]

Fidaxomicin orally 200 mg twice daily for 10 days is a valid alternative to vancomycin in patients with CDI.[38,39] Fidaxomicin was noninferior to vancomycin for initial cure of CDI in two prospective trials.[40,41] It may be useful for treating patients who are considered at high risk for recurrence (elderly patients with multiple comorbidities who are receiving concomitant antibiotics). However, it is important to note that no data on the efficacy of fidaxomicin in severe life-threatening disease are available.[14] The use of other antibiotics such as tigecycline,[14] fusidic acid, teicoplanin, rifamixin,[14] and nitazoxanide[14] has been described in the literature, but they are not currently recommended for general use.

Patients with fulminant colitis who progress to systemic toxicity require surgical intervention.

These patients are likely to have serious comorbidities, and delaying surgery in these patients leads to increased likelihood of adverse outcomes. Total colectomy is the surgical procedure of choice. However, diverting loop ileostomy with antegrade colonic lavage may be a colon-preserving alternative to total colectomy.[42,43] A prospective, nonrandomized, historical control group study was performed at the University of Pittsburgh Medical Center and the Veterans' Administration Healthcare System in Pittsburgh between June 2009 and January 2011.[44] Forty-two patients with fulminant colitis were managed by a loop ileostomy, intraoperative colonic lavage with warmed polyethylene glycol 3350/electrolyte solution via the ileostomy, and postoperative antegrade instillation of vancomycin flushes via the ileostomy. There was no significant difference in age, sex, pharmacologic immunosuppression, and Acute Physiology and Chronic Health Evaluation-II (APACHE II) scores between the studied cohort and historical controls. The operation was accomplished laparoscopically in 35 patients (83%). This treatment strategy resulted in reduced mortality compared with their historical controls. Preservation of the colon was achieved in 39 of 42 patients (93%). Of note, vancomycin antegrade enemas were continued via the ileostomy every 6 hours for 10 days, and this likely augmented the effect of the defunctioning surgery.

A retrospective multicenter study conducted under the sponsorship of the Eastern Association for the Surgery of Trauma to compare loop ileostomy with total colectomy as surgical treatment for CDI was published in 2017.[44] Data from 10 centers of patients who presented with CDI requiring surgery between July 1, 2010, and July 30, 2014, were collected. When comparing colectomy with loop ileostomy, there was no statistical difference between these two operative strategies. Univariate preprocedure predictors of mortality were age, lactate, timing of operation, vasopressor use, and acute renal failure. There was no statistical difference between the APACHE score of patients undergoing either procedure (total colectomy, 22 vs. loop ileostomy, 16). Adjusted mortality (controlled for preprocedure confounders) was

significantly lower in the loop ileostomy group (17.2% vs. 39.7%; $P=.002$).

TREATMENT OF RECURRENT CDI

Recurrence is diagnosed when CDI recurs <8 weeks after the resolution of a previous episode, provided the symptoms from the previous episode resolved after completion of the initial treatment and other causes have been excluded. Symptomatic recurrent *C. difficile* infection (RCDI) occurs in approximately 20% of patients and is challenging.[14] Therefore patients with RCDI should be treated by experienced clinicians. Antibiotics that may be used to treat the first recurrence of CDI include vancomycin (particularly if metronidazole was used for the first episode) or fidaxomicin. Antibiotic treatment options for patients with more than one recurrence of CDI include oral vancomycin therapy using a tapered and pulsed regimen.[14]

Fecal microbiota transplantation (FMT) has been considered as an alternative therapy to treat RCDI.[14] It involves infusing intestinal microorganisms (in a suspension of healthy donor stool) into the intestine of patients to restore the intestinal microbiota. The rationale of FMT is that disruption of the normal balance of colonic flora allows *C. difficile* strains to grow and produce CDI. By reintroducing normal flora via donor feces, the imbalance may be corrected and normal bowel function re-established.[42,43] Although FMT has high success rates with long-term durability,[44] a few disadvantages still exist. In particular, the manipulation of feces and the classical enteral administration methods are not only laborious but also tend to make the procedure rather unattractive for physicians and patients. FMT may be administered via enemas or as a slurry given via a nasogastric tube.

In 2016 the Food and Drug Administration (FDA) approved bezlotoxumab to reduce the recurrence of CDI in adult patients receiving antibiotic therapy for CDI who are at high risk of recurrence. Bezlotoxumab (MK-6072) is a human monoclonal antibody that reduces recurrent CDI by blocking the binding of *C. difficile* toxin B to host cells, thus limiting epithelial damage and facilitating recovery of the microbiome.[14]

Coadjuvant treatment with bezlotoxumab is generally suggested to prevent recurrences of CDI, particularly in patients with a history of CDI, caused by the 027 epidemic strain, in immunocompromised patients and in patients with severe CDI.[14]

INFECTION PREVENTION AND CONTROL

Prompt identification of patients with CDI is essential so that appropriate isolation precautions can be put into effect.[45] This is particularly important in reducing environmental contamination, as spores can survive for months in the environment,[46] despite regular use of environmental cleaning agents. An infection control "bundle" strategy should be used to successfully control CDI outbreaks. The "bundle" approach should include multifaceted interventions, including hand hygiene, isolation measures, and environmental disinfection.[14] In a healthcare setting, transmission of *C. difficile* spores occurs primarily via the contaminated hands of healthcare workers, but contact with a contaminated environment, utensils, or medical devices has also been implicated. Hand hygiene with soap and water and the use of contact precautions, along with good cleaning and disinfection of the environment and patient equipment, should be used by all healthcare workers in contact with any patient with known or suspected CDI. Hand hygiene is a cornerstone of prevention of nosocomial infections, including infection caused by *C. difficile*. Alcohol-based hand sanitizers are highly effective against non–spore-forming organisms, but they do not kill *C. difficile* spores. Though disposable glove use during care of a patient with CDI may be effective in preventing the transmission of *C. difficile*,[14] these must be removed at the point of use and the hands thoroughly decontaminated afterwards through soap and water handwashing. Patients with known or suspected CDI should ideally be placed in a private room[14] with en-suite handwashing and toilet facilities. If a private room is not available, known CDI patients may be cohort nursed in the same area,[14] though the theoretical risk of transfection with different strains exists.

CONCLUSIONS

In the last three decades the frequency and severity of *C. difficile* infection have been increasing worldwide to become one of the most common hospital-acquired infections. Appropriate management of infection requires an understanding of the various diagnostic assays and therapeutic options in addition to measures relevant to infection prevention.

KEY POINTS

- Proper antibiotic stewardship in both selecting an appropriate antibiotic and optimizing its dose and duration to prevent and cure an infection may prevent the emergence of *C. difficile.*
- The diagnosis of CDI should be based on clinical signs and symptoms in combination with laboratory tests.
- When antibiotic therapy is indicated, options include metronidazole (only in mild cases), oral or intraluminal vancomycin, and oral fidaxomicin.
- Patients with severe CDI who progress to systemic toxicity should undergo early surgical consultation and should be evaluated for potential surgical intervention.
- Resection of the entire colon should be considered to treat patients with fulminant colitis. However, diverting loop ileostomy with colonic lavage may be a useful alternative to resection of the entire colon

References for this chapter can be found at expertconsult.com.

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125

Anemia and RBC Transfusion

Erin L. Vanzant and Alicia M. Mohr

Anemia remains common in the critical care population, and its etiology is multifactorial, related to hemorrhage, hemodilution, diagnostic phlebotomy, acute inflammation, and functional iron deficiency. These factors result in decreased red blood cell (RBC) production and reduced RBC survival. This chapter will explore the problem of anemia in the critically ill patient, its causes and effects, and the use and risk of RBC transfusions in the management of anemia, with a focus on evidence-based studies. The physiologic effects of anemia are covered elsewhere.

EPIDEMIOLOGY

Anemia is defined as a hemoglobin (Hb) level of <130 g/L in men and <120 g/L in nonpregnant women.[1] In the intensive care unit (ICU) population, modest anemia is generally accepted to be a hemoglobin level of ≤100 g/L in both men and women. Large observational studies in all admitted ICU patients have demonstrated that the vast majority will experience an appreciable drop in hemoglobin. In a 2006 European study of over 1000 patients, anemia, as defined by a hemoglobin level of <130 g/L in men or <115 g/L in women, was observed in more than 80% of the patients, and by the time of discharge almost 25% had a hemoglobin level of <90 g/L.[2] Similar observations were made in a 2003 North American critical care study that involved 4892 patients.[3] In this study, 70% of patients developed a hemoglobin level of <120 g/L within 2 days of ICU admission, and 50% had a hemoglobin level of <100 g/L. By the end of the first week at least 97% of patients had a notable decrease in their hemoglobin levels.[3]

Anemia develops early within the first 2 days of ICU admission. In nonbleeding patients, an average hemoglobin drop of 5 g/L/day has been observed, with the largest decline seen in the first days after admission.[4] Persistent anemia is common after ICU discharge, with 77% of patients anemic at hospital discharge and 50% remaining anemic for up to 6 months.[3–5]

ETIOLOGY

The cause of anemia in critical illness is complex and often multifactorial. Primary mechanisms include problems with decreased RBC production, hemodilution from large-volume resuscitation, and increased RBC losses. Production issues include a suppression of bone marrow secondary to a blunted erythropoietin response during critical illness, lack of substrate availability (including iron, vitamin B_{12}, and folate), and the presence of renal failure, which leads to an absolute erythropoietin deficiency.[5,6] The blunted erythropoietin response is in part secondary to the host inflammatory response. This can lead to dysregulation of iron metabolism homeostasis, impaired proliferation of erythroid progenitor cells, and increased inflammatory mediators (interleukin [IL]-1, tumor necrosis factor [TNF]-alpha, increased hepcidin concentrations) causing an iron-restricted anemia.[7,8] The elevated hepcidin levels lead to iron sequestration in macrophages and reduce iron absorption from the gut, leading to an iron-restricted erythropoiesis.

Anemia caused by blood loss can be subdivided into disease-related and secondary causes. Disease-related causes of anemia include traumatic blood loss, coagulopathy, hemolysis, and gastrointestinal losses. Other secondary losses are primarily iatrogenic and include losses caused by diagnostic sampling, hemolysis, vascular cannulation, renal replacement therapy, and surgical procedures. Daily diagnostic sampling can be an important contributor to anemia. The average volume of blood draws in the ICU results in an average of 40 mL of blood loss per day, and up to 70 mL per day are lost as the patient's illness progresses.[6,8] Phlebotomy-related blood loss has been decreased with the introduction of new conservative techniques, with pediatric tubes, reinfusion of the discarded sample from indwelling lines, and reducing the frequency of blood tests.

CONSEQUENCES OF ANEMIA

Anemia is associated with poor outcomes, especially in the elderly and those with chronic disease.[9,10] The compensatory response of the body in acute or chronic anemia is an extra burden on critically ill patients. The supply/demand balance is particularly stressed in the critically ill anemic patient who has increased cardiac and peripheral oxygen consumption. In patients with ischemic heart disease, coronary flow may be fixed, thereby creating a mismatch between blood supply and oxygen demand. In a large retrospective administrative database study of over 75,000 patients over the age of 65 with myocardial infarction, lower hematocrit (Hct) levels were associated with significantly higher rates of shock and heart failure, in-hospital and 30-day mortality, and increased length of hospital stay.[11]

RED BLOOD CELL TRANSFUSION

Epidemiology

Anemia in critical care populations is common. The physiologic effects not only affect oxygen delivery to vital organs and tissues but also

increase cardiac workload as a consequence of natural compensatory mechanisms. These effects are further accentuated in certain high-risk populations. RBC transfusion is one of the most common therapies ordered in the ICU. It is estimated that the incidence of RBC transfusion in the ICU varies between 20% and 50%.[12] Although anemia appears to be a risk factor for both morbidity and mortality, the benefit of the augmentation of hemoglobin levels with RBC transfusion is less clear and is the focus of the discussion ahead.

PHYSIOLOGIC EFFECTS OF RBC TRANSFUSION

The negative effects of anemia on oxygen delivery are clear. Although the improved delivery of oxygen after RBC transfusions in these patients has been demonstrated in several studies, an increase in oxygen uptake and consumption by the end organs and tissue beds is less evident and is not a consistent finding. This can be explained by the various adverse factors of stored blood, like low levels of 2,3-diphosphoglycerate (2.3-DPG), with decreases in the ability of hemoglobin to unload oxygen to the tissues, the structural changes in stored blood, and the accumulation of proinflammatory cytokines. Therefore despite a strong physiologic rationale to treat anemia in critically ill patients, particularly those with evidence of end-organ ischemia, studies have failed to demonstrate reliable benefits with respect to oxygen utilization.

TRANSFUSION-RELATED COMPLICATIONS

There are infectious and noninfectious risks from RBC transfusions (Table 125.1). RBCs are tested for an extensive number of pathogens, including syphilis, hepatitis B, human immunodeficiency virus (HIV), human T-cell lymphotropic virus, hepatitis C, West Nile virus, Chagas disease, and Zika virus. In addition, storage of blood in refrigerators makes bacterial infection rare. Because of significant enhancements in donor screening and blood testing, the direct transmission of infection through a contaminated blood supply is exceedingly rare (see Table 125.1).

TABLE 125.1 Complications Associated With Allogeneic RBC Transfusion

	Complication	Risk per RBC Unit Transfused
Infectious complications	Symptomatic bacterial sepsis	1:250,000
	Death from bacterial sepsis	1:500,000
	Hepatitis:	
	A	1:2 million
	B	1:153,000
	C	1:2.3 million
	HTLV	1:4.3 million
	HIV/AIDS	1:7.8 million
	West Nile virus	<1:1 million
	Parasitic infection	1:4 million
Noninfectious complications	Urticarial reaction	1:100
	Febrile nonhemolytic reaction	1:300
	Transfusion-associated circulatory overload	1:700
	Transfusion-related acute lung injury	1:10,000
	Delayed hemolytic transfusion reaction	1:7000
	Acute hemolytic transfusion reaction	1:40,000
	Anaphylactic reaction	1:40,000
	Posttransfusion purpura	Rare

Data from Callum JL, Lin Y, Pinkerton PH, et al. *Bloody Easy 3: Blood Transfusions, Blood Alternatives and Transfusion Reactions: A Guide to Transfusion Medicine*. 3rd ed. Ontario: Ontario Regional Blood Coordinating Network; 2011.

AIDS, Acquired immunodeficiency syndrome; *HTLV,* human T-cell lymphotropic virus; *HIV,* human immunodeficiency virus; *RBC,* red blood cell.

Although changes in donor screening and blood testing have led to a significant decline in direct RBC transfusion-related infections over the past 30 years, indirect RBC transfusion-related infections have been the focus of many more recent studies. A systematic review and meta-analysis of 20 randomized trials with 7456 patients evaluated the risk of healthcare–associated infections linked to RBC transfusions and compared different liberal and restrictive transfusion strategies.[13] They found that although a restrictive transfusion strategy was not significantly associated with fewer overall healthcare–associated infections, there was a significant risk reduction in serious infection rates even when controlling for leukoreduction (number needed to treat 48, 95% confidence interval [CI] 36–71).[13] This significance was not observed in a subgroup analysis of 1475 critically ill patients. Another systematic review of randomized trials by the *British Medical Journal* to study the effect of restrictive versus liberal transfusion strategies used a subgroup meta-analysis of eight trials deemed at lower risk of bias by the authors that included 5107 patients.[14] The authors also showed a lower associated risk of infection with a restrictive transfusion strategy (relative risk [RR] 0.73, 95% CI 0.55–0.98).[14]

Noninfectious complications of RBC transfusions are far more common (see Table 125.1). These represent a spectrum from relatively benign (fever) to more severe (acute lung injury) and imminently life-threatening (hemolytic reactions).[15] With increased surveillance and studies focused on complications of transfusions, it has been recognized that transfusion-associated circulatory overload (TACO) is becoming one of the most common risks associated with RBC transfusion.[15] Patients at high risk of volume overload have the greatest danger for developing TACO. The leading cause of RBC transfusion-related morbidity is from transfusion-related acute lung injury (TRALI). This pathophysiologic process is characterized by noncardiogenic pulmonary edema leading to hypoxia. TRALI is secondary to increased lung endothelial permeability and can be caused by immune-mediated and nonimmune-mediated mechanisms.[16] Immune-mediated TRALI is caused by the presence of leukocyte antibodies in the plasma of donor blood that are directed against human leukocyte antigens and human neutrophil antigens.[17,18] Nonimmune mediation is thought to be the result of biologically active substances such as lipids and cytokines. Any blood product can trigger TRALI, but it is most commonly associated with the transfusion of products containing high plasma content, and the risk increases with the number of products transfused. In the critically ill patient, the clinical picture of TRALI is difficult to distinguish from other causes of acute lung injury. Therefore there has been a proposed update to define TRALI by an expert panel.[18] The authors used the Delphi methodology to split TRALI into two types based on a patient's risk factor for acute respiratory distress syndrome (ARDS) (Table 125.2).[18] Type I includes those without risk factors for ARDS and is defined similarly to the traditional definition. Type II includes those who may have mild ARDS or risk factors for ARDS, but have had a stable respiratory status for at least 12 hours before their transfusion and otherwise meet the definition of type I.

The exact mechanisms by which these complications occur are not understood, but are likely at least in part attributable to host immune and inflammatory responses. Central to immune-mediated reactions are donor ILs and the TNF, in addition to antibodies or activated neutrophils, fragments of cellular membranes, and soluble human leukocyte antigen, which play important roles in transfusion-induced immunomodulation

TABLE 125.2 New Consensus TRALI Definition

TRALI type I	Patients have no risk factors for ARDS and meet the following criteria: a. i. Acute onset ii. Hypoxemia (P/F <300 or SpO_2 <90% on room air) iii. Clear evidence of bilateral pulmonary edema iv. No evidence or contribution of left atrial hypertension to hypoxemia b. Onset during or within 6 hours of transfusion c. No temporal relationship to an alternative risk factor for ARDS
TRALI type II	Patients who have risk factors for ARDS (but have not been diagnosed with ARDS) or who have P/F of 200–300 but respiratory status deteriorates because of transfusion based on: a. Findings as described in a and b of TRALI type I b. Stable respiratory status in the 12 hours before transfusion

Data from Vlaar APJ, Toy P, Fung M, et al. A consensus redefinition of transfusion-related acute lung injury. *Transfusion.* 2019;59(7):2465–2476. *ARDS,* Acute respiratory distress syndrome; *P/F,* partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2); *TRALI,* transfusion-related acute lung injury.

(TRIM). TRIM is purported to predispose patients to infections and cancer recurrence.[19–21] Many Western countries across Europe and North America have adopted leukoreduction programs to reduce the effects of TRIM. TRIM may contribute to indirect infectious complications from RBC transfusions, like healthcare–associated infections that occur downstream from the point of transfusion.

Complications from massive transfusions, including coagulopathies, electrolyte disturbances, acid-base imbalances, temperature dysregulation, and citrate toxicity, are also of significant importance but are beyond the scope of this chapter.

RBC STORAGE

RBC storage encompasses the numerous physiologic and morphologic changes that occur in RBCs during storage that are a potential consequence of the storage medium.[22] Biochemical changes include depletion of 2,3-DPG (causing a reduction in oxygen unloading) and adenosine triphosphate (intracellular energy stores), *S*-nitroso-hemoglobin, and calcium. Morphologic changes include membrane phospholipid loss and redistribution, protein oxidation and lipid peroxidation, release of free hemoglobin, and microvesicle formation, which lead to RBC membrane deformation, altering the biconcave shape to a deformed spheroechinocytes.[23] Consequently, the rheologic properties of blood are altered, potentially affecting the normal passage of these deformed RBCs through the capillary microvasculature. Prolonged storage significantly impairs the ability of stored RBCs to deliver to the tissues. The effect of the storage lesion on clinical outcome has been reported in several observational studies, but these findings were not validated in more rigorous study designs.

The Canadian-led Age of Blood Evaluation (ABLE) international randomized trial was conducted to study the effect of blood storage time on clinical outcome. ABLE included 2430 patients from 64 centers across Canada and Europe and tested the effect of transfusion of fresh (stored <8 days) RBCs compared with standard-issue RBCs (oldest available compatible blood) on 90-day mortality and clinically important morbidity.[24] The investigators found no significant difference in the primary outcome of 90-day mortality among those patients who received fresh RBCs (mean age 6.1 ± 4.9 days) compared with those who received the older units (mean age 22.0 ± 8.4 days).[24] Further, there were no appreciable differences between the two groups in all of the secondary outcomes, including major illnesses, duration of life supports (respiratory, hemodynamic, and renal), and length of hospital stay or transfusion reactions.

A secondary analysis of the INFORM trial, a multicenter randomized controlled trial (RCT) that looked at all-cause hospital mortality in those with RBC transfusions greater than 35 days to those less than 7 days again found no effect between the two groups.[25] A similar study to the ABLE trial was conducted by an Australian group called the TRANSFUSE-RCT (standard issue transfusion versus fresher RBC use in intensive care). This large multicenter study included 59 centers in five countries with 4919 patients undergoing randomization.[26] The investigators compared the effect of transfusion of the freshest available versus the oldest available RBCs and the impact on 90-day mortality. They also evaluated 28-day mortality, persistent organ dysfunction, and new bloodstream infections over 180 days. The authors found no significant difference in those who received the freshest RBCs versus older blood.[26]

WHEN TO TRANSFUSE BLOOD IN THE CRITICALLY ILL

RBC transfusion remains the treatment of choice for anemia in the ICU. Various studies and trials have shown that restrictive blood transfusion protocols that use a hemoglobin trigger of <70 g/L for most critically ill patients have been found to beneficial in lowering total mortality, infections, and cardiac events. The evidence supporting a restrictive transfusion strategy for general critically ill patients is shown in Fig. 125.1. Published in 1999, the landmark Transfusion Requirements in Critical Care (TRICC) trial found no difference in 30-day mortality for critically ill patients with euvolemia, and patients should be managed with a restrictive (Hb <70 g/L) transfusion threshold.[27] This RCT included 838 ICU patients with a hemoglobin concentration of ≤90 g/L within 3 days of admission who were randomized to either a restrictive or liberal (70 g/L vs. 100 g/L) transfusion threshold strategy. The investigators found no significant difference in 30-day mortality between the groups (18.7 vs. 23.3%, $P = .11$).[27] Further, subgroup analyses showed that 30-day mortality was significantly lower in the less sick subpopulation (patients with an APACHE II score of <20) and in those critically ill patients who were less than 55 years of age.

In the euvolemic critically ill patient, improving oxygen delivery is the most common reason for administering an RBC transfusion. Specifically, in the American CRIT study,[3] a cohort of 4892 patients from 284 ICUs in 213 hospitals were observed, and low hemoglobin, active bleeding, and hemodynamic instability/hypotension were the most common indicators for transfusion (90%, 24%, and 21%, respectively). These observations were consistent with the findings of the European ABC study[9] (3534 patients, RBC transfusion rate 37%), where active bleeding (56%), anemia with diminished physiologic reserves (28%), altered tissue perfusion (17%), and ischemic heart disease (8%) were the most common reasons for transfusion.

A 2008 systematic review of 45 observational studies demonstrated an association between RBC transfusions and poor outcomes, including an increased risk of death, infection, organ dysfunction, and ARDS.[28] More recently, a systematic review of large-scale observational studies of mixed medical, surgical, ICU, and trauma patient populations (minimum 1000 patients) published between 2006 and 2010 demonstrated that RBC transfusions (as compared with no transfusion) were associated with adverse events, including mortality.[29] All of these studies, however, are subject to potential bias significantly limiting the interpretation and generalization of the results.

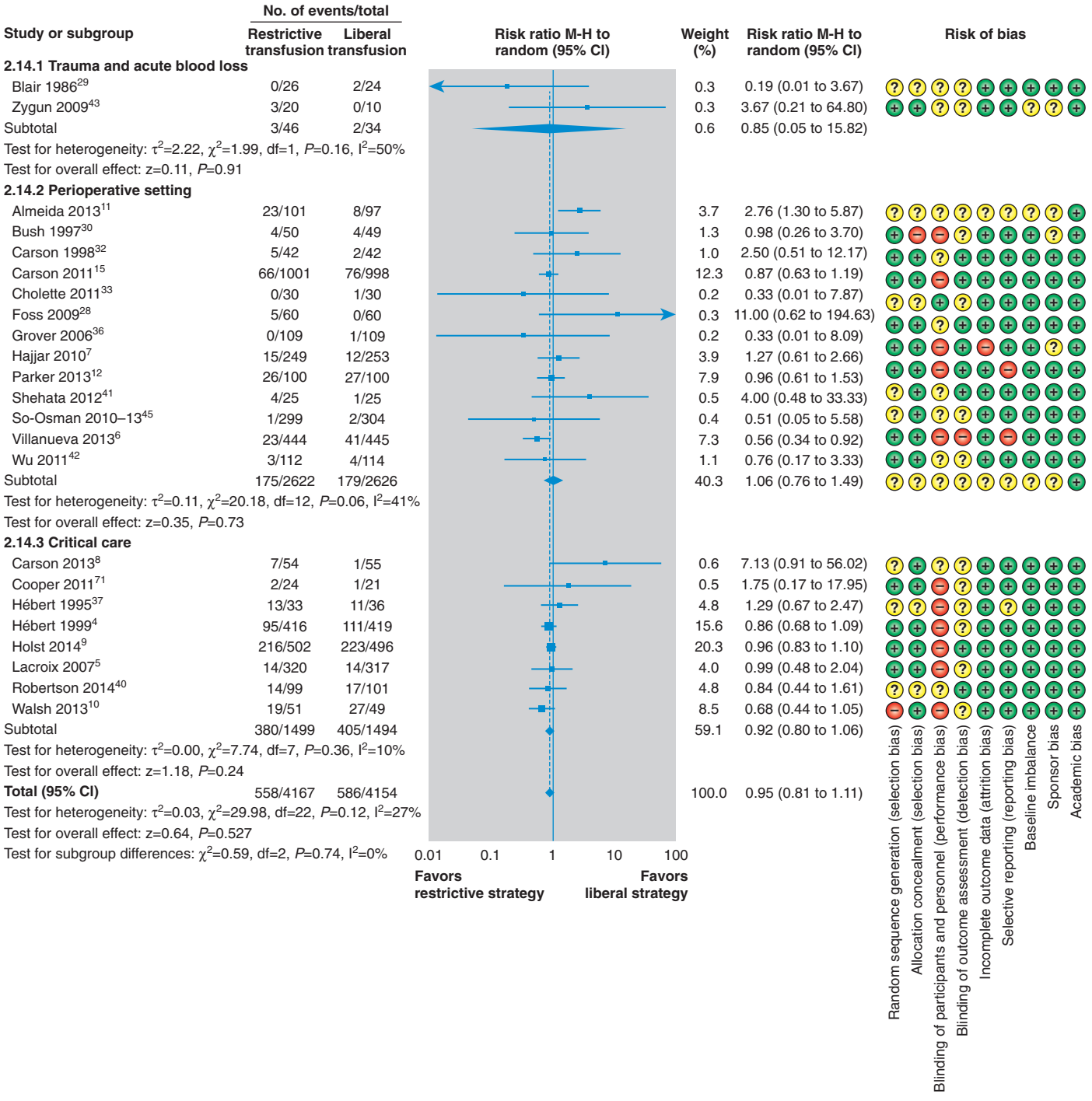

Fig. 125.1 Forest plot of the effect of restrictive versus liberal transfusion strategy on mortality stratified by patient population, presented as risk ratios with 95% confidence intervals (*CI*) and presented with risk of bias assessment. The size of the *square* represents the weight of the trial in the pooled analysis. (From Holst L, Petersen M, Haase N, et al. Restrictive versus liberal transfusion strategy for red blood cell transfusion: Systematic review of randomised trials with meta-analysis and trial sequential analysis. *BMJ.* 2015;350:h1354.)

Several systematic reviews of randomized trials of RBC transfusion in critical care and other populations exist. A comprehensive 2012 Cochrane systematic review of 19 RCTs by Carson and colleagues[30] examined transfusion thresholds and other strategies to guide transfusion. A restrictive transfusion strategy significantly decreased the exposure risk for RBC transfusion. Although the authors found that a restrictive RBC transfusion threshold was associated with reduced hospital mortality (5 studies, RR 0.77, 95% CI 0.62–0.95), no statistical significance was observed for 30-day mortality (11 studies, RR 0.85, 95% CI 0.70–1.03).[30] Furthermore, there was no statistically significant reduction in medical complications, including pneumonia (five studies), pulmonary edema (five studies), stroke (five studies), cardiac (seven studies), or venous thromboembolic events (three studies). The authors also noted the lack of literature to guide transfusion practices in certain patient populations, like those with acute

cardiac ischemia. More recently, a systematic review of restrictive versus liberal transfusion strategies for RBC transfusion by Holst and colleagues included 31 trials from a number of different clinical settings.[14] They concluded that a restrictive strategy resulted in less RBC transfusion and was not associated with less risk of death, either overall or in any of the population subgroups (see Fig. 125.1). Differences in overall mortality or fatal or nonfatal myocardial ischemia were also not observed.

A recent subanalysis of the Intensive Care Over Nations audit noted that transfusion rates in multiple regions across the world were notably lower than those reported in the ABC and CRIT studies.[31] The authors proposed that this is the result of the adaptation of a more restrictive approach to transfusion, reflecting recent literature. It is still too early to see if this trend will continue, as additional studies are being performed.

In summary, a restrictive RBC transfusion strategy leads to fewer transfusions, decreased exposure risks, and appears to not be associated with worse clinical outcomes and may in fact result in better outcomes as compared with a liberal transfusion strategy. Consequently, evidence favoring restrictive transfusion strategies has been translated into clinical practice for nearly two decades. As a result, the 2018 Patient Blood Management International Consensus Conference recommended a hemoglobin transfusion threshold of 70 g/L for stable critically ill patients.[32]

TRANSFUSION THRESHOLDS FOR SPECIFIC SUBPOPULATIONS

There are certain critical care subpopulations with distinct physiology or pathophysiologic processes that are underrepresented in the trials discussed earlier, limiting the generalization of the existing evidence to guide their anemia management with RBC transfusions.

Sepsis

A more liberal approach to RBC transfusion was previously suggested in septic shock patients with evidence of hypoperfusion/end-organ ischemia. A target hematocrit >30% was based on the significant effect on survival when introduced as part of an early goal-directed therapy bundle demonstrated by Rivers and colleagues.[33] Since this study, two other RCTs of a goal-directed therapeutic approach to patients with severe sepsis/septic shock failed to demonstrate the same survival benefit.[34,35] Transfusion rates in both of these studies were under 15%.

The specific effect of transfusion strategies on outcome in septic shock has recently been tested (liberal vs. restrictive) in the TRISS RCT.[36] In this multicenter RCT of 1005 ICU patients, the effect of a liberal (Hb trigger <90 g/L) versus a restrictive (Hb trigger <70 g/L) transfusion strategy in patients with septic shock on 90-day mortality was examined. There was no appreciable difference in the primary outcome between the two groups (RR 0.94, 95% CI 0.78–1.09) and no significant difference in ischemic events.[36] Similarly, no differences were found in subgroup analyses for age, chronic cardiovascular disease history, or illness severity. Therefore for patients with septic shock, a restrictive transfusion strategy imparts no increased risk of mortality or negative outcome and is associated with fewer RBC transfusions. The 2016 Surviving Sepsis Guidelines suggest a hemoglobin transfusion trigger of <70 g/L in the absence of extenuating circumstances, such as myocardial ischemia, severe hypoxemia, or acute hemorrhage.[37]

Acute Coronary Syndrome

Decreased myocardial oxygen delivery is the major concern in acute coronary syndrome caused by impaired coronary blood flow. In a subgroup analysis of patients with cardiovascular disease ($n = 357$) enrolled in the TRICC trial,[38] no significant difference in hospital and 30-day mortality and length of stay were found between the restrictive (Hb trigger of 70 g/L) and liberal (Hb trigger of 100 g/L) transfusion strategies. An insignificant trend toward harm was seen in those patients with severe ischemic heart disease ($n = 257$) in the restrictive strategy.[38]

The more recent FOCUS RCT of high-risk patients undergoing hip surgery ($n = 2016$, patients ≥50 years of age with a history of or risk factors for cardiovascular disease) randomized participants to either a restrictive (Hb trigger of 80 g/L) or a liberal (Hb trigger of 100 g/L) transfusion strategy.[39] The investigators found no difference between the groups for the primary outcome of death or inability to walk across the room without human assistance at 60 days. However, in a higher-risk population of patients with acute coronary syndrome or stable angina undergoing angiography, in a small pilot RCT of a restrictive versus liberal transfusion strategy, a trend toward a decrease in the primary composite outcome of death, myocardial infarction, or unscheduled need for revascularization at 30 days was observed in the liberal strategy group (risk difference: 15.0%, 95% CI 0.7–29.3%, $P = .054$).[40] Currently, the MINT trial (myocardial ischemia and transfusion) (NCT02981407) is ongoing and will aim to enroll 3500 patients with myocardial infarction and evaluate the effect of a restrictive (<80 g/L) or liberal transfusion (<100 g/L) threshold on all-cause mortality or nonfatal myocardial reinfarction within 30 days.

Cardiac Surgery

Evidence in RBC transfusion strategies in the cardiovascular surgery population is more conflicting. In the TRACS noninferiority trial[41] involving patients who had undergone cardiac surgery, a restrictive (Hct trigger <24%) compared with a liberal (Hct trigger <30%) transfusion strategy was noninferior with respect to their primary composite outcome of 30-day all-cause mortality and severe morbidity (10% vs. 11%). More recently, the large multicenter TITRe2 trial enrolled 2007 patients undergoing nonemergency cardiac surgery and examined the effect of a liberal (Hb trigger <90 g/L) versus restrictive (Hb trigger <75 g/L) transfusion strategy on a composite of serious infections or ischemic events at 3 months.[42] Although there was no significant difference in the primary outcome between the two groups, a significant increase in mortality was observed in the restrictive arm (hazard ratio 1.64, 95% CI 1.00–2.67, $P = .045$). The authors were careful not to overinterpret these secondary findings, but this strengthens the need for further trials in this higher-risk population in which a restrictive transfusion strategy may not be safe.

The subsequent Transfusion Requirements in Cardiac Surgery (TRICS)-III trial was the largest RCT of 5243 cardiac surgery patients and confirmed that a restrictive transfusion strategy was not inferior to a liberal strategy.[43] The 2019 Patient Blood Management International Consensus Conference recommends a hemoglobin threshold of 75 g/L for patients undergoing cardiac surgery.[32]

Acute Neurologic Injury

The decreased oxygen delivery associated with anemia may have more significant effects in those patients with stroke, subarachnoid hemorrhage (SAH), and traumatic brain injury (TBI). Evidence to guide RBC transfusions in these populations is lacking because both anemia and transfusion have been associated with worse outcomes. In the TRICC trial, only 67 patients with a primary neurologic diagnosis were included in the original trial.[27] A subgroup analysis of these limited patients showed no difference in outcome between the liberal and restrictive transfusion strategies.[44]

A recent systematic review of six comparative studies of RBC transfusion in a neurocritically ill population[45] found only one additional small RCT in an adult population. This small RCT included 44 patients with SAH who were randomized to either a liberal (Hb trigger of <115 g/L) or a restrictive (Hb trigger <100 g/L) RBC transfusion

strategy.[46] The study was underpowered to detect any clinically relevant outcome and used triggers that are higher than those currently practiced, which resulted in the majority of the patients receiving at least one RBC transfusion in both arms. There are no RBC transfusion strategy trials specific to an ischemic stroke population.

A RCT of 200 patients with TBI compared a liberal (Hb trigger of <100 g/L) with a restrictive transfusion strategy (Hb trigger of 70 g/L) and erythropoietin versus placebo on outcome, as measured by the Glasgow Outcome Scale (GOS), at 6 months.[47] There was no statistically significant difference between the two transfusion strategies ($P = .28$), but fewer thromboembolic events in the restrictive threshold group were reported (odds ratio [OR] 0.32, 95% CI 0.12–0.79).[47] This study does not completely answer the clinical question of the utility of liberal transfusion strategies in this patient population, as the study was underpowered to detect smaller yet clinically important outcome differences between the two transfusion groups. Although RBC transfusion rates differed in the two groups, the difference in median hemoglobin level was less than 20 g/L by day 9 and increasingly smaller by days 16, 23, and 30.

Currently two multicenter RCTs are in process, looking at transfusion thresholds in patients with TBI. The first is by a European group—the TRAIN trial (transfusion strategies in acute brain injured patients) will enroll 4610 patients with TBI, SAH, or intracranial hemorrhage to study the effect on a liberal (<90 g/L) versus restrictive (<70 g/L) transfusion trigger on neurologic outcomes (NCT02968654). A similar study is being conducted by a Canadian group—the HEMOTION trial (hemoglobin transfusion threshold)—where they plan to enroll 712 patients with moderate to severe TBI and evaluate the effect of hemoglobin thresholds (<100 g/L versus <70 g/L) on neurologic functional outcomes (NCT03260478). Although current studies do not demonstrate harm from a restrictive transfusion strategy, it remains unclear if any benefit results from a more liberal strategy in these unique patient populations.

Gastrointestinal Bleeding

In one large trial, patients with severe acute upper gastrointestinal bleeding were randomized to restrictive (Hb <70 g/L) versus liberal (Hb <90 g/L) transfusion strategies. The restrictive strategy had significantly better 6-week survival, less rebleeding, no increase in portal-pressure gradient, and reduced need for additional transfusion.[48] The 2012 American College Gastroenterology upper gastrointestinal bleeding guidelines recommend a hemoglobin greater than or equal to 70 g/L, with higher targets in patients with intravascular volume depletion or comorbidities.[49]

Alternatives to Transfusion

The knowledge of adverse effects of blood transfusion has focused current research on finding alternatives to transfusion or methods to reduce transfusion.

Erythropoiesis-Stimulating Agents

In critically ill patients, the erythropoietin response to anemia is abnormal. The bone marrow has a decreased response to erythropoietin. Corwin and colleagues,[50] in a prospective, randomized, placebo-controlled trial including 146 medical, surgical, and trauma patients, concluded that treatment with erythropoietin did not reduce the number of RBC transfusions. The use of erythropoietin was associated with a greater incidence of thrombotic events.[50] This may be caused by the fact that erythropoiesis-stimulating agents require high dosages or have delayed effect. Currently, erythropoiesis-stimulating agents are only indicated in patients with chronic kidney disease.

Iron Therapy

In critically ill patients there is an iron-restricted erythropoiesis caused by iron sequestration and decreased absorption from the gut. This suggests a role for intravenous (IV) iron therapy, but this has been challenged because of the role of iron in the growth and virulence of microbes. In a meta-analysis of five RCTs of iron supplementation (four IV, one oral iron) in adult critical care with 665 patients, the researchers found no difference in RBC transfusions, hemoglobin level, mortality, in-hospital infection, or length of stay.[51] Most recently, the IRONMAN study compared IV iron with placebo in 140 critically ill patients.[52] This study was unable to demonstrate any reduction in RBC transfusion, but patients did have higher hemoglobin levels on discharge.[52] Current evidence suggests that iron supplementation does not increase infections or adverse events, but improved patient-focused outcomes are lacking.

Blood Substitutes

The quest for blood substitutes or artificial oxygen carrier solutions as alternatives to RBC transfusions has spanned decades. Blood substitutes have not shown promising results. Cell-free hemoglobin-based oxygen carriers have various adverse effects, including nephrotoxicity, impaired perfusion, and increased rates of myocardial infarction and death.[53] Other challenging product development issues relate to the safety and cost-effectiveness of these products.

CONCLUSION

The occurrence of anemia is nearly inevitable in critically ill patients and because of its multifactorial etiology, it has impact both on morbidity and mortality. The primary etiologies include blood loss caused by bleeding and phlebotomy and defective erythropoiesis caused by systemic inflammation. The evidence supports the restrictive strategy of RBC transfusion (transfusion at Hb <70 g/L) preferably over a liberal transfusion strategy (transfusion at Hb <10 g/L) in the majority of critically ill patients. Careful consideration to individual cases must be taken in specific populations, including patients with severe cardiovascular disease and brain injury, where there is a need for more evidence. Although alternatives to RBC transfusion are lacking in the critically ill, the avoidance of unnecessary diagnostic phlebotomy should be evaluated daily.

KEY POINTS

- Anemia is common and affects almost all critically ill patients and may negatively affect organ function and patient outcome.
- Persistent anemia is common after ICU discharge, and 50% of patients remain anemic for up to 6 months.
- The etiology of anemia is multifactorial, related to hemorrhage, hemodilution, diagnostic phlebotomy, acute inflammation, and functional iron deficiency.
- RBC transfusion, the most common treatment for anemia, comes with associated infectious risks and more common noninfectious risks, including TACO, TRALI, and TRIM.
- The best evidence suggests a practice of restrictive RBC transfusion (hemoglobin trigger <70 g/L) for the majority of critically ill patients.
- Certain subpopulations of critically ill patients, such as those with cardiac disease or neurologic injury, may benefit from a more liberal trigger, but further research is still needed.
- Alternatives to blood transfusion in critically ill patients with anemia are not proven, but careful consideration of the need for diagnostic phlebotomy can be implemented daily.

References for this chapter can be found at expertconsult.com.

ANNOTATED REFERENCES

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This is a critical review of high-level studies evaluating RBC transfusion strategies with a focus on hemoglobin thresholds in the ICU. Current literature supports the use of restrictive transfusion strategies in the majority of critically ill populations, but a slightly higher threshold is recommended in cardiac surgery and those with cardiovascular disease.

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A good review article.

Napolitano LM. Anemia and red blood cell transfusion: advances in critical care. *Crit Care Clin.* 2017;33(2):345–364.
This is a review of the etiology of anemia in the ICU and current transfusion practices. Significant advances have been made in understanding the pathophysiology of anemia in the ICU. The anemia is related to high hepcidin concentration resulting in iron-restricted erythropoiesis and abnormal erythropoietin concentrations. Although a restrictive transfusion strategy is recommended to ICU patients in need of therapy for anemia, all strategies to reduce anemia and blood loss in the ICU should be implemented.

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Guidelines for Blood Component Therapy

Alexandra L. Dixon and Martin A. Schreiber

Blood component therapy is generally supportive for the correction of one or more hematologic deficiencies until the basic disease process can be controlled or corrected. Anemia is pervasive in the intensive care unit (ICU), with over 30%–50% of critically ill patients receiving a transfusion during their ICU stay.[1–3] Transfusions do not come without risk, and thus the past decade has seen a drastic shift from a product-centered focus to one of patient blood management (PBM). Defined by the AABB (previously the American Association of Blood Banks) as "an evidence-based, multidisciplinary approach to optimizing the care of patients who might need transfusion," PBM consists of a three-pillar approach: optimizing red cell mass, minimizing blood loss, and tolerating anemia. Accurate diagnosis of hematopoietic deficiencies, minimizing blood loss and unnecessary laboratory draws, and tolerance of deficiencies within limits is important. Perioperatively, this can be achieved by identifying patients at high risk of bleeding, giving close attention to surgical and anesthetic techniques (e.g., permissive hypotension, normothermia, reduction of venous pressure at the operating site) and using pharmacologic agents to minimize blood loss (eFig. 126.1). Additionally, cell salvage and hemostatic agents such as fibrin glue can be employed to avoid transfusion.

RED BLOOD CELL CONCENTRATES

Transfusion of red blood cells (RBCs) is one of the most common medical interventions performed in the United States, with over 11 million units of RBCs transfused annually.[4] RBCs are typically packed (pRBCs) with a preservative solution that allows refrigerated storage for up to 42 days. Each unit has a hematocrit of approximately 60%, and transfusion of one unit of pRBCs is typically expected to result in a hemoglobin (Hgb) increase of 1 g/dL in an adult with stable blood volume. Despite previous published guidelines, there remains significant variation in the practice of transfusing patients.[5–9] Whereas some clinicians base the decision to transfuse solely upon Hgb level, many guidelines maintain that transfusions should be given for overall clinical status, patient preference, and availability of alternative therapies.[10,11]

A recent systematic review and meta-analysis evaluating the efficacy of RBC transfusion included 31 randomized clinical trials (RCTs) with over 12,000 patients who were randomized to a higher Hgb concentration as the threshold for transfusion (referred to as *liberal transfusion;* Hgb <10 g/dL) or to a lower Hgb concentration (referred to as *restrictive transfusion;* Hgb <7–8 g/dL).[12] Patients in the restrictive group were 43% less likely to receive an RBC transfusion than those in the liberal group. Overall, there was no difference in 30-day mortality between the two groups, and results were similar among trials with thresholds of 7 and 8 g/dL. Other outcomes did not differ significantly between restrictive and liberal transfusion groups, including infection (pneumonia, wound, bacteremia), myocardial infarction, and congestive heart failure.

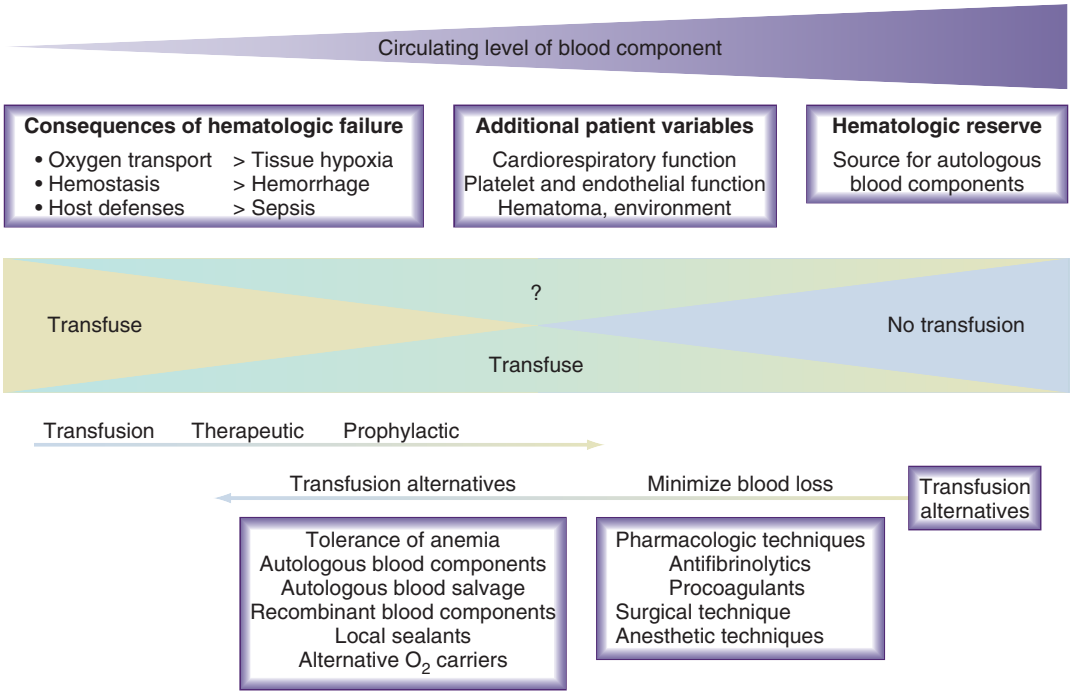
With these data in mind, the AABB recommends a restrictive RBC transfusion threshold in which transfusion is not indicated until the Hgb falls below 7 g/dL for the majority of hemodynamically stable patients, including those who are critically ill. For patients undergoing orthopedic or cardiac surgery and those with cardiovascular disease, the AABB recommends a restrictive transfusion threshold with an Hgb goal of 8 g/dL. Although they do comment that the restrictive threshold of 7 g/dL is likely comparable with 8 g/dL, RCT evidence is not available for all patient categories. These recommendations do not apply to patients with acute coronary syndrome, severe thrombocytopenia, and chronic transfusion-dependent anemia, as the evidence is insufficient in these disease processes.[10]

PLATELET CONCENTRATES

Platelet concentrates can be prepared by apheresis or from whole blood using either the buffy-coat or platelet-rich plasma methods. Whereas apheresis platelets are obtained from one donor, the buffy-coat and platelet-rich plasma methods require pooling of platelets from several donors (usually four to six). Unlike other blood components, platelets are stored at 22°C with continuous agitation and have a shelf-life of up to 5–7 days out of concern for possible bacterial growth during storage.

Thrombocytopenia is correlated with increasing illness severity, sepsis, and organ dysfunction; however, the effect of thrombocytopenia on clinically significant spontaneous hemorrhage remains unclear. Platelet transfusion strategies are driven by the need to stop (therapeutic) or prevent (prophylactic) bleeding. Although an increased risk of bleeding has been demonstrated with a platelet count below 5×10^9/L and spontaneous hemorrhage rarely occurs above 10×10^9/L, there is a general lack of evidence to support specific platelet thresholds in most critical care and surgical settings.

In patients undergoing surgical or invasive procedures, relative factors that contribute to the decision to transfuse platelets perioperatively include the type of procedure, preoperative platelet counts, degree of active or anticipated hemorrhage, and presence of antiplatelet medications or disorders that affect platelet function. For major surgeries or invasive procedures that carry an inherently elevated risk of bleeding, the platelet count should be maintained at greater than 50×10^9/L. As a significant number of patients who undergo cardiac surgery experience platelet dysfunction related to cardiopulmonary bypass, hypothermia, hemodilution, and platelet activation, prophylactic platelet transfusion should not be performed unless the patient is on antiplatelet therapy. Postoperatively, platelets should be transfused in the setting of active bleeding with a platelet count less than 50×10^9/L



eFig. 126.1 Overview of Blood Management and Where Blood Component Therapy May be Appropriate.

with no obvious source of hemorrhage.[13] For minor surgeries and minimally invasive procedures (central line placement, angiography, endoscopy, lumbar puncture, paracentesis), the platelet count should be maintained above 20–30 $\times$ 10^9/L.[14] For neurosurgical procedures and other procedures that occur within a closed, defined space (including ocular procedures), a platelet count above 100 $\times$ 10^9/L is recommended.[15]

Prophylactic platelet transfusions are recommended only for platelet counts below 10 $\times$ 10^9/L unless other factors that increase the risk of bleeding are present. In patients with qualitative defects in platelet function, platelet count is not a reliable indicator for transfusion, and transfusion decisions and monitoring of efficacy should be based on the setting and clinical features. In the setting of massive hemorrhage, the platelet count should be maintained above 50 $\times$ 10^9/L, and above 75 $\times$ 10^9/L with any associated injury to the central nervous system.[16] The transfusion of platelet concentrates is not generally considered appropriate when thrombocytopenia is the result of immune-mediated destruction or in patients with thrombotic thrombocytopenic purpura and hemolytic uremic syndrome.

FRESH FROZEN PLASMA

Fresh frozen plasma (FFP) has a shelf-life of up to a year at −18°C but requires 30 minutes or more to thaw, limiting immediate availability. Once thawed, it has a 5-day shelf-life before it must be discarded. FFP is widely used, but there are limited specific indications for its use, and there is a dearth of evidence for its efficacy in many clinical settings. FFP is frequently used to correct an abnormal international normalized ratio (INR) in nonbleeding patients. In this setting, many patients have adequate coagulation function and transfusion is unnecessary.[17] FFP may be appropriate in patients with a known coagulopathy who are bleeding or at risk of bleeding when a specific therapy or factor concentrate is not appropriate or is unavailable. This includes patients with a vitamin K deficiency or who require reversal of warfarin therapy. Additionally, FFP is generally indicated in acutely hemorrhaging patients as part of a massive transfusion protocol.

The benefit of plasma transfusion extends beyond its hemostatic effects to include reduction of vascular permeability and mitigation of inflammation after hemorrhagic shock. Severe trauma, in addition to other inflammatory conditions such as ischemia-reperfusion injury, diabetes, and sepsis, are known to result in vascular endothelial dysfunction. In vitro[18–20] and in vivo[21,22] models of hemorrhagic shock demonstrate that plasma restores microvascular integrity, in part by repair of the endothelial glycocalyx. The mechanisms of action of FFP are the subject matter of current research, but may be attributed to soluble factors, of which over 1000 are found in plasma. Many of these soluble proteins are biologically active and have unknown functions.[23]

CRYOPRECIPITATE

Cryoprecipitate is collected as the precipitate of plasma after a freeze-thaw cycle and is enriched in factors VIII and XIII, von Willebrand factor, fibronectin, and fibrinogen. Administration of cryoprecipitate is principally indicated for fibrinogen deficiency or dysfibrinogenemia when there is clinical bleeding, trauma, acute disseminated intravascular coagulation, or before invasive procedures. Currently, the American College of Surgeons Committee on Trauma recommends transfusion of cryoprecipitate to maintain fibrinogen at 180 mg/dL or greater during massive transfusion in bleeding patients.[24]

PLASMA-DERIVED PRODUCTS

Table 126.1 summarizes commonly used fresh and plasma-derived blood products. Prothrombin complex concentrate (PCC) contains concentrated vitamin K–dependent coagulation factors stored as a lyophilized powder. PCC comes as three-factor (containing factors II, IX, and X) and four-factor products (containing factors II, VII, IX,

TABLE 126.1 Blood Products

Blood Product	Main Indications
Whole blood*	Increasingly used for acute traumatic hemorrhage.
Red blood cell concentrates*	Hemorrhage and anemia.
Leukocyte-depleted blood*	In patients having febrile reactions, to avoid leukocyte immunization in selected patients (especially patients with hematologic malignancy). Universal prestorage leukodepletion is more widely used and has the added benefit of minimizing storage lesions.
Platelet concentrates*	Thrombocytopenia caused by marrow hypoplasia or platelet functional defect.
Granulocyte concentrates*	Occasionally in patients with sepsis associated with profound and prolonged neutropenia secondary to marrow suppression.
Fresh frozen plasma*	Specific or multiple plasma protein deficiencies (especially coagulation).
Cryoprecipitate*	Hypofibrinogenemia and rarely in factor VIII and von Willebrand disease, when concentrates are unavailable.[26]
4% or 5% albumin solutions†	Plasma volume expansion. Use is controversial, and the role of albumin solutions in critically ill patients remains under debate.[27]
Concentrated albumin†	Severe hypoalbuminemic states with complicating hypovolemia.
Concentrate of coagulation factors II, VII, IX, and X†	Vitamin K–dependent factor II, IX, and X deficiency and reversal of oral vitamin K antagonists.
Specific factor concentrates†	Factor VIII and IX concentrates have an established role in the management of hemophilia, but others are in the process of establishing their clinical efficacy and indications.[28–30]
	Fibrinogen concentrates for hypofibrinogenemia and dysfibrinogenemia.[28]
	Antithrombin concentrates are available for thrombophilia caused by antithrombin deficiency and are increasingly recommended in other disorders in which antithrombin may be depleted (e.g., DIC, MODS).[31]
Gamma globulin†	Generally used intravenously for replacement in hypogammaglobulinemia or in high dosages as an immune-modulating therapy.[32]
Specific immune gamma globulins†	Rhesus prophylaxis, specific infection prophylaxis and treatment.[33]

DIC, Disseminated intravascular coagulation; *MODS,* multiorgan dysfunction syndrome.
*Fresh products.
†Fractionated plasma products.

and X, in addition to the anticoagulant proteins—protein C, protein S, antithrombin, and heparin). Both three- and four-factor PCC have been shown to be superior to FFP for urgent reversal of acquired coagulation factor deficiency induced by vitamin K agonists and in correcting the coagulopathy of trauma, with four-factor PCC correcting elevated INRs more rapidly than three-factor PCC.[25] Currently, there is extensive and increased use of PCC for off-label applications, such as reversing direct oral anticoagulants.

In addition to FFP and cryoprecipitate, fibrinogen concentrate is increasingly used in the management of hypofibrinogenemic states, depending on local availability. However, because of the low quality of published clinical evidence,[34] the beneficial effect of fibrinogen concentrate remains under debate.

RECOMBINANT BLOOD PRODUCTS

Recombinant growth factors such as erythropoietin and granulocyte stimulating factor have had a major impact on managing anemia and neutropenia. Recombinant hemostatic factors, such as recombinant activated factor VII (rFVIIa), have improved the management of acquired hemophilias and other inherited bleeding diatheses. As rFVIIa tends to localize to areas of vascular injury once administered and may decrease the overall need for blood products in trauma patients, it has also been used off-label in the treatment of severe bleeding despite a lack of high-quality evidence for efficacy, as most experience has been observational and anecdotal.

BLOOD SUBSTITUTES

Significant efforts have long been ongoing to develop substitutes for RBCs and platelets. Unfortunately, neither hemoglobin-based oxygen carriers nor chemical-based products such as perfluorocarbons have yielded optimistic results, and safety concerns have plagued clinical development. However, new research does suggest that these artificial oxygen carriers may have beneficial application in other areas, such as organ preservation for transplant surgery,[35] sickle cell crisis,[36] and brain oxygenation during circulatory arrest.[37]

TRANSFUSION MANAGEMENT OF MASSIVE ACUTE TRAUMATIC HEMORRHAGE

Early definitive hemorrhage control and, when indicated, initiation of a massive transfusion protocol (MTP), have long been the tenets of treatment of severe hemorrhagic shock; however, the composition of an MTP has changed significantly in recent years. The recent conflicts in Iraq and Afghanistan led to the emergence of damage control resuscitation. This is defined as early transfusion of a balanced ratio of blood products along with the prevention and correction of coagulopathy and minimization of crystalloid fluids to prevent the known complications associated with massive crystalloid resuscitation, including acute respiratory distress syndrome, abdominal compartment syndrome, multiple organ failure, and mortality.[38] As shown by the PROMMTT study, patients transfused with plasma and platelet:RBC ratios more than 1:2 had significantly decreased 6-hour to 24-hour mortality.[39] The ideal resuscitation ratio was further validated by the PROPPR trial, which demonstrated that early transfusion of plasma, platelets, and RBCs in a 1:1:1 ratio led to improved hemostasis and fewer deaths from exsanguination than a 1:1:2 ratio.[40]

Massive transfusion (MT) is usually defined as the transfusion of ≥10 units of pRBCs within a 24-hour period. Early identification of the trauma patient who will require MT is difficult, though necessary, as early activation of an MTP is associated with decreased blood waste and improved outcomes. Although several scoring systems exist to identify trauma patients who will require an MTP, early iterations rely on laboratory values that are not available until well after the resuscitation process has begun. One scoring system that requires no laboratory data and thus can be determined almost immediately upon patient arrival is the Assessment of Blood Consumption (ABC) score, which gives 1 point for each of the following: penetrating mechanism, systolic blood pressure (SBP) <90 mm Hg, heart rate (HR) >120 bpm, and positive Focused Assessment with Sonography for Trauma (FAST) exam. A score of 2 or more is predictive of MT, with a sensitivity of 75%–90%, specificity of 67%–88%, and overall accuracy of 84%–87% for trauma patients.[41]

Although blood transfusion may be lifesaving for exsanguinating patients, it is increasingly recognized that transfusion may be an independent risk factor for delayed morbidity and mortality. Transfusion can thus be minimized with tolerance of hypotension, termed *permissive hypotension,* until hemorrhage is controlled.

Failure of hemostasis is common in acutely bleeding patients and may be complex and multifactorial. Trauma-induced coagulopathy (TIC) develops in approximately one-third of all trauma patients. Initially thought to be only the result of the iatrogenic secondary effects of hemodilution, hypothermia, and acidosis, TIC is now known to also result from multiple distinct but highly integrated pathways. Tissue hypoperfusion secondary to hypovolemic shock leads to activation of protein C, ultimately resulting in unopposed fibrinolysis and depletion of fibrinogen. Significant fibrinolysis heralds increased mortality. Conversely, fibrinolysis shutdown, or overinhibition of fibrinolysis, has also been demonstrated to be an independent predictor of adverse outcomes, including mortality, after trauma. The combination of tissue trauma and acidosis has been associated with disruption of the endothelial glycocalyx, the shedding of which appears capable of triggering systemic thrombin production and protein C activation.

NOVEL CONCEPTS FOR DAMAGE CONTROL RESUSCITATION IN TRAUMA

Never-Frozen Liquid Plasma

There is increasing interest in the use of never-frozen, or liquid, plasma to reduce waste and improve rapid availability of plasma in MTPs. Liquid plasma is approved for storage at 1°–6°C for up to 26 days with minimal degradation of clotting factor function. In vitro studies demonstrate that liquid plasma has a better coagulation profile than thawed plasma.[42] In high-volume centers, liquid plasma has the potential to replace FFP because of its superior coagulation profile, its immediate availability for MT, and its potential to reduce waste. FFP that is thawed and never used over its 5-day shelf-life is a major source of waste in most large centers.

Freeze-Dried Plasma

Freeze-dried (or lyophilized) plasma (FDP) is stored at room temperature and can be reconstituted within minutes. It can be stored for at least 1 year in the powder form. Although used extensively during World War II, US production of FDP was halted in the 1960s because of concern for pathogen transmission. FDP may be single donor or it may be pathogen reduced and come from multiple donors. There is currently no approved FDP product in the United States, though FDP is used abroad and by the deployed US military. Products are currently undergoing phase II trials in the United States.

Cold Storage Platelets

Cold storage platelets (CSPs) can be kept at 1°–6° C for up to 21 days and do not require agitation, thus reducing the burden of storage on blood banks. They undergo a spherical shape change when stored cold and are thus cleared from the circulatory system more rapidly than platelets stored at room temperature. CSPs have been shown to aggregate better and produce stronger clots than platelets stored at 20°–24°C.[43,44] CSPs are approved for military use by the Food and Drug Administration (FDA) in deployed settings and have the potential to ease platelet shortage scenarios and make platelets available in rural settings.

Whole Blood

As demonstrated by the PROPPR study, the ideal resuscitation for a trauma patient in hemorrhagic shock is a balanced 1:1:1 transfusion of plasma, platelets, and pRBCs. This "reconstituted whole blood" contains a significant amount of preservative, creating an anemic, thrombocytopenic, and coagulopathic solution even without the addition of crystalloids or artificial colloids. Contrasting this, a single 500-mL unit of fresh whole blood (WB) is diluted with only 70 mL of preservative, yielding an Hgb concentration of 13–14 g/dL, 150,000–400,000 platelets/μL, 1500 mg of fibrinogen, and nearly 100% activity of clotting factors.[45] WB provides a balanced resuscitation that simultaneously addresses oxygen debt and coagulopathy while logistically simplifying the process of transfusion by requiring only one bag as opposed to three. The use of fresh WB has been associated with decreased mortality in the military setting, and transfusion with uncrossmatched, cold-stored, low-titer group O–positive or –negative WB is currently being investigated as an alternative to component therapy in civilian trauma centers.

GOAL-DIRECTED CORRECTION OF COAGULOPATHY

There has been increased interest in viscoelastic coagulation assays such as thromboelastography (TEG) and rotational thromboelastometry (ROTEM) for the monitoring of TIC and guidance of blood product resuscitation. These assays provide real-time information on various viscoelastic properties, including time to clot initiation, clot propagation, clot strength, and clot breakdown (fibrinolysis). Many studies have validated TEG and ROTEM against standard coagulation tests, including prothrombin time (PT), INR, and activated partial thromboplastin time (aPTT). Viscoelastic assays have been shown to reduce mortality and blood product utilization in MT compared with conventional coagulation tests.[46]

HAZARDS OF ALLOGENEIC TRANSFUSION

Noninfectious risks have become the leading concern of transfusion and include the following: transfusion-associated lung injury (TRALI), transfusion-associated circulatory overload (TACO), transfusion reactions (including but not limited to allergic/anaphylactic, acute and delayed hemolytic, febrile, hypotensive, and septic transfusion reactions), alloimmunization, immunomodulation, bacterial contamination (especially of platelets), and graft-versus-host disease (GVHD). Although more detailed discussion of the complications of allogeneic blood transfusions are discussed in other chapters, TRALI and TACO deserve special mention, as they are the leading causes of transfusion-associated morbidity and mortality. Characterized by acute pulmonary edema occurring within 6 hours of transfusion, TRALI consists of pulmonary permeability (noncardiogenic) edema, whereas TACO is defined by pulmonary hydrostatic edema (cardiogenic) with signs of circulatory overload. Both syndromes are difficult to diagnose and underscored by complex and incompletely understood physiologies.

The pathophysiology of transfusion reactions can be divided broadly into the following four categories:

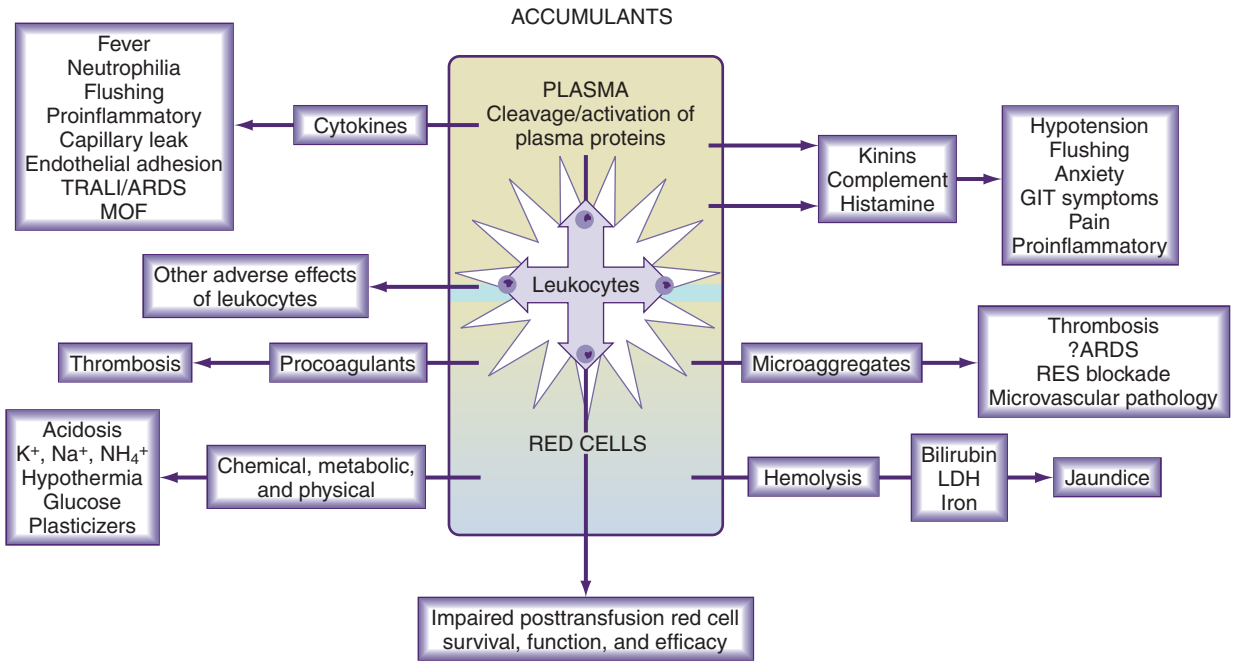
1. Reactions may occur because of *immunologic differences* between the donor and recipient, resulting in varying degrees of blood component incompatibility. In general, for a reaction to occur, the recipient needs to have been previously immunized to a cellular or plasma antigen.
2. A wide range of *infectious agents* may be transmitted by allogeneic blood component therapy. With advances in donor screening and blood product testing, the risk of transmission of infections such as human immunodeficiency virus (HIV) and viral hepatitis have been reduced to less than 1 per 10 million units of blood in developed nations. Despite this, transmission of emerging pathogens is always a threat, with the most recent example being the Zika virus, as potential donors may be viremic at the time of donation—though asymptomatic and thus not detected by donor screening.
3. *Alterations in blood products caused by preservation and storage* may result in quantitative or qualitative deficiencies in the blood components that reduce transfusion efficacy and expose the patient to potentially adverse consequences from substances that accumulate during storage (Table 126.2).
4. *Clinical, technical, and clerical errors* resulting from incorrect patient identification, failure of cold chain management, or administration errors may result in a range of hazards. Included in this group are patients who are at particular risk from lung injury and circulatory overload because of comorbidities such as cardiac compromise, poor clinical assessment of fluid and volume status, and sepsis.

A multitude of experimental and clinical studies have linked blood transfusions to a long list of unfavorable outcomes, including increased ICU admission rates, increased hospital length of stay, sepsis and infection, multiorgan dysfunction, respiratory distress and failure, venous thromboembolism, cardiac complications, stroke, renal injury, and mortality. The implication of RBC transfusion as part of the problem rather than optimal therapy has challenged long-held views about the safety of allogeneic blood transfusion. For these reasons, a precautionary approach should be adopted, with avoidance or minimization of allogeneic transfusion and the use of appropriate patient blood conservation techniques whenever possible.

BLOOD STORAGE LESIONS AND POTENTIAL CLINICAL CONSEQUENCES

In addition to the transfusion reactions and infectious risks discussed earlier, transfusion of large volumes of blood product may expose the patient to "storage lesions," or the collection of biochemical and morphologic changes that occur because of degradation of pRBCs and platelets while stored. This has been postulated to lead to deleterious effects on microvascular circulation and oxygen delivery. Storage lesions progress throughout the duration of storage, and the extent of these changes is determined by the specific blood component, preservative medium, container, storage time, and storage conditions (eFig. 126.2). RBCs stored for longer periods have alterations of the membrane resulting in increased rigidity and adherence to the endothelium, decreased levels of 2,3-bisphosphoglycerate, and decreased nitric oxide metabolism.[47,48] The storage medium itself may contain increased amounts of iron, potassium, free Hgb, and inflammatory mediators, all of which can have significant consequences.[49]

Although there is a growing literature confirming the presence of the storage lesion in vitro, the clinical significance of this continues to be debated. Previous data suggesting adverse outcomes with transfusion of older RBCs were predominantly obtained via uncontrolled observational studies. Contrasting this, a recent meta-analysis of multiple



eFig. 126.2 **Red Blood Cell Storage Lesions.** *ARDS,* Acute respiratory distress syndrome; *GIT,* gastrointestinal tract; *LDH,* lactate dehydrogenase; *MOF,* multiple organ failure; *RES,* reticuloendothelial system; *TRALI,* transfusion-related acute lung injury.

TABLE 126.2 Red Blood Cell Storage Lesions and Possible Clinical Consequences

Storage Lesion	Potential Clinical Consequences
Alterations in blood cell structure and function	
ATP depletion	Echinospherocyte formation, increased osmotic fragility, impaired RBC deformability with adverse effects on oxygen transport and delivery
Microvesiculation and loss of membrane lipid, lipid peroxidation and hemolysis, and irreversibly damaged RBCs	Reduced RBC viability and cell death Hyperbilirubinemia, LDH, increased serum iron, free radical generation, hyperkalemia
Reduced 2,3-DPG	Increased hemoglobin affinity for oxygen and impaired unloading
Decreased CD47 antigen (integrin-associated protein) expression	Reduced posttransfusion survival caused by premature clearance post transfusion
RBC adhesion to endothelial cells	Adverse effects on microcirculatory hemodynamics
Storage temperature	Hypothermia unless pretransfusion warming
Additives	
Citrate	Hypocalcemia, acid-base imbalance, initial acidosis alkalosis
Glucose	Hyperglycemia
Sodium	Hypernatremia
Cytokines: IL-1, IL-6, IL-8, TNF	Fever, hypotension, flushing
Enzymes: Myeloperoxidase, elastase, arginase, secretory phospholipase A_2	Transfusion-related immunomodulation, neutrophilia
Reactive proteins: Defensins, annexin, soluble HLA, Fas ligand, soluble endothelial cell growth factor, and others	Proinflammatory, potential "priming" for ARDS, TRALI, and MODS
Histamine and kinin accumulation	Hypotension, anxiety, flushing, pain syndromes, proinflammatory
Microaggregates and procoagulants	Blockade of reticuloendothelial system Risk factor for development of ARDS, MODS, TRALI Activation of hemostasis > DIC (?), VTE (?), arterial thrombotic events (?)

ARDS, Acute respiratory distress syndrome; ATP, adenosine triphosphate; *DIC,* disseminated intravascular coagulation; *2,3-DPG,* 2,3-diphosphoglycerate; *HLA,* human leukocyte antigen; *IL,* interleukin; *LDH,* lactate dehydrogenase; *MODS,* multiorgan dysfunction syndrome; *RBC,* red blood cell; *TNF,* tumor necrosis factor; *TRALI,* transfusion-related acute lung injury; *VTE,* venous thromboembolism.

large RCTs with over 5000 patients enrolled found that patients transfused with fresher blood (<10 days old) had no difference in adverse events outcomes or mortality when compared with patients transfused with standard-issue blood.[12] Interestingly, a trend toward increased risk of nosocomial infection was demonstrated with fresher blood (risk ratio [RR] 1.09; 95% confidence interval [CI] 1.00–1.18; $P = .04$).[12] Little data exist on transfusion of end-of-storage RBCs (older than 28 days). Further information about the storage lesion and the possible clinical implications is summarized in Table 126.2.

HYPERBILIRUBINEMIA IN THE SETTING OF MASSIVE TRANSFUSION

Hyperbilirubinemia after massive transfusion is common and deserves special mention. A significant portion of the transfused RBCs may not survive, and the resulting bilirubin load causes varying degrees of hyperbilirubinemia. Hypovolemia and shock contribute to impairment in biliary transport functions, particularly in the presence of sepsis or multiple organ dysfunction. An important rate-limiting step in bilirubin transport is the energy-requiring process of transporting conjugated bilirubin from the hepatocyte to the biliary canaliculus. Delayed excretion may lead to conjugated hyperbilirubinemia. A hemolytic transfusion reaction and resorbing hematoma also must be considered as possible causes of hyperbilirubinemia. A later increase in bilirubin at 5 days post shock may reflect ongoing injury to the liver as part of multiple organ failure.

BASIC IMMUNOHEMATOLOGY

RBC serology is a specialized area of knowledge, and with the International Society of Blood Transfusion (ISBT) now recognizing 36 human blood group systems and 346 antigens, it is not possible to expect clinicians to have more than a basic working knowledge essential for patient safety. The most well-known and important antigens for safe transfusion are ABO and D (Rh).

REGULAR AND IRREGULAR (ATYPICAL) ANTIBODIES

The four major ABO blood groups are defined by the presence or absence of the two carbohydrate antigens integral to the RBCs, A and/or B, and by the presence or absence of the naturally occurring antibodies (isoagglutinins) anti-A and/or anti-B. An individual with an antigen will lack the corresponding antibody (e.g., an individual with group A antigen will have anti-B antibodies). Of note, group A RBCs cause the most common and most dangerous ABO-incompatible hemolytic reactions.

The D antigen of the rhesus (Rh) blood group system is common and highly immunogenic, and is the second-most important antigen with regard to safe transfusion. When an Rh-negative (i.e., D-negative) patient is exposed to D-positive blood, there is a high likelihood of forming an anti-D antibody. D-negative females of childbearing age who receive D-positive blood may be at risk for hemolysis of the newborn or fetus. For this reason, the D antigen is taken into account when providing blood for transfusion to young females. Beyond the A, B, and (Rh)D antigens, it is not practical or necessary to take notice of other blood group antigens unless an atypical antibody is detected during antibody screening procedures.

Atypical antibodies are not normally present in the plasma but may be found in some people as naturally occurring antibodies or immune antibodies. Immune antibodies result from previous exposure due to blood transfusion or pregnancy. Naturally occurring antibodies are generally of minimal clinical significance. In contrast, many of the immune atypical antibodies are of major clinical significance and thus their recognition is imperative and drives pre-transfusion compatibility testing and antenatal antibody screening.

ANTIBODY SCREEN

On receipt of a blood sample by the transfusion service, the RBCs are ABO and Rh(D) typed while the serum is screened for atypical antibodies. The antibody screen is performed by incubating the patient's

serum with group O screening cells, which are RBCs obtained from two- or three-group O donors and express combinations of commonly encountered and clinically significant RBC antigens. If an atypical antibody is detected on the antibody screen, further serologic investigations are done to identify the specificity of the antibody.

CROSSMATCH (COMPATIBILITY TEST)

The crossmatch is the final compatibility test between the donor cells and the patient's serum, acting as a last check for ABO compatibility and unexpected antibodies. It can be done electronically or serologically. For a patient with a negative antibody screen with no history of a clinically significant antibody and with at least two prior ABO types performed, an electronic crossmatch (EXM) can be performed. In EXM, a computer algorithm ensures the correct ABO/RhD type blood is issued.

If the patient does not meet these criteria or EXM is not available at the institution, immediate spin crossmatch (IS XM) is performed. In IS XM, the donor RBCs are suspended in a saline solution, which is then gently mixed with the patient's serum and centrifuged before being resuspended. The presence of any hemolysis or RBC agglutination suggests possible ABO mismatch. If IS XM or antibody screen is positive, or if the patient has a history of clinically significant antibodies, an immunoglobulin G (IgG) crossmatch must be performed. In this indirect Coombs test, the donor RBCs are added to the patient's serum and incubated to allow for any immunoglobulins to coat the donor RBCs. The RBCs are then washed and treated with an antibody to human IgG before being inspected for hemolysis or agglutination.

Emergency uncrossmatched blood can be given in times of significant exsanguination with concern for possible loss of life. Group O Rh(D)-negative donors are referred to as "universal" blood donors and are ABO compatible with all recipients. This emergency uncrossmatched blood is also screened for high-titer A or B hemolysins. Although group O Rh(D)-positive blood can be used in severe hemorrhage, if the recipient is a female of childbearing age, every attempt should be made to give Rh(D)-negative blood until the patient's blood type is known.

KEY POINTS

- In general, a restrictive RBC transfusion strategy is recommended (transfuse when Hgb falls below 7 g/dL). For patients with acute coronary syndrome, RBC transfusion should be considered when Hgb is below 8 g/dL.
- The decision to transfuse RBC concentrates should be supported by the need to relieve clinical signs and symptoms of impaired oxygen transport and to prevent morbidity and mortality, with the aim of improving clinical outcomes.
- For the acutely hemorrhaging patient, resuscitation should consist of early transfusion of plasma, platelets, and RBCs in a balanced 1:1:1 ratio or liquid, cold-stored, type O WB.
- In patients undergoing surgical or invasive procedures, the decision to transfuse platelets should take into account the type of procedure, preoperative platelet counts, degree of active or anticipated hemorrhage, and presence of antiplatelet medications or disorders that affect platelet function.
- The benefit of plasma transfusion extends beyond its hemostatic effects to include reduction of vascular permeability and mitigation of inflammation after hemorrhagic shock.
- Prothrombin complex concentrate is superior to FFP in reversal of acquired coagulation factor deficiency induced by vitamin K agonists such as warfarin.
- Allogeneic transfusion can be associated with infectious and noninfectious risks, such as allergic, hemolytic, and febrile reactions, in addition to TRALI, TACO, transfusion-related immunomodulation, and GVHD.

References for this chapter can be found at expertconsult.com.

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Venous Thromboembolism

Simone Langness, Caitlin Collins, and M. Margaret Knudson

INTRODUCTION

Venous thromboembolism (VTE), which includes both deep vein thrombosis (DVT) and pulmonary embolism (PE), is a source of significant morbidity and mortality for the critically ill patient.[1] The development of DVT alone in the intensive care unit (ICU) is associated with a longer length of stay, more ventilator days, and an increased mortality rate compared with similar patients without DVT.[2] The annual costs for VTE in the United States is >$10 billion,[3] with a total economic burden as high as $69 billion.[4]

DEEP VEIN THROMBOSIS

Incidence

It is estimated that approximately 10% of patients in medical or surgical ICUs will have a DVT on admission.[5,6] The incidence of DVTs developing during ICU care is much harder to estimate but has been cited to be between 10% and 80%, depending on the patient population, predisposing factors, diagnostic method used, and prophylactic choice.[6–9] More recent studies place the estimates closer to 10%–15%[10,11] if appropriate prophylaxis is given.

Risk Factors

Several factors predispose critically ill patients to DVT (Table 127.1). Some risk factors are caused by an underlying illness, whereas others are acquired during the stay in the ICU. Each risk factor, whether intrinsic or acquired, relates to Virchow's triad of venous thrombosis: stasis, endothelial injury, and hypercoagulability.

Diagnosis

The diagnosis of DVT in critically ill and injured patients is challenging. Less than 15% of ICU patients diagnosed with DVT have associated clinical signs,[26] and many are unable to communicate symptoms because of factors such as altered mental status, sedation, or mechanical ventilation. Additionally, classically described signs such as unilateral leg swelling, local calf tenderness, dilated superficial veins, and erythema may not be present in the critically ill patient or are confounded by accompanying diseases or traumatic injuries. As such, physical examination has been shown to have little utility in the diagnosis of DVT in the ICU patient.[26]

Compression Ultrasound

Compression ultrasound (US) is the most commonly employed modality in the diagnosis of DVT, with a sensitivity of 85% and specificity of 96%[27] (Fig. 127.1). Given that DVTs in the critical setting are often clinically silent, some have advocated for routine screening of patients with US.[6] Although screening results in more DVTs diagnosed, it is also associated with increased costs and the potential for inaccurate results. Based on data from the Prophylaxis for Thromboembolism in Critical Care Trial (PROTECT), weekly screening US is not recommended.[28]

Prophylaxis

The incidence of DVT among medical-surgical ICU patients without any form of prophylaxis is estimated at around 30%.[8,11] Mechanical prophylaxis with intermittent pneumatic compression devices (PCDs) has been shown to reduce the development of DVT by approximately 30% when used in isolation compared with no prophylaxis.[29] However, when PCDs are combined with appropriate chemical prophylaxis, there appears to be no additional benefit.[30] Currently, PCD is recommended for all ICU patients in whom chemical prophylaxis is contraindicated.[31,32]

In multiple prospective randomized controlled trials and meta-analyses, chemical prophylaxis reduces the incidence of VTE in critically ill patients by approximately 50%.[33,34] The number of patients needed to receive prophylaxis in order to prevent one DVT is 20 and to prevent one PE is 52.[35] The American College of Chest Physicians (ACCP) gives a strong recommendation (Level I) for chemical thromboprophylaxis in all ICU patients.[36]

Medication Choice

Options for chemical prophylaxis for VTE prevention include unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), and argatroban. For surgery and medically ill patients, LMWH and UFH have similar efficacy and safety for DVT prophylaxis,[37,38] but LMWH is superior in the prevention of PE.[35,39] Given these findings and the lower risk of heparin-induced thrombocytopenia (HIT), LMWH should be considered the first-line approach for chemical prophylaxis for all ICU patients with adequate renal function.

For trauma patients, LMWH shows better efficacy than UFH with a risk reduction of an additional 30%.[40] LMWH administered twice daily (30 mg BID subcutaneously), typically in the abdominal fatty tissue, is the preferred medication for DVT prophylaxis for trauma patients from the ACCP and the Eastern Association for the Surgery of Trauma (EAST).[41,42]

Fondaparinux is an indirect factor Xa inhibitor. The advantage of fondaparinux is that it does not interact with platelets and therefore is a safe alternative in patients with HIT.[43]

Dosing

The optimal dosing of heparin for VTE prophylaxis in the ICU population has received recent attention. Standard dosing for UFH is 5000 U administered subcutaneously twice or three times daily. Meta-analyses evaluating the effectiveness and safety of twice-daily regimens compared with three-times-daily regimens for hospitalized patients have been mixed. Two studies suggest equivalent rates of VTE and

TABLE 127.1 Risk Factors Associated With VTE in Critically Ill Patients

Risk Factor	Pathophysiology	Notes
Age	Increased plasma concentration of specific clotting factors, impaired fibrinolytic activity.[12]	DVT risk doubles for every decade after 40[13]* *Risk of DVT for 40–49 years old = 2.5
Sepsis	Marked proinflammatory state results in dysregulated cellular responses and deposition of platelet-fibrin thrombi within vessels.[14]	RR of VTE in sepsis: 3–10.[15] *VTE incidence of 37% for patients with severe sepsis and septic shock despite >80% receiving appropriate prophylaxis.
Prolonged immobility/ neuromuscular blockade	Decreased venous blood flow from no/minimal extremity muscle contraction.	Neuromuscular blockade independently associated with incidence of DVT in multivariate analysis (OR 8.8).[16]
Central venous catheter	Direct damage to endothelium. *Polyethylene catheters, increased number of lumens, catheter size, and location all increased risk of catheter-associated VTE.[17]	Rate of catheter-associated DVT (per 1000 CVC days).[18] Internal jugular = 61 Femoral = 36 Peripheral = 27 Subclavian = 9
Genetic/acquired hypercoagulability	Reduced ability to degrade activated clotting factors.[12]	Antithrombin deficiency, proteins C and S deficiency, factor V Leiden, antiphospholipid syndrome
Obesity	Mechanical impairment of deep vein valve system. Metabolic syndrome can lead to decreased production of nitric oxide and prostacyclin, which can alter endothelial function.	RR DVT[19] (versus nonobese): 2.5 RR PE (versus nonobese): 2.2
Surgery/trauma	Direct injury to blood vessel → release of tissue factor → activation of clotting cascade.[20] Hemorrhagic shock results in hypoperfusion and stasis. Trauma → increased production of thrombin.[21]	DVT OR[22]: Femur or tibial fracture = 4.8 Spinal cord injury = 8.6 Surgery for trauma = 2.3 VTE odds ratio[23]: Lower extremity fracture with abbreviated injury score (AIS) ≥3 = 1.9 Head injury + AIS ≥3 = 1.24 Venous traumatic injury = 3.56 Surgery for trauma = 1.53
Malignancy	Direct compression of or invasion into veins. Tumors can promote the release of tissue factors → activation of clotting cascade.[24]	
Pregnancy	Increased concentration of procoagulant factors. Impairment of fibrinolytic system.[25]	

CVC, Central venous catheter; *DVT,* deep vein thrombosis; *OR*, odds ratio; *PE,* pulmonary embolism; *RR,* relative risk; *VTE,* venous thromboembolism.

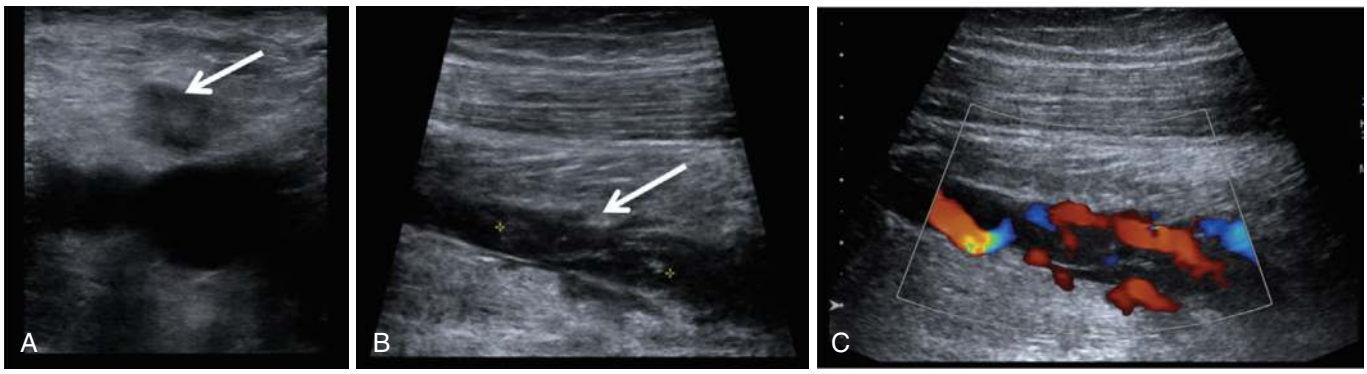

Fig. 127.1 Occlusive **(A)** and nonocclusive **(B)** deep vein thrombus (*arrows*) on compression ultrasound. Doppler ultrasound confirms nonocclusive nature of thrombus **(C)**.

major bleeding between the dosing regimens,[44,45] and a third found three times daily to be more effective (relative risk [RR] 0.27) with no increase in the incidence of major bleeding.[46]

Anti-factor Xa (anti-XA) levels can be used to evaluate the degree of thromboprophylaxis after LMWH administration. The therapeutic target for VTE prophylaxis is 0.3–0.5 IU/mL.[47] Several reports have demonstrated that approximately 50% of critically ill patients have inadequate anti-Xa levels with standard LMWH dosing (30–40 mg daily).[48–50] This has led some to argue for twice-daily dosing[51,52] or dosing based on weight,[53] thromboelastogram,[54] and/or goal anti-Xa.[55]

The etiology of subtherapeutic levels with standard LMWH in the ICU population is multifactorial but may include decreased absorption

caused by vasopressors, altered metabolism with organ dysfunction, variable albumin binding, and differences in volume of distribution caused by edema.[50,56] Obesity also plays a role in the bioavailability of heparin. There is a strong, and seemingly dose-dependent, relationship between body mass index (BMI) and failure of thromboprophylaxis. One study found a 60% increased risk of VTE for patients with BMI ≥30, suggesting that higher doses of prophylaxis may be necessary.[57] In trauma patients with massive fluid shifts, clearance of heparin-based drugs may actually increase, thus providing a rationale for more frequent dosing.

Timing of Prophylaxis

VTE prophylaxis in the critically ill patient should be initiated as soon as feasible based on the risk of hemorrhage. For the majority of patients admitted to the ICU, administration should occur at the time of admission, as delayed initiation of VTE prophylaxis by as little as 24 hours is associated with a threefold increase in VTE rates[58] in addition to increased mortality.[59] Trauma patients represent a particularly challenging population with respect to managing the risk of bleeding against the risk of VTE. The risk of VTE after injury ranges from 5% to 60% depending on injury type and patient risk.[22,23,60] PCD should be initiated immediately unless otherwise contraindicated. In patients with polytrauma, chemical VTE prophylaxis is initiated as soon as bleeding is controlled and coagulopathy corrected, as the risk of VTE increases significantly with every day it is withheld. For patients with traumatic brain injury, it is safe to start chemical VTE prophylaxis within 72 hours of injury as long as there is no expansion of bleeding on repeat imaging.[61,62] For patients with spinal cord injuries, new evidence suggests that it may be safe to initiate anticoagulants within 24–48 hours of the injury.[63] Early chemical prophylaxis is also safely given at 24–48 hours after injury in patients with solid organ injuries being managed without operation.[64,65]

Inferior Vena Cava Filter

For those who have a relative or absolute contraindication to chemical DVT prophylaxis because of high-risk bleeding, a prophylactic inferior vena cava (IVC) filter may be indicated. Additional indications for IVC filter placement include failure of or poor compliance with anticoagulation or for patients with VTE and limited cardiopulmonary reserve. Although IVC filters are highly effective at preventing PEs from lower extremity DVT, they also substantially increase the risk of DVT formation and are not effective against the formation of in situ PE or embolism from an upper extremity thrombus.[66,67] There are conflicting recommendations on the use of IVC filters in patients without a current DVT/massive PE, with some advocating their use in "high risk" trauma patients who are unable to receive chemical prophylaxis.[41]

Treatment of DVT

Although anticoagulation is the mainstay of treatment of DVT, the type and duration of anticoagulation can vary significantly, depending on the status and compliance of the patient and the perceived risk for recurrent VTE. The purpose of anticoagulation is to prevent extension of the thrombosis, embolization to the pulmonary arterial system, and the complications from chronic venous outflow obstruction.

Lower Extremity DVT

Lower extremity DVT can be classified as proximal or distal. Proximal DVTs are located in the popliteal, femoral, or iliac veins, whereas distal DVTs are confined exclusively to the calf veins (peroneal, posterior tibial, and anterior tibial). Proximal DVTs, regardless of symptomatology, are treated with anticoagulation, unless otherwise contraindicated, as they are associated with an increased rate of embolism and mortality.[68] Distal DVTs have approximately half the risk of embolization,[69] and some will resolve without intervention.[70] Management can range from observation alone to full anticoagulation, considering such factors as symptomatology, prior VTE episodes, and/or prolonged immobility. If observation is employed, routine surveillance to monitor for extension into proximal veins is recommended.[71]

Upper Extremity DVT/Catheter-Associated DVT

Upper extremity DVTs account for 5%–10% of all DVTs and include thrombus within the radial, ulnar, brachial, axillary, and subclavian veins. Thrombosis within the internal jugular vein is occasionally included as an upper extremity DVT, although rigorous definition is lacking. The incidence of PE caused by upper extremity DVT embolism is approximately 6%[72] compared with 15%–30% for lower extremity DVT.[73] Anticoagulation is recommended for upper extremity DVT in proximal vessels (axillary, subclavian, internal jugular) regardless of the etiology.

The majority of upper extremity DVTs are associated with intravenous catheter use. The increased use of peripherally inserted central catheters (PICC lines) in the management of ICU patients is associated with a corresponding increase in the incidence of upper extremity DVT. DVTs can occur as early as 1 day after central venous catheter (CVC) placement and are frequently asymptomatic. Risk factors for the development of catheter-associated DVT include catheter type, anatomic site of placement, the presence of infection, and the duration of use.[74] Data on the optimal management of CVC-related DVT are limited. Consensus opinion recommends systemic anticoagulation for a minimum of 3 months,[17,75] although 6 weeks may be adequate if the clot is small and nonocclusive.[75,76] The decision to remove the CVC should be based on whether or not the catheter is still required. Additional recommendations regarding catheter removal with associated DVT include poor positioning, infections, arm or neck swelling, and when anticoagulation is contraindicated.[75,77]

Anticoagulant Options

Initial anticoagulant therapy for DVT may include continuous heparin infusion, subcutaneous, fondaparinux, or oral factor Xa inhibitors such as rivaroxaban or apixaban. Warfarin cannot be used alone as the initial treatment of DVT because of the risk of warfarin-induced skin necrosis.[78] The determination of which anticoagulant to initiate will be dictated by comorbidities and risk of bleeding.

Intravenous heparin is the preferred initial anticoagulant for patients with renal failure (creatinine clearance [CrCl] <30), hemodynamic instability, extensive clot burden, and those with a high risk of bleeding. Rivaroxaban and apixaban are the only direct oral anticoagulants approved for initial treatment of VTE. These agents do not require pretreatment with heparin and can be useful for lower-acuity patients with low bleeding risk profiles.

All VTE events, regardless of etiology, require anticoagulation treatment for at least 3 months.[68] A transition from the initial anticoagulation regimen to a maintenance therapy is often required. Maintenance agents may include LMWH, warfarin, direct oral factor Xa inhibitors, or direct thrombin inhibitors. According to the 2016 CHEST guidelines, for patients with VTE in the absence of cancer, direct oral anticoagulants are preferred over warfarin (grade 2B), and warfarin is preferred over LMWH (grade 2C).[68]

Thrombolysis

Anticoagulation alone is sufficient treatment for the majority of patients who develop an acute DVT. However, a subpopulation of patients may benefit from reducing the venous clot burden through the administration of thrombolytic agents or with a mechanical thrombectomy. Patients who should be considered for thrombolytic therapy include those with phlegmasia cerulean dolens or massive iliofemoral

DVT. Ideal candidates for thrombolysis/thrombectomy have symptoms for <14 days, have good functional status, and have a low risk of bleeding.[68] Thrombolysis can be systemic or catheter-directed, but catheter-directed therapy is associated with a lower risk of bleeding.[79]

PULMONARY EMBOLISM

Incidence

The prevalence of PE in critically ill patients remains largely unknown. A systematic review of ICU patients reported that PE was discovered in 7%–27% of patients upon postmortem examination.[80] PE was believed to have contributed to the patient's death in 0%–12% of the cases; however, clinical suspicion of PE was present in only 30% before death, highlighting the likelihood of significant inaccuracy in current prevalence estimates. Historical estimates of PE prevalence in critically ill patients range from 7% to 50% but are largely based on autopsy studies performed between the 1960s and early 1980s.[7,81,82]

Risk Factors

PE can be considered part of a VTE spectrum, with DVT representing the requisite precursor to PE.[83] Kakkar and colleagues examined the natural history of postoperative DVT and found that approximately 20%–30% of untreated calf DVTs will eventually propagate into the thigh, at which point they pose a 40%–50% risk for PE.[84–86] Approximately 95% of pulmonary emboli arise from lower extremity DVTs.[83]

Predictive factors for the development of PE include acute medical illness, presence of meningeal hemorrhage, spine fracture, hypoxemia with partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) <300, and absence of pharmacologic VTE prophylaxis. Additionally, the use of epinephrine or norepinephrine is associated with a particularly poor prognosis among patients diagnosed with PE.[87]

Symptoms and Physiologic Derangements

Symptoms

Common symptoms of PE include pleuritic chest pain, acute-onset shortness of breath, palpitations, cough, and hemoptysis.[88,89] However, these symptoms are nonspecific and are often entirely absent in sedated and mechanically ventilated patients. The relevant clinical signs (hypoxemia, tachypnea, and tachycardia) are similarly nonspecific and frequently explained by the preexisting conditions driving their critical illness.[88] The atypical presentation in ICU patients necessitates that providers maintain a high degree of suspicion for PE with any relevant, acute changes in clinical status. More subtle clinical scenarios in which one should suspect PE include failure to wean from mechanical ventilation and persistent pyrexia without evidence of infection.[90]

Physiologic Derangements

Hypoxemia and hypocarbia are the most common signs of PE. PE causes an increase in dead space, as the corresponding lung parenchyma is ventilated but no longer perfused. Additionally, the remaining lung receives a higher proportion of blood flow but does not receive a concomitant increase in ventilation.[91] This ventilation-perfusion (V/Q) mismatch results in hypoxemia during the acute phase of PE.

Intrapulmonary shunting is a second driver of hypoxia after PE and occurs as a result of atelectasis and other causes of lung volume loss.[92] In patients with a patent foramen ovale, intracardiac shunting might also play a role. The application of positive end-expiratory pressure (PEEP) or continuous positive airway pressure can worsen the intracardiac shunting by exacerbating right and left atrial pressure gradients. Importantly, hypoxemia secondary to shunt physiology will not correct with supplemental oxygen.[91,93]

PE can result in sudden cardiovascular collapse. Acute PE decreases the cross-sectional area of the pulmonary vascular bed, thereby increasing pulmonary vascular resistance (PVR) and right ventricular (RV) afterload.[91] If severe, this can lead to RV enlargement followed by hypokinesis, ischemia, and subsequent RV failure.[93,94] In patients with already restricted cardiopulmonary reserve, even small increases in PVR can result in RV dysfunction and hemodynamic compromise.[95]

Diagnosis

When diagnosing PE, reliance on clinical impression alone is profoundly unreliable. Studies demonstrate that the sensitivity and specificity of empiric diagnosis of PE based on clinical impression alone are only 85% and 51%, respectively.[96] These data reiterate the importance of ancillary testing when PE is suspected, especially considering the potentially grave risks of therapeutic anticoagulation in a critically ill patient.

Chest X-Ray, Electrocardiogram, and D-Dimer

Chest x-ray (CXR) is most useful for quickly identifying (or ruling out) other possible conditions that mimic PE (e.g., pneumonia, atelectasis, pulmonary edema, pleural effusion, pneumothorax) but provides no utility in the diagnosis of PE.[89] Electrocardiogram (ECG) abnormalities, such as sinus tachycardia and nonspecific ST-segment and T-wave abnormalities, are frequently present in patients with acute PE.[89,97] These findings, however, lack specificity, particularly in the critically ill patient. Additional irregularities, such as atrial arrhythmias, right axis deviation, right bundle branch block, the S1Q3T3 pattern, and p-wave pulmonale, more commonly accompany a large PE and are equally nonspecific.[89,94,97] In the outpatient setting, D-dimer is routinely used as a screening test for PE, as it is associated with a negative predictive value of 99.6%.[98] However, its effectiveness in the inpatient setting, and moreover the ICU, is diminished by the fact that most patients will have elevated D-dimers for unrelated reasons, especially those who have sustained major trauma.[99]

Echocardiography

The role of transthoracic echocardiography (TTE) in the diagnosis of PE has gained momentum in the last decade. Although unable to specifically assess clot formation within the pulmonary vasculature, TTE can evaluate the physiologic consequences of PE. PE should be considered when new RV dysfunction is identified on TTE as evidence by RV dilation, hypokinesis, tricuspid regurgitation, elevated systolic pulmonary artery pressure, and paradoxical septal wall motion. Additionally, the degree of RV dysfunction documented on TTE with Doppler correlates with mortality, allowing for risk stratification and informing decisions regarding the aggressiveness of treatment interventions.[100]

V/Q Scan

The PIOPED study prospectively analyzed the diagnostic performance of V/Q scans in comparison with pulmonary angiography among hospitalized patients. Although almost all patients with PE had abnormal V/Q scans (sensitivity 98%), so did a large number of patients without PE, resulting in a specificity of only 10%.[101] Given the prevalence of both chronic and acute respiratory issues within an ICU population, the vast majority of patients will have preexisting defects in both ventilation and perfusion.[81] Attempting to identify superimposed abnormalities related to the PE would be a wasted effort. These challenges severely limit the utility of V/Q scans within an ICU setting.

Pulmonary Angiography and CT Angiogram

Although pulmonary angiography has historically been the gold standard for diagnosing PE, computed tomography pulmonary angiography (CTPA) has largely taken its place as the preferred diagnostic tool in clinical practice, with a sensitivity of 83% and specificity of 96% (Fig. 127.2).[102,103] CTPA is noninvasive, is faster, and has the

additional benefit of allowing assessment and quantification of RV dysfunction through evaluation of the LV:RV diameter ratio, interventricular septal bowing, contrast reflux into the superior and inferior vena cava, and pulmonary artery diameter.[102,104] Additionally, CTPA can detect other etiologies for the development of acute hypoxia such as pneumonia, lobar collapse, and pulmonary edema.

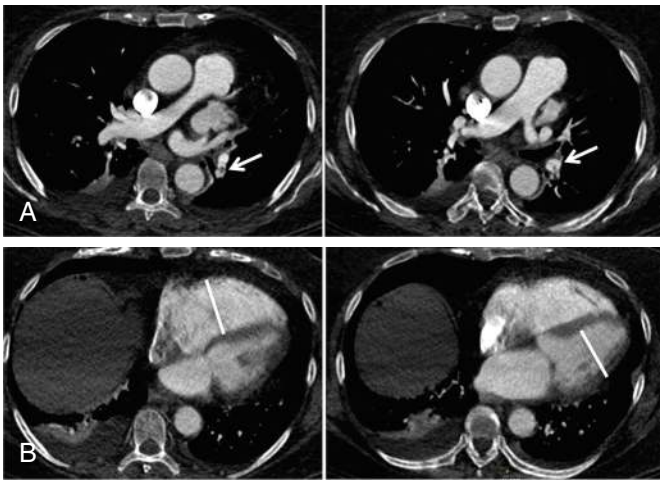

Fig. 127.2 A, Segmental pulmonary embolus (*arrows*) on computed tomography pulmonary angiogram (CTPA). **B,** Right ventricle to left ventricle ratio >1.0, suggestive of heart strain.

Treatment

The balance between the likelihood of an adverse outcome from PE and the anticoagulation/thrombolysis risk largely drives management decisions when treating ICU patients with PE. The degree of cardiovascular impact represents the best predictor of a poor outcome and is used to differentiate and treat the three main types of PE: massive PE, submassive PE with RV strain, and submassive PE without RV strain (also termed *low-risk PE*)[105] (Fig. 127.3).

Massive PE

The American Heart Association (AHA) defines massive PE as an acute PE with sustained hypotension, pulselessness, or persistent profound bradycardia (heart rate <40 beats per minute with evidence of shock). Sustained hypotension is defined as a systolic blood pressure <90 mm Hg or the need for inotropic support and cannot be the result of a cause other than PE, such as an arrhythmia, hypovolemia, sepsis, or LV dysfunction.[106]

Based on the ICOPER study, the mortality rate for patients with massive PE was 58.3% compared with 15.3% in those with PE without cardiovascular collapse.[107] In patients requiring cardiopulmonary resuscitation, the mortality rate may be as high as 65%.[108] As hemodynamic instability portends such a poor prognosis, more aggressive interventions must be considered in this patient population.

Submassive Pulmonary Embolism with Right Ventricular Strain

Submassive PE with RV strain describes patients with acute PE who are normotensive but have some evidence of RV dysfunction or myocardial

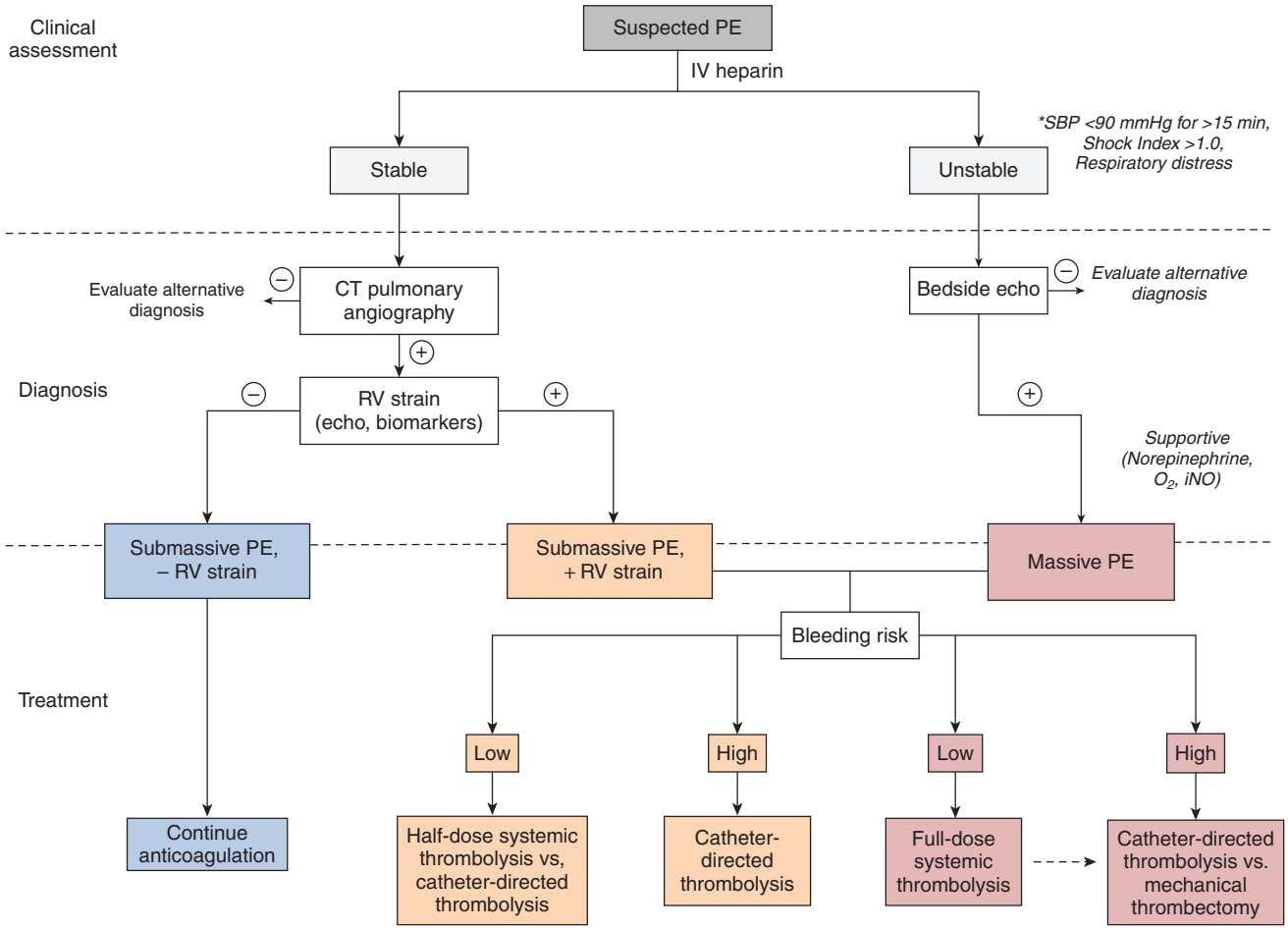

Fig. 127.3 Treatment Algorithm for Suspected Pulmonary Embolism (PE) in Critically Ill Patients.

ischemia on ECG, echocardiogram, CTPA, or laboratory work such as elevated troponin or brain natriuretic peptide.[106] This heterogeneous group spans the entire spectrum with respect to risk associated with their PE. Some patients with mild evidence of RV strain are likely to recover well with anticoagulation alone. However, others within this group behave more like patients with massive PE and thus might benefit from more aggressive and higher-risk interventions.

Submassive PE without RV Strain (Low-Risk PE)

Patients with acute PE who are hemodynamically stable and have no evidence of RV dysfunction or myocardial injury fall within the submassive PE without RV strain category and have the lowest risk of adverse outcome. In-hospital mortality for these patients is estimated at 8.1%.[108]

Anticoagulation

All patients diagnosed with PE, regardless of the severity, should receive prompt anticoagulation with UFH, LMWH, or fondaparinaux.[106] For patients with absolute contraindications to anticoagulation, an IVC filter should be placed without delay. Absolute contraindications to anticoagulation are rare but include (1) active intracranial hemorrhage and (2) uncontrolled bleeding related to conditions such as trauma, recent surgery, gastrointestinal or genitourinary pathology, or preexisting coagulopathy. Temporary contraindications should be regularly reassessed, and anticoagulation should be reconsidered as the initial contraindication abates.

Thrombolysis

Thrombolysis has been shown to more rapidly reverse RV dysfunction from PE than anticoagulation alone and confers a survival benefit in the setting of a massive PE.[88,109] For patients with submassive PE and documented RV dysfunction, a strong trend towards benefit exists based on meta-analysis, but results have varied among major studies. Thrombolysis is not recommended for patients with low-risk PE, as the risk of major bleeding outweighs the therapeutic benefit.[109]

Thrombolysis can be performed via systemic administration or using a catheter-based approach. Recent studies have found lower rates of bleeding complications with improved outcomes using catheter-based thrombolysis as opposed to systemic thrombolysis.[110,111] Despite the utility of thrombolysis in the treatment of severe PE, approximately one-third of patients with massive PE have significant contraindications to thrombolysis.[112] The prevalence of absolute contraindication is likely even higher in an ICU population. Mechanical thrombectomy and additional supportive interventions play an important role in patients who may benefit from thrombolysis but are not candidates for the therapy.

Supportive Care

Inhaled Nitric Oxide

Inhaled nitric oxide (iNO) acts as a selective pulmonary artery vasodilator, thus partially offloading RV pressure without negatively affecting systemic blood pressure.[113] Although it has been shown to be effective in reducing mean pulmonary artery pressure in the acute setting, few studies exist evaluating its use in patients with PE, and none of them are adequately powered to assess whether its use confers a mortality benefit.[113,114]

Extracorporeal Membrane Oxygenation

Extracorporeal membrane oxygenation (ECMO) represents a potential supportive intervention for massive PE. ECMO has a number of beneficial characteristics that lend to its possibilities as an adjunctive treatment. ECMO allows for offloading of the RV and can provide a bridge to other therapeutic interventions (i.e., surgical embolectomy or catheter-directed therapy).[115,116] An additional advantage of ECMO is that cannulation can be performed at the bedside. Evidence for the utility of ECMO for massive PE is primarily composed of case series, and most guidelines consider ECMO as an adjunct to thrombolysis or embolectomy.[115–117]

Future Directions

Although there are few large, prospective studies in VTE disease in ICU patients, the Consortium of Leaders in the study Of Traumatic Thromboembolism (CLOTT) group is committed to doing just that. The CLOTT group consists of 17 trauma surgeons from Level I trauma centers across the country who are funded by the Combat Casualty Care Research Program (Department of Defense) to study two important areas related to VTE in seriously injured patients. The first area of investigation relates to some work initially published by Knudson and others suggesting that pulmonary clots visualized on CTPA may in fact be de novo clots and not embolic.[118] These clots were most prevalent in patients who had sustained pulmonary injury and were not associated with lower extremity VTE.[119,120] As many of these primary pulmonary clots are detected incidentally and are frequently subsegmental, the question arises as to whether or not they need to be treated at all. This would completely change practice in the care of critically injured patients and is the central hypothesis of the CLOTT Study Part 1.

CLOTT investigators are also examining thromboelastography data that suggest that certain critically injured patients are incapable of lysing clots after injury.[121] This syndrome is referred to as *fibrinolytic shutdown,* and the risk factors for and the incidence of this new diagnosis are the central goals of the CLOTT Study Part 2. Of particular importance is the association of fibrinolytic shutdown with the development of VTE events.[122] A better understanding of this pathology could change the focus of VTE prevention in at-risk trauma patients from preventing clots from forming to assisting in clot dissolution.

KEY POINTS

- VTE is common in the critically ill patient, and chemical prophylaxis must be provided as soon as possible for risk reduction.
- Compression US and CTPA are primary modes of diagnosing DVT and PE, respectively.
- Thrombolysis or mechanical thrombectomy should be considered for proximal DVT at risk for postthrombotic syndrome and for PE with evidence of right heart strain.

References for this chapter can be found at expertconsult.com.

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Anticoagulation in the Intensive Care Unit

Jerrold H. Levy

INTRODUCTION

Patients in an intensive care unit (ICU) often have received or require anticoagulation for multiple reasons that include acute thrombotic issues, mechanical valves, venous thromboembolic prophylaxis, atrial fibrillation, ischemic cardiovascular disease, and/or extracorporeal life support. The types of anticoagulation and need for therapy vary depending on whether patients have arterial or venous thromboembolic issues. These issues are important in critically ill patients and have critical perspectives for management. The concept of anticoagulation and the various therapeutic approaches have rapidly changed over recent years, with the advent of many oral anticoagulation agents that will be considered. In addition, there are important links between coagulation and other critical physiologic responses including inflammation, that are beyond the scope of this review.[1]

ICU patients are anticoagulated for both thrombosis treatment and thromboprophylaxis. As initially mentioned, this includes a broad spectrum of potential indications. Although multiple therapeutic agents prevent or treat thrombosis in pathologic states, it is crucial to consider that all anticoagulation agents can cause bleeding. Thus causes of bleeding in an ICU setting often are the result of an acquired hemostatic defect caused by alterations in the physiologic equilibrium of procoagulant and anticoagulation balances. Under normal physiologic states in healthy patients, anticoagulation is favored because of a multitude of mediators and vascular endothelial cells. After vascular injury resulting from metabolic causes, surgery, or trauma, patients also develop procoagulant changes that alter this complex balance. As a result, hemostasis and coagulation are far more complex than the simplified coagulation cascades that most clinicians have learned or considered because of the complex equilibrium among blood cells, platelets, coagulation factors, natural inhibitors of coagulation, and the fibrinolytic system.[2–5]

In ICU settings, patients may receive anticoagulants for multiple indications that include venous thromboembolism (VTE), deep vein thrombosis (DVT), and pulmonary embolism (PE) for either prevention or therapy. Patients may also have additional problems that include acute coronary syndromes, percutaneous coronary interventions (PCIs), or with an acute ischemic stroke that are arterial issues. Arterial thrombi are mediated by platelet responses, and important interactions exist in hemostasis and thrombus formation.[6] With an arterial injury, injury or rupture of an atherosclerotic arterial plaque serves as a procoagulant focus for clot formation caused by platelet adhesion, activation, and aggregation, with the clinical end result of myocardial infarction (MI) or stroke.[7] Platelets normally circulate in an inactivated state, but after activation as described, they express glycoprotein IIb/IIIa receptors that allow fibrinogen to bind, cross-link platelets, aggregate, and form a thrombus.[7] Vascular injury causes thrombin formation but also platelet activation and the formation of the platelet-fibrinogen plug. Because platelets have a pivotal role in the pathogenesis of thrombosis after plaque rupture, antiplatelet agents, including aspirin, thienopyridines (clopidogrel, prasugrel, ticagrelor, cangrelor), and the glycoprotein IIb/IIIa inhibitors, reduce adverse events that are associated with arterial thrombotic events, including plaque rupture.[7]

Patients therefore commonly present in the ICU with underlying hemostatic disorders because of preexisting preoperative anticoagulation or antiplatelet therapy. All therapies that prevent clots from forming in pathologic states also interfere with normal hemostasis, an important mechanism to protect patients from exsanguination. Multiple anticoagulation agents are also administered in the ICU setting that include low-molecular-weight heparins (LMWHs), oral anticoagulants (vitamin K antagonists [VKAs]/warfarin and the new direct non–vitamin K oral agents apixaban, dabigatran, edoxaban, or rivaroxaban), platelet inhibitors (the thienopyridines clopidogrel, prasugrel, or ticagrelor), or parenteral direct thrombin inhibitors (bivalirudin, argatroban).[8,9] This chapter focuses on current pharmacologic anticoagulation therapies ICU patients may receive and the therapeutic perioperative and prohemostatic pharmacologic approaches that are used to treat or prevent bleeding in this setting.

ANTICOAGULATION

The basis of anticoagulation is modulating clot formation by inhibiting both thrombin activation and platelet activation.[5] Thrombin is a critical component of hemostasis (stopping bleeding) and a critical procoagulant in coagulation. Thrombin catalyzes the formation of fibrin from soluble fibrinogen but also activates factors V and VIII and platelets. Activated platelets adhere to injured vascular endothelium through a von Willebrand factor bridge between the vasculature and the platelets. Platelets also, when activated, express IIb/IIIa receptors where fibrinogen binds, causing aggregation, but also facilitate the further generation of thrombin. There are also complex humoral amplification pathways that link both inflammatory and coagulation responses to generate thrombin and prothrombotic effects.[5] Thus anticoagulation is based on inhibiting thrombin activation, platelet activation, and/or both. Current anticoagulants used to prevent clot formation will be considered. An overview of the specific targets of the different anticoagulants is shown in Fig. 128.1.

HEPARIN

Heparin, the most commonly used anticoagulant, especially in an ICU setting, is isolated from porcine intestine, where it is stored in the mast cell granules. Unfractionated heparin (UFH) is a combination of 3000- to 30,000-dalton (Da) fragments.[10] Heparin binds to antithrombin III (also called antithrombin [AT]), increasing the rate of thrombin-AT complex formation, but also inhibits other steps in coagulation.[11]

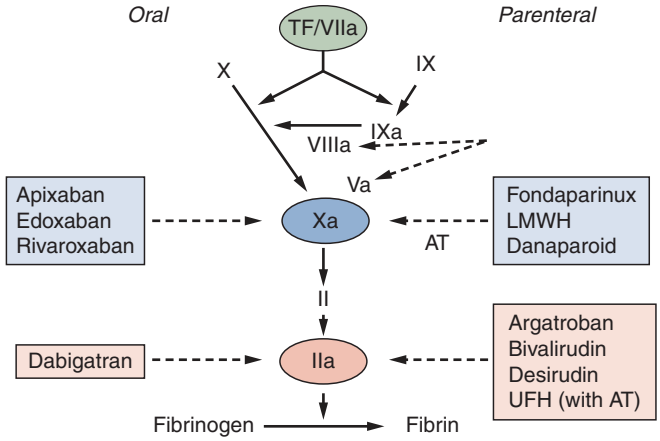

Fig. 128.1 The Sites of Action of Oral and Parenteral Anticoagulation Agents. The non–vitamin K oral anticoagulants, also called direct oral anticoagulants, include apixaban, edoxaban, and rivaroxaban. These drugs directly inhibit factor Xa, whereas dabigatran directly inhibits factor IIa (thrombin). The parenteral/intravenous anticoagulants that inhibit factor Xa include fondaparinux and low-molecular-weight heparin (*LMWH*) by antithrombin (*AT*)-cofactor dependent binding. Parenteral direct thrombin inhibitors include argatroban, bivalirudin, and desirudin that also directly inhibit thrombin, and unfractionated heparin (*UFH*) by antithrombin (AT)-cofactor dependent binding. Not shown in the figure is the mechanism of action of vitamin K antagonists (e.g., warfarin) that inhibit the posttranslational modification of coagulation factors II, VII, IX, and X to the active forms. Warfarin and its cogenders are anticoagulants because they decrease the circulating levels of critical hemostatic factors involved in coagulation.

Heparin anticoagulation has major advantages in an ICU setting, as it can be rapidly reversed with protamine, has a short half-life of ~1 hour, and is one of the few anticoagulants that can be readily administered in patients with renal dysfunction that may otherwise prolong the half-lives of most agents. One of the major side effects of UFH is heparin-induced thrombocytopenia (HIT) that can occur in ~1%–5% of ICU patients, especially postoperatively and after cardiac surgery with cardiopulmonary bypass.[12]

Low-Molecular-Weight Heparins

LMWHs are purified from UFH, with an average molecular weight of ~5000 Da. LMWHs have a longer half-life, are only partially reversible with protamine, and in patients with renal dysfunction, the effects can be greatly prolonged and should be avoided in this setting.[9] Commonly used LMWHs include enoxaparin and dalteparin.

Heparin-Induced Thrombocytopenia

HIT is a serious, prothrombotic effect of heparin that develops in 1%–3% of heparin-treated patients. HIT is an interesting paradigm where an anticoagulant produces an increased risk of thrombosis.[13] The pathophysiology of HIT is the result of a heparin–platelet factor 4 immunoglobulin G (IgG) antibody that binds and activates platelets and is associated with increased thrombotic morbidity and mortality.[13] HIT should be suspected whenever the platelet count drops >50% from baseline in 5–10 days after starting heparin (or sooner if there was prior heparin exposure) and/or new thrombosis occurring during, or soon after, heparin treatment, with other causes excluded. When HIT is strongly suspected, with or without complicating thrombosis, heparins should be discontinued, and a nonheparin alternative anticoagulant, such as a direct thrombin inhibitor (argatroban), should be initiated immediately.[13] Bivalirudin is also commonly used off-label, especially in this setting, and for HIT-positive patients requiring extracorporeal membrane oxygenation (ECMO).[14]

SYNTHETIC Xa INHIBITORS

Fondaparinux

Fondaparinux, a synthetic pentasaccharide with specific anti-Xa activity, has a long half-life and requires renal clearance and should be avoided in patients with renal dysfunction. Because of this, it is not commonly used in an ICU setting.[15]

Danaparoid

Danaparoid is one of the first anticoagulants evaluated in randomized trials in patients with HIT, was previously approved in the United States, and is currently being restudied in this setting in a randomized clinical trial with argatroban (https://clinicaltrials.gov/ct2/show/NCT03809481?term=danaparoid&draw=2&rank=1).[15]

DIRECT THROMBIN INHIBITORS: PARENTERAL AGENTS

An important major class of anticoagulants used primarily for HIT or for suspected HIT are the direct thrombin inhibitors that include bivalirudin, argatroban, and desirudin. Lepirudin is no longer available clinically. All of these parenteral direct thrombin inhibitors also vary in their binding affinities for thrombin and immunogenicity. All of the agents, except argatroban, are polypeptides, so there is a potential, but rare, risk for antibody formation and hypersensitivity responses.[15] Bivalirudin and argatroban are most often used in an ICU setting and will be considered separately.

Bivalirudin

Bivalirudin is a polypeptide with a molecular weight ~4000 Da and is approved as an anticoagulant for patients undergoing PCI with provisional use of glycoprotein IIb/IIIa inhibitor, with or at risk of HIT or HIT and thrombosis syndrome undergoing PCI, and with unstable angina undergoing percutaneous transluminal coronary angioplasty (PTCA).[15] It has also been used off-label as a replacement for heparin with ECMO. With normal renal function, the half-life is ~20 minutes but can be prolonged in patients with renal dysfunction.[15]

Argatroban

Argatroban is an injectable, synthetic, small-molecular-weight (~500 Da) direct thrombin inhibitor approved for prophylaxis or treatment of thrombosis in adult patients with HIT or as an anticoagulant in adult patients with or at risk for HIT undergoing PCI. However, for PCI, bivalirudin is currently used in this setting. The half-life is 40–50 minutes, and levels are not affected by renal dysfunction.[15] Patients with HIT often also present with acute renal failure, and all of the other agents used for acute HIT therapy are proteins that are renally eliminated. Argatroban is hepatically eliminated, so no dose adjustments are required in patients with renal dysfunction. Also, antigenicity is not an issue because of its low molecular weight.[15] We reported a study of 87 suspected HIT patients in the cardiothoracic ICU, of which 47 patients (54%) were treated with argatroban and 40 patients (46%) were not treated with argatroban. We concluded that clinical suspicion of HIT as detected by clinical probability score and thrombotic complications should prompt immediate cessation of heparin and initiation of an alternative anticoagulant such as argatroban.[16]

Desirudin

Desirudin (another recombinant hirudin) is approved in the United States for the prophylaxis of DVT, which may lead to PE in patients undergoing elective hip replacement surgery. Of note, desirudin has also been studied extensively in patients with stable angina undergoing PTCA. Because desirudin is primarily eliminated by the kidneys, patients with renal impairment require monitoring, and activated partial thromboplastin time (aPTT) can be used. However, this agent is seldom used, especially with the availability of the non–vitamin K oral anticoagulation agents.[17]

ORAL ANTICOAGULANTS

Vitamin K Antagonists: Warfarin

Warfarin is the only oral VKA agent available in the United States.[18] It is an effective anticoagulation agent by inhibiting vitamin K epoxide reductase that converts the vitamin K–dependent coagulation proteins (factors II [prothrombin], VII, IX, and X) to their active form as a posttranslational modification. One of the reasons that warfarin's onset is so slow is that it takes several days to decrease coagulation factors to the ~20%–40% level that is required for a therapeutic international normalized ratio (INR) of 2–3.[18]

Managing warfarin in the ICU setting is complicated and often bridged initially. However, in the bleeding patient, vitamin K will not immediately reverse the anticoagulant effect, and additional therapies are needed, as detailed in the guidelines for perioperative management by Douketis and colleagues in the American College of Chest Physicians (ACCP) guidelines and summarized in "ICU/Perioperative Management of Antithrombotic Therapy."[19] The ACCP guidelines also recommend the use of a four-component prothrombin complex concentrate (e.g., Kcentra/Beriplex, CSL Behring [King of Prussia, PA]; or Octaplex, Octapharma [Lachen, Switzerland]) for urgent warfarin reversal when required for bleeding or surgical interventions.[18] Additional considerations for warfarin reversal are reviewed next.

New Oral Agents: Apixaban, Dabigatran, Edoxaban, and Rivaroxaban

The non–vitamin K direct oral anticoagulation agents (DOACs) have a rapid onset, with therapeutic anticoagulation within hours of administration.[20] Dabigatran is an oral direct thrombin inhibitor, and apixaban, edoxaban, and rivaroxaban are direct factor Xa inhibitors similar to LMWH but independent of antithrombin.[17] Edoxaban has been recently approved and will not be further discussed. The new agents require dose adjustments for renal failure and will be considered separately.[17]

Apixaban

Apixaban is a factor Xa inhibitor anticoagulant approved for reducing the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation and for the prophylaxis of DVT, which may lead to PE in patients who have undergone hip or knee replacement surgery, for the treatment of DVT and PE, and for the reduction in the risk of recurrent DVT and PE after initial therapy.[20] If bleeding occurs and measurement of its effects is needed, then using a specific calibrated anti-Xa assay, similar to what is used for LMWH, is needed. However, measuring the effects of Xa inhibitors can be difficult.[17] The formulation can be crushed and given through a feeding tube if required in the ICU setting.

Dabigatran Etexilate

Dabigatran etexilate is an oral direct thrombin inhibitor currently approved to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, for the treatment of DVT and PE in patients who have been treated with a parenteral anticoagulant for 5–10 days, and to reduce the risk of recurrence of DVT and PE in patients who have been previously treated.[20] Dabigatran has a rapid onset of action and no requirement for routine coagulation monitoring.

Dabigatran's effects can be measured best by tests similar to any direct thrombin inhibitor, including aPTT values, thrombin times, diluted thrombin times, or ecarin clotting times.[17,20] A specialized assay that uses a diluted thrombin time is helpful for the specific measurement of levels when needed and is sensitive to lower levels. However, the aPTT is still a good screening test and closely correlated with more sensitive assays in the larger clinical study. Dosing should also be adjusted for patients with renal dysfunction. The capsule is specially formulated and cannot be altered or crushed for administration in an ICU setting. A specific monoclonal antibody is in clinical trials for acute reversal of dabigatran and will be discussed later.

Rivaroxaban (Xarelto)

Rivaroxaban is a direct-acting factor Xa inhibitor, which, unlike heparins, does not require antithrombin.[20] Rivaroxaban has the broadest indications that include reduction of the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation; for the treatment of DVT and PE and for the reduction in the risk of recurrence of DVT and of PE; for the prophylaxis of DVT for knee or hip replacement surgery; and in combination with aspirin to reduce major cardiovascular events in patients with chronic coronary or peripheral artery disease. Rivaroxaban has also been recently approved for VTE prophylaxis in hospitalized acutely ill medical patients. If bleeding occurs and measurement of its effects are needed, then using a specific calibrated anti-Xa assay, similar to what is used for LMWH, is needed. The formulation can be crushed and given through a feeding tube, if required, in the ICU setting.

Edoxaban (Savaysa)

Edoxaban, a direct-acting factor Xa inhibitor, is approved to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation and for the treatment of DVT and PE in patients who have been treated with a parenteral anticoagulant for 5–10 days.[20]

Other Agents

Citrate for Regional Anticoagulation

In patients with acute renal failure, citrate is increasingly used as an anticoagulant for continuous renal replacement therapy (CRRT) in ICU patients to maintain circuit and filter patency. Although heparin is often used, ICU patients are routinely coagulopathic, may have either an increased risk of bleeding or hypercoagulability, and are often at high risk for developing HIT. As a result, regional citrate is effective by locally chelating ionized calcium. The goal citrate level to inhibit clotting is 4–6 mmol/L which corresponds to a prefilter ionized calcium of <0.35 mmol/L.[21] Most of the calcium–citrate complex is removed during CRRT, and calcium is infused to maintain normocalcemia.[21]

ICU Management of the Oral Anticoagulants

In the ICU, oral therapy often is not feasible, and parenteral agents need to be considered. In renal failure, heparin and argatroban are most often used, and bivalirudin offers an alternative, but all of these agents require monitoring. The direct thrombin inhibitors are routinely monitored using partial thromboplastin times. However, for urgent reversal or management of the bleeding patients, significant concerns have been expressed about the new agents, but despite the

extensive use of LMWH in the ICU, there is no antidote available, and LMWH accumulates in renal failure, requiring dose adjustments. The Xa inhibitor agents apixaban and rivaroxaban can be used in ICU settings and administered through a feeding tube, if needed, in patients who cannot take oral medications.

In the United States, warfarin is still a problem for clinicians because the balanced prothrombin complex concentrates (PCCs) that contain all four factors (II, VII, IX, and X), like KCENTRA for immediate INR reversal, are not readily used by clinicians but are recommended in recent ACCP guidelines.[18] Vitamin K takes days to work; ~4 units of fresh frozen plasma (FFP) are required, with transfusion risk issues and volume overload; and FFP never restores the INR to baseline but usually to ~1.4–1.6, which is the baseline INR for FFP.[18]

Managing Bleeding with the New Oral Anticoagulants

If patients are acutely bleeding, the new agents, as mentioned, can be evaluated with specialized tests that should be measured in such patients. For dabigatran, thrombin times (TTs) and a diluted TT and ecarin clotting times (used in Europe) are the most sensitive. The aPTT can measure its effects, although it is not as sensitive as a TT.[20] The aPTT potentially provides a qualitative assessment of anticoagulation. Although there currently is no specific antidote to antagonize the anticoagulant effect of all of the agents, with normal renal function, these agents have a relatively short duration of effect, are direct acting, and drugs should be discontinued when risks of bleeding exceed risks of thrombosis.

With bleeding, patients should be hemodynamically and hemostatically resuscitated, and therapy should be multimodal.[20] Dabigatran can be immediately reversed with the antidote idarucizumab (Praxbind), which is widely available in most institutions and has been studied in a variety of medically ill, critically ill, and surgical patients.[22,23] For reversal of factor Xa inhibitors, including apixaban and rivaroxaban, a specific antidote currently available is andexanet alfa.[24] However, this agent has been studied primarily in patients with intracranial hemorrhage and gastrointestinal (GI) bleeding, but is approved for reversal of Xa inhibitor anticoagulation when needed as a result of life-threatening or uncontrolled bleeding. In instances of life-threatening bleeding, the off-label use of other prohemostatic agents such as PCCs has been reported.[20,25,26] As noted, PCCs are increasingly considered in guidance documents as part of a multimodal approach for bleeding management. Guidance for the use of specific reversal agents has been reported.[27]

The major concerns in the ICU are emergency procedures or major bleeding. However, newer information is available to facilitate managing patients receiving DOACs. Important management of the DOACs is discontinuing use, but if reversal is required, specific therapeutic approaches should be considered and include the application of PCCs for reversal and/or bleeding. PCCs in the United States are available in four components (KCENTRA) or three components (Profilnine and Bebulin).[18] The three-component PCCs are deficient in factor VII. Multiple reports have noted the ability of PCCs to treat DOAC-associated bleeding, and there are increasing reports on their off-label use in bleeding after surgery or traumatic injury.[28,29]

Despite concerns about NOACs and bleeding, most studies suggest patients fare better on NOACs compared with warfarin.[30] In one study of 27,419 patients treated up to 3 years, 1034 patients had 1121 major bleeds. The 30-day mortality after the first major bleed was 9.1% in the dabigatran group compared with 13.0% in the warfarin group, and dabigatran-treated patients required a shorter ICU stay compared with warfarin.[30]

PLATELET INHIBITORS

Patients with ischemic cardiovascular and atherosclerotic vascular disease are often receiving platelet inhibitors as anticoagulants—agents that also increase the risk for bleeding.[31,32] Aspirin is an irreversible platelet cyclooxygenase and thromboxane A_2 inhibitor but is also a relatively weak antiplatelet agent, and resistance can occur.[31] More potent antiplatelet agents include the $P2Y_{12}$ receptor antagonists clopidogrel, prasugrel, and ticagrelor that selectively bind to the $P2Y_{12}$ receptor to inhibit the adenosine diphosphate–dependent mechanism of glycoprotein IIb/IIIa receptor expression and platelet activation.[31,33] Clopidogrel, now a generic drug, is the major agent used. Clopidogrel and prasugrel are both prodrugs, whereas ticagrelor is a direct-acting agent. One of the clinical issues regarding clopidogrel is the potential for altered responsiveness, often defined as resistance, compared with ticagrelor, which is a direct-acting agent.[34] Dual antiplatelet therapy with aspirin and clopidogrel is standard care after revascularization by PCI with stent insertion, during acute coronary syndromes, and for percutaneous intervention.[33] Intravenous agents include the IIb/IIIa receptor antagonists abciximab, tirofiban, and eptifibatide, but also a short-acting $P2Y_{12}$ inhibitor cangrelor that is increasingly used for bridging in short-term therapy, especially in ICU settings when the patient may need intermittent procedural interventions.[32]

Glycoprotein IIb/IIIa inhibitors that include abciximab (a monoclonal Fab fragment), eptifibatide (a polypeptide), and tirofiban (a synthetic molecule) are still used as intravenous antiplatelet therapies that prevent platelet aggregation by competitive inhibition with fibrinogen and von Willebrand factor. Tirofiban and eptifibatide have relatively short half-lives of approximately 2–3 hours, compared with abciximab, a monoclonal antibody with an approximately 12-hour half-life.

Cangrelor is the most recently approved intravenous agent that has a rapid onset with a 3- to 6-minute half-life and rapid recovery within 30–60 minutes after stopping the infusion, with clearance independent of renal function. Cangrelor is often used for short-term use in ICU settings when antiplatelet effects are needed and was approved by the Food and Drug Administration as an adjunct to PCI to reduce the risk of MI, repeat coronary revascularization, and stent thrombosis in patients who have not been treated with a $P2Y_{12}$ platelet inhibitor or a glycoprotein IIb/IIIa inhibitor. Beyond the PCI program, cangrelor has also been evaluated in the clinical bridging study in patients with acute coronary syndrome or coronary stent who had received a $P2Y_{12}$ platelet inhibitor and were awaiting surgical coronary revascularization. Patients were randomized to cangrelor or placebo and reported no differences in surgery-related bleeding, and there were no safety signals. In an ICU setting, cangrelor bridging using a 0.75 mcg/kg/min infusion can be started for 3–4 days after prasugrel discontinuation and 2–3 days after clopidogrel or ticagrelor discontinuation and provides an important method for management.[35]

ICU/PERIOPERATIVE MANAGEMENT OF ANTITHROMBOTIC THERAPY

The most recent guidelines from the ACCP in 2012 recommend stopping VKAs 5 days before surgery instead of a shorter time before surgery (Grade 1B).[19]

In patients with a mechanical heart valve, atrial fibrillation, or VTE at high risk for thromboembolism, they suggest bridging anticoagulation instead of no bridging during VKA interruption (Grade 2C); in patients at low risk, they suggest no bridging instead of bridging (Grade 2C). In patients who require a dental procedure, they suggest continuing VKAs with an oral prohemostatic agent or stopping VKAs 2–3 days before the procedure instead of alternative strategies (Grade 2C).[19]

In moderate- to high-risk patients who are receiving acetylsalicylic acid (ASA) and require noncardiac surgery, they suggest continuing ASA around the time of surgery instead of stopping ASA 7–10 days

before surgery (Grade 2C). In patients with a coronary stent who require surgery, they recommend deferring surgery >6 weeks after bare-metal stent placement and >6 months after drug-eluting stent placement instead of undertaking surgery within these periods (Grade 1C); in patients requiring surgery within 6 weeks of bare-metal stent placement or within 6 months of drug-eluting stent placement, they suggest continuing antiplatelet therapy perioperatively instead of stopping therapy 7–10 days before surgery (Grade 2C).[19] In all patients, relative risk versus benefit must be considered when managing patients.

For warfarin management, the BRIDGE study randomized warfarin anticoagulation with LMWH using 100 U dalteparin/kg or placebo from 3 days before a procedure until 24 hours before, then for 5–10 days after.[36] Warfarin was stopped 5 days before the procedure and was resumed within 24 hours after. Of the 1884 patients studied, arterial thromboembolism was 0.4% in the without bridging group compared with 0.3% with bridging, and major bleeding was 1.3% in the without bridging group compared with 3.2% with LMWH bridging.[36]

For DOAC management, the Perioperative Anticoagulation Use for Surgery Evaluation (PAUSE) cohort study was a multinational study of,Ãâ3007 atrial fibrillation patients who were receiving apixaban, dabigatran etexilate, or rivaroxaban and scheduled for an elective surgery or procedure.[37] The study was designed based on pharmacokinetics, procedure-associated bleeding risk, and renal function. In low-bleeding-risk patients, DOACs were discontinued for 1 day before, and for high-risk bleeding 2 days before, and restarted 1 day or 2–3 days post procedure, respectively. Major bleeding and arterial thromboembolic events and the number of undetectable or minimal residual anticoagulant level (<50 ng/mL) at the time of the procedure were determined. There was no difference in major bleeding that occurred in 1.35% of the apixaban group, 0.90% in the dabigatran group, and 1.85% of the rivaroxaban group. The rate of arterial thromboembolism was 0.16%, 0.60%, and 0.37%, respectively, and major bleeding occurred in approximately 3% of patients.[37]

KEY POINTS

- Anticoagulation is a critical aspect of cardiovascular disease management, and patients are increasingly presenting or requiring anticoagulation in an ICU setting.
- Heparin continues to be the mainstay of therapy because of its short half-life, the ability to use with renal dysfunction, and reversibility.
- Critically ill patients receiving heparin infusion should be monitored for thrombocytopenia and the potential risk for HIT.
- Patients may require other types of anticoagulants in ICU settings, including intravenous bivalirudin and argatroban or alternative therapies.
- LMWH, although extensively used, is renally eliminated, with prolongations of the half-life in patients with renal dysfunction.
- Patients may be receiving the new non–vitamin K oral anticoagulants; currently, reversal strategies are available for emergent and urgent reversal.
- For emergent and urgent reversal of warfarin anticoagulation, PCC should be used based on guidelines and other supporting data.
- Bridging for procedural interventions in patients receiving warfarin and non–vitamin K oral anticoagulants may not be necessary based on new data and guidelines.
- New shorter-acting intravenous antiplatelet agents are available, including cangrelor, that can be used in ICU settings when patients may require frequent procedural interventions.

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Monitoring of Coagulation Status

Ashley Thompson

OVERVIEW OF EFFECTIVE COAGULATION

Components of Hemostasis

Fig. 129.1 depicts an overview of hemostasis. In a normal physiologic state, the body maintains a fine balance between hemorrhage and thrombosis through the regulation of various anticoagulant and prothrombotic systems. Four primary factors contribute to normal hemostasis. These factors are the vascular endothelium, platelets, coagulation factors, and fibrinolytic system.

The vascular endothelium is capable of evoking both antithrombotic and prothrombotic events. Under normal conditions, endothelial cells release prostacyclin and nitric oxide to inhibit platelet activation and promote vasodilation. After a tissue injury, vessel walls vasoconstrict to slow blood flow. Collagen and tissue factor (TF) are exposed and come in contact with blood. The exposed collagen initiates the accumulation and activation of platelets at the site of injury, while the TF triggers activation of coagulation factors. Once hemostasis has been obtained, the endothelium releases tissue plasminogen activator (tPA), activating fibrinolysis.[1,2]

Platelets contribute their hemostatic capacity via adhesion, activation, and aggregation.[3] Following the breach in the vessel wall, multiple signaling pathways are initiated that ultimately result in platelet activation. Once a platelet has been activated, additional platelets are recruited from the circulating blood to form a platelet plug via platelet–platelet cohesion. Thromboxane A_2, an eicosanoid produced by activated platelets, functions in an autocrine or paracrine manner to stimulate for further platelet aggregation.[4] The formation of the platelet plug is known as *primary hemostasis.*

After the nascent platelet plug is formed, it is stabilized by the formation of a fibrin mesh. The process by which this occurs is known as the *coagulation cascade* and is initiated by the exposure of tissue factor on the endothelial surface. The coagulation cascade consists of multiple factors that undergo a series of reactions that ultimately result in thrombin converting fibrinogen to fibrin.[5] The fibrin meshwork stabilizes the platelet plug, forming a clot. This stabilization phase is also known as *secondary hemostasis.*

The fourth factor in normal hemostasis is the fibrinolytic system. Once the vasculature has been repaired, plasmin breaks down the fibrin strands, resulting in clot degradation. Of note, there are antithrombotic control mechanisms that prevent spontaneous intravascular coagulation and excessive clotting. These include thrombomodulin, tPA, antithrombin, proteins C and S, and prostaglandins.[6]

Cell-Based Model of Hemostasis

The pathway by which hemostasis is obtained has traditionally been described by the extrinsic, intrinsic, and common pathways of the coagulation cascade. This classical model has been largely replaced with a "cell-based" model that incorporates the central role that cell surfaces play in coagulation. The cell-based model suggests that the process of coagulation occurs on different cell surfaces and occurs in three overlapping stages, which are initiation, amplification, and propagation.[7,8]

The initiation phase of the cell-based model occurs on the surface of TF-bearing cells (including immunostimulated endothelial cells, fibroblasts, and monocytes). The TF interacts with and activates factor VII (FVII), forming the TF–FVIIa complex. This complex activates factor IX and factor X, which leads to the generation of a small amount of thrombin. This initial thrombin is essential for the activation of platelets and factors V and VIII.

The amplification and propagation phases occur on the surface of platelets. During amplification, the procoagulant signal is shifted from the TF-bearing cells to the activated platelets. This allows for diffusion of factor IXa, which activates the intrinsic pathway and subsequently leads to large-scale thrombin generation. In the propagation phase, factor VIIIa interacts with factor IXa forming the FVIIIa/FIXa complex, which is a powerful activator of factor X. Factor Xa forms a complex with factor Va, which catalyzes prothrombin to thrombin. This FXa/Va complex is 300,000-fold more active than factor Xa alone in catalyzing prothrombin activation.[9]

BASIC NECESSARY CONDITIONS FOR PROPER HEMOSTASIS

Maintaining physiologic homeostasis between prothrombotic and excessive bleeding states requires a number of regulatory processes. Each component of the process of hemostasis can be disturbed, resulting in coagulopathy. Conditions that have been shown to cause coagulopathy include hypothermia, acidosis, and hypocalcemia.

Hypothermia may be a deliberately induced therapeutic maneuver or a consequence associated with trauma, surgery, or exposure. This can be exacerbated in patients who have sustained blood loss and are undergoing physiologic compensation with vasoconstriction. At a core temperature of less than 33°C, the coagulation cascade is impaired, platelet physiology is altered, and microvascular hypoperfusion is exacerbated.[10] In turn, this worsens the degree of acidosis. Hypothermia decreases coagulation factor activity by 10% for each degree decrease in core temperature.[11,12] Platelet adhesion is reduced by 33% at 33°C compared with 37°C and further reduced by 47% at 23°C.[13] In the nontrauma population, isolated hypothermia of 32.2°C leads to a 23% mortality rate, whereas in the trauma population, mortality approaches 100% when the core temperature reaches 32°C.[14,15]

Acidosis has been shown to be one of the most important predictors in coagulopathy.[16] The optimal pH for proteolytic activity of coagulation enzymes is well above physiologic pH.[17] When the pH drops

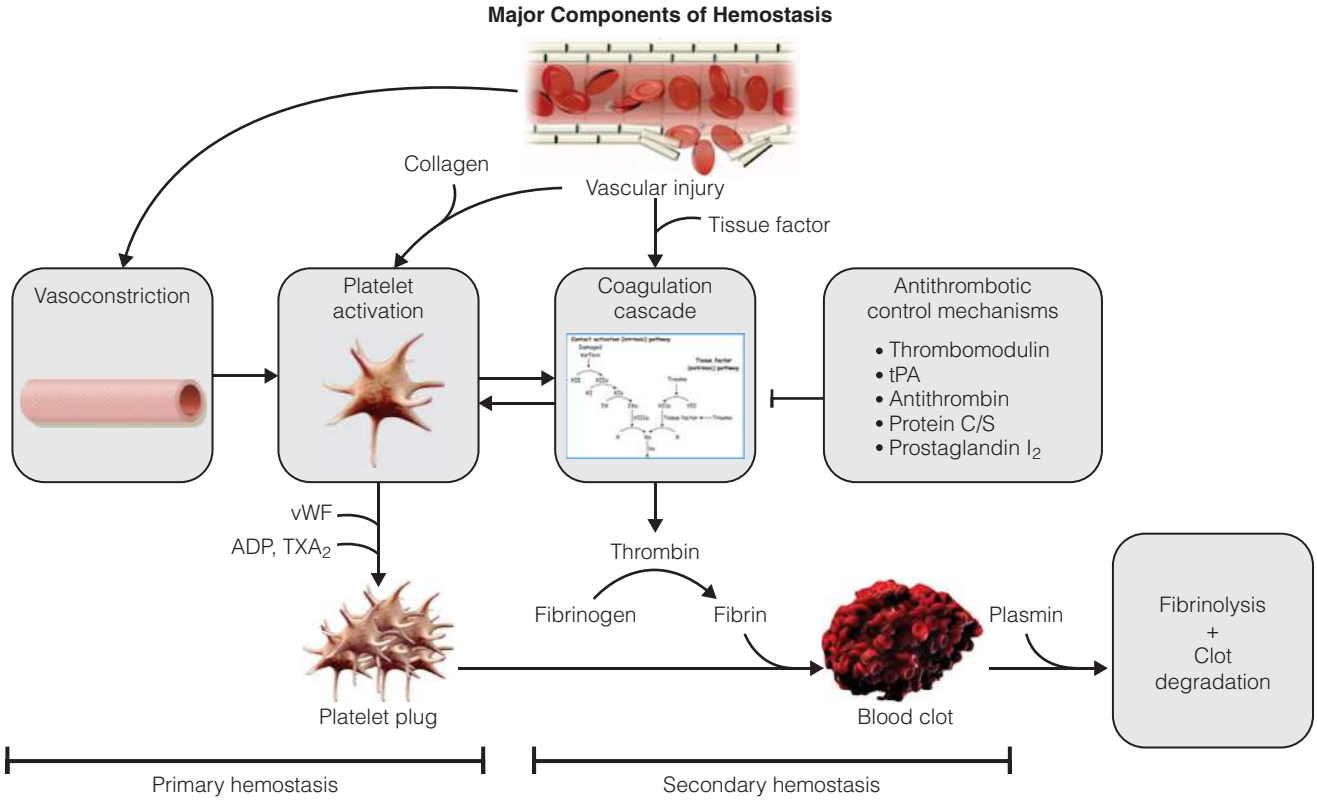


Fig. 129.1 Overview of the components of hemostasis. Immediately after vascular injury, the endothelium vasoconstricts, collagen exposure leads to platelet activation, and exposed tissue factor initiates the coagulation cascade. Activated platelets release factors, which ultimately result in the formation of a platelet plug, a process known as primary hemostasis. The coagulation cascade leads to the activation of thrombin, which promotes fibrin cross-linking. The fibrin stabilizes the platelet plug, resulting in the formation of a blood clot. This series of enzymatic reactions is known as secondary hemostasis. The clot will eventually undergo degradation via plasmin and fibrinolysis. *ADP,* Adenosine diphosphate; *tPA,* tissue plasminogen activator; *TXA_2,* thromboxane A_2; *vWF,* von Willebrand factor.

below 7.1, the ability of thrombin and fibrinogen to propagate a clot is severely diminished.[18] The activity of FVII is reduced by 90%, which leads to more blood loss and furthers the cycle. Platelets lose their ability to change shape when a patient becomes acidotic, which in turn hinders their ability to form a clot.

Ionized calcium is a necessary cofactor in the coagulation cascade. Citrate anion is capable of binding (chelating) ionized calcium, and this is how the citrate component of acid citrate dextrose (ACD) buffer used in blood storage leads to anticoagulation. Patients who have received massive resuscitation with citrated blood products should receive appropriate calcium replacement. Additionally, it has been hypothesized that hypocalcemia is associated with poor clot strength in critically ill patients, particularly for ionized calcium levels of <1.0 mmol/L.[19–21]

LABORATORY ANALYSIS FOR COAGULATION

Measures of Coagulation

Traditionally, the most commonly used clotting assays include prothrombin time (PT) or international normalized ratio (INR), activated partial thromboplastin time (aPTT), thrombin time (TT), and fibrinogen level. Each of these tests has limitations in that they are performed in plasma and do not reflect in vivo hemostasis. Therefore it is important to consider the patient's drug history, family history of coagulation disorders, and personal history of coagulopathies.

PT and aPTT are measures taken from the acellular, platelet-depleted plasma component of a citrated blood sample that has been centrifuged. The PT measures the time taken for clot formation after thromboplastin and calcium have been added to the sample. Several different thromboplastin reagents are commercially available with varying sensitivities. Therefore to standardize the PT assay, individual reagents are compared with a World Health Organization standard reference and assigned an international standardized index (ISI) value.[22] The ISI is then used to calculate the INR. The PT measures the extrinsic and common pathways and will be affected by the plasma concentrations of factors II, V, VII, and X and fibrinogen.

The aPTT measures the time taken for clot formation after the addition of calcium, phospholipid (partial thromboplastin), and a contact activator to the acellular plasma sample. aPTT evaluates the intrinsic pathway and will be prolonged with deficiencies of factors II, V, VIII, IX, X, XI, and XII or fibrinogen. Of note, the PT and aPTT are helpful in identifying factor deficiencies but cannot assess overall risk of hemorrhage.[23]

TT is measured by adding thrombin to platelet-depleted plasma and evaluating the conversion of fibrinogen to fibrin. TT may be used as a screening test for the detection of qualitative and quantitative fibrinogen abnormalities or fibrin formation disorders and is very sensitive to the presence of heparin or direct thrombin inhibitors in the sample.[24] Of the multitude of available coagulation assays, this is one of the most procedurally simple.

Fibrinogen levels can be helpful in the investigation of a prolonged PT or aPTT. Many methods have been used to measure plasma fibrinogen concentration, including gravimetric, immunologic (antigen-based),

optical, and functional assays. The most commonly used are the Clauss and prothrombin time–derived methods. The Clauss assay is a quantitative, clot-based, functional assay that measures the ability of fibrinogen to form a fibrin clot after being exposed to a high concentration of purified thrombin. This method does not measure fibrinogen directly, but determines the time until detectable clot formation.[25] Similarly, the PT-derived method is not a direct determination of plasma fibrinogen, but rather estimates fibrinogen based on absorbance changes during a prothrombin time assay. Thromboelastogram (TEG) and rotational thromboelastometry (ROTEM) are newer technologies that can be used to provide a qualitative indication of the fibrinogen concentration. These are discussed in further detail later in the chapter.

Measures of Platelet Disorders

Platelet count does not provide a functional assessment of platelets, but a low platelet count is associated with increased risk of bleeding and mortality.[26] Thrombocytopenia is defined as a platelet count below the lower limit of normal (150,000/μL). Spontaneous bleeding can occur with a platelet count less than 10,000/μL, and it is recommended that patients with counts below this level should receive a prophylactic platelet transfusion.[27] Guidelines often recommend a transfusion threshold of 50,000/μL before major surgery or if actively bleeding and 100,000/μL before surgery involving the brain or eyes.[28] Of note, a normal platelet count does not preclude platelet dysfunction.

The differential diagnosis for platelet dysfunction is broad and includes inherited syndromes in addition to acquired causes such as uremia, myelodysplasia, and drug-induced. These patients may present with ongoing bleeding in the setting of a normal platelet count. Numerous methodologies for assessment of platelet function are available. These include bleeding time, light transmission platelet aggregation (LTA), lumiaggregometry, impedance aggregometry on whole blood, platelet analysis based on flow cytometry, and platelet function methods combined with viscoelastic testing (TEG/ROTEM). The most commonly used tests rely on a platelet agonist (e.g., adenosine diphosphate [ADP], epinephrine, ristocetin, thrombin receptor agonist peptide [TRAP]), exposure to shear stress, or both to activate platelets. These tests monitor the rate of platelet aggregation through changes in light transmission, light scattering, electrical impedance, platelet aggregation on a plate, or occlusion of a tube.[29,30]

The platelet function analyzer (PFA-100) is a tool that analyzes primary hemostasis. A sample (<1 mL) of citrated blood is exposed to high shear stress within a capillary tube coated with collagen and either ADP or epinephrine. The shear stress and agonists in the membrane activate the platelets, leading to platelet aggregation. The flow rate is monitored and the time at which blood flow stops because of aperture occlusion of aggregated platelets, known as *closure time,* is reported.[31] The closure time will be abnormal in patients with congenital platelet dysfunction, von Willebrand disease, or recent aspirin ingestion. Anemia and thrombocytopenia may prolong closure time and, in general, the test is not useful in patients with a platelet count less than 80,000/μL or hematocrit <30%.[32]

The Multiplate multiple electrode aggregometry (MEA) analyzer (Roche Diagnostics, Mannheim, Germany) is a point-of-care test of platelet function that exposes platelets to platelet activators and monitors aggregation using the principle of impedance. A 300-μL sample of whole blood is obtained and diluted with saline. After incubation for 3 minutes, a platelet agonist is added and subsequent aggregation is recorded at 0.5-second intervals for 6 minutes. This test is commonly used to monitor treatment with antiplatelet agents such as aspirin and P2Y12 antagonists and has been evaluated as a potential predictor of bleeding risk in cardiac surgery and trauma patients.[33,34] Of note, unlike whole-blood clotting assays, the benefit of dedicated PFAs is their ability to reliably detect the effect of platelet antagonists.[35]

Viscoelastic Hemostatic Assays

Viscoelastic hemostatic assays (VHAs) are whole-blood tests that dynamically assess clotting time, clot strength, and clot lysis by continuously measuring the kinetics of all stages of clot formation. Two commercially available systems are available in the United States: TEG (Haemonetics, Braintree, MA) and ROTEM (Penthapharm, Basel, Switzerland). To perform these tests, a pin suspended by a torsion wire is lowered into a heated cup filled with whole blood. Either the cup (TEG) or the pin (ROTEM) is alternately rotated clockwise or counterclockwise. As the blood clots, strands of fibrin form between the cup and the pin, transmitting the torque of the cup to the torsion wire. The torque is continuously recorded and displayed as a graph.[36–38]

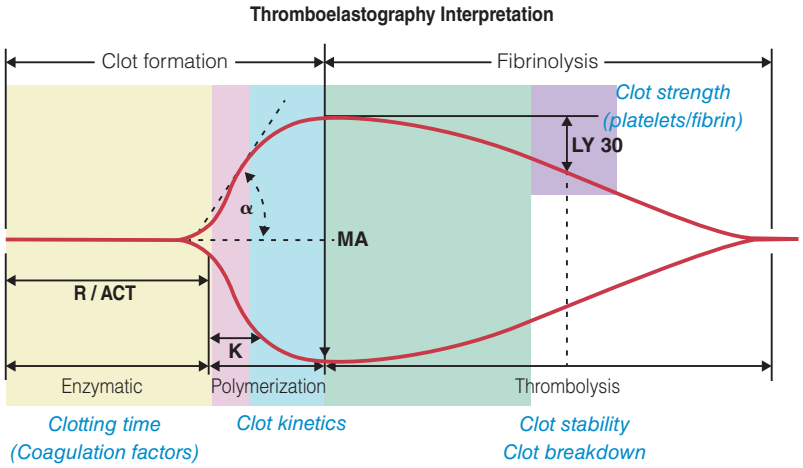
Fig. 129.2 depicts a TEG waveform and its interpretation. The data obtained from TEG and ROTEM are similar, but not interchangeable, because of differences in the methods and nomenclature. The time it takes to start forming a clot (reaction [R] time in TEG, clotting time [CT] in ROTEM) is the time from sample placement until the tracing amplitude reaches 2 mm. The kinetic time (K-time) in TEG, or clot formation time (CFT) in ROTEM, represent the time it takes for the clot to reach a fixed strength. Graphically, this is the time elapsed between the R-time and the point where the tracing amplitude reaches 20 mm. The angle is the speed of fibrin accumulation and is created from the developing curve from the point of clot initiation. Maximal amplitude (MA) in TEG or maximal clot firmness (MCF) in ROTEM is a function of the fibrin and platelet bonding. This represents the strongest point in the clot formation and correlates with platelet function. Lastly, clot dissolution is measured to evaluate for fibrinolysis. In TEG, lysis is measured at 30 and 60 minutes after the MA is recorded. In ROTEM, the lysis index 30 represents the percent reduction from MCF 30 minutes after CT.[39]

An individual's TEG/ROTEM results are compared with reference values. Deviation of these results from the reference values suggests specific disturbances of hemostasis. A prolonged R or clotting time represents a qualitative or quantitative deficiency in clotting factors, which may be corrected with the administration of fresh frozen plasma (FFP). A decreased alpha-angle or prolonged K-time/CFT indicates a fibrinogen deficiency that may be corrected with cryoprecipitate or lyophilized fibrinogen. A low MA/MCF suggests a functional or quantitative deficiency of platelets, which may be corrected with administration of desmopressin or a platelet transfusion. Increased lysis values indicate active fibrinolysis, which may be treated with fibrinolysis inhibitors such as tranexamic acid.

The primary advantage to TEG/ROTEM is the ability to deliver immediate, point-of care data for a bleeding patient using less than half of a milliliter of blood. VHAs provide a global assessment of coagulation, including coagulation factors, platelet function, and fibrinolysis. This information can be used to guide transfusion therapy and potentially decrease the use of blood products.[40,41] A 2016 Cochrane review determined that there is growing evidence that the use of TEG- or ROTEM-guided transfusion strategies may not only reduce the need for blood products but also may improve the morbidity in bleeding patients.[42]

Disseminated Intravascular Coagulation Score

Disseminated intravascular coagulation (DIC) is characterized by systemic overactivation of coagulation. Some inciting factor causes an overwhelming inflammatory response, which results in upregulation of tissue factor while simultaneously impairing physiologic anticoagulation and fibrinolysis. As a result, there is widespread fibrin deposition and microvascular thromboses. The formation of all of these clots results in consumption of coagulation factors, platelets, and anticoagulants. In laboratory studies, low platelet counts, prolonged PT/PTT, low fibrinogen levels, and elevated D-dimer can be seen.



TEG value	Normal	Description	Problem	Treatment
R-time	5–10 min	"Reaction time" = time to start forming clot	Coagulation factors	FFP
K-time	1–3 min	"Kinetic time" = time until clot reaches a fixed strength	Fibrinogen	Cryoprecipitate
α-angle	53–72 degrees	Speed of fibrin accumulation	Fibrinogen	Cryoprecipitate +/– platelets
MA	50–70 mm	"Maximum amplitude" = highest vertical amplitude of the TEG; corresponds to platelet function	Platelets	Platelets and/or DDAVP
LY 30	0–3%	Percentage of amplitude reduction 30 minutes after maximum amplitude	Excess fibrinolysis	TXA and/or aminocaproic acid

Fig. 129.2 Interpretation of thromboelastography waveform. Thromboelastography (*TEG*) is reported as a graph of the formation of a clot in a sample of whole blood. The tracing demonstrates the rate of clot formation, clot strength, fibrin cross-linking, platelet function, and the speed of clot degradation. Based on these data, the problematic components of the coagulation pathway can be identified and appropriately treated. *DDAVP,* Desmopressin; *FFP,* fresh frozen plasma; *LY 30,* lysis index 30; *TXA,* tranexamic acid.

DIC is always secondary to an underlying condition such as severe infection, solid or hematologic malignancies, trauma, or obstetric issues. Up to 35% of cases of severe sepsis may be complicated by DIC, and the severity of DIC has been shown to correlate with mortality in these patients.[43–45] In major trauma, DIC has been shown to approximately double the mortality rate.[46] A reliable diagnosis can be made using the International Society of Thrombosis and Hemostasis DIC Scoring Algorithm depicted in Table 129.1. Based on the platelet count, fibrinogen level, PT, and D-dimer, a DIC score can be calculated. A score of 5 or more has a sensitivity of 93% and specificity of 98% for diagnosing DIC.[47] The cornerstone treatment for DIC is supportive care and management of the underlying condition.

TABLE 129.1 International Society of Thrombosis and Hemostasis DIC Scoring Algorithm

DIC SCORE		
Parameter	**Value**	**Score**
PT	≤3 s	0
	3–6 s	1
	>6 s	2
Fibrinogen	>100 mg/dL	0
	<100 mg/dL	1
D-dimer	<400 ng/dL	0
	400–4000 ng/mL	2
	>4000 ng/mL	3
Platelets	>100,000/μL	0
	50,000–100,000/μL	1
	<50,000/μL	2
Score Interpretation:		
<5: Not suggestive of overt DIC, may be nonovert DIC; repeat within next 1–2 days and manage clinically as appropriate		
≥5: Compatible with overt DIC; treat for DIC as appropriate and repeat scoring daily		

DIC, Disseminated intravascular coagulation; *PT,* prothrombin time. Courtesy International Society of Thrombosis and Hemostasis, 2001.

MONITORING ANTICOAGULATION

Unfractionated Heparin, Low-Molecular-Weight Heparin, and Fondaparinux

Unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), and fondaparinux all require antithrombin (AT) activation to express their anticoagulant effect. UFH binds to and potentiates the action of AT to inactivate factor Xa, preventing the conversion of prothrombin to thrombin and of fibrinogen to fibrin. LMWH similarly binds to and accelerates the activity of AT, but with a preferential and longer-lasting effect on factor Xa. Fondaparinux is essentially a synthetic derivative of LMWH that enhances the anti-Xa activity of AT by greater than 300-fold and has no direct effect on thrombin.[48] UFH can be monitored with aPTT until higher plasma concentrations are achieved, at which time an activated clotting time (ACT) is needed to accurately assess anticoagulation.

LMWH and fondaparinux do not uniformly affect the aPTT and anti-Xa assays calibrated to the particular agent are necessary for monitoring.[49]

Vitamin K Antagonists

Vitamin K is a fat-soluble vitamin that is an essential cofactor in the conversion of clotting factors II, VII, IX, and X into their active form. Vitamin K antagonists (VKAs) have been the mainstay of long-term anticoagulation therapy for more than 50 years. The most commonly used VKA is warfarin, sold under the brand name Coumadin. VKAs have a narrow therapeutic range and therefore require regular monitoring. The degree of anticoagulation is reliably measured with the INR of the PT.

Direct Oral Anticoagulants: Dabigatran, Apixaban, and Rivaroxaban

Direct oral anticoagulants (DOACs), also collectively known as *non–vitamin K oral anticoagulants* (NOACs), are a relatively newer class of drugs shown to have equal, if not superior, efficacy while maintaining a better safety profile and requiring less monitoring than VKAs.[50] Apixaban and rivaroxaban are direct factor Xa inhibitors. Both of these drugs can alter the PT and PTT, though this effect is not reliable, and normal values do not preclude clinically relevant drug concentrations. Anticoagulation can be measured with anti-Xa assays that are calibrated for the specific drug, though routine monitoring is not indicated. Dabigatran is a direct thrombin inhibitor (DTI) and is the only oral DTI available. Similar to the factor Xa inhibitors, dabigatran is generally given at a fixed dose without monitoring. If coagulation testing is needed, dilute thrombin time and ecarin clotting time can be used to quantify plasma drug levels.[49,51]

Parenteral Direct Thrombin Inhibitors: Argatroban and Bivalirudin

Argatroban and bivalirudin are synthetic peptide-based parenteral DTIs that are most commonly used in patients undergoing percutaneous coronary interventions (PCIs) and in those with heparin-induced thrombocytopenia (HIT). DTIs prolong the aPTT, PT/INR, and ACT. Monitoring is performed using ACT or aPTT.[52] Of note, as argatroban prolongs the INR, it should be discontinued while transitioning to warfarin if the INR is greater than 4 with an aPTT within goal range.[52]

Antiplatelet Agents

Antiplatelet medications can be classified based on their mechanism of action. The most common are the platelet aggregation inhibitors, which include cyclooxygenase enzyme (COX) inhibitors (aspirin) and oral thienopyridines (clopidogrel, ticagrelor, prasugrel). Monitoring is generally not required for antiplatelet medications. If bleeding is present, bleeding time may be used to determine if a platelet transfusion is needed or if the medication requires discontinuation. Studies previously discussed regarding platelet dysfunction may also be useful in the evaluation and management of a bleeding patient on antiplatelet therapy.[26–28]

KEY POINTS

- The cell-based model of hemostasis has largely replaced the classic cascade model as the current theory of how coagulation occurs in vivo. This model suggests that the process of coagulation occurs on different cell surfaces and occurs in three overlapping stages of initiation, amplification, and propagation.
- Hypothermia, acidosis, and hypocalcemia have been associated with coagulopathy and should be corrected in bleeding patients.
- PT/INR, PTT, fibrinogen, and platelet count are routinely used in the work-up of coagulation but do not necessarily reflect in vivo hemostasis. When measuring coagulation, it is important to consider a patient's drug history, family history of coagulation disorders, and personal history of coagulopathies.
- Thrombocytopenia is associated with increased risk of bleeding and mortality. Platelets should be prophylactically transfused for platelet count <10,000/μL because of the risk of spontaneous hemorrhage. Platelet count does not provide a functional assessment of platelets.
- TEG/ROTEM provides a point-of-care assessment of coagulation, which can be used to guide transfusion therapy. The use of TEG/ROTEM may reduce the need for blood products and improve morbidity in bleeding patients.
- DIC is a condition associated with a high mortality and can be reliably diagnosed by calculating a DIC score.
- UFH, argatroban, and bivalirudin can be monitored using aPTT and ACT. Warfarin is monitored with PT/INR. LMWH, fondaparinux, apixaban, and rivaroxaban can be monitored using anti-Xa assays with normalized curves for the specific agent. TT and ecarin clotting time can evaluate dabigatran activity.

References for this chapter can be found at expertconsult.com.

ANNOTATED REFERENCES

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A reliable diagnosis of disseminated intravascular coagulation (DIC) can be made using the International Society of Thrombosis and Hemostasis DIC Scoring Algorithm. A score of 5 or more has a sensitivity of 93% and specificity of 98% for diagnosing DIC.

Hoffman M, Monroe III DM. A cell-based model of hemostasis. *Thromb Haemost.* 2001;85(6):958–965.
The cell-based model of hemostasis suggests that the process of coagulation occurs on different cell surfaces and in three overlapping stages, which are initiation, amplification, and propagation.

Wikkelsø A, Wetterslev J, Møller AM, et al. Thromboelastography (TEG) or thromboelastometry (ROTEM) to monitor haemostatic treatment versus usual care in adults or children with bleeding. *Cochrane Database Syst Rev.* 2016;2016(8):CD007871.
Thromboelastography (TEG) and rotational thromboelastometry (ROTEM) are examples of viscoelastic homeostatic assays (VHAs), which are whole-blood tests that dynamically assess clotting time, clot strength, and clot lysis by continuously measuring the kinetics of all stages of clot formation. There is growing evidence that the use of TEG- or ROTEM-guided transfusion strategies may not only reduce the need for blood products but also improve the morbidity in bleeding patients.

Wolberg AS, Meng ZH, Monroe III DM, et al. A systematic evaluation of the effect of temperature on coagulation enzyme activity and platelet function. *J Trauma.* 2004;56(6):1221–1228.
Hypothermia is associated with an increased risk of bleeding and is a significant contributing factor to the morbidity and mortality of trauma. At a core temperature of less than 33°C, the coagulation cascade is impaired, platelet physiology is altered, and microvascular hypoperfusion is exacerbated.

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Direct oral anticoagulants (DOACs) are a relatively newer class of drugs shown to have equal, if not superior, efficacy while maintaining a better safety profile and requiring less monitoring than vitamin K antagonists.

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Critical Care of the Hematopoietic Stem Cell Transplant Recipient

Robert M. Kotloff and Steve G. Peters

Hematopoietic stem cell transplantation (HSCT) is used to treat an ever-increasing array of disorders, including hematologic and lymphoid cancers; selected solid tumors; and nonneoplastic diseases, including autoimmune disorders, amyloidosis, and aplastic anemia. The main indications for autologous transplantation include multiple myeloma and lymphomas. Allogeneic transplants are most commonly performed for acute and chronic leukemia, lymphoma, and myelodysplastic syndrome. The most common graft source is peripheral blood; other graft sources include bone marrow and cord blood. A conditioning regimen is employed before transplantation to eradicate malignant cells and, in allogeneic transplantation, to induce immunosuppression that permits engraftment. The conditioning regimen can be myeloablative, reduced-intensity, or nonmyeloablative. Some patients are also given total-body irradiation for myeloablation and immunosuppression.

After HSCT, the immune system recovers along predictable patterns depending on the underlying disorder, stem cell source, and complications such as graft-versus-host disease (GVHD). Recovery occurs faster in autologous recipients, in those who receive peripheral blood stem cell grafts, and after nonmyeloablative conditioning. The posttransplant period is divided into three phases: preengraftment, early posttransplant, and late posttransplant. The preengraftment phase (0–30 days) is characterized by neutropenia and breaks in the mucocutaneous barriers. The early postengraftment phase (30–100 days) is dominated by impaired cell-mediated immunity. The impact of this cell-mediated defect is determined by the development of GVHD and the corresponding immunosuppressive medications. The late posttransplant phase (>100 days) is characterized by defects in cell-mediated and humoral immunity, in addition to function of the reticuloendothelial system in allogeneic transplant recipients.

INDICATIONS FOR ICU ADMISSION

Reflecting the multitude of potentially life-threatening complications that can punctuate the posttransplant course, the intensive care unit (ICU) is a common setting for the care of HSCT recipients. Reported rates of admission to the ICU vary widely in the published literature and are considerably higher for allogeneic compared with autologous recipients, for whom admission rates of 20%–35% have been reported in contemporary series.[1,2] Pulmonary complications represent the most common reason for ICU admission, accounting for approximately one-third of cases.[2,3] Pneumonia and sepsis-induced acute respiratory distress syndrome (ARDS) are common causes of hypoxemic respiratory failure in HSCT recipients. Noninfectious pulmonary complications also can lead to respiratory failure and ICU admission. Other common reasons for ICU admission include sepsis, cardiac events (arrhythmias, infarction, congestive heart failure), and neurologic complications (intracranial bleed, seizures, altered mental status).

COMMON INFECTIOUS COMPLICATIONS REQUIRING ICU CARE

Infectious complications are more common in patients who have undergone allogeneic transplantation because these recipients require the administration of immunosuppressive agents after transplantation to prevent or treat GVHD. In addition, GVHD itself causes an immunodeficient state by involving mucosal surfaces, the reticuloendothelial system, and bone marrow. The use of alternative hematopoietic precursor sources, such as mobilized peripheral blood stem cells, and cytokines, such as hematopoietic cell colony-stimulating factors, have shortened the period of neutropenia and decreased the frequency of infectious pulmonary complications. Additionally, effective prophylactic strategies have evolved that have further reduced the incidence of infections, in particular *Pneumocystis jiroveci* and cytomegalovirus (CMV). Nonetheless, pneumonia remains a leading cause of death after HSCT.

Bacterial Pneumonia

Bacterial pneumonia may occur at any time in the posttransplantation period but is particularly prevalent during the preengraftment period of profound neutropenia. Gram-negative pathogens, including *Pseudomonas aeruginosa,* predominate during this time.[4] *Legionella* species are an important cause of nosocomial pneumonia in some centers.

Bacterial pneumonia is commonly heralded by fever, but respiratory symptoms and signs may be absent in the neutropenic host. Presumably because of the paucity of neutrophils, chest x-ray abnormalities may be subtle or absent as well. In one series, the use of high-resolution computed tomography (CT) imaging revealed evidence of pneumonia in more than 50% of febrile neutropenic patients with normal chest radiographs.[5] Broad-spectrum antibiotics (with anti-*Pseudomonas* activity) should be initiated expeditiously in all suspected cases of bacterial pneumonia and in febrile, neutropenic patients without an identified site of infection. In choosing an antibiotic regimen, clinicians must be cognizant of the particular epidemiologic and susceptibility patterns in their hospital- and patient-associated risk factors that might increase the risk of highly resistant pathogens such as methicillin-resistant *Staphylococcus aureus,* extended-spectrum beta-lactamase-producing Enterobacteriaceae, and carbapenemase-producing organisms.

Aspergillus

Although the incidence of invasive aspergillosis has declined significantly with widespread implementation of azole prophylaxis, it remains one of the most devastating complications of HSCT and one of the leading causes of infectious death in this group. Allogeneic transplant recipients in particular are at increased risk for invasive

aspergillosis caused by neutropenia during the preengraftment phase and the administration of immunosuppressive agents to both prevent and treat GVHD. The reported frequency of invasive aspergillosis in the allogeneic population varies between 5% and 15% compared with 0%–8% among autologous HSCT recipients.[6]

Invasive aspergillosis is confined to the lungs in the majority of cases, but sinusitis and central nervous system involvement also occur with some frequency. Cough and dyspnea are the most common presenting symptoms. Pleuritic chest pain and hemoptysis are important, albeit nonspecific, clues to the presence of invasive aspergillosis, reflecting the tendency of the organism to invade blood vessels and cause pulmonary infarction. Fever may be absent in up to two-thirds of patients.

Initial radiographic findings include single or multiple nodules, cavities, and subsegmental or segmental consolidation. CT imaging is more sensitive in detecting abnormalities and can do so at an earlier stage of infection. A highly characteristic CT finding is the halo sign, a rim of low attenuation representing edema or hemorrhage that surrounds a pulmonary nodule. In one study, the halo sign was present in over 90% of neutropenic patients with invasive pulmonary aspergillosis when CT scans were performed at the onset of fever.[7]

Establishing a definitive diagnosis of invasive pulmonary aspergillosis remains difficult, and up to 30% of cases are unrecognized antemortem.[8] The recovery of *Aspergillus* species on cultures of bronchoalveolar lavage fluid is highly suggestive of invasive infection in the HSCT population, but sensitivity is only 27%–57%, with the lowest yields reported for peripheral nodular lesions.[9,10] Transthoracic fine-needle aspiration of accessible focal lesions has a yield of 50%–67%, but performance of this procedure is often precluded by the presence of severe thrombocytopenia.[11,12] An enzyme-linked immunosorbent assay that detects galactomannan, a fungal cell wall component released during invasive disease, has been introduced into clinical practice as a diagnostic tool, albeit with its own limitations. Among HSCT patients with proven or probable cases of invasive aspergillosis included in a meta-analysis, the pooled sensitivity, specificity, and positive and negative predictive values of serum galactomannan testing were 82%, 86%, 65%, and 65%, respectively.[13] Galactomannan testing of bronchoalveolar lavage (BAL) fluid appears to offer greater sensitivity than the serum assay, without sacrificing specificity.[9,14,15] Current practice guidelines from the Infectious Disease Society of America endorse the use of both serum and BAL galactomannan assays in the diagnosis of invasive aspergillosis in the HSCT population (strong recommendation; moderate-quality evidence).[10]

Voriconazole is the treatment of choice for invasive aspergillosis, based on demonstration of superior efficacy and less toxicity compared with amphotericin B.[16] A multicenter registry of HSCT recipients documented partial or complete response at 12 weeks in 64% of patients with invasive aspergillosis, the majority of whom were treated with voriconazole either alone or in combination with an echinocandin.[17] The mortality rate at this time point was 36%, a dramatic reduction from rates in excess of 80% reported in the 1990s. Liposomal amphotericin B and isavuconazole are alternative options for patients in whom voriconazole is contraindicated or not tolerated. The echinocandins (caspofungin, micafungin), used either alone or in combination with another antifungal agent, are considered to be salvage therapy for severe or refractory cases. Surgical resection of localized disease is sometimes used as an adjunct to antifungal therapy in refractory cases or in the setting of massive hemoptysis.

Cytomegalovirus

The risk of CMV pneumonia is far greater after allogeneic compared with autologous HSCT, a consequence of the need to administer immunosuppressive drugs to the former recipient group. The vast majority of episodes of CMV disease result from reactivation of latent virus in seropositive recipients. Seronegative patients who receive stem cells from a seropositive donor have a lower risk of posttransplantation CMV disease than do seropositive recipients, a situation that contrasts with that seen after solid organ transplantation. In the preprophylaxis era, the onset of CMV pneumonia almost invariably occurred between engraftment and day 100. The use of prophylaxis has dramatically reduced the incidence of CMV pneumonia to approximately 5% among allogeneic HSCT recipients but has also shifted the onset of disease to later in the posttransplantation course.

The clinical presentation of CMV pneumonia is not distinctive. Nonproductive cough, fever, and hypoxemia are typical, with rapid progression to respiratory failure in some cases. The chest radiograph most often demonstrates bilateral interstitial opacities, but focal or diffuse consolidation and nodular opacities may also be seen. Ground-glass opacities are commonly demonstrated by high-resolution CT. The diagnosis of CMV pneumonia is most definitively established by demonstration of viral inclusion bodies in specimens obtained by either transbronchial lung biopsy or BAL, but the yield of both of these techniques is low. In association with compatible clinical and radiographic features, detection of virus in BAL fluid by rapid culture technique or polymerase chain reaction (PCR) is considered diagnostic in this patient population. However, in cases lacking the classic features, these results must be interpreted with caution because viral shedding into the respiratory tract can occur in the absence of invasive disease. Identification of a high viral load in peripheral blood provides additional supportive evidence in the appropriate setting.

The combination of ganciclovir and high-dose intravenous immunoglobulin (IVIg) or CMV-specific immunoglobulin is standard of care for treatment of CMV pneumonia in HSCT recipients, though the need for the immunoglobulin preparations has recently been questioned.[18] Foscarnet is reserved for patients unable to tolerate ganciclovir and those infected with ganciclovir-resistant strains.

Community Respiratory Viruses

As a group, the community respiratory viral pathogens—respiratory syncytial virus (RSV), influenza A and B, parainfluenza, and human metapneumovirus—account for the majority of non-CMV viral respiratory infections in both autologous and allogeneic HSCT recipients. With the exception of parainfluenza virus, which occurs year-round, the other viruses occur predominantly in the late fall, winter, and early spring. These viruses most commonly present as upper respiratory tract infections, but all have the propensity to progress to involve the lower respiratory tract (LRTI; i.e., bronchiolitis or pneumonia) and to lead to respiratory failure.

Among patients with RSV infection, the risk of progression to LRTI approaches 80% for those who are less than 1 month posttransplant or still in the preengraftment stage but falls to less than 40% for those beyond this critical period.[19] Once LRTI develops, mortality from untreated RSV infection approximates 80%. Published studies, chiefly retrospective or prospective but nonrandomized, suggest that ribavirin alone or in combination with IVIg or RSV-specific monoclonal antibody (palivizumab) decreases mortality among HSCT recipients with RSV LRTI.[20] Aerosolized ribavirin has been used in most studies, but favorable results have also been reported with intravenous and oral administration. There is currently no consensus on the approach to treating RSV LRTI, but published guidelines endorse the use of aerosolized ribavirin and IVIg for HSCT recipients with LRTI.[21,22]

Ribavirin has been used in the treatment of LRTI with parainfluenza and human metapneumovirus, but there is no compelling evidence of efficacy. Patients with LRTI from influenza are commonly treated with the neuraminidase inhibitor oseltamivir, but its efficacy in

HSCT recipients has not been established. Postinfluenza bacterial pneumonias, typically with *S. aureus* or *Pneumococcus,* should be considered in patients who develop a second wave of fever associated with evidence of consolidation on imaging.

COMMON NONINFECTIOUS COMPLICATIONS REQUIRING ICU CARE

Acute Pulmonary Edema

Acute pulmonary edema is a common but potentially overlooked cause of pulmonary dysfunction during the neutropenic phase after HSCT. Noncardiogenic pulmonary edema has many contributory factors, including total-body radiation, induction drugs, aspiration, transfusion-related acute lung injury, and sepsis. Patients who develop hydrostatic/cardiogenic pulmonary edema have often received large volumes of fluid for medications, total parenteral nutrition, and multiple blood product transfusions. Cardiac dysfunction resulting from chemotherapeutic agents used during induction can also contribute to volume overload, as can renal impairment.

Engraftment Syndrome and Periengraftment Respiratory Distress Syndrome

Engraftment syndrome is characterized in its full expression by a combination of fever, erythrodermatous rash, diarrhea, diffuse capillary leak, and noncardiogenic pulmonary edema occurring coincident with neutrophil recovery.[23] This syndrome has been described most frequently after autologous HSCT, with a reported incidence of 7%–53%.[24,25] A similar presentation after allogeneic transplantation has been described but must be distinguished from acute GVHD. The term *periengraftment respiratory distress syndrome* (PERDS) has been applied to the subset of patients with engraftment syndrome who manifest hypoxemia and pulmonary opacities on chest radiographs.

The etiology of engraftment syndrome is poorly understood; release of proinflammatory cytokines during engraftment is postulated to play a principal role. The use of granulocyte–macrophage colony-stimulating factor has been identified in some studies as a risk factor for engraftment syndrome.[26]

Signs and symptoms of PERDS begin within 5 days preceding or after neutrophil engraftment. Dyspnea is universally present, accompanied by hypoxemia of varying severity. Frank respiratory failure requiring mechanical ventilator support develops in approximately one-third of patients with PERDS. The majority of patients are febrile; other clinical features of engraftment syndrome may be present, including a maculopapular rash, hypoalbuminemia, ascites, and peripheral edema. Bilateral pulmonary infiltrates are seen on chest x-ray and CT scan but are nonspecific. The diagnosis of PERDS is based on the presence of compatible clinic-radiographic features; onset in the periengraftment period; and the exclusion of infection, volume overload, diffuse alveolar hemorrhage (DAH), and other entities that share similar features. Early recognition and treatment with high-dose corticosteroids has been associated with rapid clinical improvement, even among patients requiring mechanical ventilation.[23,27]

Diffuse Alveolar Hemorrhage

In the context of HSCT, DAH is considered to be a manifestation of widespread alveolar injury of noninfectious etiology. DAH occurs with a frequency of 1%–5% among autologous HSCT recipients and 3%–7% among allogeneic HSCT recipients and, because of the high rate of associated respiratory failure, is a common indication for ICU admission in these patient populations.[28,29] DAH is most commonly observed within the first month, often during the periengraftment phase, but later onset is encountered in up to 47% of cases.[28,29] Older age, allogeneic donor source, severe acute GVHD, total-body irradiation, myeloablative conditioning regimen, and renal insufficiency have been identified as risk factors.[29] Although thrombocytopenia is common, platelet counts are not lower than those found in patients without DAH, and aggressive platelet transfusion does not result in improvement in respiratory status.[30]

The pathogenesis of DAH in HSCT recipients remains obscure. Postmortem investigations have shown that the majority of patients with DAH have evidence of diffuse alveolar damage.[30,31] It is likely that DAH, like idiopathic pneumonia syndrome (IPS) and PERDS, is part of a spectrum of acute lung injury induced by conditioning chemotherapy, radiation, and occult infection. The fact that many cases occur at the time of engraftment suggests that neutrophil influx into the lung may accentuate the injury and in some way precipitate hemorrhage.

Patients present with dyspnea, nonproductive cough, fever, and diffuse pulmonary infiltrates, but hemoptysis is notably rare. An otherwise unexplained drop in hemoglobin provides an important clue to the presence of DAH. The majority of patients require ICU admission and mechanical ventilation. Diagnosis centers on the bronchoscopic demonstration of progressively bloodier BAL fluid from at least three lobes or greater than 20% hemosiderin-laden macrophages in the BAL fluid and the exclusion of underlying infection. However, these criteria have been demonstrated to lack both sensitivity and specificity when using postmortem examination as the gold standard.[31]

Early descriptions using supportive therapy alone documented mortality rates of 80%–100%.[30,32] Retrospective case series subsequently suggested that administration of high-dose corticosteroids improved the survival rate,[32,33] but more recent single-center case series continue to document 60-day mortality rates in the range of 75%–80% even with this intervention.[29,34] Successful outcomes have been reported with the addition of recombinant factor VIIa[35,36] or aminocaproic acid[37] to high-dose steroids, but evidence to date is conflicting,[34] and use of these adjuvant therapies cannot be endorsed. Onset of DAH within the first 30 days of transplantation and autologous HSCT are associated with the most favorable outcomes.[29] Death is usually a result of superimposed multisystem organ failure or sepsis rather than respiratory failure from refractory hemorrhage.[28]

Idiopathic Pneumonia Syndrome

The term *idiopathic pneumonia syndrome (IPS)* applies to HSCT patients presenting with widespread alveolar injury in the absence of an identifiable infectious etiology. More recently, the definition was updated to additionally require exclusion of cardiac dysfunction, renal failure, and iatrogenic volume overload as the etiology for pulmonary dysfunction.[38] The updated diagnostic criteria, which continue to rely chiefly on BAL studies to exclude infection, are listed in Box 130.1. Adding to the ambiguity of the definition, some authorities include PERDS and DAH in the spectrum of IPS, whereas others treat them as distinct entities.

The incidence of IPS in the first 120 days after allogeneic HSCT with myeloablative conditioning historically has been reported in the range of 3%–15%.[39] With advances in transplant practices and better detection of underlying infectious etiologies, its incidence appears to be declining.[40] A recent report detected potential infectious pathogens, predominantly viral, in the BAL fluid of almost 60% of patients labeled as having IPS, challenging the fundamental definition of the entity as a noninfectious form of lung injury.[41] However, BAL alone does not distinguish between viral shedding, colonization, and true infection, so the implications of this study remain uncertain. Among allogeneic recipients, the incidence appears to be lower after nonmyeloablative versus conventional high-dose conditioning

BOX 130.1 Criteria for Diagnosing Idiopathic Pneumonia Syndrome

I. Evidence of widespread alveolar injury
- Multilobar infiltrates on routine chest radiographs or computed tomography
- Symptoms and signs of pneumonia (cough, dyspnea, tachypnea, rales)
- Evidence of abnormal pulmonary physiology
  - Increased alveolar to arterial oxygen difference
  - New or increased restrictive pulmonary function test abnormality

II. Absence of active lower respiratory tract infection based upon:
- Bronchoalveolar lavage cultures, cytology, polymerase chain reaction, and other studies negative for significant bacterial, viral, and fungal pathogens
- Transbronchial biopsy if condition of the patient permits

III. Absence of cardiac dysfunction, acute renal failure, or iatrogenic fluid overload as etiology for pulmonary dysfunction

Modified from Panoskaltsis-Mortari A, Griese M, Madtes DK, et al. An official American Thoracic Society research statement: noninfectious lung injury after hematopoietic stem cell transplantation: idiopathic pneumonia syndrome. *Am J Respir Crit Care Med.* 2011;183:1262–1279.

regimens, lending support to the belief that toxicity from intensive chemotherapy and radiation contributes significantly to pathogenesis. Acute GVHD has been identified as a risk factor for IPS, suggesting that alloimmune mechanisms may also come into play. IPS also occurs after autologous HSCT, but the frequency appears to be lower than that among recipients of allogeneic HSCT. It remains unclear whether the source of stem cells (bone marrow vs. peripheral blood vs. umbilical cord blood) affects the frequency of this complication.

The median time to onset of IPS has been reported to be 19 days, with the majority of cases occurring within the initial 120 days.[39] Patients with IPS present with dyspnea, fever, nonproductive cough, increasing oxygen requirements, and diffuse radiographic infiltrates. When obtained, lung biopsy specimens reveal two main patterns: diffuse alveolar damage and interstitial pneumonitis. The course is typically rapid, with up to two-thirds of patients progressing within several days to respiratory failure requiring mechanical ventilation.[39] Combined mortality in six of the larger published case series was 74%,[42] and the mortality rate among those requiring mechanical ventilation may exceed 95%.[39] Mortality at 120 days in a large contemporary study was 46%, suggesting that survival may be improving, possibly the result of advances in the care of critically ill patients.[40]

Beyond supportive care, there is no proven treatment for IPS. High-dose corticosteroid therapy is commonly administered, but substantiation of benefit is lacking. Based on evidence that anti–tumor necrosis factor therapy mitigates acute lung injury in murine models of IPS,[43] etanercept, a soluble tumor necrosis factor-alpha–binding protein, has been administered to patients with IPS. Two case series, encompassing a total of 37 patients treated with a combination of corticosteroids and etanercept, demonstrated high clinical response rates and improved short-term survival.[44,45] A subsequent prospective trial randomizing adults to either corticosteroids plus etanercept or corticosteroids alone aimed to enroll 120 patients but succeeded in accruing only 34 patients.[46] Acknowledging that it was underpowered to draw a definitive conclusion, the study nonetheless failed to demonstrate any difference in response rates or survival between the two groups. A more recent nonrandomized phase II trial involving 28 pediatric patients demonstrated a response rate (defined as survival to day 28 of the study plus complete discontinuation of supplemental oxygen support for >72 consecutive hours) of 71%.[47]

OUTCOMES AFTER ICU ADMISSION

Most of the published experience with HSCT requiring ICU admission has focused on allogeneic recipients, who have a significantly higher incidence of complications leading to critical illness. Historically, the prognosis of HSCT patients admitted to the ICU has been poor.[48–50] In particular, HSCT patients requiring mechanical ventilation for respiratory failure have experienced the poorest outcomes, leading some authorities in the past to consider this as a futile intervention.[51] In one of the largest studies involving 348 mechanically ventilated HSCT recipients at the Fred Hutchinson Cancer Research Center between 1986 and 1990, survival at 6 months was only 3%.[52] In another study from the same center, investigators found no survivors among ventilated patients with acute lung injury and either hepatic and renal insufficiency or hemodynamic instability necessitating vasopressors.[53]

More recent studies have reported improved outcomes for allogeneic HSCT recipients requiring ICU admission.[1,2] In particular, short-term survival rates in the subgroup who received mechanical ventilation approximate 15% in a contemporary series.[1] One likely reason for these favorable trends is the greater use of reduced-intensity conditioning regimens. These reports are encouraging, and despite the fact that survival rates remain disappointingly low, it can be argued that a trial of mechanical ventilation in select groups of HSCT recipients is reasonable.

There is limited experience with venovenous extracorporeal membrane oxygenation (VV-ECMO) in the allogeneic HSCT population. The largest experience of 37 patients comes from a consortium of 12 European centers.[54] The etiology of respiratory failure was pneumonia in 80%. Overall survival to hospital discharge was 19%; time from transplant was a discriminating factor, with a survival rate of only 4% among patients within 240 days of transplant compared with 46% for those further out. Pending further studies, VV-ECMO should be applied in a highly selective fashion and only with the understanding by the patient and/or family that this life-sustaining measure will be withdrawn if continuation is deemed to be futile.

To inform the appropriate use of the ICU and mechanical ventilation, a number of studies have attempted to identify factors predictive of outcome. Specific pre-ICU characteristics, including age, sex, primary disease, type of transplant, and conditioning regimen, have not proven to be reliable predictors.[50,55,56] Admission to the ICU within the engraftment period has been associated with a more favorable prognosis compared with later admission, particularly for recipients requiring mechanical ventilation.[56] Factors during the ICU course that have been associated with unfavorable outcomes are the need for mechanical ventilation, need for renal replacement therapy, presence of multiple organ failure, hyperbilirubinemia, use of vasopressors, and grade 3–4 acute GVHD.[1,2,56–58] Notably, the combination of mechanical ventilation with hepatic and renal dysfunction continues to portent nearly universal mortality.[59,60]

Well-known instruments used to prognostically stratify patients at the time of admission to the ICU, such as Acute Physiology and Chronic Health Evaluation (APACHE) II and APACHE III, and the Sequential Organ Failure Assessment have limited prognostic value in the HSCT patient population. As a result, indices specific to allogeneic HSCT have been developed. One such index, based on factors present at the time of initiation of mechanical ventilation, classifies patients with a creatinine <2 mg/dL and platelet count >20 × 10^9/L in a favorable category, with an overall survival at 100 days post mechanical ventilation of 29%, compared with only 5% for those not meeting both of these criteria.[61] The Hematopoietic Cell Transplantation–specific Comorbidity Index (HCT-CI) appears to be useful as a predictive instrument for in-hospital mortality among patients admitted to

the ICU within 100 days of their transplant. In one study, mortality was 46% for those with an HCT-CI score of 0–1 compared with 69% for those with a score ≥4.[62]

These predictive factors and indices allow for some stratification of risk but fall short of defining patients for whom ICU care and mechanical ventilation would be inappropriate. This is best accomplished through daily assessment of the critically ill patient's status and response to therapy, close communication between the ICU and transplant teams, and awareness of the patient's preferences and goals of care.

KEY POINTS

- ICU admission in the post-HSCT period is common; pulmonary complications, both infectious and noninfectious, represent the leading cause of ICU admission.
- Bacterial pneumonia is particularly common during the neutropenic preengraftment phase after both allogeneic and autologous HSCT.
- Because of the requirement for administration of immunosuppressive agents, allogeneic HSCT recipients are particularly predisposed to opportunistic infections, including CMV and invasive aspergillosis.
- Noninfectious pulmonary complications leading to respiratory failure include PERDS, DAH, and IPS.
- Outcomes after ICU admission are improving. However, the status of the underlying disease; presence of multiple organ failure; a need for mechanical ventilation, pressors, or renal replacement therapy; and absence of improvement after initial supportive measures may all contribute to poor prognosis and should be taken in context with the wishes and advance directives of the patient and proxy.

References for this chapter can be found at expertconsult.com.

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Cardiovascular and Endocrinologic Changes Associated With Pregnancy

Marie R. Baldisseri

Fundamental to the management of a critically ill pregnant woman is a detailed knowledge of the normal physiologic changes that occur during gestation and immediately after delivery. Some of these physiologic adaptations are from the hormonal changes associated with pregnancy, and others are to support the mother and the growing fetus.[1] Clinicians must have a good understanding of the extent of these changes, which occur in all pregnant women, to appropriately diagnose and treat critically ill patients whose additional pathology complicates the distinct metabolic homeostasis and hemodynamics of the normal pregnant state. It is important to recognize that these physiologic changes add a level of complexity to diagnosis and management in the critically ill pregnant woman. The normal baseline physiologic changes of pregnancy often alter the presentation of a disease process or illness that presents during pregnancy, and they can unmask a previously silent disease process of the woman. The normal physiologic maternal adaptations will change the interpretation of clinical and diagnostic examination findings in the pregnant woman. Subsequently, the endpoints of treatment can be significantly different from those for nonpregnant patients. To detect early signs of deterioration in a critically ill pregnant patient, modified early obstetric warning score (MEOWS) charts have been introduced in some obstetric centers.[2,3]

Some of the physiologic changes associated with pregnancy occur early in the normal course of gestation, whereas others occur during the middle or later stages. To render the most effective care of critically ill pregnant patients, the clinician must be aware of the timing of important physiologic changes. They affect almost all organ systems to varying degrees, depending in part on the gestational age of the fetus. Hemodynamic, metabolic, hormonal, and structural changes all occur during pregnancy and allow for the natural growth and development of the fetus. The healthy pregnant woman adapts remarkably well to these changes, as does the fetus, allowing the two to coexist symbiotically without harm to the other. However, if the pregnant woman is ill, either from a preexisting underlying disease process or from a new pathologic process that occurs during the pregnancy, the normal physiologic adaptive mechanisms of pregnancy are often insufficient to maintain the normal healthy union between mother and fetus. Depending on the severity of the underlying process or new illness, the hemodynamic ramifications to the pregnant woman and her fetus can be devastating and life threatening.

CARDIOVASCULAR CHANGES IN PREGNANCY

Cardiovascular and blood volume changes are among some of the more significant changes that occur in pregnancy (Table 131.1). These changes are primarily adaptive mechanisms, allowing the pregnant woman to accommodate her additional metabolic needs in addition to those of the fetus during gestation and immediately after delivery. Cardiac output is significantly increased during pregnancy by as much as 50% compared with nonpregnant values. Cardiac output is increased by 15% in twin pregnancies and in multiple gestations.[4] An increase in cardiac output is seen as early as the first 6–8 weeks of pregnancy. A series of meta-analyses of singleton pregnancies found that cardiac output peaks during the early third trimester: 1.5 L/min (31%) above nonpregnant values.[5] Cardiac output can increase by 75% by the end of the third trimester. The early increase in cardiac output is primarily the result of a significant increase in stroke volume. However, stroke volume decreases as the pregnancy advances because of aortocaval compression by the uterus and the pressure of the fetal presenting part on the common iliac vein. Caval compression occurs because the large, gravid uterus rests on the vena cava, decreasing venous return to the heart and therefore effectively decreasing ventricular preload. In the latter half of pregnancy, a progressive increase in the maternal heart rate by 15–20 beats/min is primarily responsible for maintaining the elevated cardiac output. The additional increase in cardiac output before labor and delivery is caused by a further increase in heart rate. Resting cardiac output either is maintained or decreases slightly as term approaches.[6,7]

Influence of Body Position

Venous return is further compromised with changes in body position, particularly if the pregnant patient is supine. As a result, cardiac output can be diminished by as much as 25%–30%. The effects of changes in body position are most obvious in the latter half of pregnancy when the fetal size and gravid uterus can effectively tamponade the vena cava, the abdominal aorta, and the iliac arteries. This phenomenon is exaggerated in women with poorly developed venous collaterals. With compression of the vena cava in the supine position, these women exhibit signs of severe hypoperfusion (hypotension and bradycardia), a phenomenon described as the *supine hypotensive syndrome of pregnancy*. Symptoms quickly resolve after the patient is repositioned to the left lateral recumbent position.[8] Cardiac output can decrease by

TABLE 131.1 Normal Hemodynamic Changes During Pregnancy

Physiologic Parameter	Term Pregnancy	Labor and Delivery	Postpartum
Cardiac output	Increases 30%–50%	Increases 50%	Increases 60%–80% within 15–20 min
Blood volume	Increases 30%–50%	Additional 300–500 mL with each contraction	Decreases to baseline
Heart rate	Increases by 15–20 beats/min	Increase depends on stress and pain relief	Decreases to baseline
Blood pressure	Decreases by 5–10 mm Hg in midpregnancy	Increase depends on stress and pain relief	Decreases to baseline
Systemic vascular resistance	Decreases	Increases	Decreases to baseline
Oxygen consumption	Increases by 20%	Increases with stress of labor and delivery	Decreases to baseline
Red blood cell mass	Increases by 15%–20%	—	—

30%–40% in patients with this syndrome. This vasovagal phenomenon underscores the influence of maternal body position on the hemodynamic alterations occurring in pregnancy.

Hemodynamic changes associated with decreases in preload and cardiac output are less pronounced when the gravid uterus is minimally compressing the vena cava, which is optimally achieved by maintaining the pregnant woman at greater than 20 weeks' gestation in the left lateral position when recumbent. Alternatives to this position, less optimal than the left lateral position but preferable to the supine position, are a left lateral tilt to 15 degrees or manual displacement of the gravid uterus. The latter maneuver of left uterine displacement can be performed by manually moving the uterus away from the midline to the left side when the patient is supine. This maneuver is particularly useful when performing cardiac compressions in a pregnant patient. In the supine position, the gravid uterus, which accounts for as much as 10% of the cardiac output, hinders successful resuscitation because of its adverse effects on intrathoracic pressure and venous return. Although hemodynamics are best in the left lateral position, it is difficult to achieve optimal chest compressions with the patient in this position. Acceptable alternatives are to perform cardiac compressions with the patient supine but with concurrent manual displacement of the uterus to the other side; it is also satisfactory to place a firm wedge under the right hip of the patient.[9,10]

Oxygen Consumption and Ventricular Performance

As cardiac output progressively increases, maternal oxygen consumption also increases. However, the increase in cardiac output is seen earlier than the rise in maternal oxygen consumption. Accordingly, the arteriovenous oxygen difference actually narrows early in pregnancy. The arteriovenous oxygen difference widens at the end of gestation. By term, there is a 20% increase in maternal oxygen consumption, mostly as a result of the increase in metabolic needs of the fetus. The increase in oxygen consumption is also a result of maternal increased work of ventilation during pregnancy, maternal increase in myocardial oxygen demand, and maternal increase in renal oxygen consumption. Oxygen extraction also gradually increases throughout gestation. The increase in cardiac output is probably the result of a combination of factors, including increased uterine blood flow, increased maternal circulating blood volume (and hence ventricular preload), and possibly estrogen- and prolactin-induced augmentation of myocardial contractility. Ventricular dynamics are improved during pregnancy as a direct result of the action of steroid hormones on the pregnant myocardium. In animal models, estrogens have been shown to increase cardiac output and decrease peripheral vascular resistance.[11] Echocardiographic studies performed in healthy pregnant women have demonstrated a decrease in the preejection period of left ventricular systole but an increase in the left ventricular end-diastolic dimension.[12–14] It may be that a combination of improved myocardial contractility and increased ventricular diastolic area may be responsible for increases in cardiac output during normal pregnancy.[15]

Hemodynamic Changes During Labor and Delivery

Although cardiac output remains relatively constant in the third trimester, there is a significant increase during active labor and immediately after delivery. With each uterine contraction, cardiac output dramatically increases as an additional 300–500 mL of maternal blood volume from the uterus is returned to the heart. Cardiac output can rise to 50% greater than normal when the pregnant woman is pushing in the second stage of labor. The amount of blood returned to the heart is accentuated in the supine position. When the pregnant patient is supine, uterine contractions can cause a 25% increase in cardiac output, a 15% decrease in maternal heart rate, and a 30%–35% increase in stroke volume. In the lateral recumbent position, the hemodynamic changes associated with uterine contractions are less pronounced; cardiac output and stroke volume may rise by only 6%–7%, and there may be only a small change in maternal heart rate. Cardiac output may be preferentially diverted to the heart if there is partial obstruction of the abdominal aorta by the uterus during contraction.

The hemodynamic changes seen during labor and delivery are influenced by anesthetic and analgesic techniques. The increase in cardiac output is less if caudal anesthesia is used.[16,17] Within the immediate 20–30 minutes after delivery of the fetus and placenta, there is an even greater increase in cardiac output, because blood is no longer diverted to the uteroplacental vascular bed. Approximately 500 mL is redirected to the maternal circulation in the so-called *autotransfusion effect of pregnancy.* This effect can increase cardiac output by 60%–80% after aortocaval compression is removed and blood volume is increased. Many of the physiologic changes of pregnancy resolve and revert to normal within several days after delivery. Cardiac output returns to normal within 2 weeks to 3 months after delivery as sodium and water balances normalize.

Blood Volume Changes

The changes in maternal blood volume during pregnancy are significant. Plasma volume increases by 30%–50% by the end of gestation. This value is increased in the multigravida patient compared with primigravidas, but the exact mechanism responsible for this effect is unclear. The increase in blood volume can be as high as 70% with twin pregnancies. An increase of 10%–15% in blood volume is seen as early as the sixth week of gestation. Blood volume is maximal at 30–34 weeks, after which the value plateaus until term.[18] Others have suggested that blood volume continues to increase until term.[19] Ventricular filling pressures do not increase despite the large increases in plasma volume.[20] This is most likely the result of vasodilatation with

concurrent decreases in systemic and pulmonary vascular resistance in addition to a normal heart adapting to chronic volume overload.

The increase in blood volume is a striking adaptive mechanism that permits additional blood flow to the uterus and other maternal organs, in particular the kidneys. Uterine blood flow increases to 100 mL/min by the end of the first trimester and reaches 1200 mL/min at term. Both sodium and water retention contribute to the increase in plasma volume. Total body water increases by approximately 6.5–8 L. Most of this increase is seen in the extracellular space and is preferentially distributed in the lower extremities. The total increase in body water includes approximately 3.5 L of amniotic fluid, placental fluid, and water in the fetus. The relative hypervolemia leads to a mild reduction in the serum sodium concentration (135–138 mEq/L) and in serum osmolality (approximately 280 mOsm/L). The maternal blood volume increases by 1–2 L. Red blood cell (RBC) mass accounts for only 300–400 mL of the increase in total blood volume.

Plasma renin and aldosterone levels are elevated during pregnancy despite expansion of the maternal blood volume. Activation of the renin–angiotensin–aldosterone system may result from the concomitant decrease in peripheral vascular resistance and the increase in vascular capacitance seen as early as the first 6 weeks of pregnancy.[6] Both estrogens and progesterone increase aldosterone levels, increasing sodium and water retention.[21] At 12 weeks of gestation, atrial natriuretic peptide levels also increase, most likely in response to the increase in plasma volume.

The increase in blood volume is an adaptive mechanism that provides some level of protection for the inevitable blood loss that accompanies delivery of the fetus and placenta.[22,23] Average blood loss during vaginal delivery is 500 mL; average blood loss during cesarean delivery is approximately 1000 mL. Although providing some degree of protection from peripartum blood loss, the increased plasma volume associated with pregnancy also can lull the clinician into a false sense of security. A pregnant woman can lose up to 35% of her blood volume before the usual signs of hypovolemia and acute hemorrhage are obvious. Although the pregnant woman may appear to have stable vital signs up to this point, the fetus may be severely compromised and deprived of adequate maternal blood flow. Tachycardia, hypotension, and other signs of hemodynamic instability are late manifestations of a significant deficit in maternal blood volume.

Physiologic Anemia of Pregnancy

Accompanying the increase in blood volume is an increase in RBC mass stimulated by increased circulating levels of erythropoietin. The RBC mass increases during the second trimester and continues to increase progressively throughout the pregnancy. However, the increase of 15%–20% in RBC mass is disproportionate to the 30%–50% increase in blood volume. As a result, the hematocrit decreases, resulting in the "physiologic hemodilutional anemia" of pregnancy. Hemodilution is most notable during the 30th to 34th gestational weeks. The hemoglobin concentration can decrease by as much as 9%. In the second trimester, the hemoglobin level can decrease to 11–12 g/100 mL, compared with the normal nonpregnant value of 13–14 g/100 mL. The decrease in blood viscosity associated with the anemia of pregnancy allows for a decrease in resistance to blood flow that improves placental perfusion. The hematocrit decreases until the end of the second trimester but increases later in the pregnancy, when the increase in RBC mass is proportionate to the increase in plasma volume. The hematocrit stabilizes at that point or even increases slightly as term approaches.

The degree of change in RBC mass during pregnancy depends in part on whether iron is supplemented. With the increase in RBC mass, there is a need for additional iron to prevent the development of iron-deficiency anemia. Maternal requirements for iron can increase to 5–6 mg/day. The fetus uses iron from maternal stores to prevent fetal anemia, but the presence of significant maternal iron-deficiency anemia has been shown to result in a higher incidence of fetal complications, including preterm labor and late spontaneous abortions.[24]

Renal Blood Flow During Pregnancy

Under the influence of circulating hormones, there is a preferential redistribution of blood flow to the uterus, breast, and kidneys during pregnancy. Each kidney increases in length and weight, and the renal pelvis and ureters dilate, leading to urinary stasis that predisposes pregnant women to frequent urinary tract infections.[25] The glomerular filtration rate (GFR) increases by 50%, and renal blood flow increases by 60%–80% above pre-pregnancy levels.[26] Changes in GFR and renal blood flow occur by the sixth week of gestation. The increase in renal blood flow plateaus early in pregnancy and remains unchanged or decreases slightly as term is approached. Urine flow and sodium excretion are increased and are influenced by position, especially in late pregnancy. Flow rates and the sodium excretion rate are significantly higher in the lateral recumbent position compared with the supine position. Concentrations of serum creatinine and blood urea nitrogen are reduced proportionately to the increase in GFR. Glycosuria may also occur during pregnancy as a result of the increase in GFR and impaired tubular reabsorption of glucose.

Changes in Blood Pressure and the Vascular System

Systolic and diastolic blood pressures usually decrease by 5–10 mm Hg below the patient's baseline blood pressures in the second trimester and may normalize to nonpregnant values by term.[27] Arterial blood pressure decreases as early as the sixth week of pregnancy; the lowest diastolic pressures are recorded during the second trimester. By the eighth week of gestation, diastolic blood pressure decreases by approximately 10%. Diastolic pressure reaches a nadir at 16–24 weeks and is typically 5–10 mm Hg less than normal. After the 16th to 24th gestational weeks, blood pressure progressively increases and is back to baseline by term. With the increase in venous return associated with uterine contractions and the additional factors of pain, anxiety, and stress during labor and delivery, an increase in blood pressure usually occurs during this time. Although earlier studies showed that blood pressure decreases during pregnancy, recent studies have demonstrated progressive increases in blood pressure during pregnancy, particularly in obese and overweight women.[28,29] The decrease in blood pressure during pregnancy is associated with a significant decrease in peripheral vascular resistance. Decreased systemic vascular resistance begins as early as the 5th week of gestation and plateaus between the 20th and 32nd weeks, after which it slowly increases to pre-pregnancy values by term.[30] The decrease in arteriolar tone is influenced by several factors, including hormonal changes that induce vasodilatation and lack of responsiveness to the pressor effect of angiotensin II.[31] There is evidence for blood vessel remodeling in pregnancy, leading to increased venous compliance.[32,33] During pregnancy, circulating levels of numerous endogenous procoagulant and anticoagulant proteins change, leading to a hypercoagulable state. As a consequence, the risk of venous thrombosis increases during pregnancy. The reported incidence is 0.7 cases per 1000 women, and this rate increases threefold to fourfold in the postpartum period.[34]

The treatment of choice for severe hypotension resulting from acute hemorrhage, sepsis, or other critical illness during pregnancy is aggressive fluid resuscitation. When hypotension is refractory and unresponsive to fluids, vasopressors should be used to prevent the detrimental consequences of hypotension to both the mother and fetus as a result of inadequate uterine blood flow. Most vasopressors increase maternal blood pressure at the expense of fetal blood flow, inducing vasoconstriction of the uterine vessels. There are few human

studies of these agents in pregnant women. However, animal studies have indicated that ephedrine and dopamine increase uterine blood flow to the uteroplacental circulation while at the same time increasing maternal blood pressure.[35]

Structural Remodeling of the Heart

The heart is dramatically remodeled during the first few weeks of pregnancy. There is enlargement of all four chambers. The valvular annular diameters increase, as do the thickness and volume of the left ventricular wall. End-diastolic volume increases, although end-diastolic pressure remains unchanged.[14] Transthoracic echocardiography and cardiovascular magnetic resonance have demonstrated an increase in left ventricular end-diastolic volume from 95 to 115 mL and 98 to 125 mL, respectively.[36] There is also increased left ventricular mass from 111 to 163 g and 121 to 179 g, respectively.[36] Chamber enlargement, particularly of the left atrium, may be a predisposing factor for supraventricular and atrial arrhythmias. Nonspecific ST-T–wave changes may also be found in the asymptomatic pregnant woman.

As the uterus enlarges and the diaphragm elevates, the heart is rotated upward and to the left. The apical impulse on physical examination is heard best over the fourth intercostal space, lateral to the midclavicular line. Left axis deviation is seen on the electrocardiogram as a result of the rotation of the heart. Because of the displacement of the heart, pregnant women may appear to have cardiomegaly on the chest radiograph. In addition, lung markings may be more prominent, suggesting vascular congestion. These changes can be similar to those seen in patients with heart disease. Even in women with no underlying cardiac pathology, the normal physiologic changes of pregnancy can result in signs and symptoms that are difficult to differentiate from those associated with cardiac disease. Symptoms such as fatigue, decreased exercise tolerance, peripheral edema, palpitations, chest pain, dyspnea, and orthopnea are common complaints as pregnancy advances.

New murmurs often appear during pregnancy. Systolic flow murmurs and a third heart sound are common but are soft. Mild pulmonic and tricuspid regurgitation occurs in more than 90% of healthy pregnant women.[37,38] One-third of pregnant women have evidence of clinically insignificant mitral regurgitation. Diastolic, pansystolic, and late systolic murmurs are rare in normal pregnancy and may indicate underlying heart disease. As a result of the mild four-chamber dilatation, clinically insignificant mitral, tricuspid, and mitral regurgitation is seen. Bruits originating from the internal mammary artery and venous hums with diastolic components are common during pregnancy. These findings can initially confuse the diagnosis of a more serious underlying cardiac illness.

Cardiac Disease and Pregnancy

In women with significant cardiac pathology, the hemodynamic aberrations associated with pregnancy can be life threatening. The incidence of significant cardiac disease in pregnancy is less than 2% but is increasing.[39,40] Cardiovascular disease in pregnancy has been reported as the leading cause of maternal mortality in North America.[36] Advances in medical therapy and in cardiac surgery, including transplantation, have allowed female cardiac patients to survive to childbearing age and to have successful term pregnancies.[41] For women with severe cardiac problems such as pulmonary hypertension, Eisenmenger syndrome, severe mitral stenosis, or Marfan syndrome (in which the risk of aortic dissection is high during pregnancy), the physiologic changes of pregnancy can increase both maternal and fetal morbidity and mortality by transiently or permanently worsening the underlying heart disease.[42] Increases in blood volume, stroke volume, cardiac output, and heart rate and the decrease in systemic vascular resistance are poorly tolerated by pregnant women with severe underlying cardiac disease. Maternal mortality is less than 1% for patients with less severe cardiac problems, but it increases to 50% if pregnancy is associated with the presence of underlying primary pulmonary hypertension or cyanotic disorders such as Eisenmenger syndrome.[43,44]

Approximately 90% of pregnant women with cardiac disease are rated as New York Heart Association (NYHA) functional class I or class II. These patients tolerate the hemodynamic changes of pregnancy and can be managed well with medical therapy, although the incidence of heart failure and arrhythmias tends to be higher in this group of patients.[45] The 10% of pregnant patients with NYHA functional class III or IV heart disease accounts for 85% of cardiac deaths.[46] Fetal morbidity and mortality are increased in these patients, and there is a higher incidence of prematurity, miscarriage, and intrauterine growth retardation.[47] Cardiac telemetry, fetal monitoring, and hemodynamic monitoring are usually necessary for these high-risk patients during labor and delivery and, because of the large changes in intravascular volume after delivery, during the first few postpartum days.

ENDOCRINE AND METABOLIC CHANGES IN PREGNANCY

There are numerous endocrine and metabolic alterations during pregnancy, many of which are directly attributable to hormonal signals originating from the fetoplacental unit. Maternal adaptations to hormonal changes that occur during pregnancy directly influence the growth and development of the fetus and placenta. In pregnancy, there is also a change in the normal hormonal feedback mechanisms that control the synthesis and release of hormones. As with cardiac disease, the presentation of endocrine and metabolic disorders may be difficult to differentiate from the normal hypermetabolic state of pregnancy.

Hypothalamic and Pituitary Alterations

As in the nonpregnant state, the hypothalamic–pituitary axis is responsible for regulating many aspects of metabolism. Circulating levels of most of the releasing hormones of the hypothalamus increase during pregnancy because of increased production by the placenta rather than increased production and release by the hypothalamus. The target organ of the hypothalamus, the pituitary gland, undergoes remarkable structural and metabolic changes in pregnancy. Its size increases almost threefold secondary to estrogen stimulation. Gonadotropin and growth hormone production decrease during pregnancy. However, synthesis of adrenocorticotropic hormone (ACTH), prolactin, and thyroid-stimulating hormone (TSH) increases.

Free and bound cortisol levels are increased in pregnancy, even though circulating ACTH concentrations are elevated. These changes suggest that the normal negative feedback loop between ACTH and cortisol concentrations is altered in the pregnant state.[48] Free plasma cortisol concentrations may be two to three times higher than normal at term. Diurnal variation of cortisol is blunted but maintained throughout pregnancy. The clinical signs of weakness, peripheral edema, glucose intolerance, and weight gain associated with Cushing disease are sometimes difficult to differentiate from the clinical features of normal gestation. The symptoms of Cushing disease are exacerbated by pregnancy but often resolve after delivery. Improved outcomes are seen with surgical therapy intrapartum if pituitary or adrenal tumors are discovered during the course of the pregnancy.[42,49] In normal pregnancy, cortisol release may not be suppressed with a low intravenous dose (1 mg) of dexamethasone. An 8-mg dose of dexamethasone is usually needed to suppress cortisol secretion if a tumor is present. In patients with occult adrenal insufficiency, a life-threatening adrenal crisis may be precipitated by the stress of labor and delivery. The signs and symptoms of adrenal insufficiency during pregnancy may be nonspecific and difficult to recognize, but with the stress

of labor, these symptoms are exaggerated. The clinical diagnosis is made in conjunction with laboratory evidence of a low cortisol level or even a low-normal level and no increase in the plasma cortisol concentration with an ACTH stimulation test. Immediate treatment with stress doses of hydrocortisone is indicated in these patients.

In preparation for lactation, circulating prolactin levels progressively increase to about 10 times normal during the course of pregnancy, secondary to stimulation of the anterior pituitary by placental estrogens and progesterone. The dramatic increase in plasma prolactin concentration may lead to an increase in the size of preexisting pituitary adenomas larger than 1 cm.[50] Symptoms resulting from an increase in prolactin secretion usually subside within 6 weeks after delivery if the patient is not breastfeeding.

The thyroid gland increases the production of thyroid hormones during pregnancy. TSH secretion is transiently decreased in the first trimester, but circulating TSH concentrations are usually increased by term. Circulating levels of thyroxine (T_4) and triiodothyronine (T_3) increase as a result of a twofold estrogen-stimulated increase in the synthesis of thyroxine-binding globulin. Levels of free (dialyzable) T_4 and free T_3 are unchanged. In 15% of women, the thyroid gland increases in size and volume. Pregnant women who obtain sufficient dietary iodine (more than 200 μg daily) have no untoward complications from the changes in thyroid function.[51,52] Patients with preexisting hypothyroidism should increase their levothyroxine daily dose by 30% early in pregnancy.[53]

Posterior pituitary hormones are altered in pregnancy. Circulating oxytocin levels increase, but the vasopressin concentration remains essentially unchanged. Plasma osmolality decreases by 5–10 mOsm/kg, suggesting that the threshold for secretion of vasopressin decreases during gestation. Although vasopressin levels remain unchanged, some women develop transient diabetes insipidus during pregnancy.[54]

Changes in Glucose Metabolism

Early in pregnancy, increased levels of estrogens and progesterone influence glucose metabolism primarily by inducing pancreatic beta-cell hyperplasia and increased insulin secretion. Placental hormones control glucose metabolism later in the pregnancy in response to the increased nutritional and metabolic demands of the fetus. Circulating glucose and insulin levels fluctuate widely depending on the nutritional state of the mother. Morning fasting levels of glucose can decrease to less than 55 mg/dL. Fasting blood glucose levels decrease by 10%–20% because of increased peripheral glucose use, decreased hepatic glucose production, and increased consumption of glucose by the fetus.

Pregnant women with diabetes mellitus experience more hypoglycemic episodes in the first trimester because hepatic gluconeogenesis is decreased during this period. Insulin secretion increases during pregnancy. There is a relative state of insulin resistance, as evidenced by postprandial maternal hyperglycemia.[55] Normally, women adapt to the state of relative insulin resistance during pregnancy. However, those women with marginal pancreatic reserve or preexisting insulin resistance caused by obesity may not produce sufficient insulin, leading to the development of gestational diabetes mellitus. Pregnant women with preexisting diabetes mellitus require as much as 30% more insulin than before pregnancy. There is a close correlation between maternal blood glucose levels and glucose uptake and use by the fetus because glucose crosses the placental barrier. Poor maternal glucose control worsens fetal morbidity. For patients with preexisting insulin-dependent diabetes mellitus, fetal and neonatal mortality rates have decreased significantly, from 65% to between 2% and 5%, as a result of implementing strict metabolic glucose control with insulin.[56]

Lipid metabolism is accelerated in pregnancy, and the circulating concentrations of triglycerides and cholesterol increase. Increased production of triglycerides allows for maternal consumption while sparing glucose for use by the fetus.[57] Lipolysis is stimulated in adipose tissue, and there is a release of glycerol and fatty acids that decreases maternal glucose use, additionally sparing glucose for the fetus.

KEY POINTS

- Normal pregnancy is associated with many physiologic changes that occur at different stages throughout pregnancy and affect almost all maternal organ systems. These changes may alter the presentation of a maternal disease process, confound the diagnosis, or alter the endpoints of treatment.
- Cardiac output, primarily as a result of augmented blood volume and, to a lesser extent, by the heart rate, is increased significantly up to the early third trimester. During labor and delivery, cardiac output is further increased with uterine contractions and the "autotransfusion" effect of increased preload after delivery of the fetus and placenta. This increase in preload can be particularly dangerous to those women with fixed or low cardiac output states, resulting in acute and precipitous respiratory insufficiency with pulmonary edema.
- Maternal body position directly affects cardiac output and stroke volume. In the supine position, the gravid uterus causes aortocaval compression and decreased preload. After the 20th week of gestation, pregnant women should not be placed supine, but rather in the left lateral recumbent position, which maximizes maternal hemodynamics. During cardiac resuscitation, the pregnant patient should be placed in this position, or manually displace the uterus to the left, to improve the efficacy of cardiac compressions.
- Blood volume increases by 30%–50% by the end of gestation. However, RBC mass increases by only 15%–20%, creating the "physiologic anemia" of pregnancy.
- A pregnant woman can lose up to 35% of her blood volume before tachycardia and hypotension occur as a result of acute hemorrhage or severe hypovolemia.
- A decrease in the diastolic blood pressure by 10% is seen in the second trimester, secondary to the decrease in systemic vascular resistance. By the end of pregnancy, blood pressure levels should increase to prepartum values.
- Blood vessel remodeling and changes in the coagulation system during pregnancy, including an increase in most clotting factors, makes the pregnant woman hypercoagulable and more susceptible to venous thromboembolism throughout pregnancy and in the postpartum period.
- Remodeling of the heart causes enlargement of all four chambers. The pregnant woman may be more susceptible to supraventricular and atrial arrhythmias because of left atrial enlargement.
- Pregnant patients with mild to moderate cardiac disease usually tolerate the hemodynamic changes of pregnancy. Those patients with pulmonary hypertension and right-to-left shunts have mortality rates as high as 50%.
- There are numerous endocrine and metabolic alterations during pregnancy that primarily affect the hypothalamus, pituitary, and adrenal glands. As with cardiac disease, the presentation of a patient with endocrine and metabolic disorders may be difficult to differentiate from the normal hypermetabolic state of pregnancy.
- Cushing syndrome can be exacerbated by pregnancy, and acute adrenal crisis may be precipitated by the stress of labor and delivery.
- Large fluctuations in glucose and insulin levels are seen in pregnancy, depending on the nutritional state of the mother. Fasting glucose levels can decrease by 10%–20%.
- During pregnancy, there is increased insulin secretion, with a relative state of insulin resistance.
- Obese women with insulin resistance and women with marginal pancreatic reserve can develop gestational diabetes mellitus.

References for this chapter can be found at expertconsult.com.

ANNOTATED REFERENCES

Burt CC, Durbridge J. Management of cardiac disease in pregnancy. *CEACCP*, 2009;9:44.
This article is an excellent review of cardiac disease in pregnancy, focusing on the different causes of cardiac disease and their management in pregnancy. Cardiac disease is the most common cause of mortality in pregnancy and may present with cardiovascular decompensation during pregnancy, at the time of delivery, or immediately postpartum. The goals of therapy are early risk assessment, optimization, regular monitoring for deterioration, planning of delivery, and surveillance for deterioration in the immediate postpartum period. Vaginal delivery with low-dose regional analgesia and careful fluid management is the preferred method of delivery, and cesarean section deliveries should be reserved for obstetric indications.

Clark SL, Cotton DB, Lee W, et al. Central hemodynamic assessment of normal term pregnancy. *Am J Obstet Gynecol*. 1989;161:1439.
This landmark paper presents central hemodynamic data obtained with the use of a pulmonary artery catheter during pregnancy and after delivery. Ten primigravida patients in late pregnancy (between the 36th and 38th weeks of gestation) underwent pulmonary artery catheter and arterial catheter placement. These same patients were restudied with a pulmonary artery catheter at 11–13 weeks after delivery. All measurements were performed with the patient in the left lateral recumbent position. The authors found significant decreases in systemic vascular resistance, pulmonary vascular resistance, colloid oncotic pressure, and colloid oncotic pressure–pulmonary capillary wedge pressure gradient in the third-trimester measurements ($P < .05$*). A significant rise in cardiac output and heart rate was seen in all patients before delivery (*$P < .05$*). No significant changes in pulmonary capillary wedge pressure, central venous pressure, left ventricular stroke work index, or mean arterial pressure were found. Although blood volume and preload are elevated in pregnancy and end-diastolic volume increases, there were no substantial increases in the filling pressures of the heart as measured by the pulmonary artery catheter, suggesting a decrease in afterload with the decrease in the systemic and pulmonary vascular resistance.*

Panchal AR, Bartos JA, Cabanas JG, et al. Part 3: Adult basic and advanced life support: 2020 American Heart Association guidelines for cardiopulmonary and cardiovascular care. *Circulation*. 2020;142:S366–S468.
Recommendations and guidelines for cardiopulmonary resuscitation (CPR) and advanced cardiac life support (ACLS) drug administration in pregnancy are presented by the American Heart Association (AHA). Although cardiac arrest in women is a relatively rare event, the incidence has been increasing. The most common causes are hemorrhage, trauma, pulmonary embolism, amniotic fluid embolism, sepsis, complications of anesthesia, and severe preeclampsia. Relief of aortocaval compression is critical to improve the quality of cardiac compressions. Standard ACLS measures and drugs should be used during a cardiac arrest in a pregnant woman. Perimortem cesarean delivery has been shown to improve both maternal and neonatal outcomes when ROSC is not quickly achieved. Case reports using extracorporeal membrane oxygenation (ECMO) and TTM have shown favorable outcomes.

Snow V, Qaseem A, Barry P, et al. Management of venous thromboembolism: A clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. *Ann Intern Med.* 2007;146:204.
Recommendation 4: There is insufficient evidence to make specific recommendations for types of anticoagulation management of venous thromboembolism (VTE) in pregnant women. During pregnancy, women have a fivefold increased risk for VTE compared with nonpregnant women. Clinicians should avoid vitamin K antagonists in pregnant women, because these drugs cross the placenta and are associated with embryopathy between 6 and 12 weeks' gestation, in addition to fetal bleeding (including intracranial hemorrhage) at delivery. Neither low-molecular-weight heparin (LMWH) nor unfractionated heparin crosses the placenta, and neither is associated with embryopathy or fetal bleeding.

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Surgery during pregnancy is relatively common. This review of the literature focuses on relevant issues such as maternal safety during nonobstetric surgery in pregnancy, teratogenicity of anesthetic drugs, avoidance of fetal asphyxia, prevention of preterm labor, the safety of laparoscopy, and the need to monitor the fetal heart rate, and will finally give a practical approach to manage these patients.

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Hypertensive Disorders in Pregnancy

Marie R. Baldisseri

Hypertensive disorders associated with pregnancy are the most common medical diagnoses in pregnancy, occurring in approximately 6%–8% of pregnancies.[1,2] Guidelines from the Society of Obstetricians and Gynecologists have classified hypertension of pregnancy into two categories: (1) preexisting chronic hypertension or (2) preeclampsia superimposed on either gestational hypertension or preexisting chronic hypertension.[3] The National High Blood Pressure Education Working Group on High Blood Pressure in Pregnancy classified hypertension as (1) chronic hypertension; (2) preeclampsia-eclampsia; (3) preeclampsia superimposed on chronic hypertension; and (4) gestational hypertension, which is transient during pregnancy, or chronic hypertension identified in the latter half of pregnancy.[1] In 2015 the American College of Obstetricians and Gynecologists Committee on Obstetrics defined a hypertensive obstetric emergency as acute-onset, severe hypertension persistent for 15 minutes or longer.[4]

Gestational hypertension, including preeclampsia, occurs de novo after 20 weeks of gestation. Chronic hypertension is defined as blood pressure >140/90 mm Hg either occurring before the pregnancy or manifesting before the 20th week of gestation.[5,6] Chronic hypertension is present in up to 22% of women of childbearing age and occurs more commonly in women older than 35 years of age. Approximately 1% of pregnancies are complicated by chronic hypertension, 5%–6% by gestational hypertension, and 1%–2% of all pregnancies are associated with preeclampsia. Preeclampsia occurs in 20%–25% of women with preexisting chronic hypertension.

Preeclampsia, which is usually seen after 20 weeks' gestation, is seen more frequently, although not exclusively, in the older parturient. Preeclampsia is most often observed in younger women (<18 years) and in the older parturient (>35 years). Predisposing factors for the development of hypertension and/or preeclampsia during pregnancy include a family history of hypertension or preeclampsia, preexisting diabetes mellitus, black race, obesity (body mass index [BMI] ≥30), vascular or renal disorders, primigravid state, preeclampsia with a previous pregnancy, migraine history, and multiple gestational pregnancies.[7] Smoking during pregnancy may actually decrease the incidence of hypertension and preeclampsia during pregnancy, although this is controversial.[8] Hypertensive disorders in pregnancy are a significant leading cause of maternal mortality and morbidity, particularly when preeclampsia is superimposed on preexisting chronic hypertension. A pregnancy-related mortality of 7.4% was reported as a result of hypertensive disorders in the United States from 2011 to 2013.[9] The risk of recurrent preeclampsia during subsequent pregnancies is approximately 18%. Those who develop preeclampsia earlier during pregnancy have been shown to be at risk for cardiovascular disease later in life.[10] Women with hypertensive pregnancy disorders are at both immediate and long-term risk for cardiovascular complications.[11]

BLOOD PRESSURE MEASUREMENTS IN PREGNANCY

The definition of hypertension during pregnancy has been controversial in the past. *Hypertension* is now most commonly defined as a blood pressure (BP) greater than 140/90 mm Hg. Recently, there has been a consensus that the degree of increase in systolic blood pressures (SBPs) and diastolic blood pressures (DBPs) may actually be more important than the baseline values. Many authors now agree that significant hypertension in pregnancy is defined by an increase of at least 30 mm Hg in the SBP and an increase in the DBP of at least 15 mm Hg. Treatment of a DBP greater than 110 mm Hg or an SBP greater than 160 mm Hg is advocated because of the increase in maternal complications with this degree of hypertension.[12]

Sustained (rather than transient) increases in BP are the key risk factors; accordingly, BP should be measured on at least two separate occasions at least 4–6 hours apart. BP measurements should be made in a standardized fashion (e.g., with the patient sitting in the same position) at each evaluation. Measurements in the upper arm in the recumbent position may yield false-low values because of aortal and caval compression by the gravid uterus. BP is best recorded with the patient in the sitting position or in the inferior arm in the lateral recumbent position. Many automated BP cuffs are accurate during pregnancy but may underestimate BP measurements in preeclamptic women. Manual BP readings are best suited for this group.

PHYSIOLOGIC CHANGES IN PREGNANCY

Essential to the management of hypertension in pregnancy is an understanding of the normal physiologic changes in cardiac output, vasomotor tone, and systemic BP that occur. During pregnancy, cardiac output can increase by 50% up to the early third trimester. The increase in cardiac output during this time is primarily caused by increased maternal blood volume, with a small increase in maternal heart rate. Cardiac output plateaus for the remainder of the pregnancy until labor. An increase in cardiac output is seen with each uterine contraction. Cardiac output increases again during the immediate postpartum period after delivery of the fetus and the placenta. It is during this period that cardiac output is highest because of the *autotransfusion effect* (see Chapter 154).

Systemic vascular resistance, and consequently BP, decreases during the second trimester. Increased synthesis of vasodilating prostaglandins may play a role in the regulation of BP and uterine blood flow in pregnancy. In a normal pregnancy, vascular resistance is determined by a proper balance of the effects of vasoconstricting and vasodilating factors, including prostaglandins. This balance may be disturbed in hypertensive states, owing to inadequate prostaglandin synthesis. In pregnancy-related hypertensive states, there is a paradoxical increase in

the systemic vascular resistance compared with pregnancy without hypertension. It is noteworthy that all patients with newly acquired or preexisting hypertension in pregnancy have a relative decrease in DBP during the second trimester, reflecting a relative decrease in systemic vascular resistance. Indeed, BP normalizes during the second trimester in some patients with preexisting hypertension.

CAUSES OF HYPERTENSION IN PREGNANCY

There are multiple causes of hypertension during pregnancy (Box 132.1). The most common hypertensive states are gestational hypertension without the presence of proteinuria, essential chronic hypertension, and preeclampsia (i.e., gestational hypertension with significant proteinuria). This classification is clinically useful to the practitioner, but the risk from systemic hypertension is significant for all three conditions, regardless of the specific cause of high BP. Hypertension during pregnancy is associated with an increased risk of death for both the mother and fetus. Severe maternal hypertension during pregnancy is associated with placental abruption and intrauterine growth retardation.[13]

Preeclampsia is defined as primarily diastolic hypertension that occurs transiently during the pregnancy, usually manifesting after the 20th gestational week, and resolves within 1–2 months after delivery. Women who develop preeclampsia have a high rate of recurrence of hypertension with subsequent pregnancies and often develop chronic hypertension at a later time.

Essential chronic hypertension (i.e., hypertension that was present before the pregnancy, whether diagnosed or undiagnosed) persists in the postpartum period and accounts for approximately one-third of all cases of hypertension during pregnancy. Essential chronic hypertension may manifest during the first 20 weeks of pregnancy. Women who develop hypertension without proteinuria in the last trimester of pregnancy may have essential hypertension, either unmasked or precipitated by the pregnancy. In these cases of de novo presentation of hypertension, care must be exercised to rule out other nonpregnancy-related causes of hypertension, such as renal artery stenosis, polycystic kidneys, glomerular or interstitial renal disease, pheochromocytoma, coarctation of the aorta, primary aldosteronism, Cushing syndrome, hyperthyroidism, and hyperparathyroidism. Previously undiagnosed essential chronic hypertension is a consideration, particularly in older multiparous women. As the age of parturients has increased, the incidence of essential hypertension in pregnant women has also increased. For some patients, the initial diagnosis of hypertension may be made during a routine prenatal visit with an obstetrician. For some patients, this prenatal visit is their first encounter with a physician as an adult. Essential hypertension should be suspected if there is a family history of hypertension, diabetes, or obesity. If there is a suspicion of preexisting essential hypertension, cardiac echocardiography should be performed to evaluate for left ventricular hypertrophy, which would suggest that hypertension has been a problem for an extended period. If BP extremes are avoided with treatment, there is no significant worsening of maternal and perinatal outcomes for pregnant patients with essential hypertension. Complications related to intrapartum hypertension (e.g., placenta previa, placental abruption, and preeclampsia) are less likely with judicious treatment of elevated BP. Patients with essential hypertension have not been shown to have a higher incidence of preeclampsia, particularly if the BP is well controlled. In general, mortality and morbidity are not increased in patients with uncomplicated mild chronic hypertension. However, morbidity and mortality are both increased in those patients with severe uncontrolled hypertension, and this is further complicated by superimposed preeclampsia.[14]

BOX 132.1 Causes of Hypertension in Pregnancy

1. Pregnancy-induced hypertension (gestational hypertension without proteinuria)
2. Essential hypertension
   - Preeclampsia (gestational hypertension with proteinuria)
   - Primary aldosteronism (Conn syndrome)
   - Renal artery stenosis
   - Coarctation of the aorta
   - Pheochromocytoma
   - Cushing syndrome
   - Cocaine use
   - Methamphetamine use

PATHOLOGY OF PREECLAMPSIA

Preeclampsia is a pregnancy-related multisystem disease process that usually occurs after the 32nd week of gestation. Systemic hypertension and significant proteinuria (i.e., 0.3 g or greater in a 24-hour urine collection) are invariably present. Clinical onset is usually characterized by rapid weight gain associated with generalized edema, followed by onset of hypertension or proteinuria or both. The incidence of preeclampsia in the United States ranges from 5% to 7%. The highest frequency occurs in young primigravidas, and the second highest incidence is in older multiparous women, a group that has a higher maternal mortality rate than the young primigravidas. The incidence is higher in patients with preexisting hypertension or renal vascular disease, and the symptoms may present earlier than the 32nd gestational week in these patients. Diastolic hypertension is most often seen in association with preeclampsia. It is less common to record SBP values greater than 160 mm Hg. If the SBP is greater than 200 mm Hg, the clinician should consider the possibility of underlying essential hypertension, which may be superimposed on the preeclamptic state. Because preeclampsia is a multisystem disease process, it may imitate or mask other pathologic conditions, and a thorough investigation to rule out other coexisting pathologies should be carried out. Familial prevalence of preeclampsia has been reported.[15,16] In some cases, preeclampsia manifests 1–7 days after delivery.[17,18] Most commonly, if preeclampsia is present during the postpartum period, it manifests as the HELLP syndrome, a severe variant of the preeclamptic spectrum of diseases.[19] This syndrome always includes some, if not all, of the following features: microangiopathic hemolytic anemia (H), elevated liver enzymes (EL), and low platelets (LP). The syndrome can develop without substantial BP changes or with no significant changes compared with BP readings taken during the pregnancy.

A significant elevation of BP in the second trimester is associated with an increased risk of preeclampsia later in the pregnancy.[20] One-third of pregnant women with mean arterial pressures greater than 90 mm Hg in the second trimester develop preeclampsia later during pregnancy. Only 2% of women with mean arterial pressures less than 90 mm Hg develop preeclampsia. Relatively mild hypertension early in pregnancy, which might be ignored in nonpregnant patients, should not be overlooked or dismissed in the parturient. As many as 25% of all pregnant women have slightly elevated BPs in the last month of pregnancy, but the incidence of preeclampsia is also highest during this period. Accordingly, clinicians must remain vigilant when faced with new-onset hypertension and look for other signs and symptoms that might suggest the presence of the preeclamptic syndrome.

The exact pathogenesis of preeclampsia is still unknown, although it is believed to be related to endothelial cell injury and dysfunction

that occurs in most maternal organs as a result of toxic substances released from a poorly perfused placenta. Genetic and immunologic factors also have been implicated in the pathogenesis of preeclampsia.[21] The generalized vasospasm that occurs in preeclampsia is responsible for many of the organ-specific signs and symptoms apparent in this multisystem disease. Widespread vasospasm is associated with increased circulating levels of vasoconstrictors, increased sensitivity to angiotensin II, and decreased levels of vasodilators. An imbalance in circulating angiogenic factors is emerging as a prominent mechanism that mediates endothelial dysfunction and the clinical signs and symptoms of preeclampsia.[22] There is an imbalance in the ratio of prostacyclin to thromboxane production that contributes to the pathogenesis of preeclampsia, although preeclampsia is not simply a state of prostacyclin deficiency. This idea has prompted studies of low-dose aspirin to prevent development of preeclampsia. Duley and colleagues reviewed 59 trials involving 37,560 women that examined the use of antiplatelet agents in preeclampsia. Antiplatelet agents, including low-dose aspirin, showed moderate benefits when used for the prevention of preeclampsia and its consequences, decreasing preterm births, fetal and neonatal deaths, and small-for-gestational-age babies. However, they recommended that further information would be required to assess which women are most likely to benefit, when treatment is best started, and at what dose.[23] The US Preventive Services Task Force (USPSTF) conducted a systematic evidence review that showed lower risks with the use of aspirin at a dose of 60–150 mg daily.[24] In a randomized, double-blind, placebo-controlled trial of low-dose aspirin vs. placebo in patients at high risk for developing preeclampsia, preterm preeclampsia occurred in only 1.6% of the patients as compared with the placebo group (4.3%).[25] The maternal organs most affected in preeclampsia are the kidneys, brain, liver, and hematologic system. Despite a lack of understanding of the exact pathogenesis of preeclampsia, significant improvements in the identification of the disease, monitoring, and management of these complex cases has improved perinatal and maternal morbidity and mortality. If vasospasm affects the uteroplacental bed, the incidence of intrauterine growth retardation, stillbirths, and neonatal deaths increases.[26]

Peripheral edema is a common symptom and complaint of pregnant women that cannot be ignored, because it may herald the onset of preeclampsia. The majority of women with preeclampsia present with generalized edema, and significant weight gain is the first symptom. However, because peripheral edema is a ubiquitous symptom during pregnancy, it is no longer considered a hallmark trait of preeclampsia. Preeclampsia is often manifested initially by peripheral edema that is usually accompanied by a gradual increase in BP. Sodium retention is partly responsible for edema formation and hypertension. In normal pregnancy, the glomerular filtration rate increases by as much as 50%. There is a concomitant increase in sodium reabsorption by the renal tubules and a 60%–80% increase in renal blood flow. Renal blood flow increases because of the increase in cardiac output and a decrease in renal vascular resistance. In preeclampsia, sodium retention is caused by a decrease in the glomerular filtration rate, possibly resulting from a vasospasm of the renal vasculature, commonly seen in preeclampsia. Renin and aldosterone secretion decrease in patients with preeclampsia, probably as a result of extracellular volume expansion and associated edema. The exact cause of the decreased activity of these factors is unknown, but it may be related to decreased renal prostaglandin synthesis, increased systemic BP, or the expansion of extracellular volume. In spite of the decreased levels of renin and aldosterone, sensitivity to angiotensin II is increased, a factor that may play a role in the pathogenesis of hypertension in preeclampsia.[27] Vascular maladaptation with increased vasomotor tone, endothelial dysfunction, and increased sensitivity to angiotensin II and norepinephrine in preeclampsia may be explained on the basis of angiotensin II–mediated mechanisms. Although sodium retention occurs in preeclampsia, blood volume actually can be diminished compared with that in normotensive pregnant patients.[28] Plasma volume contracts as extracellular fluid is preferentially shifted from the vascular space to the interstitium. However, the decrease in plasma volume does not indicate volume depletion in patients with preeclampsia. In contrast to hypovolemic patients, cardiac output is increased and central venous and pulmonary capillary wedge pressures are normal to high in patients with preeclampsia.[29] These data can guide the management of preeclampsia, because efforts should be directed to control BP rather than injudicious volume resuscitation.

Hyperuricemia in preeclampsia occurs at least in part because of decreased renal excretion of uric acid. However, the development of hyperuricemia frequently predates increases in serum blood urea nitrogen and creatinine, suggesting that other mechanisms are involved as well. Hyperuricemia has been used as a marker of severity of preeclampsia, and it is a risk factor for fetal mortality.[30]

CLINICAL PRESENTATION OF PREECLAMPSIA

The severity of illness is defined as mild, moderate, or severe depending on the presenting signs and symptoms and associated comorbidities. Because the nature of the process is multisystemic, preeclampsia may manifest with a wide spectrum of organ-specific abnormalities in addition to the general findings of edema, hypertension, and proteinuria. The pathologic abnormalities associated with preeclampsia are not necessarily secondary to hypertension, and thus the severity of preeclampsia does not always correlate with the degree of BP elevation.[20] BP elevations are classified as mild, moderate, or severe. Hypertension in preeclampsia may result from increases in systemic vascular resistance and cardiac output.

In mild preeclampsia, SBP is 130–140 mm Hg and DBP is 80–95 mm Hg. Peripheral edema is minimal, and there is a lack of associated visual or cerebral symptoms. In moderately severe preeclampsia, the SBP may increase to as high as 150–160 mm Hg, and the DBP can be as high as 110 mm Hg. An increase in SBP of 25 mm Hg or more and an increase in DBP of 15 mm Hg or more suggests the presence of moderate to severe preeclampsia. Peripheral edema, hyperreflexia, and visual symptoms are often present with moderately severe preeclampsia. In severe forms of preeclampsia, the SBP is greater than 160 mm Hg and the DBP is 110 mm Hg or greater. In severe preeclampsia, there are signs of multiple organ system involvement. Pulmonary, cardiac, renal, and neurologic disturbances may be present. Severe renal involvement in preeclampsia leads to glomeruloendotheliosis, which manifests as marked proteinuria (excretion of greater than 5 g protein daily). Oliguria (urine output less than 500 mL/day) is also common, and the serum creatinine concentration is usually greater than 1.6 mg/dL. Acute renal failure is relatively rare, although clinical evidence of renal involvement in preeclampsia significantly increases perinatal mortality.[31] Hepatic involvement is manifested by epigastric or right upper quadrant pain with elevated circulating levels of bilirubin and transaminases. Severe preeclampsia itself is the most common cause of hepatic tenderness and liver dysfunction in pregnancy.[32] Severe hepatic pathology can result in subcapsular hematomas and lacerations that may require surgical intervention. Neurologic changes may include persistent headaches, visual disturbances, focal neurologic deficits, and severe hyperreflexia with or without clonus. Computed tomography of the brain may exhibit cerebral edema, especially in the occipital region.

Severe preeclampsia associated with central nervous system irritability, manifesting as generalized tonic-clonic seizures not caused by other cerebral pathology, is defined as *eclampsia*.[33] Eclampsia can

occur without significant hypertension or proteinuria. Cardiovascular and respiratory changes can manifest as pulmonary edema, resulting from iatrogenic fluid overload; acute systolic left ventricular failure; or diastolic left ventricular dysfunction secondary to chronic essential hypertension. Pulmonary edema may also result from increased capillary permeability or from a decrease in colloid osmotic pressure that occurs to some extent during normal pregnancy but can be accentuated by preeclampsia.[34] Hematologic disturbances consist of thrombocytopenia, disseminated intravascular coagulation, and hemolysis.

It is unknown whether preeclampsia leads to persistent chronic hypertension after delivery, although it seems that this is unlikely. Nevertheless, an episode of preeclampsia may identify a subgroup of women with an increased risk of the eventual development of essential hypertension at a later time. Women with preeclampsia have been shown to have an increased risk of death resulting from cardiovascular disease later in life, independent of other measured risk factors.[35] These findings reinforced previously reported recommendations that a history of preeclampsia be used to target women at risk for cardiovascular disease. Debate continues as to whether the presence of preeclampsia or the duration of the disease process may be responsible for influencing factors that later lead to the development of essential hypertension. Women who develop preeclampsia superimposed on previously undiagnosed essential hypertension or underlying renal disease are predisposed to the later development of essential hypertension.

OTHER CAUSES OF HYPERTENSION IN PREGNANCY

Some of the less common causes of hypertension are listed in Box 132.1.

Primary aldosteronism in pregnant women has been reported, but is uncommon. The treatment of hypertension in these patients is directed toward medical management during the pregnancy and postpartum operative intervention if an adenoma is present.

Renal artery stenosis can be associated with preeclampsia. Medical therapy with antihypertensive agents is recommended. Although ideal therapy for these patients would include angiotensin-converting enzyme (ACE) inhibitors, these agents are contraindicated during pregnancy, and other alternatives must be employed.[36]

Coarctation of the aorta is a rare cause of hypertension. It may be previously undiagnosed and then initially diagnosed during a patient's first pregnancy. It can be associated with preeclampsia. The greatest risk to these patients is aortic rupture caused by cystic medial necrosis of the aortic wall. This risk is amplified because the normal physiologic changes of pregnancy place further stress on the abnormal aorta. Increases in BP, cardiac output, and the strain of labor with contractions can increase this risk. Aggressive medical management with antihypertensive medications, including beta-adrenergic blockers, improves the outcome of these high-risk patients.

Pheochromocytoma is a rare cause of hypertension, but patients have a poor outcome if the tumor is not diagnosed and treated. These patients can present with nausea, vomiting, profuse diaphoresis, severe headache, generalized weakness, palpitations, and seizures. The immediate causes of sudden death are secondary to pulmonary edema, cerebral hemorrhage, and cardiovascular collapse. Because there is a risk of significant morbidity and mortality to both mother and fetus, it was previously recommended that immediate surgical intervention be carried out during pregnancy. Currently, most experts advocate medical therapy with alpha- and beta-adrenergic blockade during pregnancy and tumor removal after delivery.

Illicit drug use, particularly from cocaine and methamphetamine, during pregnancy has been shown to result in worse maternal and fetal outcomes. The use of cocaine during pregnancy is associated with maternal migraines, epileptiform seizures, premature rupture of membranes, spontaneous miscarriages, and aggravating and worsening preexisting maternal chronic hypertension leading to hypertensive crises.[37,38] Methamphetamine use during pregnancy can worsen preexisting chronic hypertension and gestational hypertension with preeclampsia.[39] Continued use of methamphetamines during pregnancy results in shorter gestational ages and lower birth weights.[40]

GENERAL TREATMENT PRINCIPLES

Many of the treatments of pregnancy-related hypertension states are based on expert opinion and observational studies and not randomized controlled trials, However, the goal of treatment, using general and specific pharmacologic therapies, is to prevent severe maternal cardiovascular and cerebrovascular complications and to prevent perinatal morbidity and mortality.[41] The benefits of a well-balanced, low-salt diet and exercise have been shown to decrease the incidence and severity of hypertension. Bennett and colleagues conducted a retrospective analysis of women who had prior bariatric surgery before becoming pregnant. These patients had lower rates of hypertensive disorders in subsequent pregnancies.[42] Previously, some experts were concerned that aggressive management of hypertension in pregnancy might be detrimental, perhaps because hypertension improved uterine blood flow. These concerns appear to be unfounded, because later studies showed that uterine blood flow either increases or shows no change after hypertension is controlled. Nevertheless, caution must be exercised to ensure that the treatment of hypertension during pregnancy does not induce hypotension, which adversely affects maternal hemodynamics and compromises fetal well-being. There is a significant correlation between maternal BP control and fetal morbidity, and evidence now suggests that antihypertensive treatment for severe hypertension results in an improved perinatal outcome. The development of mild hypertension or preeclampsia at or near term is associated with minimal maternal and neonatal complications. However, the onset of severe gestational hypertension and/or severe preeclampsia early in gestation is associated with significant maternal and perinatal complications.[43] General recommendations for management and monitoring of hypertension in pregnant patients include the stabilization and treatment of acute changes in BP. Specific goal-directed therapy is indicated for various organ system abnormalities that may be present, particularly in those patients with moderate to severe preeclampsia. If proteinuria is not present and there is no suspicion of preeclampsia, conservative management on an outpatient basis is usually adequate. Immediate hospitalization with bedrest is recommended for patients presenting with proteinuria if there is a high index of suspicion for the diagnosis of preeclampsia.

ANTIHYPERTENSIVE DRUG THERAPY

There is now an extensive pharmaceutical armamentarium available for the treatment of both acute hypertensive episodes and chronic hypertension in pregnancy. In 1979 the US Food and Drug Administration (FDA) established categories for all drugs with potential and actual adverse effects on the fetus.[44] Although helpful to the clinician, these categories most often did not reflect current scientific knowledge regarding specific teratogenic effects of the drugs. In 2015 the FDA removed the pregnancy letter categories (A, B, C, D, and X) and now requires that the Pregnancy and Lactation Labeling Rule (PLLR) format be used to assist healthcare providers in assessing the benefits and the risks of specific medications. The PLLR includes a comprehensive summary and discussion of the risks of a medication and relevant information to guide clinicians about the use of specific medications during pregnancy and lactation.[45] However, many clinicians continue

to use the preexisting pregnancy letter category system because the PLLR is somewhat confusing and cumbersome and is not widely used in the United States to make prescribing decisions.

Most newer antihypertensive drugs used during pregnancy have not been extensively studied in animals and women. The decision to use them during pregnancy should be based on the potential benefit of using them versus the potential risks to the fetus. Prazosin, alpha-methyldopa, hydralazine, nifedipine, and labetalol have been safely used for many years in pregnant patients without significant fetal risk. Because most antihypertensive drugs are used later in pregnancy, the potential teratogenic effects of these drugs are not usually a major concern. However, if treatment is initiated for patients with preexisting essential hypertension or early-onset gestational hypertension, teratogenic effects must be considered when choosing antihypertensive drugs. It may be necessary to change the antihypertensive therapy early in pregnancy if the patient is taking drugs that could increase the risk of fetal abnormalities.

The goal of hypertensive therapy in pregnancy is the prevention of maternal complications such as intracerebral hemorrhage, stroke, and decompensated heart failure. There are no convincing data to determine the optimal BP goal with drug therapy. There is also disagreement concerning the proper normal values for BP during pregnancy, but most agree that acute treatment is mandated if (1) the SBP is greater than 160 mm Hg or the DBP is 105 mm Hg or greater or (2) if the SBP is more than 30 mm Hg greater than the baseline value or the DBP is more than 15 mm Hg greater than the baseline. For women with preexisting chronic hypertension, a BP of more than 160/100 should be targeted. If acute and urgent drug therapy management is required, some patients may need to be hospitalized, depending on their compliance with drug therapy and the urgency of lowering the BP based on concomitant organ system involvement. For patients presenting with SBP 140 mm Hg or higher and DBP 90 mm Hg or higher, urgent drug therapy should be implemented if there is concurrent evidence of symptoms, underlying essential hypertension, or end-organ involvement. If the patient presents after the 24th gestational week and fetal viability is ascertained, both cardiac and fetal telemetry may be required. For patients presenting with SBP less than 140 mm Hg and DBP less than 90 mm Hg and no evidence of significant proteinuria, management and treatment can be provided on an outpatient basis, with frequent office visits and close maternal and fetal assessments. If the hypertension is refractory to standard therapy, hypertension worsens despite adequate drug therapy, or the suspicion of preeclampsia arises, immediate hospitalization is recommended.

Conservative drug therapy is advocated for moderately severe preeclampsia, but the ideal treatment of choice for severe preeclampsia and associated end-organ involvement is immediate delivery of the fetus. Delay in delivery for patients with severe preeclampsia and end-organ involvement before 34 weeks' gestation results in serious maternal and fetal complications, and perinatal outcomes have been shown to be worse.[46,47] Conservative management with vigilant monitoring and assessment of these patients should be performed in a hospital setting. If the fetus is of mature gestational age, factors influencing the decision to deliver are dependent on the progression of the disease process, assessment of fetal lung maturity, and the status of the cervix. The conservative management of preeclamptic patients at a gestational age less than 24 weeks is associated with serious maternal complications, and termination of the pregnancy should be considered.[48,49]

Updated guidelines in 2015 from the American College of Obstetricians and Gynecologists Committee on Obstetric Practice[4] recommend the following:

- In addition to parenteral hydralazine and labetalol, oral nifedipine and/or oral labetalol (200 mg) may be considered as a first-line therapy, particularly if there is no intravenous (IV) access.
- Parenteral labetalol should be avoided in women with asthma, heart disease, or congestive heart failure.
- Magnesium sulfate is not recommended as an antihypertensive agent but is the drug of choice for seizure prophylaxis in severe preeclampsia and for controlling seizures in eclampsia.
- Although sodium nitroprusside can be used for treatment in emergent situations, there is a risk of cyanide and thiocyanate toxicity in the mother and fetus and increased intracranial pressure with potential worsening of cerebral edema in the mother.

During pregnancy, the clinician must decide when to use antihypertensive medications and what level of BP to target. The choice of antihypertensive agents is more limited in pregnancy, because not all available antihypertensive drugs have been adequately evaluated in pregnant women, and some agents are contraindicated.[50] A first-line drug still used today in pregnant patients, although less commonly in the general populace, is oral alpha-methyldopa, a central alpha-2-adrenergic agonist. Historically this has been a first-line drug of choice for many obstetricians in the past, and there has been little evidence to convince them otherwise. The starting dose is 250 mg orally two to three times a day for the first 48 hours of treatment. Dosing can be increased every 2 days until the desired BP level is achieved. The maximum daily dose is 4 g. Beta-adrenergic blocker therapy with oral labetalol, a combined alpha- and beta-adrenergic antagonist, has become popular as a single-agent antihypertensive. The recommended initial dose is 100 mg orally twice daily. The dose can be increased as indicated, either semiweekly or weekly, and the maintenance dose is usually 200–400 mg administered twice daily. The benefits of the beta-adrenergic blockade make this an attractive drug for parturients with underlying chronic essential hypertension and possible cardiac and vascular involvement. Diuretics also may be used, although care must be exercised to prevent excessive fluid loss, which can exacerbate the decrease in blood volume associated with preeclampsia. As mentioned previously, ACE inhibitors and angiotensin II receptor antagonists should be avoided intrapartum because these agents can increase perinatal morbidity and mortality.

For acute and emergent drug therapy for severe hypertension, IV antihypertensive drugs should be used; IV infusions are particularly attractive because they provide rapid control of BP and can be titrated easily. IV hydralazine, a direct arteriolar vasodilator, remains the standard for many obstetricians, although other drugs may be preferable because hydralazine may decrease BP precipitously.[51] Excessive lowering of BP is a particular problem when hydralazine is administered to preeclamptic patients with contracted blood volume. If hydralazine is used, it should be given as 5- to 10-mg IV boluses every 15–30 minutes until BP is controlled. Onset of the hypotensive effect is 10–20 minutes, and the duration of action is about 8 hours. Infusions of hydralazine are difficult to titrate and may be associated with increased incidence of fetal distress.

IV labetalol, a nonselective beta- and alpha-adrenergic receptor blocker, is also commonly used for the acute management of hypertension.[52] Labetalol rapidly decreases the BP but not at the expense of uteroplacental blood flow. Labetalol crosses the placenta but rarely causes significant neonatal bradycardia. An initial IV bolus of 10 or 20 mg should be given, followed by boluses of 40–80 mg at 10- to 15-minute intervals as needed to control hypertension. Labetalol also can be given by continuous IV infusion; the usual dose is 1–4 mg/min. Contraindications to the use of labetalol are the same as those for other beta-adrenergic antagonists, notably heart block and acute asthma.

Sodium nitroprusside is a potent arterial and venous vasodilator that quickly decreases BP. Rapid titration with a continuous IV infusion can be instituted starting at a dose of 0.25–0.5 μg/kg/min and adjusted every few minutes and titrated to effect. Invasive arterial

monitoring is often recommended in conjunction with its use. As with all potent vasodilators, care must be taken when using sodium nitroprusside, because patients with volume depletion may be particularly sensitive to its effects. Despite a paucity of data, concern regarding the risks of fetal cyanide toxicity prompts some practitioners to avoid using this drug in pregnant patients. Careful attention to dosing and duration of use should minimize the risk of toxicity.

Other less frequently used agents include IV nitroglycerin, oral clonidine, and beta-adrenergic blockers other than labetalol. IV nitroglycerin is easily titrated and is especially attractive for the management of patients with pulmonary edema. However, its antihypertensive potency is somewhat limited. IV infusions of nicardipine and clevidipine (calcium channel blockers) have been used in pregnancy, although there are limited data to support this usage.[53] Oral clonidine, a centrally acting alpha-2-adrenergic agonist, is an effective antihypertensive drug, but concerns about the risk of rebound hypertension after cessation limit its use.

There remains considerable debate concerning the use of beta-adrenergic blockers in pregnancy because of the potential risks of fetal bradycardia and a decrease in perfusion to the uteroplacental bed. Beta-blockers have been used during pregnancy without evidence of teratogenic effects. Although there is limited experience, they are considered as indicated in pregnant women with hypertension, mitral stenosis with pulmonary hypertension, coarctation of the aorta, ischemic heart disease, and supraventricular and ventricular arrhythmias and can be continued during delivery.[1,54] Esmolol has been used widely for heart rate control in pregnancy, but its efficacy is limited as an antihypertensive agent.

MANAGEMENT OF HYPERTENSION DURING LABOR AND DELIVERY

Management of hypertension during labor and delivery is directed toward avoiding acute and maternal complications. Antihypertensive drug therapy with a judicious use of IV fluids is of paramount importance to avoid unnecessary complications. Postpartum monitoring is advocated for high-risk, chronically hypertensive patients. Hypertension associated with preeclampsia usually resolves spontaneously within a few weeks after delivery. These patients are at risk for the development of acute complications, such as hypertensive encephalopathy, pulmonary edema, and acute renal failure. The choice of antihypertensive medications or the doses used may have to be adjusted after delivery, and minute amounts of all antihypertensive agents are found in breast milk. Although limited data are available, adverse perinatal effects have not been observed with the more commonly used drugs, such as alpha-methyldopa, hydralazine, and the various alpha-adrenergic blockers.[54]

KEY POINTS

- Hypertensive disorders associated with pregnancy are not uncommon and can either predate the pregnancy or be precipitated or unmasked by the pregnancy.
- BP measurements should be consistently taken in either the sitting position or in the inferior arm in the lateral recumbent position with each evaluation and should be repeated in 4–6 hours.
- Treatment is recommended if the SBPs are 160 mm Hg or higher or the DBPs are 110 mm Hg or higher, or with lower BPs if the patient is symptomatic.Elevated BPs caused by essential hypertension may transiently improve during the second trimester of pregnancy.
- Consistently elevated SBPs greater than 200 mm Hg should prompt the practitioner to consider undiagnosed chronic hypertension or some of the less common causes of hypertension such as primary aldosteronism, renal artery stenosis, pheochromocytoma, or illicit drug use.
- Preeclampsia most often appears after the 32nd week of gestation and resolves with delivery of the fetus.
- Preeclampsia can be superimposed on chronic hypertension.
- Preeclampsia may initially present during pregnancy or after delivery as the HELLP syndrome.
- Hypertension with BP elevation of 140/90 mm Hg or higher and proteinuria are the principal characteristics of preeclampsia. Edema is no longer a criterion for preeclampsia.
- Preeclampsia is a multisystem disease. Severe preeclampsia manifests with signs and symptoms of end-organ involvement.
- The antihypertensive drugs most frequently used in pregnancy have not been associated with significant fetal abnormalities.
- First-line oral antihypertensive drugs for moderate hypertension are alpha-methyldopa and labetalol.
- Parenteral antihypertensive agents are used for more severe elevations of BP. The agents most commonly employed are labetalol, hydralazine, and sodium nitroprusside in addition to IV nicardipine and clevidipine infusions.
- Caution should be exercised with the administration of hydralazine, particularly in patients with decreased plasma volume.

References for this chapter can be found at expertconsult.com.

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In 2006 the American Association of Clinical Endocrinologists (AACE) proposed guidelines for the diagnosis and treatment of hypertension, focusing on identifying and managing hypertension relating to or coinciding with endocrinopathies. These guidelines are based on positive data from randomized clinical trials. They recommended diuretics, beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and calcium channel blockers (CCBs) for treating hypertension in patients, particularly those with diabetes mellitus.

Magee L, Chan C, Waterman EJ, et al. Hydralazine for treatment of severe hypertension in pregnancy: meta-analysis. *BMJ.* 2003;327:955.
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Magee LA, Helewa M, Moutquin JM, et al. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. *J Obstet Gynaecol Can.* 2008;30:S1.
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Acute Pulmonary Complications During Pregnancy

Cornelia R. Graves

During pregnancy, the respiratory system undergoes a number of changes and is subject to functional and anatomic stresses. The critical care provider must remember these changes to appropriately care for the maternal-fetal unit. Although the need for ventilatory support is rare in pregnancy, respiratory insufficiency, which may complicate up to 1 in 500 pregnancies, is still the most common indication in pregnancy for admission to a critical care unit.[1]

In this chapter, the unique physiologic changes that occur during pregnancy are addressed and guidance is provided to critical care specialists who may encounter pregnancies that are complicated by acute pulmonary complications.

PULMONARY PHYSIOLOGY IN PREGNANCY

A number of physiologic changes affect respiration during pregnancy. Normal pregnancy is associated with a 20% increase in oxygen consumption and a 15% increase in metabolic rate. During the first trimester, minute ventilation is increased, whereas the respiratory rate remains the same. Although one might assume that the lung volume during pregnancy would decrease owing to a rise in the maternal diaphragm, the tidal volume (VT) is actually increased by 40% over baseline values. The increase in VT is thought to be caused by the increase in circulating progesterone that affects the respiratory center.[2] Arterial blood gas measurements reflect respiratory alkalosis compensated for by metabolic acidosis that results in a relatively normal pH. $PaCO_2$ usually ranges from 28 to 32 mm Hg. Functional residual capacity (FRC), residual volume, and total lung volume are decreased near term. Because of this decrease, respiratory distress occurs more rapidly in the gravid than in the nongravid state. The function of the large airways, as measured by forced expiratory volume in 1 second (FEV_1) and peak expiratory flow rate (PEFR), is essentially unchanged throughout pregnancy.[3] Oxygen consumption reaches 20%–33% above baseline by the third trimester. Airway hyperemia and edema occur during pregnancy as a result for human placental growth hormone, resulting in the possibility of a difficult or failed intubation.[4]

Colloid osmotic pressure is decreased by 20%. This change in hydrostatic pressure results in a propensity for pregnant patients to develop cardiogenic and noncardiogenic pulmonary edema.

Dyspnea on exertion is common, especially in the third trimester of pregnancy, making the diagnosis of respiratory problems more difficult than that in the nongravid state.

Fig. 133.1 illustrates the graphic relationship of pulmonary changes.

ASTHMA

Epidemiology

Asthma is one of the most common pulmonary problems in pregnant women; recent studies have reported that approximately 8% are affected.[5] The disease is characterized by hyperactive airways, leading to episodic bronchoconstriction. The role of inflammatory mediators in the pathogenesis of asthma has become apparent in recent years, leading to the early use of antiinflammatory medications in the treatment of exacerbations.

Effects of Asthma on Pregnancy

Asthma may be triggered by environmental allergens, medications—especially aspirin or nonsteroidal antiinflammatory drugs (NSAIDs)—or stress. Most exacerbations are marked by cough, wheezing, and dyspnea. Rapid therapeutic intervention at the time of an exacerbation is imperative to prevent impaired maternal and fetal oxygenation because uncontrolled asthma can increase maternal morbidity. In several studies, even after controlling for confounding variables, adverse pregnancy outcomes are more pronounced in patients with asthma. These include low birth weight, preeclampsia, preterm birth, and stillbirth.[6,7] Although historical data have shown an increase in death and low birth weight, Fitzsimmons and colleagues observed low birth weight in only those patients treated for status asthmaticus.[8] In addition, Schatz and colleagues noted that intrauterine growth restriction was directedly related to lung function as measured by FEV_1.[9]

However, a recent meta-analysis of 40 studies demonstrated that maternal asthma is associated with an increase in low-birth-weight infants, intrauterine growth restriction, preterm delivery, and preeclampsia when controlled for all variables.[10]

Effect of Pregnancy on Asthma

Numerous studies have observed that the course of asthma may be affected by pregnancy. Gluck and colleagues found that, on average, asthma improved in 36% of women during pregnancy, remained unchanged in 41%, and worsened in 23%.[11] Schatz and colleagues, in an analysis of 366 pregnancies in which patient status was followed by objective criteria, found that asthma improved in 28% of women, remained unchanged in 33%, and worsened in 35%. Fifty-nine percent of the patients had similar asthma control in successive pregnancies.[9] Asthma exacerbations are not uniformly distributed in pregnancy. Observational studies have found that exacerbations were most frequent before 24 weeks' gestation.[11]

Fetal sex may influence asthma in pregnancy. In one study, mothers who gave birth to boys were more likely to report improved asthma symptoms.[12] Dodds and colleagues found that the use of medications to treat asthma was less common in mothers of boys.[13] Although a number of hypotheses have been proposed, including alterations in progesterone levels and the role of leukotrienes, changes in not one of these mediators can explain the varied course of pregnant asthmatics.[14]

Management

The National Asthma Education and Prevention Program issued specific guidelines regarding asthma treatment. In 1993 the Working

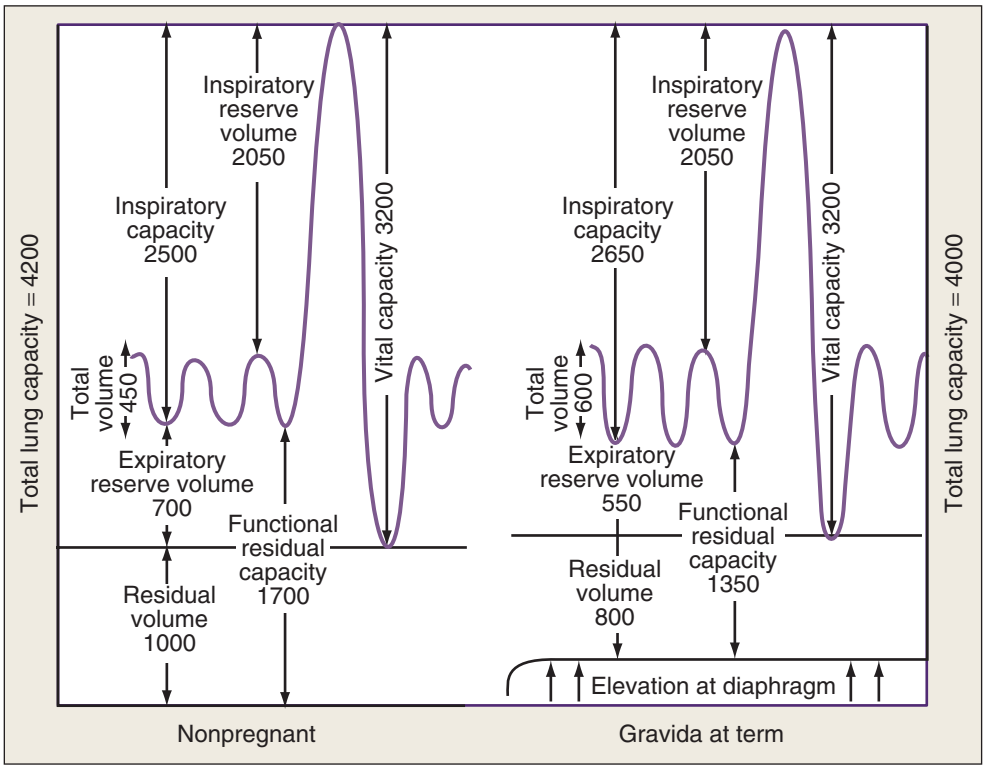

Fig. 133.1 Respiratory changes in pregnancy.

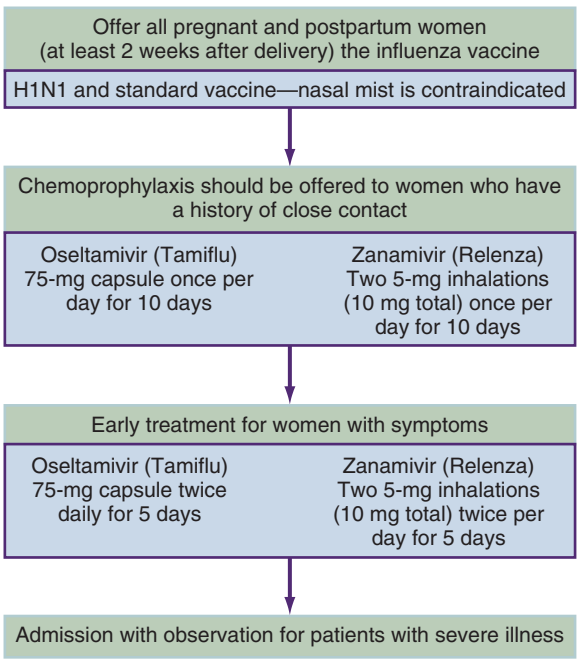

Fig. 133.2 Treatment during pregnancy.

Group on Asthma and Pregnancy established criteria for diagnosis and treatment among the gravid population (Fig. 133.2).[15]

The goals of treatment during pregnancy are to control exacerbation and prevent status asthmaticus, thereby reducing maternal and fetal hypoxemia. The initial step in treatment involves monitoring pulmonary function, and FEV_1 is the single best measure. A physical examination and chest radiography are poor measures of disease severity. A portable handheld peak flow meter gives a quick, accurate assessment by measuring PEFR. Most authorities believe that airways remain essentially unchanged throughout pregnancy; therefore every patient with asthma should be given a peak flow meter and be educated in its use. The patient should obtain a baseline PEFR during a quiescent period. The severity of disease is determined by the occurrences of exacerbations and changes in FEV_1 and PEFR. The PEFR can be used as a guide to refer the patient for emergency care.

Pharmacologic therapy is the mainstay of asthma treatment. Most drugs used in the treatment of asthma are thought to be safe in pregnancy. Inhaled beta-agonists are the most frequently used in asthma treatment. A prospective study of inhaled beta-agonists in 259 pregnancies showed no change in the rate of congenital malformation, perinatal mortality, low birth weight, or complications of pregnancy.[16] There is little role for the use of oral beta-agonists, which may cause more adverse systemic symptoms and are not more effective than inhaled drugs.

Inhaled corticosteroid therapy remains the mainstay of antiinflammatory treatment of asthma. Corticosteroids have also been advocated as first-line therapy in patients with mild asthma.[17] Studies have demonstrated that with asthma, those taking an inhaled corticosteroid were four times less likely than their nontreated counterparts to suffer an exacerbation.[18] Another randomized study noted that there was a 55% reduction in readmission rates because of acute asthma in patients using inhaled beclomethasone.[19] Inhaled corticosteroids can increase the effectiveness of beta-adrenergic agents by inducing the formation of new beta receptors. Because beclomethasone is the most studied of the inhaled corticosteroids in pregnancy, it is recommended as first-line therapy.[19] However, if patients are well controlled on other corticosteroid preparations, it is suggested they be continued on their current medication because all inhaled corticosteroids are labeled by the US Food and Drug Administration (FDA) as pregnancy class C. Other

BOX 133.1 Treatment of Asthma in Pregnancy

Mild Asthma
Characterized by FEV_1 or PEFR ≥80%
Brief (<1 hour) exacerbations
Treatment: inhaled beta-2-agonist

Moderate Asthma
Characterized by FEV_1 or PEFR range from 60% to 80%
Exacerbations more than twice per week; exacerbations may last for several days, and occasional emergency care needed
Treatment: inhaled corticosteroids and inhaled beta-2-agonist

Severe Asthma
Characterized by FEV_1 or PEFR <60% of baseline
Continuous symptoms, limited activity, frequent exacerbations and nocturnal symptoms, occasional hospitalization and emergency treatment needed
Treatment: inhaled corticosteroids, inhaled beta-2-agonist, sustained-release theophylline; oral corticosteroid taper for active symptoms

FEV_1, Forced expiratory volume in 1 second; *PEFR,* peak expiratory flow rate.

antiinflammatory medications used in the treatment of asthma (e.g., cromolyn sodium and nedocromil sodium) appear to be less effective than inhaled corticosteroids in reducing symptoms.

Systemic corticosteroids should be reserved for the periodic treatment of acute asthma exacerbations. Chronic oral corticosteroid therapy may increase the risks of gestational diabetes mellitus, preterm labor, low-birth-weight infants, and preeclampsia; however, it is evident that the benefits of controlled severe asthma outweigh the potential risks to the mother and fetus.

Intravenous corticosteroids have no increased benefits over oral corticosteroids in the treatment of acute exacerbations.[20] Methylprednisolone, hydrocortisone, and prednisone are safe for use in pregnancy, unlike betamethasone or dexamethasone, because very little active drug crosses the placenta.

Leukotriene pathway moderators have been shown to improve pulmonary function, as measured by FEV_1.[21] Zafirlukast and montelukast are rated as FDA category B; however, these drugs have not been frequently used in pregnancy, and their role is undetermined.

The treatment of asthma requires providing patient education in the preconceptional period and during the pregnancy for optimum outcome. Box 133.1 shows a suggested schematic for the treatment of asthma in pregnancy.

STATUS ASTHMATICUS

Status asthmaticus is a rare complication in pregnancy. Diagnosis is established by a PaO_2 of less than 70 mm Hg, a $PaCO_2$ of greater than or equal to 35 mm Hg, or a measured expiratory flow of less than 25% of expected. Because of impending respiratory failure, these patients should be managed in a critical care unit. Aggressive treatment of status asthmaticus is mandatory to protect the mother and fetus. Maternal mortality may be as high as 7% and fetal mortality as high as 11% despite adequate treatment. Epinephrine is not contraindicated in pregnancy during a respiratory emergency. Criteria for intubation in gravida with status asthmaticus include (1) inability to maintain a PaO_2 of greater than 60 mm Hg despite supplemental oxygen; (2) inability to maintain a PCO_2 of less than 40 mm Hg; (3) evidence of maternal exhaustion, with worsening acidosis (pH <7.2) despite intensive bronchodilator therapy; and (4) altered maternal consciousness.[15]

When traditional treatment proves to be ineffective, a number of therapies have been reported to be beneficial. The use of a helium–oxygen mixture that has been reported to be effective in studies in nonpregnant women has been used safely in pregnancy.[22]

Some drugs used in labor and delivery may increase the risk of inducing asthma in susceptible patients. 15-Methylprostaglandin $F_{2\alpha}$, ergonovine, and methylergonovine should be avoided. Prostaglandins E_1 and E_2 and oxytocin have very little effect on bronchospasm.

PULMONARY EDEMA

Pulmonary edema can be divided into two categories during pregnancy. *Cardiogenic pulmonary edema* is the result of high intravascular pressures creating a hydrostatic pressure gradient that results in extravasation of fluid into lung tissues despite the integrity of normal lung microcirculation. *Noncardiogenic pulmonary edema* is the result of a leaky pulmonary capillary bed despite normal intravascular pressures. During pregnancy, the distinction between these two types of edema may be blurred owing to disease states that exacerbate the hypo-oncotic state of pregnancy.

Etiology

There are a number of causes of pulmonary edema in pregnancy. Some are pathologic in their process; others are the result of idiopathic causes. One of the most common associations with pulmonary edema during pregnancy is hypertensive disease. In patients with hypertensive disease, pulmonary edema may be cardiogenic because of fluid overload or left ventricular dysfunction or noncardiogenic because of decreased oncotic pressure.

Another common cause of pulmonary edema in pregnancy is tocolytic therapy. Most cases described have resulted from the intravenous use of beta sympathomimetics. The use of magnesium sulfate therapy and the use of corticosteroids in association with tocolysis for preterm labor have been shown to exacerbate the condition. The incidence of edema is increased in multiple gestations and in patients with subclinical infection.

Underlying cardiovascular disease is also another cause of pulmonary edema during pregnancy. The increased cardiac output and heart rate that occur in pregnancy increase the gradient across a stenotic mitral value, which may lead to acute pulmonary edema.

Peripartum cardiomyopathy may also present as pulmonary edema in pregnancy; therefore cardiac imaging is recommended in all patients who present with acute refractory pulmonary edema in pregnancy.

Other causes of acute pulmonary edema in pregnancy include amniotic fluid embolism, aspiration, and the need for massive transfusion after hemorrhage.[23]

Treatment

The treatment of pulmonary edema during pregnancy depends on its etiology. The cause is best determined by the use of pulmonary artery catheterization and measurement of pulmonary capillary wedge pressure. Although all patients may not require this intervention, it is recommended in patients in whom the clinical picture may be unclear (e.g., those with hypertensive disease) and in those who do not respond to standard diuretic therapy.

For patients who do not improve rapidly with diuretic therapy, intubation and ventilation with positive pressure is recommended. In addition to the use of diuretic therapy, reduction of preload and afterload may be achieved by the use of vasodilators such as nitrates, hydralazine, or calcium channel blockers. All are safe for use in pregnancy.

Box 133.2 shows a guide for the treatment of patients with pulmonary edema.

BOX 133.2 Treatment in Patients With Pulmonary Edema

1. Determine the etiology, stop fluids, tocolysis, etc.
2. Treat with a diuretic (the author prefers furosemide in increments of 10- to 20-mg intravenous [IV] push).
3. Consider the use of morphine sulfate for patient comfort, 1- to 2-mg IV push q2–3h.
4. Proceed with hemodynamic monitoring if the patient does not rapidly respond to the earlier measures.
5. Consider intubation and mechanical ventilation with positive pressure for those patients with noncardiogenic pulmonary edema and those patients with cardiogenic pulmonary edema who need further support.

ACUTE RESPIRATORY DISTRESS SYNDROME

Etiology

The causes of acute respiratory distress syndrome (ARDS)[24–27] in pregnancy include preeclampsia, sepsis, aspiration, pyelonephritis, intrauterine infections, acute fatty liver of pregnancy, and amniotic fluid embolism.[28] In a review of 83 cases of ARDS associated with pregnancy, it was noted that among the causes of ARDS, 35 cases were attributed to uniquely obstetric conditions.[29] In addition, it was noted that varicella pneumonia and pyelonephritis were associated with ARDS. These conditions rarely trigger ARDS in immunocompetent adults. De Vaciana and colleagues pointed out that the development of lung injury in pregnancy correlates with known physiologic changes, including increased blood volume, decreased colloid osmotic pressure, and an unchanged critical lung closing volume despite a diminished FRC.[30]

Management

Management of ARDS includes diagnosis, maternal stabilization, fetal monitoring, investigation and treatment of underlying causes, and in many cases, evaluation for delivery. ARDS is a rare occurrence in the pregnant patient, with an estimated incidence of 16–70 per 100,000 pregnancies.[29]

Maternal stabilization includes intubation for mechanical ventilation if necessary. The clinician should consider intubation sooner rather than later in the presence of respiratory deterioration, keeping in mind that a decreased FRC exacerbates respiratory distress.

Contemporary thinking regarding the treatment of ARDS has found that a lung-protective ventilator strategy is the first therapy that has been found to improve outcomes. It has been noted in numerous studies that decreasing the VT from the standard of 12 mL/kg to 6 mL/kg or less and peak inspiratory pressures to less than 30 cm H_2O from 50 cm H_2O have resulted in decreased morbidity and mortality in patients with ARDS.[31] There has been considerable discussion in the literature concerning permissive hypercapnia and its use in preventing lung injury. However, there have been no controlled studies in pregnancy, and it is the opinion of the author that increasing $PaCO_2$ in pregnant patients should be undertaken with caution.

Judicious use of fluids is important in the management of ARDS. Although some authors have advocated the use of fluid restriction, clinicians must consider the volume-dependent status in pregnancy. It is recommended that fluid management be carefully guided by the use of hemodynamic monitoring.

Although oxygenation is important, it should be noted that oxygen should be used at the lowest concentration possible because it is toxic to the lung tissue in high doses. The goal of therapy is to keep the SaO_2 higher than or equal to 95%.

BOX 133.3 Management of the Patient With ARDS

1. Evaluate the patient in respiratory distress; calculate PaO_2/FiO_2 ratio; consider intubation if ≤200 mm Hg. The PEEP or CPAP mask is not recommended in pregnancy, owing to the high risk of aspiration.
2. Set tidal volume at 8–9 mL/kg to prevent increased peak pressures. Given recent evidence, aim to keep peak pressures less than 40 cm H_2O.
3. Use PEEP, starting at 5–8 cm H_2O to assist in recruiting alveoli.
4. Aim to keep FiO_2 less than 60%; keep SaO_2 greater than or equal to 95%.
5. Use a pulmonary artery catheter to assist in fluid management and to guide hemodynamic parameters.
6. Consider the use of tocolysis only after the patient has been adequately hydrated and oxygenated.
7. Consider delivery if indicated for obstetric conditions or if continuing the pregnancy has no clear benefit.

ARDS, Acute respiratory distress syndrome; *CPAP,* continuous positive airway pressure; *FiO_2,* fraction of inspired oxygen; *PaO_2,* partial pressure of oxygen; *PEEP,* positive end-expiratory pressure; *SaO_2,* oxygen saturation.

A number of other methods have been discussed in the treatment of ARDS, including inhaled nitric oxide, prostacyclin, surfactant, and inverse ratio ventilation. Currently, these modalities cannot be recommended because they have not been shown to decrease morbidity and mortality. The indications for prone positioning in pregnancy should be the same as for any other patient with severe ARDS.[32]

Fetal surveillance during ARDS may be more difficult because drugs used to sedate the mother can affect fetal heart rate and variability. Sedatives, anxiolytics, hypnotics, and nondepolarizing agents are not contraindicated in pregnancy. In addition, preterm contractions and labor may present a problem because of maternal hypoxemia. Clinicians are cautioned against starting tocolytic therapy before achieving adequate maternal oxygenation. If tocolysis is needed, beta-agonists such as terbutaline should be avoided because of the risk of increased pulmonary capillary permeability and increased demands on cardiac load. Magnesium sulfate is not strictly contraindicated, but it may also increase pulmonary capillary permeability. The use of NSAIDs may be the best choice for tocolysis because they have been proven to improve ARDS in animal models.[33] Consultation with a maternal-fetal specialist is recommended to assist intensivists in caring for these complex patients.

The timing of delivery of the patient with ARDS is a question that must be addressed by clinicians. Some authors advocate delivery after maternal stabilization, citing the possible "therapeutic effect" of delivery. Tomlinson and colleagues failed to demonstrate any significant benefit to delivery.[33] It is this author's opinion that delivery should be considered on a case-by-case basis, carefully weighing the risk/benefit ratio to the mother and fetus.

Extracorporeal membrane oxygenation (ECMO) support has been used successfully in pregnancy. One case series in pregnancy demonstrated an 88.9% chance of maternal survival and a 77% chance of fetal survival for patients who required support. In this series, four people delivered on ECMO, and if the fetus was viable, survival was 100%.[34]

Box 133.3 shows a reasonable management scheme for a patient with ARDS.

EMBOLISM

Because of the hypercoagulable changes in the coagulation cascade associated with pregnancy, there is an increased risk of venous

thromboembolism. It has been estimated that clinically symptomatic pregnancy-related venous thromboembolism occurs in 1–2 per 1000 pregnancies. Maternal age (>40 years) and ethnic and genetic factors may increase this risk. Postpartum thromboembolism is 3–5 times more common than antepartum thromboembolic events. A cesarean section confers a risk of 3–16 times that of a vaginal delivery.

Clinical signs of a pulmonary embolism include unexplained tachycardia, dyspnea, diaphoresis, and a nonproductive cough. The work-up for a suspected pulmonary embolism should include normal laboratory studies (arterial blood gases) and an electrocardiogram in conjunction with radiographic testing.[35] Pregnancy should not prevent obtaining appropriate radiographic studies. In patients with a high clinical index of suspicion for thromboembolic phenomena, a definitive diagnosis is imperative (Box 133.4). Ventilation-perfusion scans are recommended as the first diagnostic test. Spiral computed tomography has replaced ventilation-perfusion scanning in almost all centers as an initial test. Pulmonary angiography is still the gold standard for offering a definitive diagnosis. All of the aforementioned tests use less than the 5 rad of radiation exposure that has been associated with fetal teratogenesis. The use of an abdominal shield further decreases fetal exposure.

D-dimer levels have not been shown to be useful for the diagnosis of a thromboembolism during pregnancy because they may be elevated in the absence of a thrombus.[35] However, in a prospective study involving pregnant women with suspected pulmonary embolism, pulmonary embolism was ruled out if none of the three adapted YEARS criteria were met and the D-dimer level was less than 1000 ng/mL or if one or more of the three criteria were met and the D-dimer level was less than 500 ng/mL.[36]

Low-molecular-weight heparin (weight-based dosing BID) is the anticoagulant of choice in antepartum patients. Warfarin should be avoided during pregnancy, if possible. Unfractionated heparin can also be used. Neither of these drugs crosses the placenta, owing to the size of the drug molecule. Patients on low-molecular-weight heparin should be monitored with factor Xa levels to ensure a therapeutic level.

Warfarin may be used in the second and third trimesters in patients in whom heparin therapy may be contraindicated. Coumarins may be difficult to reverse and are not routinely recommended during pregnancy. All anticoagulants can be used in the postpartum period and are compatible with breastfeeding.[37]

The goals for therapy during the antepartum and postpartum periods (6–8 weeks postdelivery) should be an activated partial thromboplastin time of 2.0–2.5, a factor Xa level of 0.6–1.1, or an international normalized ratio (INR) of 2.5–3.0.

An amniotic fluid embolism is a rare phenomenon that may initially present as severe respiratory distress. Risk factors include rapid labor, multiple gestation, polyhydramnios, and uterine rupture. Patients with an amniotic fluid embolism usually have symptoms of acute respiratory distress, cardiovascular collapse, and profound disseminated intravascular coagulation. Treatment is supportive; however, maternal mortality may be as high as 80%.

BOX 133.4 Treatment of Pulmonary Embolism in Pregnancy

1. Begin therapy immediately based on strong clinical suspicion while awaiting complete diagnostic work-up.
2. Establish the diagnosis with appropriate diagnostic imaging test.
3. Maintain maternal and fetal oxygenation.
4. Administer intravenous heparin and maintain full anticoagulation for 7–10 days before changing to subcutaneous injections (antepartum) or warfarin (postpartum). Oral anticoagulation should be continued 6–8 weeks after delivery.
5. Keep the international normalized ratio, activated partial thromboplastin time, or factor Xa level in the therapeutic range.

PNEUMONIA

Concern over the H1N1 virus has reinforced the seriousness of influenza infection in pregnant patients. Historical data have shown that during an influenza pandemic, mortality rates among pregnant women are unusually high. Neuzil and colleagues noted that even during a normal season, compared with their postpartum counterparts, pregnant women were more likely to be hospitalized.[38] The risk of hospitalization was highest in the third trimester, with women nearly five times more likely to be hospitalized than the postpartum control group. Influenza-related morbidity occurs in 10.5 of 10,000 pregnant women, compared with 1.91 of 10,000 in nonpregnant controls. Influenza pneumonia mortality in pregnancy has been noted to range from 12.5% to 42.1%.[39]

Contemporary management of influenza infection in pregnancy includes the use of antiviral medications for preventing and treating the disease. Amantadine and rimantadine have been shown to be effective in shortening the course and duration of disease in influenza A and influenza B. Recently, oseltamivir (Tamiflu) and zanamivir (Relenza) have been recommended for the prevention of influenza infection. Current Centers for Disease Control and Prevention (CDC) guidelines recommend that treatment be initiated for pregnant women (including patients until 2 weeks postpartum) with documented exposure to influenza virus and those patients who present with symptoms in the first 48 hours of illness, regardless of their gestational age. Medication should be started at the first sign of symptoms; awaiting confirmation of the diagnosis and delaying therapy could result in rapid progression of the disease. In the 2009 flu season, 6% of deaths were in pregnant women, even though only 1% of the population is pregnant at any given time. Data suggest that the use of antiviral medications significantly reduces perinatal morbidity and mortality. Since 1995 the CDC has recommended that all pregnant women receive influenza immunizations. There has been some discussion regarding the use of thimerosal, which is used in the standard influenza vaccine; most authorities feel that the thimerosal-free vaccine, when available, is preferable.

It is the opinion of the author that all pregnant patients who present with respiratory symptoms after exposure to viral illness should be hospitalized for observation.[39–41] Changes in maternal respiratory physiology during pregnancy can make progression from mild respiratory distress to severe respiratory distress rapid and unpredictable[38] (see Fig. 133.1).

Since first being identified in December 2019, the novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly spread around the globe. Data from 8207 pregnant women in the United States suggest that the symptoms of COVID-19 are similar to the nonpregnant population, with most presenting with cough (>50%) and shortness of breath (30%). Chronic lung disease, diabetes mellitus, and cardiovascular disease were more commonly reported among pregnant women than among nonpregnant women. Among women with COVID-19, hospitalization was approximately six times higher. After adjusting for age, presence of underlying medical conditions, and race/ethnicity, pregnant women were significantly more likely to be admitted to the intensive care unit and receive mechanical ventilation. The risk of death in pregnancy was noted to be significantly higher that in the non pregnant population.[42] We are still learning about this virus in pregnancy—the use of

steroids and remdesivir in pregnancy has been associated with improved outcomes.[43]

CONCLUSION

Because of the rare need for mechanical ventilation, there are no randomized controlled trials to determine the treatment modalities that are most effective in pregnancy. A retrospective study noted a maternal mortality rate of 14% and a fetal mortality rate of 11% in patients who required mechanical ventilation during pregnancy. The critical care specialist, maternal-fetal medicine specialist, anesthesiologist, and other members of the healthcare team should work closely to provide coordinated care.[44] Understanding the physiologic changes during pregnancy, combined with aggressive treatment of early pathologic changes, will assist in providing improved management in gravid patients with potentially lethal pulmonary complications.

KEY POINTS

- Physiologic changes in pregnancy affect the management of respiratory disease, making the pregnant patient more susceptible to respiratory compromise.
- Caution should be used when considering treatment for preterm labor in patients requiring respiratory support. Correction of oxygenation is usually more effective than pharmacologic therapy.
- The need for mechanical ventilatory support does not mandate delivery of the fetus. Most studies do not report significant maternal improvement after delivery.
- Pregnancy is a hypercoagulable state that increases the risk of thromboembolic phenomena.
- Care should be taken to carefully evaluate pregnant patients with viral pneumonia for acute respiratory symptoms.
- Amniotic fluid embolism is a rare cause of respiratory complications in pregnancy.
- ECMO support has been used successfully in pregnancy with excellent maternal and fetal survival.
- The identification of pulmonary embolism in pregnancy may be enhanced by using the adjusted YEARS algorithm, which re-evaluates the use of D-dimer in pregnancy.
- Asthma is the most common respiratory complication in pregnancy and should be controlled in pregnancy in order to avoid perinatal complications.
- As respiratory complications in pregnancy are rare, assembly of a multidisciplinary team is essential to improve maternal and fetal outcomes.

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Postpartum Hemorrhage

Cornelia R. Graves

Obstetric hemorrhage remains a leading cause of maternal mortality and morbidity worldwide, with most deaths occurring in the postpartum period. Recognition of blood loss in obstetric hemorrhage can be challenging. Therefore interventions focused at the patient level, provider and unit level, and system level are imperative in order to provide optimal patient care. In smaller centers, guidelines to establish which patients should be triaged to a higher level of care should be considered. In all centers, a plan for evaluating and managing obstetric hemorrhage, which may include assessing additional resources, should be in place in order to reduce maternal morbidity and mortality.

DEFINITION

The commonly accepted definition of *postpartum hemorrhage* (PPH) is excessive and life-threatening bleeding after 20 weeks of gestation, which occurs at the time of delivery of the fetus or placenta. Primary PPH is excessive blood loss within 24 hours of delivery. Secondary PPH is any abnormal or excessive bleeding that occurs between 24 hours and 12 weeks after delivery. Most commonly, bleeding occurs in the third stage of labor, which refers to the time between delivery of the fetus and delivery of the placenta after its separation and expulsion from the uterus. Defining excessive bleeding is somewhat problematic because it can be difficult to determine the exact amount of blood loss, and clinicians tend to underestimate blood loss. With a normal vaginal delivery, blood loss is typically 500 mL or less; after a normal cesarean section, it is usually 800–1000 mL. Blood loss greater than these amounts has been used to define PPH. However, uncomplicated vaginal and cesarean deliveries can occasionally occur with greater amounts of blood loss but without hemodynamic compromise. Therefore a more comprehensive definition of PPH is bleeding (regardless of the volume of shed blood) that is severe enough to cause hemodynamic compromise.

A decrease in hematocrit greater than 10% as a diagnostic criterion has also been widely accepted as a definition of PPH. The hematocrit level initially may be in the low-normal to normal range despite excessive bleeding, because hematocrit does not change quickly in response to rapid hemorrhage. The hematocrit is also determined in part by the volume of infused resuscitation fluid. Because the parturient's blood volume is increased by 30%–50%, the signs of tachycardia and hypotension may not manifest until blood loss exceeds 1500 mL. If the patient is hemodynamically unstable but the amount of blood visualized externally is relatively insignificant, occult sites of internal bleeding should be suspected immediately.

INCIDENCE AND MORTALITY

Maternal mortality has significantly decreased over the past 50 years in developed countries, in part because of improvements in obstetric care. However, in the United States maternal mortality rose to a high of 17.4 per 100,000 in 2018. Much of this increase was associated with rising rates of hemorrhage. This increase was the highest among developed countries. Racial and ethnic gaps exist between non-Hispanic black (37.1 deaths per 100,000 live births), non-Hispanic white (14.7), and Hispanic (11.8) women.[1]

In the United States, the rate of PPH increased 26% between 1994 and 2006 primarily because of increased rates of atony. In contrast, maternal mortality from postpartum obstetric hemorrhage has decreased since the late 1980s and accounted for slightly more than 11% of maternal mortalities (approximately 1.7 deaths per 100,000 live births) in 2009. This observed decrease in mortality is associated with increasing rates of transfusion and peripartum hysterectomy.[2–4] Worldwide, obstetric hemorrhage is the leading cause of maternal mortality, causing 24% of maternal deaths, or an estimated 127,000 maternal deaths annually. PPH is the most common type of obstetric hemorrhage and accounts for the majority of the 14 million cases that occur each year. In developing countries, PPH may cause up to 40% of all maternal deaths.

PATHOPHYSIOLOGY

At term, blood flow to the uterus and placenta increases to 600–1200 mL/min, accounting for 10% of the maternal cardiac output. To stem the flow of blood and provide immediate hemostasis after delivery of the fetus, the uterus begins to contract. Myometrial contraction is the primary mechanism for both placental separation and hemostasis. The myometrial muscle fibers of the uterus simultaneously contract and retract, causing compression and occlusion of the blood vessels. Uterine atony results when this adaptive mechanism fails and the myometrial fibers are unable to contract and retract normally. Excessive bleeding from the uterus and lower genital tract from many causes, including lacerations, placental anomalies, and trauma, is directly related to the increase in blood flow to the uterus and placenta. At term, there is a physiologic increase in the circulating concentrations of various clotting factors. This adaptive response also helps control the bleeding that is a normal consequence of delivery. However, these factors are overwhelmed by the excessive bleeding of PPH.

PRESENTATION

PPH often manifests as brisk and excessive flow of blood from the uterus. Maternal hemodynamics may be unaltered initially. If the bleeding is left untreated, typical presenting signs of hypovolemic shock (i.e., tachycardia, tachypnea, and hypotension) become apparent. Bonnar described the symptoms related to PPH in relation to the amount of blood loss (Table 134.1).[5] However, the signs and symptoms of

TABLE 134.1 Presentation of Symptoms in Postpartum Hemorrhage

Percent Blood Loss (mL)	Systolic Blood Pressure (mm Hg)	Signs and Symptoms
Stage I: 10–15 (500–1000)	Normal	Tachycardia, palpitations, dizziness
Stage II: 15–25 (1000–1500)	Low to normal	Tachycardia, weakness, diaphoresis
Stage III: 25–35 (1500–2000)	70–80	Restlessness, pallor, oliguria
Stage IV: 35–45 (2000–3000)	50–70	Collapse, air hunger, anuria

hemorrhagic shock may not occur immediately and may extend over a longer period if shed blood is sequestered in the uterus. Occult bleeding occurs most frequently with retained placental fragments; uterine atony; and concealed hematomas in the pelvis, perineum, or retroperitoneal space. Occult hemorrhage in the uterus or hematomas should be suspected in patients who are in the third stage of labor with hemodynamic instability but little or no evidence of external bleeding. Signs and symptoms of excessive bleeding also may be delayed because of the relative hypervolemic state of the patient and by the position of the patient after delivery with the legs elevated in stirrups.

CAUSES

Obtaining a detailed antenatal history is important in helping to determine a possible cause of PPH. Because obstetric hemorrhage is difficult to predict, it is important for all institutions that deliver obsterical care to have protocols in place to manage and treat obstetrical hemorrhage. Risk assessment tools are readily available and have been shown to identify 65%–80% of patients who may experience PPH. However, it should be remembered that risk factors may change during the labor process, so constant assessment is essential in order to attempt to identify patients at risk.[6]

A history of prior bleeding episodes associated with heavy menses or with dental or surgical procedures should raise the possibility of an underlying coagulation or bleeding disorder. Significant predisposing risk factors for the development of PPH include previous episodes of PPH, multiparity, and multiple fetuses. Women with a prior history of PPH can have up to a 15% risk of recurrence with subsequent pregnancies.[6] Risk factors associated with the development of PPH are listed in Box 134.1. Early recognition of these risk factors may aid in the diagnosis and subsequently in the management of PPH. A randomized controlled trial (RCT) comparing oxytocin administration before and after delivery of the placenta found that birth weight, labor induction with augmentation, chorioamnionitis, use of magnesium sulfate infusions, and previous episodes of PPH increased the risk of developing PPH.[7] However, a significant number of patients with PPH have no obvious predisposing factors.[8]

Potential causes of PPH are listed in Box 134.2. Risk factors for obstetric causes at the time of admission should be identified and reassessed during the intrapartum and postpartum process. The most frequent cause of PPH is uterine atony after delivery of either the fetus or placenta. Bleeding is from the uterine vessels or from the placental site of implantation if the placenta has been delivered. The incidence of uterine atony is approximately 1 in 20 deliveries. Uterine atony can lead to rapid and severe PPH. Overdistention of the uterus secondary to multiple gestation, fetal macrosomia, or polyhydramnios is a major predisposing risk factor for the development of uterine atony. Other predisposing factors are retained placenta, chorioamnionitis, uterine structural abnormalities, and muscle fatigue after prolonged or stimulated labor. General anesthesia, particularly with halogenated anesthetics, and magnesium sulfate infusions can inhibit effective uterine contractions and lead to uterine atony. The diagnosis of uterine atony is a clinical diagnosis made by assessing the tone of the uterus and its size by manually palpating the uterus externally. Bimanual examination of the uterus also can be performed to diagnose uterine atony. A boggy uterus associated with heavy vaginal bleeding or with an appreciable increase in the size of the uterus is diagnostic of uterine atony. The size of the uterus may be larger than normal because of accumulated blood within it.

Lacerations of the lower genital tract are the second most frequent cause of PPH. Lacerations of the vagina and cervix can result from a number of causes. These lesions occur most commonly as a result of prolonged or tumultuous labor, particularly with uterine hyperstimulation with oxytocic agents. Nevertheless, lacerations can occur spontaneously as well. They are seen in deliveries associated with

BOX 134.1 Predisposing Risk Factors for Obstetric Hemorrhage

Low Risk
No previous uterine incision
Singleton pregnancy
<4 previous vaginal births
No known bleeding disorder
No history of PPH

Moderate Risk
Prior cesarean section or uterine surgery
Multiple gestation
>4 previous vaginal births
Chorioamnionitis
History of previous PPH
Polyhydramnios
Large uterine fibroids

High Risk
Placenta previa or low lying
Suspected accreta or percreta
HCT <30 *and* other risk factors
Platelets <100,000
Active bleeding on admission
Known coagulopathy

HCT, Hematocrit; *PPH,* postpartum hemorrhage.

BOX 134.2 Causes of Postpartum Hemorrhage

Uterine atony
Cervical or vaginal lacerations
Retention of placental fragments
Placental anomalies
Traumatic hematomas of the perineum or pelvis
Coagulation disorders
Uterine rupture
Uterine inversion

instrumentation, such as forceps deliveries, or with extrauterine or intrauterine manipulations of the fetus. Attempts to remove the placenta or placental fragments manually or with instrumentation can lead to traumatic lesions or hematomas. Excessive vaginal bleeding or traumatic hematomas can result from these lacerations. Careful examination with palpation of the vagina and cervix may reveal the presence of lacerations.

Retention of placental fragments or the entire placenta can lead to severe and life-threatening hemorrhage, which may be immediate or delayed depending on the extent of accumulated blood in the uterus. The most common definition of retention of the placenta in utero is when part or all of the placenta is retained in the uterus for more than 30–60 minutes after delivery of the fetus. Retained placenta is more likely to occur with a preterm gestation of less than 24 weeks.

Placental abnormalities (i.e., placenta accreta, placenta increta, and placenta percreta) have been associated with retained placenta and failure of complete separation of the placenta from the uterus. If the placenta has been delivered, it is imperative to closely examine the placenta to look for missing fragments, a finding that suggests retained placental tissue.

Another less frequent cause of PPH is uterine rupture. Rupture is more common in patients with prior cesarean incisions and in those with any prior operative procedures of the uterus (e.g., intrauterine device placement, laparoscopy, hysteroscopy). Uterine rupture may manifest with severe and acute abdominal pain and hemodynamic instability, but there may not be significant bleeding initially. Uterine inversion is relatively uncommon but may be associated with blood losses of up to 2 L.

A defect in hemostasis resulting from an underlying coagulopathy should be considered if the uterus is contracting normally and manual exploration has excluded either placental retention or uterine rupture. Disseminated intravascular coagulation (DIC) associated with placental abruption (premature separation of a normally implanted placenta), the HELLP syndrome (*h*emolysis, *e*levated *l*iver enzymes, and *low p*latelets), intrauterine fetal death, acute fatty liver of pregnancy, sepsis, or amniotic fluid embolism may precipitate PPH. The incidence of severe DIC associated with PPH is estimated at 0.1% of pregnancies.[9]

Amniotic fluid embolism syndrome (AFES) is a catastrophic condition that can occur either during the pregnancy or after the delivery. AFES manifests with acute respiratory failure, cardiogenic shock, and/or DIC.[10] As much as 80% of these patients develop DIC, and in some, DIC is the major clinical abnormality. Oozing from intravenous (IV) or skin puncture sites, mucosal surfaces, or surgical sites should raise the suspicion of DIC; confirmation of the diagnosis is made by laboratory coagulation studies. Although the coagulation profile is unlikely to be abnormal with acute postpartum bleeding in the absence of DIC, coagulation parameters are clearly abnormal in the presence of DIC, regardless of the cause. In late pregnancy, the circulating fibrinogen level usually is two to three times the normal prenatal value, but fibrinogen concentration is dramatically decreased if DIC is present. Preexisting or pregnancy-acquired disorders of coagulation are relatively infrequent causes of significant PPH.

DIAGNOSTIC STUDIES

Although the diagnosis is obvious with significant and excessive bleeding after delivery, not all patients present with immediate bleeding because of hematoma formation or accumulations in the interior of the uterus. Bedside ultrasonography can be used for the detection of clots, hematomas, and retained placental products. For patients who are at high risk for development of PPH, periodic ultrasound examinations during pregnancy can offer invaluable information concerning the extent and progression of placental disease. Angiography with selective arterial embolization can be used both diagnostically and therapeutically. Bleeding sites can be visualized and embolized simultaneously. For evaluation of a proven or suspected case of PPH, the following laboratory studies are almost always indicated: complete blood count with platelet count, coagulation studies with prothrombin and activated partial thromboplastin times, fibrinogen, and fibrin split products. D-dimer may be of limited use, as it may be elevated in normal pregnancies. With acute hemorrhage, the measurements of hemoglobin concentration and hematocrit may also be of limited use.

PREVENTION

There has been much controversy concerning the preferred methods of managing the third stage of labor in terms of decreasing bleeding complications. The debate concerns active versus expectant management. Expectant management consists of waiting for separation and expulsion of the placenta, with minimal intervention except for gentle fundal massage. Active management of the third stage of labor involves three components. The first consists of administering a uterotonic drug, usually oxytocin, immediately after delivery of the fetus to promote contraction of the uterus and subsequent expulsion of the placenta. The second maneuver consists of gentle traction on the umbilical cord after the uterus is well contracted and then using countertraction against the uterine fundus.[11] The third maneuver is uterine massage after delivery of the placenta.

Manual external uterine massage should be performed immediately to stimulate uterine contractions and express clots if uterine atony is suspected or confirmed. If the uterus does not respond to vigorous manual external massage and the rapid administration of oxytocin, bimanual massage with one hand on the uterus and the other hand placed anterior to the cervix in the vagina should be performed. Aggressive uterine manipulation can result in uterine inversion. Direct pressure should be maintained over visible perineal, vaginal, or cervical lacerations. These general treatment measures can control excessive bleeding and even stop the hemorrhage in a significant proportion of patients.

The two modalities were compared in five RCTs in a Cochrane meta-analysis of studies enrolling more than 6000 women. A 60% decrease in PPH was associated with active management of the third stage of labor.[12]

GENERAL TREATMENT MEASURES

Many deaths associated with PPH may have resulted because clinicians underestimated the extent of blood loss and failed to provide rapid and aggressive resuscitation with fluids and blood products. Several authors have suggested the use of specific management protocols for the care of patients with PPH.[5,13,14] These guidelines can expedite rapid diagnosis and management of obstetric hemorrhage. Quantification of blood loss during delivery has been recommended, as it gives a better assessment of blood loss. Several current toolkits are available to assist medical personnel in managing the weighing of pads and laps in order to give an accurate assessment.[15] Simulation may also be used to assist the team in responding more quickly to this emergency.[36]

A general assessment of the patient, evaluation of vital signs, a detailed physical examination, and a review of the obstetric delivery details are all necessary for the clinician to formulate a comprehensive evaluation and critique of the situation. The general treatment measures for PPH are the same as those for any patient with acute hemorrhage (Box 134.3). Oxygen should be administered routinely. At least two large-caliber IV lines should be placed immediately. Central venous access is usually unnecessary unless peripheral access cannot be

BOX 134.3 General Treatment Measures for Postpartum Hemorrhage

Oxygen administration
Gentle massage of the uterine fundus
Placement of large-caliber intravenous catheters for rapid and aggressive fluid resuscitation with isotonic solutions using the "3:1 rule"
Blood product administration depending on the extent of bleeding and coagulation abnormalities

TABLE 134.2 Therapeutic Response to Initial Fluid Resuscitation

Response	Description	Follow-Up Treatment
Rapid response	<20% of blood volume lost	No additional fluids or blood are needed.
Transient response	20%–40% of blood volume lost; responds to initial fluid bolus but later has worsening vital signs	Continue fluids and consider blood transfusions.
Minimal or no response	Ongoing severe hemorrhage with >40% blood volume lost	Continue aggressive fluid and blood product replacements.

obtained quickly. Aggressive volume resuscitation should be instituted immediately, because this intervention can be lifesaving in patients with ongoing bleeding and hemodynamic instability. Either normal saline or lactated Ringer's solution is the preferred fluid for aggressive resuscitation. Isotonic electrolyte solutions provide transient intravascular volume expansion. Monitoring of changes in blood pressure, heart rate, and pulse pressure can help the clinician to determine the amount of blood loss, particularly in cases in which bleeding is internal (Table 134.2).

Initiation of transfusion therapy should be undertaken in the setting of ongoing blood loss. In the setting of PPH, hemoglobin and hematocrit will not reflect blood loss. Vital signs may also be difficult to follow, as maternal vital signs may lag behind actual loss. In patients with ongoing blood loss of 1500 mL or more, preparation should be made for transfusion. The use of tranexamic acid (TXA) should be considered. In a large, randomized trial (WOMAN) 1 gram of TXA was noted to reduce the risk of maternal mortality rates. The data suggest that for every 15-minute delay in treatment, there was a decrease in survival by 10%.[37] When given after 3 hours, there was no change in maternal mortality. The dose may be repeated in 30 minutes or if hemorrhage recurs within 24 hours. The use of TXA did not increase the risk of thrombosis. It is the opinion of the author that TXA should be started when the need for transfusion is being considered. The use of prophylactic TXA has not been well established. Preliminary studies suggest that prophylactic application during cesarean section may reduce blood loss; however, RCTs are pending.[16]

Delay in replacing blood loss in pregnancy may lead to an increased risk of coagulopathy and multisystem organ failure. Most of the literature governing blood product replacement in pregnancy has been taken from the trauma literature. The current recommendation is for packed red blood cells and fresh frozen plasma in a 1:1 ratio.[17] In women with a consumptive coagulopathy, early administration of cryoprecipitate and fresh frozen plasma should be considered. A normal fibrinogen level in pregnancy is higher than in the nonpregnant patient; therefore coagulopathy should be suspected in patients with a fibrinogen less than 200 mg/dL.

BOX 134.4 Blood Product Replacement

Crossmatched blood.
Type-specific or "saline crossmatched" blood.
Compatible ABO and Rh blood types.
Administration of tranexamic acid (1 g) when there is a need for massive transfusion. May repeat in 30 minutes if needed.
Rh-negative blood is preferable if typed blood is not available.
Warm the blood, if possible, especially if the rate of infusion is >100 mL/min or if the total volume transfused is high; cold blood is associated with an increased incidence of arrhythmias and paradoxical hypotension.
Administer calcium if blood is transfused rapidly at >100 mL/min because of the binding of calcium by anticoagulants in banked blood.
Give fresh frozen plasma (FFP) and 10 units of packed red blood cell (PRBC) transfusions in a 1:1 ratio when possible.
Give 10–12 units of platelets if the platelet count decreases to $<50 \times 10^9$/L.
Cryoprecipitate can be given to replace fibrinogen in addition to the FFP.
Consider 60–120 μg/kg intravenous bolus injection of recombinant activated factor VII (rFVIIa).

As in trauma, emergent use of O Rh–negative blood should be available for use. Each hospital and unit should establish protocols based on the resources available.

Although cell salvage or autologous blood transfusion may be used in patients with anticipated hemorrhage (i.e., placenta accreta), the emergent nature of PPH often limits its use.[18] The previous concerns for amniotic fluid contamination are no longer an issue with new filtration techniques.

Recombinant activated factor VII (rFVIIa) has been recommended in cases of refractory PPH that has not responded to medical measures, including blood product administration.[19] Although supported by few and uncontrolled studies, the available data suggest a potential role of rFVIIa in the management of severe PPH before performing a definitive hysterectomy. A management protocol has been provided (Box 134.4).

SPECIFIC TREATMENT MEASURES

Oxytocic (uterotonic) drugs administered IV, intramuscularly, or intramyometrially are used to stimulate the uterus by producing rhythmic contractions and controlling the degree of hemorrhage. Dosing regimens for oxytocic drugs are listed in Table 134.3.

Oxytocin (Pitocin) remains first-line therapy for most obstetricians. Prophylactic oxytocin, given either before or after placental delivery, decreases the incidence of PPH up to 40%.[20] It is also used prophylactically after delivery of the fetus but before delivery of the placenta to decrease the duration of the third stage of labor and the amount of blood loss. In an RCT, the incidence of PPH was similar, regardless of whether oxytocin was given before or after placental delivery.[7] Additionally, the incidence of retained placenta was similar for patients treated with oxytocin before or after delivery of the placenta. Oxytocin should be used with caution in patients with hyperactive uterine contractions or hypertension, because the pressor effect of sympathomimetic drugs can increase if they are used with oxytocin.

Methylergonovine (Methergine) is now considered second-line therapy. It is a direct uterotonic agent that reduces uterine bleeding and shortens the third stage of labor. Hypertension is a relative contraindication for the use of Methergine. Carboprost tromethamine (Hemabate), a synthetic prostaglandin similar to prostaglandin $F_{2\alpha}$ but

TABLE 134.3 Dosing Regimens for Oxytocic Drugs

Drugs	Regimens
Oxytocin (Pitocin)	5-unit IV bolus
	Add 20–40 units oxytocin to 1 L of fluids
	10 units intramyometrially
Methylergonovine (Methergine)	0.2 mg IM every 2–4 h
Ergonovine maleate (Ergotrate)	100–125 μg IM or intramyometrially every 2–4 h
	200–250 μg IM
	Total dose 1.25 mg
Carboprost (Hemabate)	250 μg IM or intramyometrially every 15–90 min
	Total dose 2 mg
Misoprostol	800 μg PR or 800 μg of sublingual misoprostol

IM, Intramuscular; *IV,* intravenous; *PR,* per rectum.

with a longer duration, produces myometrial contractions that induce hemostasis at the placentation site, reducing postpartum bleeding. It is used in some centers as a second-line uterotonic agent. Asthma is a relative contraindication to the use of carboprost. Carboprost has been shown to be effective in decreasing PPH refractory to oxytocin and ergonovine. Misoprostol, prostaglandin E_1, causes uterine contractions, and rectal administration of this drug has been shown to be useful in refractory PPH. Although oxytocin is considered the standard of care for treating PPH, it is not always viable or available, particularly in resource-poor clinical settings, because of refrigeration requirements and the need for IV administration. In a large randomized prospective trial, the efficacy and acceptability of 800 μg of sublingual misoprostol were compared with 40 IU of IV oxytocin to control postpartum bleeding.[21] The primary endpoints were cessation of active bleeding within 20 minutes and additional blood loss of 300 mL or more after treatment. The findings suggested that sublingual misoprostol is a viable alternative to 40 IU of IV oxytocin for treatment of primary PPH after oxytocin prophylaxis during the third stage of labor. Misoprostol stopped bleeding as rapidly as oxytocin and with a similar quantity of additional blood loss.

The practice of uterine packing to control bleeding remains somewhat controversial. Although this practice had been abandoned for many years, it has recently resurged as an effective method for tamponade of bleeding from the uterus. Balloon occlusion catheters have been used in the treatment of PPH.[22] Recent data suggest that balloon tamponade is an effective method for controlling hemorrhage, and in 80% of cases, hysterectomy was averted. When a specific uterine balloon catheter is not available, placement of a Sengstaken-Blakemore tube or a large Foley catheter can also be used to control bleeding.[23]

If there is a suspicion of retained placenta, examination of the uterus is both diagnostic and therapeutic. The uterus must be explored digitally and retained placental fragments removed either manually or with instruments. Because this procedure can be difficult and quite painful, it may be necessary to use regional or general anesthesia to obtain optimal visualization and manipulation of the uterus. Administration of oxytocic drugs should continue during manual extraction of placental fragments. Administration of broad-spectrum antibiotics has been recommended whenever there is manipulation or instrumentation of the uterus.

Compression of the abdominal aorta against the vertebral column, which can be achieved by pressing a fist on the abdomen cephalad to the umbilicus, can be a lifesaving temporizing maneuver to control hemorrhage before surgery in the presence of fulminant bleeding with severe hemodynamic compromise. If there is persistent and significant bleeding despite the therapeutic measures described, consideration should be given to arteriography with selective arterial embolization. This procedure requires the expertise of an interventional radiologist and may not be readily available in many hospitals. Successful embolization of the bleeding sites can be accomplished, obviating the need for surgical intervention.[24] In addition, fertility can be preserved with this procedure.[25] Prophylactic placement of embolectomy catheters in patients at high risk for PPH to minimize the procedural delay in the presence of active bleeding has also been used in some centers. If embolization is unsuccessful, balloon catheter occlusion of the hypogastric and iliac arteries has been successfully performed as a temporizing measure before surgery.[26–28] Complications are minimal, and postprocedural fever appears to be the most common complication of the procedure.

SURGICAL THERAPY

Surgical therapy is reserved for cases not amenable to medical therapy. Patients with ongoing hemorrhage despite aggressive medical therapy are candidates for operation. Surgery is the treatment of choice for uterine rupture. Lacerations, if visible, are directly repaired and oversewn. Lacerations high in the vaginal vault or in the cervix may require operative repair, primarily for improved visualization of the lesions. Hematomas of the lower genital tract are incised and drained. Arterial embolization of vaginal and vulvar lesions has been used. Hematomas of the broad ligament and in the retroperitoneal space are often managed conservatively if there is only minimal further expansion of the hematoma, but surgical exploration or embolization is mandated if additional significant bleeding occurs. Radiographic imaging with computed tomography, magnetic resonance imaging, and/or ultrasonography is a useful adjunct to monitor the expansion of these hematomas.

Ligation of the uterine, ovarian, or internal iliac (hypogastric) arteries can be performed. The uterine arteries provide 90% of uterine blood flow. Ligation of these arteries can often control bleeding with success rates of up to 92% and a complication rate of 1%.[29] If hemostasis is not achieved with uterine artery ligation, the ovarian and internal iliac arteries can be ligated as well. Ligation of the internal iliac arteries is technically more difficult, and success rates range from 40% to 100%.[29,30] Ligation of the internal iliac arteries usually is done only if ligation of the uterine and ovarian arteries has proved unsuccessful in halting bleeding.

Uterine compression sutures running through the full thickness of both uterine walls (posterior and anterior) have recently been described for the surgical management of atonic PPH.[31–33] The different uterine suture techniques have proved to be valuable and safe alternatives to hysterectomy in the control of massive PPH. In contrast, hysterectomy remains the definitive surgical therapy to control bleeding. Hysterectomy is required if bleeding continues despite ligation of the internal iliac arteries. Subtotal or total hysterectomy is curative in PPH. In cases of uterine rupture, it is the only surgical option, and nonsurgical modalities are only temporizing measures until the patient can be brought to the operating room. In developed countries, the incidence of postpartum emergent hysterectomy is approximately 1 in 2000 deliveries. Rossi and colleagues reviewed 24 articles that included 981 cases of emergency postpartum hysterectomy. They found women at highest risk of emergency hysterectomy are those who are multiparous, who had a cesarean delivery in either a previous or the present pregnancy, or who had abnormal placentation.[34]

COMPLICATIONS

Serious morbidity may follow PPH. Complications from postpartum bleeding include hematologic abnormalities such as DIC and dilutional coagulopathy from massive fluid resuscitation and/or massive transfusion (more than 10 units of packed red blood cells). Dilutional coagulopathy occurs when more than 80% of the original blood volume has been replaced. Life-threatening complications of hemorrhagic shock, including renal failure and liver failure, acute respiratory distress syndrome (ARDS), and pituitary necrosis (Sheehan syndrome), can occur. Sheehan syndrome can result from severe PPH that causes permanent hypopituitarism from avascular necrosis of the pituitary gland.[35]

PROGNOSIS

The prognosis of PPH depends on many factors, some of which are directly related to prompt diagnosis and treatment. The cause of bleeding, the duration of bleeding, and the extent of bleeding all affect the likelihood of a good outcome.

KEY POINTS

- PPH is defined as excessive bleeding after a vaginal or cesarean delivery that can be associated with hemodynamic instability if the bleeding is severe.
- Every center that performs obstetric care should have a protocol in place to manage patients with obstetric hemorrhage.
- The usual signs of tachycardia and hypotension associated with severe bleeding may not manifest early because of the relative hypervolemic state of pregnancy.
- Occult bleeding occurs most frequently with retained placental fragments; uterine atony; and concealed hematomas in the pelvis, perineum, or retroperitoneal space.
- Many women have predisposing factors leading to the development of PPH. Ongoing evaluation of the patient in the antepartum, intrapartum, and postpartum period is essential for risk identification.
- The most frequent cause of PPH is uterine atony, which occurs in 1 of every 20 deliveries. Risk factors for uterine atony include overdistention of the uterus, retained placenta, uterine muscle fatigue, and use of halogenated anesthetic agents.
- DIC is associated with placental abruption, the HELLP syndrome, acute fatty liver of pregnancy, intrauterine fetal death, sepsis, and amniotic fluid embolism.
- The early use of TXA has been shown to reduce maternal morbidity and mortality.
- Aggressive resuscitation leads to improved outcomes. Transfusion should be considered early. Current recommendations suggest 1:1 placement of red blood cells to plasma to prevent consumptive coagulopathy.
- Placenta accreta spectrum, defined as abnormal invasion of the placenta into the uterine wall, is associated with significant maternal morbidity and mortality. Optimal management involves a standardized approach with a comprehensive multidisciplinary care team accustomed to managing this condition.

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Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State

Jan Gunst and Greet Van den Berghe

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are endocrine emergencies occurring in diabetes patients. Both conditions require prompt, adequate treatment to avoid mortality. In patients with known diabetes mellitus, both conditions are most commonly triggered by noncompliance with diabetes treatment or infection. Nevertheless, any condition that induces severe insulin resistance and elevated counterregulatory hormones may trigger DKA or HHS, including severe trauma, myocardial infarction, and stroke. DKA and HHS may be the presenting syndrome of previously unknown or new-onset diabetes.[1,2]

PATHOPHYSIOLOGY

DKA and HHS are caused by an absolute or relative, respectively, insulin deficiency in the presence of elevated counterregulatory hormones (glucagon, cortisol, growth hormone, and catecholamines) (Fig. 135.1).[2] This constellation leads to increased hepatic gluconeogenesis and glycogenolysis and reduced peripheral glucose utilization in insulin-dependent tissues. The resultant hyperglycemia induces glycosuria once above the renal threshold, leading to osmotic diuresis and significant losses of water and electrolytes, in particular potassium and phosphate. In cases of (nearly) absolute insulin deficiency or very severe insulin resistance with substantially elevated counterregulatory hormones, lipolysis is activated, and free fatty acids are oxidized to ketone bodies in the liver. Ketones by themselves may aggravate osmotic diuresis, and accumulation of ketone bodies induces ketoacidosis. In patients with residual insulin effect, hepatic ketogenesis is suppressed. As a result, hyperglycemia and associated fluid and electrolyte losses further aggravate, eventually leading to a hyperosmolar hyperglycemic state, characterized by severe dehydration and alterations in mental state. As DKA can only develop in cases of minimal insulin effect, it mainly occurs in patients with type 1 diabetes, whereas HHS develops in patients with type 2 diabetes. DKA usually develops rapidly (within 24 hours), whereas HHS develops more insidiously over days.[2]

In the vast majority of cases, DKA patients present with severe hyperglycemia (>200–250 mg/dL [11.1–13.9 mmol/L]).[2] However, some diabetes patients at risk—taking sodium-glucose co-transporter 2 (SGLT2) inhibitors, pregnancy, excessive alcohol intake, prolonged fasting, chronic liver disease—may develop ketoacidosis in the absence of elevated blood glucose concentrations.[3] Several pathophysiologic mechanisms may contribute to the so-called "euglycemic DKA" or "DKA with lower-than-anticipated glucose levels," including increased urinary glucose losses, glucose uptake by the fetus, and insufficient gluconeogenesis because of lack of substrate or liver disease.[3]

DIAGNOSIS

In most cases, the diagnosis of a hyperglycemic emergency is obvious after taking a history and performing a clinical examination and is confirmed by laboratory examination (Table 135.1). Apart from diagnosing DKA/HHS, the precipitating event also should be sought, which often needs additional diagnostic tests.[2]

Clinical Features

Patients with DKA/HHS present with polyuria and clinical signs of volume depletion and weight loss, which are accompanied by polydipsia in alert patients.[2] Nausea, vomiting, and abdominal pain frequently occur in DKA patients but not in HHS patients.[2,4] DKA patients usually present with Kussmaul respiration because of metabolic acidosis, with a fruity breath scent resulting from exhaled acetone.[5] Patients with HHS and severe DKA typically have decreased consciousness secondary to the pronounced metabolic alterations and volume depletion. Focal neurologic deficits and seizures may also occur in HHS.[5]

Key Diagnostic Criteria

DKA patients usually present with the classic triad of severe hyperglycemia (the "D" in DKA), ketosis ("K"), and metabolic acidosis ("A"). The key diagnostic criterion in DKA is a significant elevation in circulating ketone concentrations.[6]

Three ketones are produced in DKA: acetoacetate, a ketoacid produced by the liver; beta-hydroxybutyrate, a hydroxyacid formed by reduction of acetoacetate; and acetone, a true ketone that is formed by decarboxylation of acetoacetate and that is exhaled.[6] Increased ketogenesis can be confirmed by measuring increased circulating ketone concentrations or by detecting ketonuria. The preferred diagnostic test is the direct measurement of blood beta-hydroxybutyrate, however, for several reasons.[6] First, beta-hydroxybutyrate is the most abundant circulating ketone in DKA, exceeding values of 3 mmol/L (31 mg/dL). Second, the alternative test, the nitroprusside test, which semiquantitatively detects acetoacetate in blood or urine, may yield false-positive and false-negative results. Finally, acetoacetate testing may not be reliable to monitor therapy during DKA. Indeed, because beta-hydroxybutyrate is converted into acetoacetate during treatment to be excreted in the urine, rise in acetoacetate concentrations may falsely give the impression of insufficient treatment response.[6]

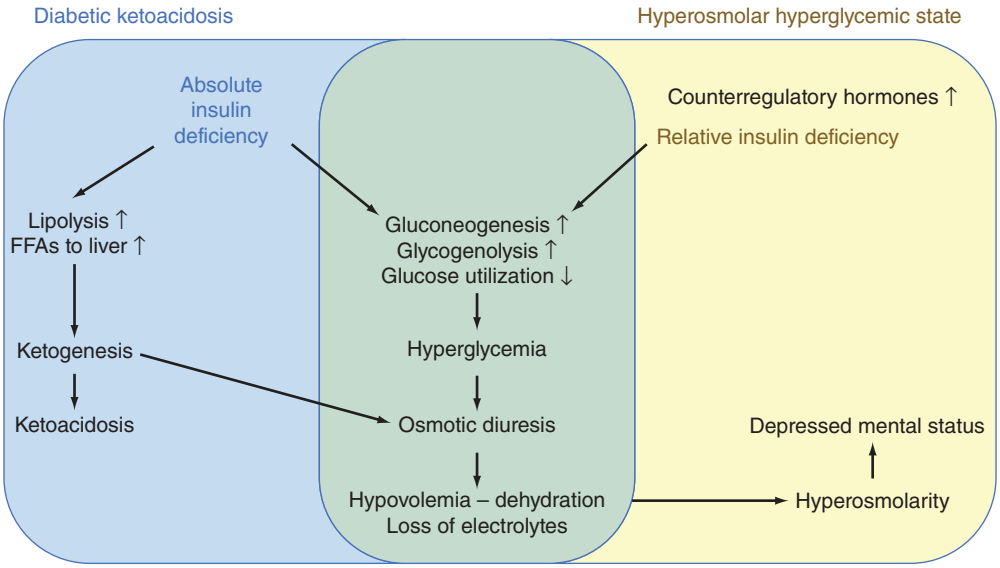

Fig. 135.1 Pathophysiology of Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State. Insulin deficiency, either absolute or relative, and a concomitant increase in counterregulatory hormones (glucagon, growth hormone, cortisol, and catecholamines) stimulate gluconeogenesis and glycogenolysis and attenuate glucose utilization. The ensuing hyperglycemia induces osmotic diuresis, leading to large fluid and electrolyte losses. When insulin deficiency is absolute, lipolysis is activated and free fatty acids (*FFAs*) are used for hepatic ketogenesis, which aggravates osmotic diuresis. The resultant clinical picture is diabetic ketoacidosis, with the classic triad of hyperglycemia, ketonemia, and metabolic acidosis. When residual insulin effect is present, ketogenesis is inhibited, allowing a further increase in blood glucose concentrations and associated fluid and electrolyte losses. The resultant hyperosmolarity is accompanied by profound alterations in mental status, characteristic of hyperosmolar hyperglycemic state.

The traditional blood glucose cutoff of DKA is 200–250 mg/dL (11.1–13.9 mmol/L), and in most cases, admission blood glucose is even considerably higher.[5,7] However, in patients with additional risk factors—SGLT2 inhibitors, pregnancy, excessive alcohol intake, prolonged fasting, chronic liver disease—DKA may develop without severe hyperglycemia.[3] Moreover, pseudonormoglycemia may develop in cases of severe hyperlipidemia.[5]

The third diagnostic criterion of DKA is metabolic acidosis (pH <7.3 and HCO_3^- <18 mmol/L) with elevated anion gap, explained by the accumulation of ketones. Metabolic acidosis can be classified as mild (pH 7.25–7.3 and HCO_3^- 15–18 mmol/L), moderate (pH 7.0–7.24 and HCO_3^- 10–14.9 mmol/L), or severe (pH <7.0 and HCO_3^- <10 mmol/L).[5]

HHS is characterized by more severe hyperglycemia (>540–600 mg/dL [30–33.3 mmol/L] and often >1000 mg/dL [55.6 mmol/L]) and hyperosmolarity (serum osmolality >320 mmol/kg) in the absence of significantly elevated ketone concentrations and metabolic acidosis.[5,8] However, mild ketonemia may develop. The laboratory alterations in HHS are typically accompanied by severely impaired mental status (stupor, coma).[2]

Other Laboratory Abnormalities

DKA and HHS patients may have secondary organ damage because of volume depletion, including acute kidney injury. Acute kidney injury is usually more pronounced in HHS patients, because of a more protracted time course before admission and more severe volume depletion.[5] Although patients have a potassium and phosphate deficit, admission serum potassium and phosphate are often normal or elevated as a result of insulin deficiency, hypertonicity, and acidemia. Severe hyperlipidemia caused by lipolysis may lead to pseudohyponatremia and pseudonormoglycemia in DKA. Because infection is a common trigger for DKA and HHS, patients often have increased inflammatory parameters upon admission. C-peptide is low in DKA patients because of absolute insulin deficiency, whereas C-peptide is usually in the normal range in HHS patients.[5]

TREATMENT

Initial treatment consists of fluid resuscitation, insulin therapy, potassium supplementation, and treatment of the precipitating cause (Box 135.1). Other treatments, including bicarbonate and phosphate substitution, are controversial. After resolution of ketoacidosis and HHS, insulin therapy should be switched to maintenance therapy.[5,7,8]

Fluid Resuscitation

DKA and HHS patients have profound volume depletion, with an approximate water deficit of 100 mL/kg and 100–200 mL/kg body weight, respectively.[1] Fluid resuscitation is essential to restore volume homeostasis and tissue perfusion. Moreover, it will directly reduce blood glucose by dilution and reducing counterregulatory hormones.[1] Restoration of peripheral perfusion is also a prerequisite to obtain sufficient perfusion of tissues with insulin-dependent glucose uptake (skeletal muscle and adipose tissue).

Isotonic saline has been recommended as initial resuscitation fluid, although infusion of large volumes may induce hyperchloremic metabolic acidosis.[5,7,8] No large randomized controlled trial has investigated whether balanced crystalloids are clinically superior in this patient population, however.[9] Guidelines recommend to administer 1000–1500 mL normal saline during the first hour, after which the fluid infusion rate is titrated according to hemodynamics and readouts of peripheral perfusion (urinary output, skin perfusion, etc.).[5,7,8] In general, fluid rates of 250–500 mL are recommended after the first

TABLE 135.1 Clinical and Diagnostic Features in Patients With Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State

Diabetic Ketoacidosis	Hyperosmolar Hyperglycemic State
Precipitant Factors	
Noncompliance with insulin treatment	Noncompliance with treatment
Infection	Infection
New-onset (type 1) diabetes	New-onset (type 2) diabetes
Other	Other (corticosteroids, excess diuretics, etc.)
Course of Illness	
Rapid (in general <24 hours)	Insidious (days)
Clinical Findings	
Polyuria, polydipsia, dehydration, hypovolemia	Polyuria, dehydration, hypovolemia
Nausea, vomiting, abdominal pain	Depressed mental status up to coma
Fruity odor of breath, Kussmaul respiration	
Diagnostic Laboratory Criteria	
Blood glucose >200–250 mg/dL*	Blood glucose >540–600 mg/dL*
AND elevated ketones in blood or urine	AND serum osmolality >320 mmol/kg
AND metabolic acidosis	NO significant ketosis
(pH<7.3 and HCO_3^- <18 mmol/L)	NO metabolic acidosis
Concomitant Laboratory Abnormalities	
Elevated anion gap	Variable anion gap
Low C-peptide	Normal C-peptide
	Acute kidney injury

*For conversion of blood glucose concentrations in mg/dL to mmol/L, divide by 18. American Diabetes Association guidelines recommend the highest reported blood glucose cutoff for both diabetic ketoacidosis and hyperosmolar hyperglycemic state, UK guidelines the lowest.[5,7,8] In patients at risk—taking sodium-glucose co-transporter 2 (SGLT2) inhibitors, pregnancy, excessive alcohol use, decreased caloric intake, chronic liver disease—ketoacidosis may develop in the absence of elevated blood glucose concentrations (euglycemic diabetic ketoacidosis).[3]

BOX 135.1 Protocol for Initial Management of Patients Admitted With Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State

Fluids
- Administer 1000–1500 mL 0.9% NaCl during the first hour
- After first hour: titrate infusion rate according to hemodynamics and adjust the type of fluid depending on electrolyte status and blood glucose concentration:
  - In general 250–500 mL/h
  - Normal or high corrected serum Na concentration[1]: 0.45% NaCl
  - Low corrected serum Na concentration: 0.9% NaCl
  - Add dextrose 5% to IV fluid when blood glucose <200–250 mg/dL[2] (DKA) or 250–300 mg/dL (HHS)

Insulin
- Initiate 0.1 U/kg/h through continuous IV infusion (hold in case of hypokalemia)
- Measure blood glucose every 1–2 hours
- Increase insulin by 1 U/h if blood glucose does not decrease by at least 50 mg/dL/h
- When blood glucose <200–250 mg/dL (DKA) or 250–300 mg/dL (HHS): reduce insulin to 0.02–0.05 U/kg/h IV and add dextrose to IV fluid
- Maintain blood glucose between 150 and 200 mg/dL until resolution of ketoacidosis (DKA) or between 200 and 300 mg/dL until HHS has resolved

Potassium
- Measure potassium and other electrolytes every 2–4 hours: universal potassium deficit – target K^+ = 4–5 mmol/L
- If K^+ <3.3 mmol/L: hold insulin and administer 20–40 mEq/h until K^+ >3.3 mmol/L
- If 3.3 mmol/L < K^+ <5.2 mmol/L: administer 20–40 mEq in each liter of IV fluid
- If K^+ >5.2 mmol/L: no supplementation, check after 2 hours

Identify and Treat Precipitating Cause

DKA, Diabetic ketoacidosis; *HHS,* hyperosmolar hyperglycemic state; *IV,* intravenous.
[1]For each 100 mg/dL glucose above 100 mg/dL, add 1.6 mmol/L Na to obtain a corrected serum Na value.
[2]For conversion of blood glucose concentrations in mg/dL to mmol/L, divide by 18.

hour. At the same time, the fluid type may need to be adapted according to the electrolyte status and the blood glucose concentration.[5,7,8] When the corrected serum sodium concentration is normal or high, it is recommended to switch to 0.45% sodium chloride. In addition, when blood glucose falls below 200–250 mg/dL (11.1–13.9 mmol/L) in DKA or 250–300 mg/dL (13.9–16.7 mmol/L) in HHS, dextrose 5% should be added to the intravenous fluid to allow continued insulin treatment to suppress ketogenesis while avoiding hypoglycemia.[5,7,8]

Insulin Therapy

A second mainstay of treatment is insulin therapy.[2] Insulin is administered through continuous intravenous infusion at a rate of 0.1 U/kg/h after eventual correction of hypokalemia. An initial bolus of insulin is not needed, because fluid resuscitation by itself will reduce blood glucose, as described earlier.[1] Blood glucose should be measured every 1–2 hours, and insulin is adjusted if needed. The goal is to lower blood glucose by 50–100 mg/dL per hour (2.8–5.6 mmol/L/h).[2] The insulin dose is decreased to 0.02–0.05 U/kg/h and dextrose 5% is added to the intravenous fluid when blood glucose falls below 200–250 mg/dL (11.1–13.9 mmol/L) in DKA or 250–300 mg/dL (13.9–16.7 mmol/L) in HHS to further suppress ketogenesis with insulin while preventing hypoglycemia.[5,7,8] Blood glucose concentrations are kept between 150 and 200 mg/dL (8.3 and 11.1 mmol/L) until resolution of ketoacidosis or between 200 and 300 mg/dL (11.1 and 16.7 mmol/L) until HHS has resolved.[5,7,8]

Most cases of DKA are treated with intravenous insulin. In mild cases, subcutaneous insulin may be considered as an alternative.[6] Because these patients are generally not admitted to an intensive care unit, this option falls beyond the scope of this chapter.

Potassium Supplementation

Although serum potassium upon admission is often normal or elevated, DKA and HHS patients have a potassium deficit, usually in the range of 3–5 mEq/kg.[1] Because treatment of DKA/HHS will lower

potassium levels by an intracellular shift induced by insulin, correcting acidosis and restoring volume homeostasis, monitoring of serum potassium concentrations and adequate supplementation are crucial. Guidelines recommend adding 20–40 mEq per liter of intravenous fluid unless the patient has hyperkalemia.[5,7,8] When the patient has hypokalemia, it is recommended to hold insulin therapy until serum potassium levels are above 3.3 mmol/L.

Treatment of the Precipitating Cause

Besides supportive measures, treatment of the precipitating cause of DKA/HHS is crucial. A variety of conditions may precipitate DKA or HHS. In patients with previously known diabetes, nonadherence to antidiabetic therapy and infection are predominant causes.[2] Hence, treatment of the DKA/HHS patient often involves treatment of a precipitating infection.

Other Initial Treatments

Bicarbonate treatment in DKA is controversial. A systematic review including three randomized controlled trials did not identify clinical benefit.[10] Moreover, bicarbonate treatment increases the risk of hypokalemia and may paradoxically worsen intracellular acidosis.[1,5] Guidelines recommend to only consider bicarbonate in patients with severe acidosis (pH <7.0).[5,7]

Likewise, phosphate supplementation in DKA and HHS patients is controversial, despite the universal phosphate depletion (on average, 1.0 mmol/kg body weight).[5] Randomized controlled trials have not shown benefit of routine phosphate supplementation on clinical outcome, although these trials may have been underpowered to detect a clinical benefit.[11–13] Phosphate concentrations generally recover after resuming oral intake, and intravenous phosphate supplementation may precipitate hypocalcemia, especially when administered at high doses.[9] Therefore routine supplementation to DKA patients has been discouraged.[5] Nevertheless, when patients have profound and/or potentially symptomatic hypophosphatemia, as expressed by severe muscle weakness, supplementation may be indicated.[5]

As DKA and HHS are procoagulant states, patients are at risk for venous thrombosis. Therefore prophylactic administration of low-molecular-weight heparin is indicated.[8]

Switch to Maintenance Therapy

Intravenous insulin should be continued until DKA and HHS have resolved. Resolution of DKA has been defined as blood glucose concentrations below 200 mg/dL (11.1 mmol/L), plus two of the following: pH >7.3, bicarbonate ≥ 15 mmol/L, and/or anion gap ≤ 12 mmol/L. Resolution of HHS has been defined as normal serum osmolality and regained mental status.[2]

After resolution of DKA/HHS, maintenance antidiabetic therapy should be initiated in consultation with an endocrinologist. In view of the short half-life of intravenous insulin, the intravenous insulin infusion should be continued for at least 2 hours to prevent rebound hyperglycemia or ketoacidosis. In patients with previously unknown diabetes, insulin can be initiated at a total dose of 0.5–0.7 U/kg/day.[1]

COMPLICATIONS AND OUTCOME

Before the discovery of insulin, DKA was a lethal condition. In current intensive care, mortality has declined to less than 1%, however.[14] In contrast, mortality of HHS is estimated at 10%–20%.[15,16] The higher mortality of HHS may be related to the higher risk profile of these patients, who are generally older and have more comorbidities.[2] Nevertheless, the insidious time course of HHS, with more severe dehydration and secondary organ damage, may also contribute to the higher mortality risk.

Common complications of DKA/HHS treatment include hypokalemia, hypoglycemia, and hyperchloremic metabolic acidosis.[2] Indeed, insulin treatment induces an intracellular shift of potassium in a condition in which total potassium stores are already low. Therefore, insulin treatment should be temporarily withheld if hypokalemia develops. A considerable number of patients may develop transient hyperchloremic metabolic acidosis after the infusion of large amounts of normal saline. Although this condition can potentially be prevented by infusion of balanced crystalloids,[9] no large randomized controlled trial has compared normal saline with balanced crystalloids in DKA/HHS, and current guidelines still recommend normal saline.[5,7,8]

The most feared complication of DKA is cerebral edema. This condition most often occurs in DKA episodes in children, with a prevalence of 0.3%–1%.[17,18] In adults and patients with HHS, the condition is very rare. Once cerebral edema develops, mortality rates are high (20%–40%), and survivors are at risk for long-term sequelae. Clinical symptoms include new or worsening headache, gradually decreased consciousness, irritability, and seizures.[5] When cerebral edema is suspected, prompt treatment with mannitol (0.5–1.0 g/kg) has been recommended before computed tomography is obtained.[2] Traditionally, development of cerebral edema has been attributed to rapid normalization of hyperosmolarity by fluid therapy and blood glucose lowering.[5] Therefore, gradual correction of hyperglycemia and fluid deficits has been recommended, especially in critically ill children. Nevertheless, more recent evidence has questioned the role of fluid therapy in mediating the risk of cerebral edema. Indeed, a large randomized controlled trial with 2-by-2 factorial design found no impact of fluid administration rate or the sodium chloride content on the neurologic outcome of children admitted with DKA ($n = 1389$).[19] This may suggest that the risk of cerebral edema is possibly related to the initial severity of DKA, rather than to DKA treatment. Potential mediators are hypocapnia-induced cerebral vasoconstriction, hypovolemic shock–induced neurologic damage, inflammatory damage to the brain, and damage caused by intracellular acidosis.[18,20–22]

PREVENTION OF RECURRENT EPISODES

After initial treatment, patients should be instructed on how to prevent recurrent DKA/HHS.[1] This includes instructions on appropriate antidiabetic therapy and on adaptations of treatment in conditions of metabolic stress.

Concern has arisen regarding the potentially increased incidence of euglycemic DKA with the introduction of SGLT2 inhibitors.[23,24] However, the overall incidence of DKA in patients taking such drugs remains low, and both professional societies and regulatory authorities have concluded a favorable risk-benefit profile.[25] Nevertheless, to attenuate the risk of DKA, patients taking SGLT2 inhibitors should avoid periods of prolonged starvation, ketogenic diets, and excessive alcohol intake, and SGLT2 inhibitors should be withheld in hospitalized patients who are fasted.[25]

CONCLUSION

DKA and HHS are hyperglycemic emergencies that require prompt treatment by intravenous fluids, insulin infusion, and potassium supplementation. In addition, the precipitating event should be sought and treated. In contemporary intensive care, DKA mortality is relatively low, whereas mortality of HHS remains elevated, which may partially be related to the higher intrinsic risk profile of these patients.

KEY POINTS

- DKA and HHS are endocrine emergencies that are caused by an absolute (DKA) or relative (HHS) insulin deficiency in the presence of elevated counterregulatory hormones.
- In patients with known diabetes, the most common precipitants of DKA and HHS are noncompliance with diabetic treatment and infection.
- Key diagnostic criteria for DKA are the classic triad of severe hyperglycemia (D), elevated blood ketone concentrations (K), and metabolic acidosis (A).
- In patients at risk—taking SGLT2 inhibitors, pregnancy, excessive alcohol intake, prolonged fasting, chronic liver disease—ketoacidosis may develop in the absence of elevated blood glucose concentrations (euglycemic diabetic ketoacidosis).
- Key diagnostic criteria for HHS are severe hyperglycemia and hyperosmolarity and changes in mental state.
- Both DKA and HHS are characterized by large fluid and potassium deficits, although serum potassium concentrations may be normal or high upon admission.
- The initial treatment consists of fluid resuscitation, insulin therapy, potassium supplementation, and treatment of the precipitating cause.
- After initial glucose lowering with insulin therapy and fluid resuscitation, blood glucose should be maintained at 150–200 mg/dL (DKA) or 200–300 mg/dL (HHS) with insulin treatment until ketoacidosis or HHS has resolved.
- The most severe complication of DKA is cerebral edema, which is most prevalent in children and which requires prompt treatment with mannitol.
- In contemporary intensive care, mortality of DKA is <1%, whereas mortality of HHS remains at approximately 10%–20%, which is at least partially related to a higher risk profile of HHS patients (older age, more comorbidities).

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Adrenal Insufficiency

Herwig Gerlach

During stress response, the central nervous system (CNS) induces activation of both the sympathoadrenergic system (by release of catecholamines) and the hypothalamic-pituitary-adrenal (HPA) axis (by release of steroid hormones, glucocorticoids [GCs], and mineralocorticoids), with the target of maintaining homeostasis by influencing metabolic, cardiovascular, immunologic, and endocrine functions. In this context, the adrenal gland plays a key role, combining the location for synthesis and expression of catecholamines, GCs, androgenic hormones, and factors of the renin-angiotensin-aldosterone (RAA) system. Acute and chronic inflammatory diseases include stimulation of the HPA axis by the immune system, thereby leading to morphologic and functional changes, especially of the adrenal cortex. This phenomenon has been described for acute infectious diseases and for sepsis and septic shock.

Over 60 years ago, the seminal observation was made that administering an adrenal cortical steroid extract to a patient with progressive, active rheumatoid arthritis slowed progression of the disease. This soon led to the development of synthetic adrenal cortical steroids, which gained a remarkable reputation in the treatment of a wide range of inflammatory and autoimmune disorders. However, it soon became apparent that this efficacy did not come without a cost in terms of potentially serious adverse effects. In patients with sepsis and septic shock, negative results of trials with high doses of GCs evoked skepticism over the years. Meanwhile, several randomized trials revealed contradictory results with low doses of corticosteroids in patients with septic shock. Hence, there is still controversy about which patients profit best from this therapy and how to define and evaluate adrenal gland disorders.[1–4]

ANATOMY OF THE ADRENAL GLAND

The two paired adrenal glands are located in the retroperitoneal soft tissue near the top of each kidney. In neonates, the adrenal glands are relatively large (approximately one-third of the kidney's size) compared with other organs. In the postnatal period, the cortex portion shrinks, leading not only to a relatively but also an absolutely smaller size of the organ. In adults, each adrenal gland weighs 4–5 g, has a flat form with a sagittal diameter of less than 1 cm, a transverse diameter of 3 cm, and a craniocaudal diameter of 4–5 cm. The right gland has a triangle/pyramid-like shape, whereas the left gland has a half-moon shape.

Circulatory supply to the adrenals, with a flow rate of about 5 mL per minute, is maintained by up to 50 arterial branches from the aorta, renal arteries, and inferior phrenic arteries for each gland. Blood flow is directed from the capsule into the subcapsular arteriolar plexus through the cortex toward the medulla, where a single vein drains the blood entering the vena cava or the renal vein. Direct blood supply to the medulla is maintained by medullary arteries.

The adrenal cortex receives afferent and efferent innervation. Direct contact of nerve terminals with adrenocortical cells has been suggested, and chemoreceptors and baroreceptors present in the adrenal cortex infer efferent innervation. Diurnal variation in cortisol secretion and compensatory adrenal hypertrophy are influenced by adrenal innervation. Splanchnic nerve innervation has an effect in regulating adrenal steroid release. The adrenal medulla secretes the catecholamines epinephrine and norepinephrine, both of which affect blood pressure, heart rate, sweating, and other activities regulated by the sympathetic nervous system. The adrenal cortex is divided into three layers: (1) the zona glomerulosa, just under the capsule; (2) the zona fasciculata, the middle layer; and (3) the zona reticularis, the innermost, netlike patterned area with reticular veins draining into medullary capillaries. The zona glomerulosa exclusively produces the mineralocorticoid aldosterone; the zonae fasciculata and reticularis produce GCs and androgens.[5]

PHYSIOLOGY OF THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

The adrenal glands are part of a complex system that produces interacting hormones to maintain physiologic integrity, especially during the stress response.[6,7] This system, the *HPA axis,* includes the hypothalamic region that produces corticotropin-releasing hormone (CRH), which stimulates the pituitary gland. The pituitary gland is composed of two major structures: the adenohypophysis (anterior pituitary) and neurohypophysis (posterior pituitary). The anterior pituitary is responsible for the secretion of corticotropin (adrenocorticotropic hormone [ACTH]), thyroid-stimulating hormone (TSH), growth hormone (GH), beta-lipotropin, endorphins, prolactin, luteinizing hormone (LH), and follicle-stimulating hormone (FSH). The posterior pituitary secretes vasopressin (antidiuretic hormone [ADH]) and oxytocin. Corticotropin regulates the production of corticosteroids by the adrenal glands. Hypothalamic neurons receive input from many areas within the CNS; they integrate these inputs and initiate an output to the anterior pituitary via the median eminence. The median eminence secretes releasing hormones into a hypophyseal portal network of capillaries that connect the median eminence with the pituitary hormones.

The anterior pituitary gland secretes adrenocorticotropin (ACTH) under stimulation from hypothalamic CRH. ACTH, in turn, stimulates the synthesis and release of GCs, mineralocorticoids, and androgenic steroids from the adrenal gland. In terms of a feedback loop, ACTH release is inhibited by GCs, which act on both the pituitary corticotropic cells and hypothalamic neurons. ACTH is also released during stress, independent of the circulating serum cortisol level. CRH, vasopressin, and norepinephrine act synergistically to increase ACTH release during

stress. Endorphinergic pathways also play a role in ACTH regulation. Acute administration of morphine stimulates release of ACTH, whereas chronic administration blocks secretion of ACTH. ACTH and cortisol are secreted normally in a diurnal pattern, with the lowest concentrations between 10:00 PM and 2:00 AM and highest levels around 8:00 am. Samples obtained at different times can provide useful dynamic information regarding HPA function. Loss of diurnal rhythm may indicate hypothalamic dysfunction.

The HPA axis is stimulated not only by physical or psychic stress but also by peptides such as ADH and cytokines. Thus the HPA axis plays an important role during infections and immunologic disorders.[8,9] Via interaction with the RAA system regulating fluid and salt balance, synthesis of androgens (e.g., dehydroepiandrosterone) with a possible impact on immunomodulation, and the sympathoadrenergic system, the HPA axis is probably the most important organ of the stress response. Stimulation of the immune system by infections induces the release of proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, or IL-6. After a cascade, these cytokines stimulate both the hypothalamus and the anterior pituitary gland, which ultimately leads to the release of GCs. IL-6 is also able to induce a steroid release directly from the adrenal gland. The adequate increase of GC levels during inflammation is a crucial factor for an appropriate stress response. In acute infections, this release maintains metabolic and energy integrity. If the process is chronic, the HPA axis develops an adaptation, which induces typical clinical manifestations such as hypercatabolic states; hyperglycemia; and suppression of androgens, growth, and thyroid hormones. These changes, however, may increase the risk of secondary infections. Increased cortisol levels suppress higher regulatory levels of the HPA axis in terms of a negative feedback loop. Hence, after major surgery or during sepsis and septic shock, high cortisol and low ACTH levels are detectable.[10,11] Even the infusion of dexamethasone or CRH is not able to suppress increased cortisol levels in these patients.[12,13] Several investigations have demonstrated that adrenal cortisol synthesis in critically ill patients is not regulated by ACTH, but by paracrine pathways via endothelin, atrial natriuretic peptide, or cytokines such as IL-6.[14–16] IL-6 directly induces the adrenal cortex to release cortisol, which, in chronic courses, can worsen the prognosis.[17]

CELLULAR RESPONSE TO ADRENOCORTICAL HORMONES AND RELATED DRUGS

Cortisol, the major free circulating adrenocortical hormone, is a hydrophobic hormone and circulates in the bloodstream bound to protein. Cortisol-binding globulin (or transcortin)–protein complexes account for about 95% of circulating cortisol, but only the free form is biologically active with a plasma half-life of 60–120 minutes. Cortisol is metabolized by hydroxylation in the liver, and metabolites are excreted in the urine. Steroid hormones enter the cytoplasm of cells, where they combine with a receptor protein. Metabolic, immunologic, and hemodynamic responses to adrenocortical steroid hormones are regulated in a highly complex manner that includes transactivation, transcription, posttranscriptional/translational regulation, and nongenomic effects. The immediate nongenomic effects of steroid hormones are primarily attributed to mineralocorticoids (aldosterone), with rapid activation of the sodium-proton exchanger, increase in intracellular Ca^{++} levels, and activation of second messenger pathways.[18,19] A randomized trial in patients during cardiac catheterization revealed that within minutes after aldosterone injection, cardiac index and arterial pressure increased significantly for 10 minutes and returned to baseline thereafter.[20] Interestingly, the genomic effects of aldosterone seemed to be mediated by binding to GC receptors (GRs) and not to mineralocorticoid receptors.[21] There is evidence that GC, like cortisol, also modulates immune functions by rapid, nongenomic effects via nonspecific interactions with cellular membranes and specifically binding to membrane-bound GRs.[22] Nonspecific membrane effects have been demonstrated for inhibition of sodium and calcium cycling across plasma membranes by impairing Na^+/K^+-ATPase and Ca^{++}-ATPase. Moreover, the rapid activation of lipocortin-1 and inhibition of arachidonic acid release after GC were independent of GR translocation. Finally, high-sensitivity immunofluorescence staining revealed membrane-bound GRs on circulating B lymphocytes and monocytes.[22]

The multiple mechanisms by which GCs modulate cellular responses include mainly genomic pathways.[23–25] Nongenomic effects are thought to account for immediate immune effects of high doses of GC, whereas membrane-bound receptors probably mediate low-dose GC effects. The classic model is that GCs bind to the cytoplasmic ligand-regulated GC receptor alpha (GRα), which is an inactive multiprotein complex consisting of two heat shock proteins (hsp90) acting as molecular chaperones, in addition to other proteins (Fig. 136.1). Upon GC binding to GRα, a conformational change causes dissociation of hsp90, with subsequent nuclear translocation of GRα homodimers, binding of GRα to GC response elements (GREs) of DNA, and transcription of responsive genes (transactivation) such as lipocortin-1 and beta-2-adrenoreceptors. Alternatively, GRα may bind to negative GRE (nGRE) and repress transcription of genes (transrepression) such as pro-opiomelanocortin (POMC). More important, transrepression without direct binding of GRα to GRE by protein-protein interactions of GRα with transcription factors, nuclear factor kappa B (NF-κB), and AP-1 has been recognized as a key step by which GC suppresses inflammation.[26] In turn, synthesis of TNF-α, IL-1β, IL-2, IL-6, IL-8, inducible nitric oxide synthase (iNOS), cyclooxygenase (COX)-2, cell adhesion molecules, and growth factors is inhibited and apoptosis promoted.[27] In addition, NF-κB repression may be mediated by GC-induced up-regulation of the cytoplasmatic NF-κB inhibitor, IκBα (see Fig. 136.1), which prevents translocation of NF-κB.[28] Clinical investigations provide support for the presence of endogenous GC inadequacy in the control of inflammation and peripheral GC resistance.[29] With GC treatment, the intracellular relations between the NF-κB and GRα signaling pathways change from an initial NF-κB–driven and GRα-resistant state to a GRα-sensitive one. However, data are conflicting and probably do not explain the early (<2 hours) suppressive effects of GC, but may account for the longer-term dampening effect of GC on inflammatory processes.[23]

Besides transcriptional regulation, posttranscriptional, translational, or posttranslational processes have been described for GC-induced modulation of COX-2, TNF-α, GM-CSF, IL-1β, IL-6, IL-8, and interferon gamma (IFN-γ).[23] Furthermore, GCs act at multiple levels to regulate iNOS expression via (1) decreased iNOS gene transcription and messenger RNA (mRNA) stability; (2) reduced translation and increased degradation of the iNOS protein by the cysteine protease, calpain[30]; (3) limitation of the availability of the NOS cofactor, tetrahydrobiopterin; (4) reduced transmembranous transport and de novo synthesis of the NOS substrate, L-arginine; and (5) lipocortin-1–induced inhibition of iNOS.[31,32] Together, these complex mechanisms result in the ability of GC to inhibit inflammation and to stabilize hemodynamics. Finally, GRs have been found in nearly every nucleated cell in the body, and because each cell type has specific responses to GC, it follows that GCs have many effects in the body, equally true of endogenously produced GC hormones or exogenously administered GC medications. Both increase hepatic production of glucose and glycogen and decrease peripheral use of glucose. Steroids also affect fat and protein metabolism. They increase lipolysis both directly and

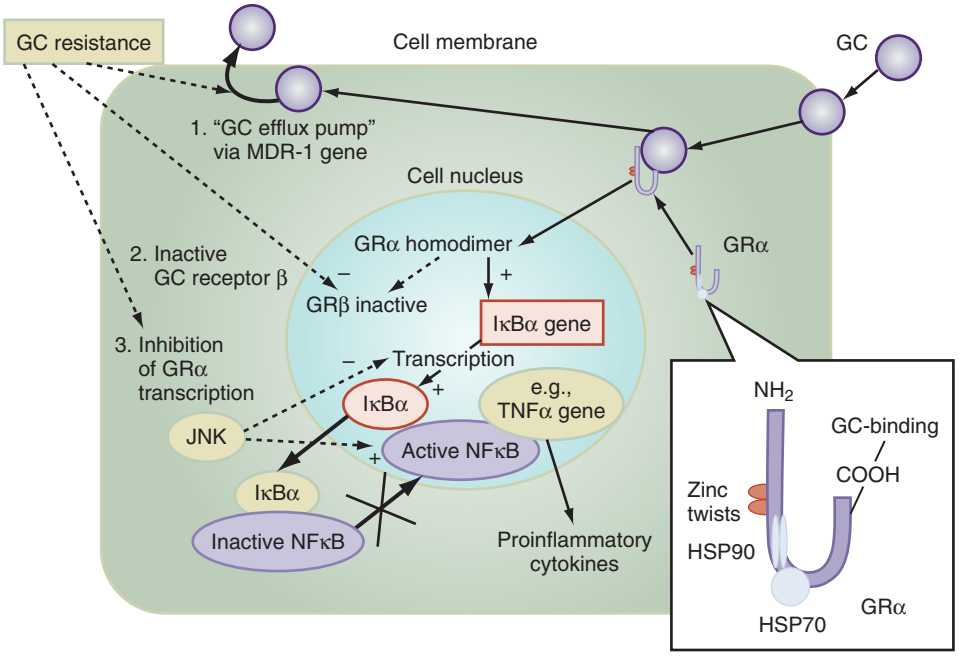

Fig. 136.1 Cellular mechanisms of glucocorticoid effects *(right)* and glucocorticoid resistance *(left).* After passive transport through the cell membrane, GCs bind to the intracellular GC receptor alpha (GRα), which is sequestered in the cytoplasm and bound to the HSP complex that comprises chaperone molecules HSP70 and HSP90. Binding of GC to GRα allows formation of a homodimer that is transported into the nucleus. GR-mediated transcription induces inhibitor kappa B alpha (IκBα), which binds to and inhibits nuclear factor kappa B (NF-κB). Thus GC inhibits the NF-κB–mediated synthesis of proinflammatory cytokines like tumor necrosis factor alpha (TNF-α). Impaired GC sensitivity (GC resistance) includes three major pathways *(dotted arrows)*: (1) decreased cytoplasmatic GC concentrations secondary to increased P-glycoprotein–mediated efflux of GC caused by overexpression of the MDR-1 gene; (2) increased expression of a truncated splice variant of the GR that is unable to transactivate GC-sensitive genes (GRβ); and (3) activation of proinflammatory mediators via upstream kinases (JNK), which can directly inhibit GR transcription activity. *GC,* Glucocorticoids; *GR,* glucocorticoid receptor; *HSP,* heat shock protein; *JNK,* c-Jun N-terminal kinase; *MDR-1,* multidrug resistance gene 1.

indirectly by elevating free fatty acid levels in the plasma and enhancing any tendency toward ketosis. GCs further stimulate peripheral protein metabolism, using the amino acid products as gluconeogenic precursors.

DEFINITIONS OF ADRENAL INSUFFICIENCY

The adrenal glands may stop functioning when the HPA axis fails to produce sufficient amounts of the appropriate hormones. *Primary adrenal insufficiency* is defined by the inability of the adrenal gland to produce steroid hormones even when the stimulus by the pituitary gland via corticotropin is adequate or increased. Primary adrenal insufficiency affects 4–6 out of 100,000 people. The disease can strike at any age, with a peak between 30 and 50 years, and affects males and females about equally. In 70% of cases, the cause is a primary destruction of the adrenal glands by an autoimmune reaction ("classical" Addison disease or autoimmune adrenalitis), with about 40% of patients having a history of associated endocrinopathies. Most adult patients have antibodies against the steroidogenic enzyme, 21-hydroxylase,[33] but their role in the pathogenesis of autoimmune adrenalitis is uncertain. In the other 30%, the adrenal glands are destroyed by cancer, amyloidosis, antiphospholipid syndrome, adrenomyeloneuropathy, acquired immunodeficiency syndrome (AIDS), infections (e.g., tuberculosis, cytomegaly, fungi), or other identifiable diseases (Box 136.1). In these cases, the typical morphologic changes of the adrenal cortex are atrophy, inflammation, and/or necrosis. In primary adrenal insufficiency, the whole adrenal cortex is involved, resulting in a deficiency of GCs, mineralocorticoids, and adrenal androgens.[34,35]

Secondary adrenal insufficiency is characterized by adrenal hypofunction caused by the lack of pituitary ACTH or hypothalamic CRH. Diseases of the anterior pituitary that can cause secondary adrenal insufficiency include neoplasms (e.g., craniopharyngiomas, adenomas), infarction (e.g., Sheehan syndrome, trauma), granulomatous disease (e.g., tuberculosis, sarcoidosis), hypophysectomy, and infection.[36] Causes also include hypothalamic dysfunction, such as after irradiation or surgical intervention (see Box 136.1). Because aldosterone secretion is more dependent on angiotensin II than on ACTH, aldosterone deficiency is not a problem in secondary adrenal insufficiency. Selective aldosterone deficiency can occur as a result of depressed renin secretion and angiotensin II formation.[34] Rarely, patients have an isolated deficiency of CRH,[37] and lymphocytic hypophysitis with subsequent adrenal insufficiency has been described in women.[38] These disorders may lead to an isolated ACTH deficiency.[34]

The so-called *tertiary adrenal insufficiency,* which is often summarized together with secondary forms, commonly occurs after withdrawal of exogenous GCs. Many of these patients do well during normal activities but are unable to mount an appropriate GC response to stress. This effect depends on the dose and duration of treatment and varies greatly from person to person. It should be anticipated in any patient who has been receiving more than 30 mg of hydrocortisone per day (or 7.5 mg of prednisolone, or 0.75 mg of dexamethasone per day)

BOX 136.1 Etiology of Adrenal Insufficiency

Primary Adrenal Insufficiency

- Autoimmune adrenalitis (Morbus Addison), often with concomitant endocrinopathies
- Hemorrhage (trauma, anticoagulants)
- Infarction, thrombosis
- Tumors
- Infections (tuberculosis, cytomegaly, fungi, AIDS)
- Amyloidosis, hemochromatosis, sarcoidosis
- Congenital hyperplasias or hypoplasias
- Congenital ACTH resistance
- Adrenomyeloneuropathy

Secondary Adrenal Insufficiency (Lesions of Pituitary and/or Hypothalamic Regions)

- Tumors
- Hemorrhages, apoplexy
- Infections, inflammations
- Autoimmune lesions
- Trauma, surgery
- Radiation
- Congenital syndromes (e.g., familial CBG deficiency)

ACTH, Adrenocorticotropin; *AIDS,* acquired immunodeficiency syndrome; CBG,

for more than 3 weeks.[35] If supraphysiologic doses of GCs have been administered to a patient for more than 1–2 weeks, the drug should be tapered to allow for adrenal gland recovery. It may take 6–12 months for the adrenal glands to recover fully after prolonged use of exogenous GCs.[39] Because ACTH is not a major determinant of mineralocorticoid production, the basic deficit in adrenal insufficiency is that of deficient GC production. It is important that neither the dose of applied GCs, nor the time of treatment, nor the basal plasma level of cortisol allows sufficient assessment of the function of the HPA axis. Several drugs have also been described to induce adrenal insufficiency, either by directly affecting adrenocortical steroid release (e.g., fluconazole, etomidate)[40,41] or by enhanced hepatic metabolism of cortisol (e.g., rifampicin, phenytoin).[35]

Isolated hypoaldosteronism is quite rare and should be suspected in cases of hyperkalemia in the absence of renal insufficiency. The main causes for isolated deficiency of aldosterone secretion are congenital deficiency of aldosterone synthetase, hyporeninemia caused by defects in the juxtaglomerular apparatus, or treatment with angiotensin-converting enzyme inhibitors that lead to loss of angiotensin stimulation. Other forms of hypoaldosteronism usually occur in patients with chronic renal disease and/or diabetes mellitus.

RELATIVE ADRENAL INSUFFICIENCY

The aforementioned forms of adrenal insufficiency, which lead to an absolute deficiency of steroid production, are rare in critically ill patients (0%–3%).[42] To reflect the notion that subnormal adrenal corticosteroid production during acute severe illness can also occur without obvious structural defects in the HPA axis, deficiency syndromes caused by a dysregulation have been termed *functional adrenal insufficiency*.[43] Functional adrenal insufficiency can develop during the course of critical illness and is usually transient.[35] Decreased levels of GCs occur much more often; these levels might be sufficient in normal subjects but are too low for stress situations, owing to higher need, and

BOX 136.2 Values Indicating Normal Adrenocortical Function

- Plasma cortisol (7:00–8:00 AM): 5–25 μg/dL (135–700 nmol/L)
- Plasma adrenocorticotropin (ACTH) (7:00–8:00 AM): <70 pg/mL
- Urine excretion rate of free cortisol: 20–90 μg/d
- Urine excretion rate of 17-hydroxycorticosteroid (17-OHCS): 4–10 mg/d

are associated with a worse outcome.[44] This led to the concept of *relative adrenal insufficiency* (RAI). The major cause of RAI is inadequate synthesis of cortisol caused by cellular dysfunction. Hence, in contrast to absolute adrenal insufficiency, the morphologic changes in the adrenal glands associated with RAI may be minor, sometimes characterized by cellular hyperplasia within the adrenal cortex. This is often combined with peripheral GC resistance of the target cells, which is caused by inflammatory events and aggravates the clinical course, although the absolute cortisol serum levels might be normal.[45] In septic shock, RAI may be the result of impaired pituitary corticotropin release, attenuated adrenal response to corticotropin, and reduced cortisol synthesis (Fig. 136.2).[35,46,47] In addition, cortisol transport capacity may be reduced, and response to cortisol may be impaired at the tissue level by cytokines modulating GC receptor affinity to cortisol and/or GREs.[48,49] In clinical trials, it was demonstrated that prolonged treatment of systemic inflammation in patients with severe acute respiratory distress syndrome (ARDS) with methylprednisolone can improve the decreased GC response by increasing the GC receptor affinity and reducing the NF-κB–mediated DNA binding and transcription of proinflammatory cytokines.[29] Thus if RAI can be identified, treatment with supplemental corticosteroids may be of benefit.[35] Prevalence of RAI in the critically ill varies from 0% to 77% with different definitions, cutoff values, study populations, and adrenal function tests[34,35,46,50,51] and may be as high as 50%–75% in septic shock.[52]

EVALUATION OF ADRENAL INSUFFICIENCY

In clinical practice, assessment of adrenal function is difficult, especially in critically ill patients, because the diurnal rhythm is disrupted. Values indicating normal adrenocortical function are listed in Box 136.2. Normally, serum cortisol concentrations in the morning (8:00 AM) of less than 3 μg/dL (80 nmol/L) are strongly suggestive of absolute adrenal insufficiency,[53] and values below 10 μg/dL (275 nmol/L) make the diagnosis likely. Basal urinary cortisol and 17-hydroxycorticosteroid excretion is low in patients with severe adrenal insufficiency but may be low-normal in patients with partial adrenal insufficiency. Generally, baseline urinary measurements are not recommended for the diagnosis of adrenal insufficiency. To differentiate among primary, secondary, and tertiary adrenal insufficiency in cases of low cortisol, it is recommended to measure plasma ACTH concentrations simultaneously. Inappropriately low serum cortisol concentrations in association with increased ACTH concentrations are suggestive of primary adrenal insufficiency, whereas the combination of low cortisol and ACTH concentrations indicates secondary or tertiary disease. This diagnosis, however, should be confirmed by stimulation of the adrenal gland with exogenous ACTH. In secondary or tertiary adrenal insufficiency, the adrenal glands release cortisol, whereas in primary adrenal insufficiency, the adrenal glands are partially or completely destroyed and do not respond to ACTH.

ACTH stimulation tests usually consist of administering 250 μg (40 international units) of ACTH (so-called *high-dose ACTH stimulation test*). For long-term stimulation tests, which are preferred for differentiating between secondary and tertiary adrenal insufficiency,

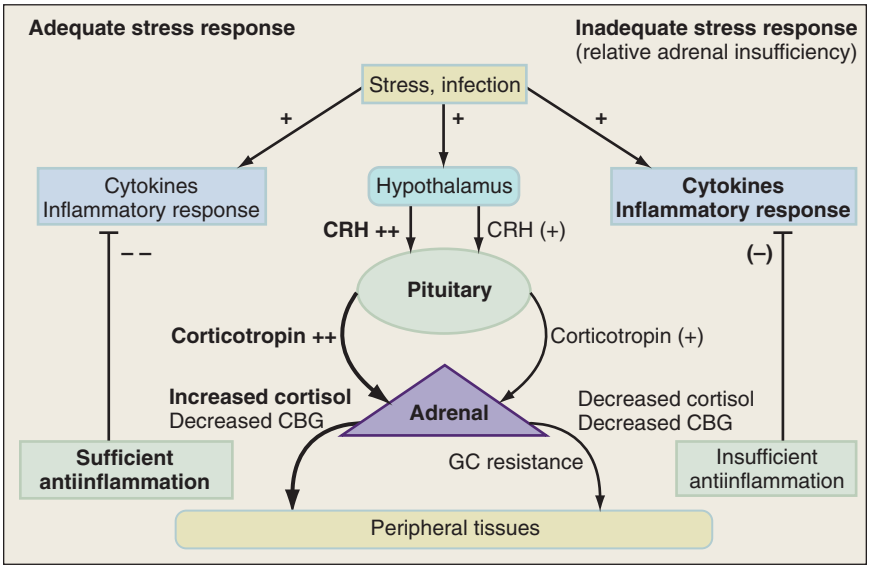

Fig. 136.2 Concept of relative adrenal insufficiency (RAI). Unlike in an adequate stress response *(left)*, RAI may occur when causal or additional factors impair the function of the hypothalamic-pituitary-adrenal (HPA) axis. This may be the result of microcirculatory failure, additional drugs like antibiotics, anesthetic drugs, infections, long-term use of steroids, or hemorrhages. Impaired HPA axis function results in an insufficient antiinflammatory response and an increased inflammatory response. Plus (+) denotes activation; minus (−), inhibition. *CBG,* Cortisol-binding globulin; *CRH,* corticotropin-releasing hormone; *GC,* glucocorticoids.

250 μg of ACTH are infused either over 8 hours or over 2 days.[54] Serum cortisol and 24-hour urinary cortisol and 17-hydroxycorticosteroid (17-OHCS) concentrations are determined before and after the infusion. This test may be helpful in distinguishing primary from secondary/tertiary adrenal insufficiency. In primary adrenal insufficiency, there is a minimal to no response of plasma or urinary cortisol and urinary 17-OHCS. Increases of these values over the 2–3 days of the test are indicative of a secondary/tertiary cause of adrenal insufficiency. In normal subjects, the 24-hour urinary 17-OHCS excretion increases threefold to fivefold above baseline. Serum cortisol concentrations reach 20 μg/dL (550 nmol/L) at 30–60 minutes and exceed 25 μg/dL (690 nmol/L) at 6–8 hours post initiation of the infusion. At present, this approach is used frequently because clinical manifestations of adrenal insufficiency combined with basal cortisol levels, short-term ACTH stimulation tests, and CRH tests (see later discussion) usually provide sufficient information.

A short-term stimulation test with 250 μg ACTH, mostly used for patients who are not critically ill, determines basal serum cortisol levels and the induced-response concentration 30 and 60 minutes after intravenous (IV) administration of ACTH. The advantage of the high-dose test is that pharmacologic plasma ACTH concentrations can be achieved by either IV or intramuscular injection.[55] This dose of ACTH, however, may be too high to identify mild cases of secondary adrenal insufficiency or chronic deficiencies.[56] Furthermore, it should not be used when acute secondary adrenal insufficiency (e.g., Sheehan syndrome) is presumed, because it takes several days for the adrenal cortex to atrophy, and it will still be capable of responding to ACTH stimulation normally. In these cases, a low-dose ACTH test or an insulin-induced hypoglycemia may be required to confirm the diagnosis of adrenal insufficiency.[57,58] A rise in serum cortisol concentration after 30–60 minutes to a peak of 18–20 μg/dL (500–550 nmol/L) or more is considered a normal response to a high-dose ACTH stimulation test and excludes the diagnosis of primary adrenal insufficiency and almost all cases of secondary adrenal insufficiency except those of recent onset.[59–61]

To further differentiate between secondary and tertiary adrenal insufficiency, laboratory investigations may be augmented by a CRH stimulation test. In both conditions, cortisol levels are low at baseline and remain low after CRH. In patients with secondary adrenal insufficiency, there is little or no ACTH response, whereas in patients with tertiary disease, there is an exaggerated and prolonged response of ACTH to CRH stimulation that is not followed by an appropriate cortisol response.[62,63] In the past, the HPA axis was also tested by a stimulated hypoglycemia test. After administering 0.1 units of insulin per kilogram body weight, inducing a hypoglycemic state of less than 40 mg/dL serum glucose, an intact HPA axis is associated with a serum cortisol concentration of more than 20 μg/dL. Nowadays, this procedure is considered obsolete because of the high risk of symptomatic hypoglycemia.

In critically ill patients, primary causes of absolute or RAI are multiple and often undetectable if no specific hypothesis exists. Volume-resistant septic shock or any other form of life-threatening hypotension with an increased need for catecholamines indicates the need to evaluate adrenal function. Previously, a serum cortisol value less than 20 μg/dL was suggestive of the diagnosis of adrenal insufficiency.

Several factors complicate investigations of the HPA axis in patients with critical illness. A short-term ACTH stimulation test may be performed in critically ill patients suspected of having adrenal insufficiency. However, in most patients, RAI will be present, especially in patients with sepsis and septic shock. A clear definition of RAI is still missing, and the pathophysiology is rather complex, which makes it difficult to define clear cutoffs for both basal serum cortisol concentrations and incremental increases after short-term ACTH stimulation tests. Proposed cutoff points may depend on different methods used to measure cortisol, with variations when compared with high-performance liquid chromatography (HPLC) as the reference method.[64] In addition, considering free cortisol or an increase in free cortisol in response to ACTH could increase the accuracy of adrenocortical function tests.[48] Furthermore, extrapolating the diagnosis from reference values obtained from healthy people or patients with HPA disorders

may be misleading, because normal or high-normal cortisol concentrations in septic shock may indicate inadequate adrenal response to stress. In a large series of patients, receiver operating characteristic curve (ROC) analysis reached the highest sensitivity (68%) and specificity (65%) for a reference value of less than 9 μg/dL (incremental increase) to detect nonresponders.[52] Basal cortisol of 34 μg/dL and an incremental increase of 9 μg/dL after stimulation were the best cutoff points to discriminate between survivors and nonsurvivors. The higher the basal plasma cortisol and the weaker the cortisol response to corticotropin, the higher the risk of death. Some investigators have questioned the discriminative power of the incremental increase of cortisol after stimulation in patients with high basal cortisol values, as increases may reflect adrenal reserve more than adrenal function. Hence, RAI was defined based on the hemodynamic response when a randomly measured cortisol was less than 25 μg/dL.[46]

Routine use of the low ACTH stimulation test in critically ill patients cannot be recommended at present, although the low-dose test is preferred in patients with secondary or tertiary adrenal insufficiency.[65] After stimulation with 250 μg ACTH, circulating corticotropin concentrations are 40–200 pg/mL during stress but may be as high as 60,000 pg/mL.[35] Stimulation of the adrenal gland with low doses of ACTH (1 μg) was shown to increase sensitivity and specificity to detect adrenal insufficiency in patients with HPA disorders who respond normally to traditional high-dose stimulation.[35,66–69] The test is performed by measuring serum cortisol concentrations immediately before and 30 minutes after IV injection of ACTH at a dose of 1 μg (160 mIU) per 1.73 m^2 body surface.[34] This dose stimulates maximal adrenocortical secretion up to 30 minutes post injection and in normal subjects results in a peak plasma ACTH concentration about twice that of insulin-induced hypoglycemia.[70] A value of 18 μg/dL (500 nmol/L) or more at any time during the test is indicative of normal adrenal function. The advantage of this test is that it can detect partial adrenal insufficiency that may be missed by the standard high-dose test.[57,58]

Using the 1-μg ACTH stimulation test to identify patients with RAI in septic shock has been proposed, but the 1-μg stimulation test has not been well validated in critically ill patients or patients with septic shock.[34,35] In addition, studies evaluating low-dose and high-dose ACTH stimulation tests in septic shock may have been flawed by methodologic problems. At present, using the 1-μg ACTH stimulation test cannot be recommended routinely until further data from well-designed randomized studies in septic shock patients are available.

The current recommendation is to use a three-level therapeutic guide for evaluating RAI in critically ill patients, especially those with septic shock. Patients with a random basal cortisol below 15 μg/dL will likely benefit from low-dose corticosteroid therapy, whereas corticosteroid replacement is unlikely to be helpful when basal cortisol is above 34 μg/dL. When a random basal cortisol value is between 15 and 34 μg/dL, adrenocortical stimulation with 250 μg ACTH should discriminate responders (incremental increase ≥9 μg/dL) from nonresponders (<9 μg/dL). However, it has been pointed out that no cutoff values are entirely reliable.[35]

CLINICAL SYMPTOMS

About 25% of patients with adrenal insufficiency present with adrenocortical crisis.[34] The symptoms are nonspecific and include sudden dizziness, weakness, dehydration, hypotension, and shock (Box 136.3). In many cases, the clinical picture may be indistinguishable from shock because of loss of intravascular fluid volume. Other features such as anorexia, nausea, vomiting, diarrhea, abdominal pain, and delirium may be present, but they are also common in patients with other acute illness. Hence, these symptoms may not be helpful in establishing the diagnosis of adrenal insufficiency and are often misleading. Hypoglycemia is rare in acute adrenal insufficiency but more common in secondary adrenal insufficiency; it is a common manifestation in children and women with the disorder. For patients in the intensive care unit (ICU), it remains extremely difficult to recognize acute, absolute adrenal insufficiency based on clinical symptoms. However, if the diagnosis is missed, the patient will probably die, so the threshold for laboratory investigations in cases of unexplained catecholamine-resistant hypotension should be low. It is important to be mindful that the onset of an acute adrenocortical crisis is not necessarily the acute beginning of the underlying disease itself. The preceding course is often gradual and may go undetected until an acute illness, stress, trauma, pregnancy, or other conditions precipitate adrenal crisis.[34,71]

BOX 136.3 Clinical Manifestations of Adrenal Insufficiency

Acute Adrenal Insufficiency

- Acute apathy
- Nausea, vomiting
- Fever
- Acute dehydration, tachycardia
- Craving for salt
- Hypotension, shock

Chronic Adrenal Insufficiency

- Weakness, fatigue
- Lack of appetite
- Orthostatic hypotension
- Weight loss, anorexia
- Hyperpigmentation (only in primary Addison disease caused by increased ACTH)
- Vitiligo
- Nonspecific gastrointestinal symptoms (diarrhea, nausea, abdominal pain)
- Nonspecific pain (myalgia, arthralgia, headaches)
- Nonspecific psychological symptoms (depression, lack of concentration, confusion, psychosis)
- Hypoglycemia
- Hyponatremia
- Hyperkalemia
- Acidosis, prerenal azotemia
- Lymphocytosis, eosinophilia

ACTH, Adrenocorticotropin.

Typical symptoms of primary adrenal insufficiency, such as hyperpigmentation, scanty axillary and pubic hair, hyponatremia, or hyperkalemia, may be diagnosed in the acutely ill patient. Adrenal crisis can occur in patients receiving appropriate doses of GCs if their mineralocorticoid requirements are not met.[72] After spontaneous events leading to primary adrenal insufficiency (e.g., hemorrhage, myocardial infarction, adrenal vein thrombosis), these signs are absent. If an acute adrenal crisis is suspected, a blood sample should be obtained to confirm the diagnosis. The main clinical problem is hypotension and shock caused by acute mineralocorticoid deficiency. However, GC deficiency may also contribute to hypotension by decreasing vascular responsiveness to angiotensin II, norepinephrine, and other vasoconstrictive hormones, reducing the synthesis of renin substrate and increasing production and effects of prostacyclin and other vasodilatory hormones.[73,74] Finally, panhypopituitarism may be associated with symptoms, owing not only to a lack of corticotropin but also TSH, gonadotropin, and GH.

In chronic adrenal insufficiency, the major clinical features (see Box 136.3) may be detected but may also be absent if adrenal gland

insufficiency develops over a prolonged period. There is a stage characterized by normal basal steroid secretion but an inability to respond to stress; hence, the patient may be asymptomatic. In other cases, there may also be signs and symptoms suggestive of other hormone deficiency, such as decreased thyroid and gonadal function. Independent of the underlying cause, the most common clinical manifestations are general malaise, fatigue, weakness, anorexia, weight loss, nausea, vomiting, abdominal pain, arthralgia, postural syncope, diarrhea that may alternate with constipation, hypotension, electrolyte abnormalities (hyponatremia, hyperkalemia, metabolic acidosis), decreased axillary and pubic hair, and loss of libido and amenorrhea in women.[34,71]

In primary adrenal insufficiency, hyperpigmentation and autoimmune manifestations (vitiligo) are typically the result of increased ACTH concentrations, whereas these findings are not seen in secondary or tertiary adrenal insufficiency. Another specific symptom of primary adrenal insufficiency is a craving for salt.[35] Typical laboratory abnormalities are hyponatremia, hyperkalemia, acidosis, slightly elevated creatinine concentrations, mild normocytic anemia, and, rarely, hypercalcemia.[35]

In secondary adrenal insufficiency, because production of mineralocorticoids by the zona glomerulosa is generally preserved, dehydration and hyperkalemia are not present, and hypotension is less prominent than in primary disease. Especially in the early stages, the onset of chronic adrenal insufficiency is often insidious, and the diagnosis may be difficult. Some patients initially present with gastrointestinal symptoms such as nausea, vomiting, diarrhea, and abdominal cramps.[35,75] In other patients, the disease may be misdiagnosed as depression or anorexia nervosa.[76,77] Hyponatremia and increased intravascular volume may be the result of an "inappropriate" increase in vasopressin secretion. Decreased libido and potency and amenorrhea may occur. Hypoglycemia is more common in secondary adrenal insufficiency, possibly the result of concomitant GH insufficiency, and in isolated ACTH deficiency. Clinical manifestations of a pituitary or hypothalamic tumor, such as signs and symptoms of deficiency of other anterior pituitary hormones, headache, or visual field defects, may also be present.[34,71] Finally, in young patients suspected of having adrenal insufficiency, delayed growth and puberty point to the presence of hypothalamic-pituitary disease, as would headaches, visual disturbances, or diabetes insipidus in patients of any age.[35,36] Laboratory screening in patients with chronic adrenal insufficiency usually reveals hyponatremia, hypoglycemia, lymphocytosis, and eosinophilia.[35]

THERAPEUTIC APPROACHES

Treatment of adrenal insufficiency involves addressing the precipitating cause (e.g., tumor, infection) and hormone replacement. In acutely ill patients, if the diagnosis of adrenal crisis is suspected but not known, blood should be obtained for measurement of cortisol concentrations, followed by the administration of 250 μg of ACTH in patients with an unknown history. Replacement therapy should be started immediately while awaiting the results of testing.[78] Dexamethasone (1 mg every 6 hours) may be given as the initial GC replacement, because it does not cross-react with cortisol in the plasma while adrenal testing is being performed. Patients are usually treated with IV fluids in the form of isotonic saline to restore intravascular volume and replace urinary salt losses. Dextrose infusion may be added to prevent hypoglycemia. Hydrocortisone (100-mg IV bolus or over 30 minutes, followed by continuous infusion of 10 mg/hr, or 50 mg every 4 hours, or 75–100 mg every 6 hours, resulting in a total daily dose of 240–300 mg hydrocortisone) is frequently given for hormonal replacement.[34,78] However, equivalent GC doses of methylprednisolone or dexamethasone may also be used. Typically, mineralocorticoid replacement therapy is not required in adrenal crisis as long as the patient is receiving isotonic saline. Prophylactic use of antibiotics is not beneficial, but specific infections should be treated aggressively with appropriate antibiotic therapy.

Once the patient is stable, GCs can be tapered to maintenance doses. Long-term replacement doses consist of hydrocortisone, usually 30 mg/d, with two-thirds (20 mg) given in the morning and one-third (10 mg) given at night, or prednisone 7.5 mg in a similar regimen (5 and 2.5 mg, respectively). The daily dose may be decreased to 20 or 15 mg of hydrocortisone as long as the patient's well-being and physical strength are not reduced.[34] The goal should be to use the lowest dose that relieves the patient's symptoms in order to prevent weight gain and osteoporosis.[34,78,79] If the patient continues to experience weakness or other symptoms of GC deficiency, the dose can be increased. Excessive GC therapy should be avoided so as to minimize complications. In addition, mineralocorticoid effect is provided with fludrocortisone (50–100 μg orally daily) to prevent sodium loss, intravascular volume depletion, and hyperkalemia, especially when the dose of hydrocortisone decreases below 100 mg/d. Therapy can be guided by monitoring blood pressure, serum potassium, and plasma renin activity, which should be in the upper normal range.[34,61] Clinical response, however, is the best indicator of the adequacy of replacement. Excessive mineralocorticoid replacement may cause congestive heart failure, alkalosis, hypokalemia, or hypertension. Patients receiving prednisone or dexamethasone may require higher doses of fludrocortisone to lower their plasma renin activity to the upper normal range, whereas patients receiving hydrocortisone, which has some mineralocorticoid activity, may require lower doses. The mineralocorticoid dose may have to be increased in the summer, particularly if patients are exposed to temperatures above 29°C (85°F). In cases of isolated hypoaldosteronism, treatment includes liberal sodium intake and daily administration of fludrocortisone. In patients with secondary adrenal insufficiency caused by panhypopituitarism, replacement with other hormones may also be necessary. In women, the adrenal cortex is the primary source of androgen in the form of dehydroepiandrosterone and dehydroepiandrosterone sulfate. Although the physiologic role of these androgens in women has not been fully elucidated, their replacement is being increasingly considered in the treatment of adrenal insufficiency.[80,81]

Once the patient is stable and on maintenance doses of steroids, ACTH testing can be repeated to document adrenal recovery. Patients with primary adrenal insufficiency require lifelong GC and mineralocorticoid replacement therapy and should carry a card containing information on current therapy, in addition to some type of bracelet or necklace with recommendations for treatment in emergency situations. One of the important aspects of the management of chronic primary adrenal insufficiency is patient and family education. Patients should understand the reason for lifelong replacement therapy; the need to increase the dose of GCs during minor or major stress; and how to inject hydrocortisone, methylprednisolone, or dexamethasone in emergencies. Patients should also have supplies of dexamethasone sodium phosphate and be educated about how and when to administer it. The survival rate for patients with chronic primary adrenal insufficiency has gone from 2 years or less before the availability of steroid replacement to that of the normal population now that GCs are readily available. In acute adrenal insufficiency, prompt recognition and treatment usually result in a favorable outcome, provided the underlying disease process can be treated.

GLUCOCORTICOID REPLACEMENT IN PATIENTS WITH SEPTIC SHOCK

In patients with sepsis and septic shock, the clinical course is extremely varied. The impact of the primary disease, in addition to immunologic factors (including cytokines) associated with sepsis, affect the HPA

axis. In contrast to the early phase of septic shock, adrenal cortisol release may recover, thus leading to RAI with absolute steroid levels around or even above normal range.[82] In refractory septic shock, the prevalence of RAI may be as high as 50%–75%.[52] Furthermore, dynamic testing is not always available in ICUs, making it difficult for the physician considering hormone replacement therapy, because decisions have to be made within hours in severe forms of septic shock to improve prognosis.

Proposed mechanisms of protection from high-dose GCs include improvement of hemodynamic, metabolic, endocrine, and phagocytic functions, resulting in the maintenance of normal morphologic-functional status of tissues including brain, liver, heart, kidneys, and adrenals.[83] In addition, GCs are recognized to inhibit key features of inflammation: endothelial cell activation and damage; capillary leakage; granulocyte activation; adhesion and aggregation; complement activation; and formation and release of eicosanoid metabolites, oxygen radicals, and lysosomal enzymes.[84–89]

However, in only one long-term prospective study in humans receiving high doses of methylprednisolone (30–60 mg/kg) or dexamethasone (2– 4 mg/kg), including 179 bacteremic septic shock patients over a period of 8 years, were experimental results confirmed and mortality reduced from 38% to 10%.[90] Evidence from another study suggested that prolongation of treatment might have been beneficial, because shock reversal and improved survival occurred after a bolus GC application in an early time window but vanished after several days.[91] Two meta-analyses included 9 and 10 randomized trials, respectively, of patients with severe sepsis and septic shock who received up to 42 g of hydrocortisone equivalent or more; both concluded that high doses of corticosteroids were ineffective[92] or harmful.[93] This was confirmed by a large randomized trial in 1987.[94] High-dose GCs were associated with increased risk of secondary infections, mortality,[93] and incidence of renal and hepatic dysfunction.[95] Taken together, these results suggest that high-dose GCs are not effective in septic shock.

Similar to studies of high-dose GC treatment, numerous randomized controlled trials with low-dose corticosteroids in patients with septic shock also confirmed shock reversal and reduction of vasopressor support within a few days after initiation of therapy in most patients.[96–101] In a crossover study, mean arterial pressure and systemic vascular resistance increased during low-dose hydrocortisone treatment and heart rate, cardiac index, and norepinephrine requirement decreased significantly.[102] All effects were reversible with cessation of hydrocortisone. Some studies indicated that corticosteroid-induced increase of sensitivity to norepinephrine was more pronounced in patients with RAI than in patients without RAI.[46,101] There are multiple potential mechanisms by which corticosteroids may modulate vascular tone. Considerable evidence confirms that cytokine-induced formation of nitric oxide (NO) plays a central role in vasodilation, catecholamine resistance, maldistribution of blood flow, and mitochondrial and organ dysfunction and that the amount of NO production correlates with shock severity and outcome.[103,104] In a crossover trial, norepinephrine requirement could be reduced by administering low-dose hydrocortisone in nearly all patients within 1–2 days. Hydrocortisone treatment also induced a significant and prolonged decline of nitrite/nitrate levels, which significantly correlated with reduction of norepinephrine requirements during hydrocortisone infusion.[102] Considering the complex genomic and nongenomic actions of corticosteroids described earlier, it is probable that NO is not the only target.

GCs modulate the stress response in a very complex manner that includes not only antiinflammatory and immunosuppressive actions to protect the host from overwhelming inflammation but also immune-enhancing effects.[27] Markers of the inflammatory response, antiinflammatory response, granulocyte, monocyte, endothelial activation, antigen-presenting capacity, and innate immune response were investigated in septic shock patients.[102] Hydrocortisone significantly attenuated inflammatory and antiinflammatory responses and granulocyte, monocyte, and endothelial activation. Monocyte HLA-DR expression was depressed, but receptor down-regulation was limited and was followed by a rebound increase after drug withdrawal.[102] The immune effects of low-dose hydrocortisone treatment in septic shock may thus be characterized as immunomodulatory rather than immunosuppressive.

Although data on outcomes in septic shock patients after low-dose corticosteroid treatment are limited, up to 300 mg hydrocortisone per day may improve survival. In some trials with low-dose corticosteroids,[96–100] 28-day all-cause mortality was reduced, whereas in high-dose trials, there was no significant effect. In a multicenter trial in 300 patients with severe volume and catecholamine-refractory septic shock, survival time was significantly increased in patients with RAI but not in responders to ACTH.[97] Similar results were obtained for ICU and hospital mortality but not for 1-year follow-up. Significant increases of serious adverse events during treatment with low-dose hydrocortisone have not been reported. The incidence of gastrointestinal bleeding, superinfections, or hyperglycemia has not been different in patients treated with corticosteroids or placebo, and wound infections were even less frequent in patients treated with low-dose hydrocortisone.[97] However, these findings were not confirmed by another large randomized trial, the Corticosteroid Therapy of Septic Shock (CORTICUS) trial,[105] which used different inclusion criteria. Only patients who were successfully resuscitated by volume therapy plus vasopressors were included.[105] These contradictory results led the Surviving Sepsis Campaign in the recent 2016 guidelines to recommend against the use of low-dose GCs for patients who are responding adequately to volume plus vasopressor therapy—that is, those who are no longer hypotensive.[106] Only in the minority of patients, when a stabilization of blood pressure cannot be obtained by using volume plus vasopressors, continuous low-dose hydrocortisone might be considered.[106] These recommendations were confirmed by the two largest randomized controlled trials on low-dose corticoids in septic shock, both published in 2018: The first one (APROCCHSS trial), which was comparable to the first low-dose steroid trial from 2002,[97] used combined glucocorticoid and mineralocorticoid therapy in vasopressor-resistant septic shock, and an improved survival could be demonstrated.[107] The second one (ADRENAL trial) was similar to the CORTICUS trial,[105] used only glucocorticoids in patients with septic shock (vasopressor resistance was not required), and failed to show any outcome benefit.[108] Based on these results, the aforementioned recommendations by the Surviving Sepsis Campaign were not adapted.[106]

Treatment with low-dose hydrocortisone may induce an increase of sodium levels within a few days, and hypernatremia with values over 155 mmol/L have been reported during prolonged treatment.[100] Nevertheless, the indication for low-dose corticosteroids should be weighed against possible risks, and treatment should be limited to the duration of volume- and vasopressor-restrictive hypotension.

Dosing of hydrocortisone in septic shock is similar to that in adrenal crisis (100 mg initial bolus, followed by 200–300 mg per day), and the dose should be tapered once the patient stabilizes. Hydrocortisone is the synthetic equivalent to the physiologic final active compound, cortisol, so treatment with hydrocortisone directly replaces cortisol independently from metabolic transformation. In contrast to dexamethasone, hydrocortisone has intrinsic mineralocorticoid activity. A recent randomized trial demonstrated that the addition of oral fludrocortisone to low-dose hydrocortisone has no benefit in septic shock patients.[109] It has not been established whether a weight-adjusted regimen (e.g.,

0.18 mg/kg/hr)[56] of continuous hydrocortisone infusion is superior to a fixed regimen; moreover, a comparative study of bolus versus infusion regimens has not been performed so far. Patients should be weaned from low-dose hydrocortisone over several days to avoid hemodynamic and immunologic rebound effects. In patients with septic shock, abrupt cessation of low-dose hydrocortisone was followed by significant reversal of many hemodynamic and immunologic effects observed during corticosteroid therapy, even after a short treatment period of 3 days.[102] Adrenal function tests with 250 μg ACTH can be performed in patients with septic shock; however, at present this approach cannot be recommended to exclude responders or patients with high random cortisol values from low-dose corticosteroid therapy.[35] When basal serum cortisol concentrations are less than 15 μg/dL in septic shock, low-dose hydrocortisone replacement is recommended; levels of over 34 μg/dL are considered sufficient. Between 15 and 34 μg/dL, an incremental increase of less than 9 μg/dL serum cortisol makes RAI likely, and therapy may be considered according to the clinical state.[35] Other recommendations use a randomly assigned cutoff level of below 25 μg/dL serum cortisol.[46] The routine use of the low ACTH stimulation test (1 μg ACTH) cannot be recommended at present until further data from well-designed randomized studies in septic shock patients are available. Most importantly, it has to be realized that all the aforementioned studies were performed in patients with catecholamine-resistant septic shock. To date, there are no data justifying the use of low-dose steroids in patients with sepsis. Significant effects on outcome have been observed only in patients with systolic blood pressure below 90 mm Hg despite vasopressor therapy.[97] It is not yet known whether low-dose corticosteroids are also effective in patients with less severe shock. Sufficient data on the dose-response characteristics of GCs in septic patients are still lacking, and the current recommended strategy using 200–300 mg hydrocortisone per day is based on empiric recommendations; further investigations are needed.

FURTHER IMPLICATIONS FOR ANESTHESIA AND CRITICAL CARE

Surgical stress increases serum cortisol levels fivefold to sixfold postoperatively, with return to normal at 24 hours unless stress continues. Patients who have received GCs equivalent to 30 mg/d cortisol for longer than 3 weeks may have impairment in this stress response, and steroid supplementation should be considered. However, short-term treatment of heterogeneous groups of patients with critical illness is controversial, and supraphysiologic doses of GCs are not beneficial and may even be harmful.[110] Hence, outside the situations in which benefit has been proved, supraphysiologic doses of GCs (e.g., 30 mg methylprednisolone per kilogram of body weight per day) in patients with critical illness are not indicated. Whereas early treatment with dexamethasone was suggested to decrease morbidity in bacterial meningitis,[111,112] a recent meta-analysis was less enthusiastic.[113] The positive effects of steroid treatment on tissue-specific resistance to GCs have already been described. However, despite the frequent suggestion that unexplained intraoperative hypotension and even death reflect unrecognized hypocortisolism, there is no evidence that primary adrenal insufficiency is a likely explanation for this response.

Patients with known chronic adrenal insufficiency must be advised to double or triple the dose of hydrocortisone temporarily whenever they have any febrile illness or injury.[34] In stressful situations or during major surgery, trauma, burns, or medical illness, high doses of GCs up to 10 times the daily production are required to avoid an adrenal crisis, although no data from randomized trials are available. A continuous infusion of 10 mg of hydrocortisone per hour or the equivalent amount of dexamethasone or prednisolone eliminates the possibility of GC deficiency. This dose can be halved on the second postoperative day, and the maintenance dosage can be resumed on the third postoperative day. However, it is important with regard to possible detrimental effects and the possibility of decreased resistance to infections that this treatment not be used for prolonged periods in the absence of evidence of corticosteroid insufficiency. General perioperative management should include avoidance of etomidate as an anesthetic drug (selection of other drugs and muscle relaxants is not influenced by the presence of treated hypocortisolism); infusion of sodium-containing fluids; minimal doses of any anesthetic drugs to avoid increased sensitivity to drug-induced myocardial depression; invasive monitoring of hemodynamics, glucose, and electrolytes; and decreased initial doses of muscle relaxant while monitoring the effect using a peripheral nerve stimulator. Especially when acute adrenal insufficiency has been detected in a critically ill patient with a previously unknown disorder, thorough diagnostic evaluation is required, even after improvement.

The control of cortisol secretion in response to stress is more complex than originally thought. Interactions between corticotropin-releasing factor (CRF), vasoactive intestinal polypeptide, arginine vasopressin, catecholamines, and other hormones involved in the control of cortisol secretion have been described.[114] Alpha-2-adrenergic receptor antagonists (e.g., clonidine), which are widely used in ICUs, may suppress the cortisol response to surgical stress. On the other hand, increases in intracranial pressure stimulate cortisol release without increasing ACTH levels, and adrenalectomy, but not adrenal demedullation, increases the permeability of brain tissue to macromolecules.[115] Evidence also suggests that white blood cells may release ACTH-like peptides that can stimulate adrenal gland secretion of cortisol and that primary adrenal insufficiency is associated with increases in serum levels of angiotensin-converting enzyme.[116]

Multiple interactions between drugs and the HPA axis have to be considered if absolute or RAI is suspected. Moreover, in patients with hepatic dysfunction, GC doses should be tapered, especially when using prednisone, because hydroxylation to the active component needs considerable metabolic capacity. Special attention is required in the concomitant use of GCs with other drugs, because of potential interactions and because some drugs may affect the metabolism of steroids, which may lead to a decreased or increased GC effect on their target tissues.[117,118] GCs decrease blood levels of aspirin, coumarin anticoagulants, isoniazid, insulin, and oral hypoglycemic agents, whereas cyclophosphamide and cyclosporine levels may be increased. Conversely, antacids, carbamazepine, cholestyramine, colestipol, ephedrine, mitotane, phenobarbitone, phenytoin, and rifampicin decrease GC blood concentrations, whereas concentrations are increased by cyclosporine, erythromycin, oral contraceptives, and troleandomycin. Furthermore, the combination of exogenous GC administration and amphotericin B, digitalis glycosides, and potassium-depleting diuretics may induce or worsen hypokalemia, warranting frequent monitoring of potassium levels. Finally, the general risk of immunosuppression by GCs precludes any use of vaccines from live attenuated viruses to avoid severe generalized infections.[117,118]

CONCLUSION

Underproduction of adrenal hormones can lead to serious illness. GCs play a critical permissive role in intermediary metabolism, are counterregulatory in relation to insulin, modulate inflammatory and immune responses, and optimize cardiovascular and CNS function. Therefore diseases with a primary adrenocortical dysfunction or those leading to secondary adrenal insufficiency may have severe sequelae, which often are life threatening. The concept of RAI in critically ill patients with functional disorders of the HPA axis has gained attention. Especially in patients with sepsis and septic shock, this phenomenon is suspected of

having a major impact on the severity of illness and prognosis. Both absolute adrenal insufficiency and RAI should be diagnosed by using adequate laboratory investigations. In most cases, testing the basal level of cortisol, combined with a short-term stimulation test with 250 μg ACTH, can identify the disease. In patients with critical illnesses, however, it continues to be difficult to diagnose RAI.

In cases of suspected adrenal crisis with severe volume- and catecholamine-resistant shock, immediate replacement therapy is indicated. If the diagnosis is questionable, dexamethasone should be administered to allow an appropriate diagnostic evaluation. Once the diagnosis of adrenal insufficiency is made, hydrocortisone is the preferred therapy, because it provides both glucocorticoid and mineralocorticoid effects. After stabilization, the dose of GCs should be tapered down to a total of 20–35 mg hydrocortisone per day or equivalent. Randomized controlled trials of high-dose GCs failed to improve outcome from sepsis and septic shock. However, prolonged treatment of refractory septic shock with low doses of corticosteroids is only considered a therapeutic option if the patient does not respond to volume replacement and vasopressor therapy.

KEY POINTS

- The definition of adrenal insufficiency is based on the inability of the adrenal gland to produce adrenocortical steroid hormones.
- The main cause of *primary adrenal insufficiency* (70%–80%) is an autoimmune disorder that induces morphologic destruction of more than 90% of the adrenal cortex. The result is a critically decreased synthesis of steroids, with typical clinical manifestations.
- *Secondary adrenal insufficiency* is characterized by reduced stimulation of the intact adrenal gland caused by low ACTH levels (hypothalamic-pituitary insufficiency), which also results in reduced cortisol levels.
- *Tertiary adrenal insufficiency* is caused by long-term treatment with steroid hormones, which induces feedback inhibition of the HPA axis.
- The definition of *relative adrenal insufficiency* (RAI) in critically ill patients is based on plasma cortisol levels. The critical threshold is a basal cortisol level of 18–25 μg/mL without preceding stimulation.
- Clinical manifestations of adrenal insufficiency are usually nonspecific and include weakness, anorexia, orthostatic hypotension, and general gastrointestinal symptoms. Typical signs of primary forms are hyperpigmentation caused by increased ACTH levels, vitiligo in cases of autoimmune disorders, and hyperkalemia. Secondary forms cause milder symptoms as a result of maintained mineralocorticoid effects.
- Evaluation of adrenal insufficiency generally includes measurement of basal serum cortisol concentrations and the incremental increase after stimulation with ACTH. A high-dose test (250 μg ACTH) is preferred, which uses 30- and 60-minute cortisol levels after stimulation. Long-term tests or low doses (1 μg ACTH) are only used for special indications. Basal values for serum cortisol of less than 3 μg/dL indicate severe, absolute hypocortisolism warranting immediate intervention. In critically ill patients, basal cortisol levels of less than 18–25 μg/mL have been recommended as an indication for low-dose replacement therapy.
- Acute adrenal insufficiency (Addisonian crisis) requires immediate intervention. Establishing IV access, infusion of saline, monitoring serum glucose, and administering dexamethasone after drawing a blood sample may be lifesaving. ACTH stimulation tests should be used for diagnosis. Once the results after stimulation are known, hydrocortisone therapy is preferred for its mineralocorticoid effects.
- Chronic adrenal insufficiency may require long-term replacement therapy with glucocorticoids and mineralocorticoids (for primary forms). Any physical or emotional stress must be considered as possibly harmful, with the need for 3–10 times increased doses of glucocorticoids.
- In patients with septic shock who are not adequately responding to volume and vasopressor therapy, replacement with low-dose hydrocortisone (200–300 mg/d) may be considered, although optimal dosing and timing have yet to be established. A preliminary ACTH test in these patients is no longer recommended.

References for this chapter can be found at expertconsult.com.

ANNOTATED REFERENCES

Annane D, Bellissant E, Bollaert PE, et al. Corticosteroids in the treatment of severe sepsis and se ptic shock in adults: A systematic review. *JAMA.* 2009;301:2362-2375.
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In contrast to the aforementioned study, this randomized trial did not show any benefit of low-dose hydrocortisone therapy in septic shock; however, these patients were responsive to vasopressor therapy, which underlines the relevance of thorough patient selection.

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Thyroid Disorders

Angela M. Leung and Alan P. Farwell

NORMAL THYROID HORMONE ECONOMY

Regulation

Synthesis and secretion of thyroid hormone is under the control of the anterior pituitary hormone thyrotropin (or thyroid-stimulating hormone [TSH]). Consistent with a classic negative feedback system, TSH secretion increases when serum thyroid hormone levels fall and decreases when they rise (Fig. 137.1). TSH secretion is also under the regulation of the hypothalamic hormone thyrotropin-releasing hormone (TRH). The negative feedback of thyroid hormone is targeted mainly at the pituitary level, but also likely affects TRH release from the hypothalamus. In addition, input from higher cortical centers can affect hypothalamic TRH secretion.

Under the influence of TSH, the thyroid gland synthesizes and releases thyroid hormone. Thyroxine (3,5,3′,5′-tetraiodothyronine, or T_4, which is 65% iodine by weight) is the principal secretory product of the thyroid gland, comprising about 90% of secreted thyroid hormone under normal conditions.[1] Although T_4 may have direct actions in some tissues, it primarily functions as a hormone precursor that is metabolized in peripheral tissues to the transcriptionally active 3,5,3′-triiodothyronine (T_3, which is 59% iodine by weight).

Metabolic Pathways

The major pathway of metabolism of T_4 is by sequential monodeiodination.[2] At least three deiodinases, each with its unique expression in different organs, catalyze deiodination reactions involved in the metabolism of T_4. Removal of the 5′-, or outer ring, iodine by type I iodothyronine 5′-deiodinase (D1) or type II iodothyronine 5′-deiodinase (D2) is the "activating" metabolic pathway leading to the formation of T_3. Removal of the 5′-, or inner ring, iodine by type III iodothyronine deiodinase (D3) is the "inactivating" pathway that produces the metabolically inactive thyroid hormone 3,3′,5′-triiodothyronine (reverse T_3 or rT_3). D1 is found most abundantly in the liver, kidneys, and thyroid. It is up-regulated in hyperthyroidism and down-regulated in hypothyroidism. D2 is found primarily in the brain, pituitary, and skeletal muscle and is down-regulated in hyperthyroidism and up-regulated in hypothyroidism. D3 is expressed primarily in the brain, skin, and placental and chorionic membranes. The actions of D3 also include inactivation of T_3 to form T_2, another inactive metabolite. Under normal conditions, about 41% of T_4 is converted to T_3, about 38% is converted to rT_3, and about 21% is metabolized via other pathways, such as conjugation in the liver and excretion in the bile.[3,4]

T_3 is the metabolically active thyroid hormone and exerts its actions via binding to chromatin-bound nuclear receptors and regulating gene transcription in responsive tissues.[5] It is important to note that only around 10% of circulating T_3 is secreted directly by the thyroid gland, whereas more than 80% of T_3 is derived from the conversion of T_4 in peripheral tissues.[1,2] Thus factors that affect peripheral T_4-to-T_3 conversion will have significant effects on circulating T_3 levels. Serum levels of T_3 are approximately 100-fold less than those of T_4, and like T_4, T_3 is metabolized by deiodination to form diiodothyronine (T_2) and by conjugation in the liver. The half-lives of circulating T_4 and T_3 are 5–8 days and 1.3–3 days, respectively.[3]

Serum Binding Proteins

Both T_4 and T_3 circulate in the serum as hormones bound to several proteins synthesized by the liver.[4] Thyroid-binding globulin (TBG) is the predominant transport protein and binds to approximately 80% of the circulating serum thyroid hormones. The affinity of T_4 for TBG is about 10-fold greater than that of T_3, which accounts in part for the higher circulating T_4 levels as compared with T_3 levels. Other serum binding proteins include transthyretin, which binds about 15% of T_4 but little, if any, T_3; and albumin, which has a low affinity but a very large binding capacity for T_4 and T_3.[6] Overall, 99.97% of circulating T_4 and 99.7% of circulating T_3 are bound to plasma proteins.

Role of the Free Thyroid Hormones

Essential to an understanding of the regulation of thyroid function and the alterations of circulating thyroid hormones seen in critical illness is the "free hormone" concept, which is that only the unbound hormone has metabolic activity. Although overall thyroid hormone production is regulated by the pituitary, serum thyroid function is affected by changes in the free thyroid hormone concentrations. Alterations in either the concentrations of binding proteins or the binding affinity of thyroid hormones to their serum binding proteins have significant effects on total serum hormone levels, owing to the high degree of binding of T_4 and T_3 to these proteins. However, despite these changes, binding effects do not necessarily translate into clinically significant thyroid dysfunction.

THYROID HORMONE ECONOMY IN CRITICAL ILLNESS

Widespread changes in thyroid hormone economy in critically ill patients[7,8] occurs as a result of (1) alterations in peripheral metabolism of thyroid hormones, (2) alterations in TSH regulation, and (3) alterations in the binding of thyroid hormone to TBG.

Peripheral Metabolic Pathways

There is considerable variation in the transcriptional and translational activities of genes important for thyroid hormone metabolism during acute illness.[9] One of the initial alterations in thyroid hormone metabolism in acute illness is the acute inhibition of D1, which results in the impairment of T_4-to-T_3 conversion in peripheral tissues.[10] D1 is

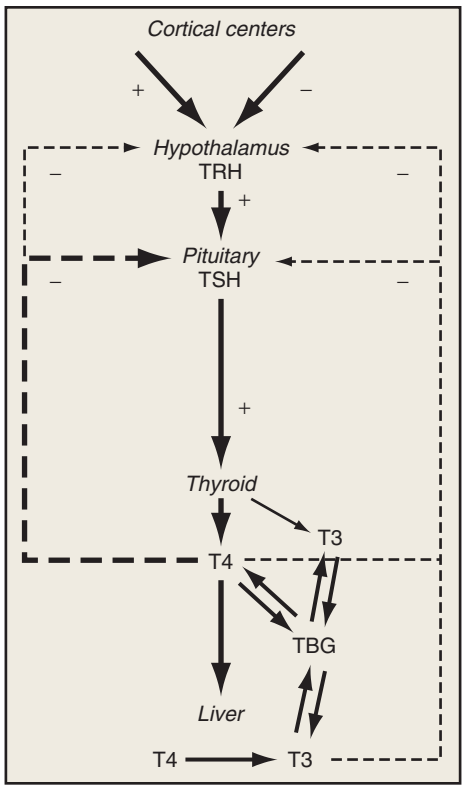

Fig. 137.1 Diagram of the hypothalamic-pituitary-thyroid axis. Inhibitory effect of T_4 and T_3 on TSH secretion is shown by dashed line and minus sign, and stimulatory effects of TRH on TSH secretion and TSH on thyroid secretion are shown by solid lines and plus signs. T_4 and T_3 may also have an inhibitory effect on TRH secretion.

inhibited by a wide variety of factors, including acute illness (Box 137.1),[2] resulting in the acute decrease in T_3 production in critically ill patients. In contrast, inner ring deiodination by D3 may be increased by acute illness, resulting in increased levels of rT_3.[11] Additionally, because rT_3 is subsequently deiodinated by D1, degradation of rT_3 decreases, and levels of this inactive hormone rise in proportion to the fall in T_3 levels. There may also be potential roles of other T_4 metabolites like 3,5-diiodothyronine (3,5-T2) and 3-iodothyronamine (3-T1AM) in critical illness, but this remains unclear.[12]

Nondeiodinative pathways may play an important role in critical illness, as sulfoconjugation and alanine side chain deamination/decarboxylation are increased, resulting in increased levels of T_3-sulfate and Triac, respectively, although thyroid hormone hypermetabolism may not entirely be the result of these processes in critical illness.[13] Triac, which binds to the thyroid hormone receptor and has weak thyromimetic activity, increases locally during illness and fasting. An increase in Triac production in the pituitary may be a factor in decreasing TSH levels during illness.

Finally, in critical illness, there is impaired transport of T_4 to peripheral tissues, such as the liver and kidney, where much of the circulating T_3 is produced. This further contributes to the decrease in the production of T_3.[14,15] Interestingly, increased expression of the thyroid hormone transporters OATP1C1 and MCT8 in animal models[16] and increased expression of MCT8 and MCT1 in the liver and muscle in human studies involving critical illness have been observed.[17] The mechanisms underlying the decrease in tissue transport during critical illness has yet to be more fully elucidated.

BOX 137.1 Factors That Inhibit Type 1 5′-Deiodinase Activity (D1)

Acute and chronic illness
Caloric deprivation
Malnutrition
Glucocorticoids
Beta-adrenergic blocking drugs (e.g., propranolol)
Oral cholecystographic agents (e.g., iopanoic acid, sodium ipodate)
Amiodarone
Propylthiouracil
Fatty acids
Fetal/neonatal period
Selenium deficiency
Hepatic disease

BOX 137.2 Factors That Decrease Pituitary Secretion of TSH

Acute and chronic illness
Adrenergic agonists
Caloric restriction
Carbamazepine
Clofibrate
Cyproheptadine
Dopamine and dopamine agonists
Endogenous depression
Glucocorticoids
Insulin-like growth factor (IGF)-1
Metergoline
Methysergide
Opiates
Phenytoin
Phentolamine
Pimozide
Rexinoids
Somatostatin and its analogs
Serotonin
Surgical stress
Thyroid hormone metabolites

Thyrotropin Regulation

It has long been recognized that serum TSH levels are usually normal in the early phases of acute illness.[18,19] Decreased TRH secretion caused by inhibitory signals from higher cortical centers, impaired TRH metabolism,[20] alteration of pulsatile TSH,[21] and the decrease or absence of a nocturnal TSH surge[21,22] may all further lower TSH levels. Serum levels of leptin, the *ob* gene product that has been shown to vary directly with thyroid hormone levels, also falls as illness progresses[23] and hypothalamic TRH secretion falls, which in turn lead to lowered TSH levels. The decrease of hypothalamic TRH gene expression in animal models, however, is not associated with increased serum T_4 and T_3 levels.[16] Finally, certain thyroid hormone metabolites that are increased during acute nonthyroidal illness may play a role in the inhibition of TSH and TRH secretion.[7]

Common medications used in the treatment of critically ill patients may also have inhibitory effects on serum TSH levels (Box 137.2). Van den Berghe and colleagues reported that intravenous (IV) administration of dopamine for 15–21 hours can acutely decrease TSH, whereas

TABLE 137.1 Factors That Alter Binding of T_4 to Thyroid-Binding Globulin

	Increase Binding	Decrease Binding
Drugs	Estrogens	Glucocorticoids
	Methadone	Androgens
	Clofibrate	L-Asparaginase
	5-Fluorouracil	Salicylates
	Heroin	Mefenamic acid
	Tamoxifen	Phenytoin
	Raloxifene	Furosemide
		Heparin
		Anabolic steroids
Systemic Factors	Liver disease	Inherited
	Porphyria	Acute illness
	HIV infection	NEFAs
	Inherited	

HIV, Human immunodeficiency virus; *NEFA,* Nonesterified free fatty acid.

its withdrawal results in a 10-fold increase in serum TSH levels.[24] Other medications that can inhibit TSH secretion include glucocorticoids, rexinoids, and somatostatin.[25]

Serum Binding Proteins

The affinity of thyroid hormones binding to transport proteins and the concentration of serum binding proteins are altered with acute illness (Table 137.1). Serum levels of transthyretin and albumin decrease, especially during prolonged illness, malnutrition, and in high catabolic states. TBG levels may be increased, as seen with liver dysfunction, or decreased, as seen with severe or prolonged illness.[26]

An acquired binding defect of T_4 to TBG is commonly seen in patients with critical illness. This is thought to result from the release of some as yet unidentified factor from injured tissues that has the characteristics of unsaturated nonesterified fatty acids (NEFAs),[27] which also inhibit T_4-to-T_3 conversion.[28] In systemically ill patients, NEFA levels rise in parallel with the severity of the illness,[29] and drugs such as heparin stimulate the generation of NEFA.[30] Many drugs, including high-dose furosemide, antiseizure medications, and salicylates, also alter the binding of T_4 to TBG.[25] The alteration in serum binding proteins in critical illness makes estimating free hormone concentrations challenging.

EVALUATION OF THYROID FUNCTION IN CRITICALLY ILL PATIENTS

Diagnostic Tests

Thyrotropin Assays

Abnormal thyroid function tests caused by nonthyroidal illness have been reported in up to approximately 70% of acutely ill patients.[31,32] In a study of 1580 hospitalized patients, only 24% of patients with suppressed TSH values (i.e., TSH levels below the limit of detection) and 50% of patients with TSH values over 20 mU/L were found to have thyroid disease.[33,34] More importantly, none of the patients with subnormal but detectable TSH values and only 14% of patients with elevated TSH values less than 20 mU/L were subsequently diagnosed with intrinsic thyroid dysfunction. A review by Kaptein and colleagues suggested that patients with isolated increased TSH concentrations in the setting of chronic cardiac, hepatic, or renal disease usually do not persist or progress to overt hypothyroidism.[35]

The development of sensitive third-generation TSH assays has led to small improvements in discerning between overt hyperthyroidism and nonthyroidal illness.[33] Overall, however, although a normal TSH level has a high predictive value of normal thyroid function, an abnormal TSH value alone is not helpful in evaluating thyroid function in critically ill patients.

Serum T_4 and T_3 Concentrations

Measurement of free thyroid hormone concentrations in patients with nonthyroidal illness is similarly fraught with difficulty.[36] The gold standard for determination of free hormone levels is equilibrium dialysis. However, this technique is labor intensive, time consuming, and rarely used. The most commonly available laboratory tests for thyroid hormone concentrations are free T_4 index, free T_4, and free T_3 that are measured by analog methods; however, these methods are estimates of free hormone concentrations and thus subject to inaccuracies.[37,38]

The free T_4 index (FT4I) is determined by multiplying the total T_4 concentration by the T_3 or T_4 resin uptake, which is an inverse estimate of serum TBG concentrations.[38] Free T_4 levels can also be measured by the analog method, a less expensive alternative to the FT4I[39]; the two tests are likely comparably,[40] and in a healthy population, there is a close correlation between the FT4I and free T_4 levels. However, in critically ill patients, this association is no longer seen, mainly because of difficulties in estimating TBG binding with resin uptake tests. Despite this, the sensitivity of the FT4I in a large study of hospitalized patients was 92.3%, compared with 90.7% for the sensitive TSH test.[33]

Of the serum thyroid function tests, serum T_3 concentrations are affected to the greatest degree by alterations in thyroid hormone economy during acute illness. Therefore there is no indication for routine measurement of serum T_3 levels in the initial evaluation of thyroid function among critically ill patients. This test should be obtained only if thyrotoxicosis is clinically suspected in this setting (i.e., in the presence of a suppressed sensitive TSH and elevated [or high normal] FT4I or free T_4 values). The total T_3 assay is preferable to the free T_3 (analog) assay, owing to the variability among laboratories with the latter test,[41] although there are limited data reporting the utility of free T_3 levels in predicting mortality in the ICU.[42] Similarly, although there is some evidence that ICU patients with lower serum rT_3 levels have higher risks of mortality,[15,43,44] rT_3 levels are generally unreliable and are difficult to distinguish between intrinsic thyroid dysfunction and nonthyroidal illness.[45]

Serum Thyroid Autoantibodies

Autoantibodies to thyroglobulin and thyroid peroxidase (TPO), two intrinsic thyroid proteins, are commonly ordered serum tests.[46] Increased serum titers of either or both of these antibodies indicate the presence of autoimmune thyroid disease, but the presence of thyroid autoantibodies alone does not necessarily indicate thyroid dysfunction, as they are present in up to 26% of the general population.[47,48] Thyroid autoantibodies do, however, add to the sensitivity of abnormal TSH and FT4I values in diagnosing known intrinsic thyroid disease.[33,34]

Imaging Studies

Imaging studies are rarely essential for the diagnosis of thyroid disorders in critically ill patients. Occasionally, functional analysis of thyroid glands using the radioisotope ^{123}I may be useful in patients with suspected thyrotoxicosis and equivocal laboratory tests. However, these studies are labor intensive, and managing the underlying acute illness often overshadows the benefits of obtaining these studies. Anatomic studies such as ultrasound, isotopic imaging, computed tomography

(CT), and magnetic resonance imaging (MRI) are useful in the evaluation of thyroid nodules and goiter, but these conditions are rarely the cause of acute illness; as such, these radiologic studies are not usually helpful in critically ill patients.

Diagnosis

Routine serum thyroid function screening of an ICU population is not recommended because of the high prevalence of abnormal thyroid function tests and low prevalence of true thyroid dysfunction. When thyroid function tests are ordered in hospitalized patients, they should only be done if there is a high clinical index of suspicion for thyroid dysfunction. Whenever possible, it is best to defer evaluation of the thyroid-pituitary axis until patients have recovered from the acute illness. Because every test of thyroid hormone function can be altered in critically ill patients, no single test can definitively rule in or rule out the presence of intrinsic thyroid dysfunction.

If there is a high clinical suspicion for intrinsic thyroid dysfunction in critically ill patients, reasonable initial tests should include either serum free T_4 index or free T_4 and TSH measurements. Assessment of these values in the context of the duration, severity, and stage of illness will allow the correct diagnosis in most patients. For example, a mildly elevated TSH coupled with a low FT4I or free T_4 is more likely to indicate primary hypothyroidism early in an acute illness, as opposed to the same values obtained during the recovery phase of the illness. Similarly, the combination of an elevated TSH and low-normal FT4I or free T_4 is more likely to indicate thyroid dysfunction in hypothermic, bradycardic patients than the tachycardic, normothermic individuals. If both the FT4I or free T_4 and TSH are normal, thyroid dysfunction is effectively eliminated as a significant contributing factor. If the diagnosis is still unclear, measurement of thyroid antibodies is helpful as a marker of intrinsic thyroid disease and increases the sensitivity of both the FT4I or free T_4 and the TSH. Only in the case of a suppressed TSH and a mid- to high-normal FT4I or free T_4 are measurements of serum T_3 levels indicated.

NONTHYROIDAL ILLNESS

In patients without underlying thyroid dysfunction, critical illness causes multiple nonspecific alterations in thyroid hormone concentrations that relate to the severity of the illness.[8,49] Proposed mechanisms of nonthyroidal illness include the induction of a central hypothyroidism arising from decreased TSH production, an acute phase response leading to thyroid binding alterations within the circulation, and impaired function of thyroid hormone transporters across cell membranes.[50]

The alterations in thyroid hormone parameters represent a continuum of changes that depends on the severity of the illness and can be categorized into several distinct stages (Fig. 137.2).[51] The wide spectrum of changes observed often results from the differing points in the course when serum thyroid function tests are obtained. Importantly, these changes are rarely isolated and are often associated with alterations of other endocrine systems, such as the hypothalamic-pituitary-gonadal and -adrenal axes.[17] Thus sick euthyroid syndrome should not be viewed as an isolated pathologic event, but as part of a coordinated systemic reaction to illness involving both the immune and endocrine systems.

The effect of nonthyroidal illness has been studied in several acute and chronic diseases. Some investigators have postulated an association between hypothyroidism and chronic kidney disease, although the thyroid function abnormalities in this patient population with a chronic illness may represent a component of nonthyroidal illness.[52] Others have reported that the presence of nonthyroidal illness portends worsened overall prognosis in patients with coexisting end-stage renal disease,[53] cardiorenal syndrome,[54] and enterocutaneous fistulas[55] and in burn patients.[43] There is limited literature regarding the optimal treatment of nonthyroidal illness in children who are hospitalized in the ICU.[56–58]

Low T_3 State

Common to all of the abnormalities in thyroid hormone concentrations seen in critically ill patients is a substantial depression of serum T_3 levels, which can occur as early as 24 hours after the onset of illness. Over half of patients admitted to the medical service will demonstrate depressed serum T_3 concentrations.[33,34] As noted earlier, multiple pathways contribute to the development of the low T_3 state in critical illness, including decrease in peripheral T_4-to-T_3 conversion through inhibition of type 1 deiodinase, increase in T3-to-T2 conversion through increased type 3 deiodinase expression, increase in T3 sulfation, and increase in Triac formation. This results in marked reduction of T_3 production and rT_3 degradation,[59] thereby leading to reciprocal changes in serum T_3 and serum rT_3 concentrations. The low T_3 state has been

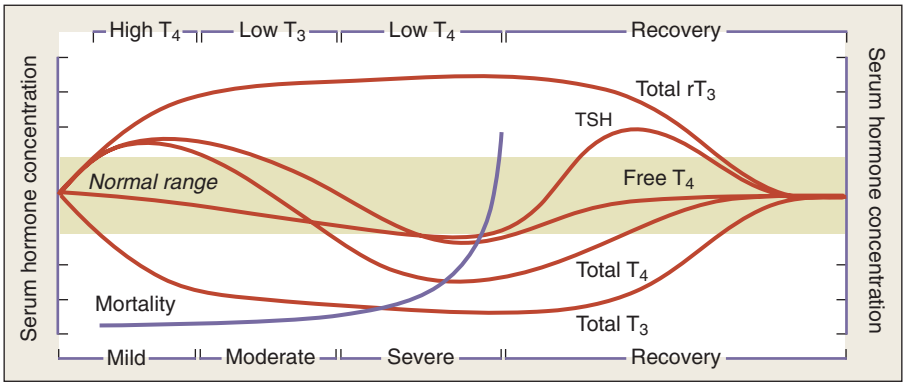

Fig. 137.2 Alterations of serum thyroid hormone concentrations in critical illness. Schematic representation of the continuum of changes in serum thyroid hormone concentrations in patients with nonthyroidal illness. Alterations become more pronounced with increasing severity of illness and return to normal range as illness subsides and the patient recovers. A rapidly rising mortality accompanies the fall in total and free T_4 concentrations. *rT_3,* reverse triiodothyronine (3,3′5′-triiodothyronine); *T_3,* 3,5,3′-triiodothyronine; *TSH,* thyroid-stimulating hormone (thyrotropin). (From Farwell AP. Sick euthyroid syndrome in the intensive care unit. In Irwin RS, Rippe JM, eds. *Intensive Care Medicine,* 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

described as a predictor of both all-cause and cardiac mortalities in critical care patients with acute decompensated heart failure.[60] During critical illness, T_3 levels are also abnormally low in peripheral tissues.[44] Moreover, thyroid hormone receptor expression is decreased in acute nonthyroidal illness,[61] possibly in response to the decrease in tissue T_3 levels.

High T_4 State

Serum T_4 levels may be elevated early in acute illness because of either the acute inhibition of type 1 deiodinase or increased TBG levels. This is seen most often in the elderly and in patients with psychiatric disorders. As the duration of illness increases, nondeiodinative pathways of T_4 degradation increase serum T_4 levels to the normal range.[34]

Low T_4 State

As the severity and duration of the illness increase, serum total T_4 levels decrease into the subnormal range. Contributors to this decrease in serum T_4 levels are (1) a decrease in the binding of T_4 to serum carrier proteins; (2) a decrease in serum TSH levels, leading to decreased thyroidal production of T_4; and (3) an increase in nondeiodinative pathways of T_4 metabolism. The decline in serum T_4 levels correlates with prognosis in the ICU, with mortality increasing as serum T_4 levels drop below 4 μg/dL and approaching 80% in patients with serum T_4 levels below 2 μg/dL.[62–64] Despite marked decreases in serum total T_4 and T_3 levels in critically ill patients, free hormone levels have been reported to be normal or even elevated,[50] providing a possible explanation for why most patients appear eumetabolic despite thyroid hormone levels in the hypothyroid range. Thus the low T_4 state is unlikely to be a result of a hormone-deficient state and is probably more of a marker of multisystem failure in critically ill patients.

Recovery State

As acute illness resolves, so do the alterations in thyroid hormone concentrations.[65] This stage may be prolonged and is characterized by modest increases in serum TSH levels. Full recovery with restoration of thyroid hormone levels to the normal range may require several weeks or months after hospital discharge. One study reported that 35 of 40 patients with nonthyroidal illness after coronary artery bypass grafting were able to regain normal thyroid function 6 months after surgery.[66]

Treatment of Nonthyroidal Illness

The question of whether nonthyroidal illness in critically ill patients represents pathologic alterations in thyroid function that negatively affect these patients or simply reflects multisystem failure (i.e., respiratory, cardiac, renal, hepatic failure) is still debatable in both adults[67–70] and children.[49] However, in most studies, thyroid hormone replacement therapy has been shown to not be beneficial,[69,71] including in pediatric patients.[72]

Initial evidence suggested a beneficial effect of liothyronine (L-T_3) on increasing organs available for harvest from brain-dead patients,[73] such that L-T_3 was included in hormonal preservation of organs before transplant.[74] However, a subsequent meta-analysis, including prospective studies, failed to confirm any beneficial effect.[75] Although L-T_3 normalizes serum T_3 levels[76] and improves hemodynamic and neurohumoral parameters in patients with dilated cardiomyopathy[77] and impaired myocardial function[78] slightly, these benefits may represent a pharmacologic effect of T_3 rather than a physiologic replacement hormonal effect. Most recently, T_3 has been used in the setting of a myocardial infarction in a small series of patients with borderline low/low T_3 levels with no adverse effects and a suggestion of a decrease in regional wall motion abnormalities.[79] These studies involving patients with congestive heart failure and myocardial infarction are more remarkable for a lack of deleterious effect of L-T_3 treatment than for any sustained clinical benefit. In any event, future studies are warranted in this patient population.

Therapies other than thyroid hormone replacement have been shown to be beneficial options in the management of nonthyroidal illness. One randomized multicenter clinical trial reported that the use of *N*-acetylcysteine (NAC) was able to prevent serum thyroid function derangements, consistent with nonthyroidal illness among patients after an acute myocardial infarction.[80] The findings suggest that NAC, a potent intracellular antioxidant, is able to reduce oxidative stress, presumed as a causative factor of nonthyroidal illness.[81] Changes in thyroid hormone parameters occurring postoperatively have been prevented by early institution of nutritional support.[82] Finally, some investigators have suggested that patients with prolonged critical illness may represent a different disease entity than those with acute disease,[9,49] and treatment with hypothalamic-releasing factors should be tested in future trials.[49] In summary, in the absence of any clinical evidence of hypothyroidism, there does not appear to be any compelling evidence for the use of thyroid hormone therapy in patients with decreased thyroid hormone parameters related to sick euthyroid syndrome.

THYROID STORM

Thyroid storm is an acute, life-threatening complication of hyperthyroidism and represents the extreme manifestation of the disease.[83,84] Historically, thyroid storm was associated with surgery for hyperthyroidism.[85] Currently, because of better recognition of the disease and improved perioperative management, thyroid storm is rare, accounting for an incidence of 0.20–0.76 per 100,000 hospitalized patients.[86–88] Most often, thyroid storm is precipitated by an intercurrent medical problem in untreated or partially treated hyperthyroid patients.[89] The diagnosis of thyroid storm is a clinical one; there are no distinctive laboratory features, and thyroid hormone concentrations are similar to those observed in uncomplicated thyrotoxicosis. Although the cause of rapid clinical decompensation is unknown, a sudden inhibition of thyroid hormone binding to plasma proteins by the precipitating factor, causing a rise in free hormone concentrations in the already elevated free hormone pool, may play a role in the pathogenesis of thyroid storm.[90]

Clinical Manifestations

Thyroid storm is primarily a clinical diagnosis; as such, the varying incidence of this disorder in patient series likely results from the strictness of the diagnostic criteria. Clinical features are similar to those of thyrotoxicosis but more exaggerated (Box 137.3). Cardinal features of thyroid storm include fever (temperature usually >38.5°C), tachycardia out of proportion to the fever, and mental status changes.[91] Tachyarrhythmias, especially atrial fibrillation in the elderly, are common. Nausea, vomiting, diarrhea, agitation, and delirium are frequent presentations. Vascular collapse and shock caused by dehydration and cardiac decompensation are poor prognostic signs, as is the presence of jaundice.[92] Multiorgan failure has been reported.[93] Coma and death may ensue in up to 20% of patients, frequently the result of cardiac arrhythmias, congestive heart failure, hyperthermia, or the precipitating illness.[94] Involvement of the central nervous system may portend a worsened prognosis.[95,96]

Most patients display the classic signs of Graves disease, the most common cause of thyrotoxicosis, with ophthalmopathy and a diffusely enlarged goiter as the usual manifestations. In the elderly, atypical signs and symptoms may include severe myopathy, profound weight loss, apathy, and a minimally enlarged goiter.[97]

BOX 137.3 Clinical Features of Thyroid Storm

- Fever (as high as 105.8°F)
- Tachycardia/tachyarrhythmias
- Mental status changes
- Delirium/agitation
- Congestive heart failure
- Tremor
- Nausea and vomiting
- Diarrhea
- Sweating
- Vasodilatation
- Dehydration
- Hepatomegaly
- Splenomegaly
- Jaundice

BOX 137.4 Precipitating Factors for Thyroid Storm

- Surgery
  - Thyroidal
  - Nonthyroidal
- Infections
  - Pneumonia
  - Upper respiratory
  - Enteric
  - Other
- Stress
- Trauma
- Diabetic ketoacidosis
- Labor
- Cardiac disease
- Iodinated intravenous contrast agents
- Radioactive iodine (^{131}I) therapy

Precipitating Factors

In the past, thyroid storm was frequently associated with surgery for hyperthyroidism (Box 137.4), with symptoms beginning a few hours after thyroidectomy in patients prepared for surgery with potassium iodide alone. Most of these cases occurred in patients who were not appropriately prepared for surgery by current standards. Certain clinical and socioeconomic factors have also been suggested to be associated with complicated hyperthyroidism, including lack of insurance, age younger than 30 or older than 50, and serum T_4 concentrations greater than twice the upper limit of normal.[98] Because of better recognition of the disease, preoperative treatment with thionamides to deplete the gland of thyroid hormone before surgery, and improved perioperative management with beta-blockade, thyroid storm now is rarely a postoperative complication of thyroid surgery.

Currently, thyroid storm appears most commonly after infection, causing the thyrotoxic state to decompensate.[89] Pneumonia, upper respiratory tract infections, and enteric infections are common precipitating infections. Other precipitating factors include stress, trauma, nonthyroidal surgery, diabetic ketoacidosis, labor, heart disease, and iodinated contrast studies in unrecognized or partially treated hyperthyroid patients.[99–102] Iatrogenic thyroid storm has also been reported as a result of thyroid hormone overdose.[103,104] Thyroid storm associated with gestational trophoblastic disease and TSH-secreting pituitary adenoma are uncommon.[105,106] Thyroid storm occurring after ^{131}I therapy is extremely rare.[107] When reported, radioiodine-induced thyroid storm usually occurs if there was no pretreatment with antithyroid drugs. Tyrosine kinase inhibitors, used for the treatment of various cancers, has also been described to precipitate thyroid storm.[108]

Diagnosis

The diagnosis of thyroid storm is based primarily on clinical judgment. The Burch-Wartofsky[109] and Akamizu[86] scoring systems may be helpful in distinguishing the likelihood of thyroid storm in patients presenting with hyperthyroid symptoms. These scoring systems use criteria that include temperature, central nervous system effects, gastrointestinal effects, cardiovascular effects, and precipitant history to assist in the diagnosis.

There are no distinct laboratory abnormalities apart from elevated thyroid hormone concentrations, which are similar to those found in uncomplicated thyrotoxicosis. Serum T_3 concentrations are often elevated to a greater degree than serum T_4 concentrations, owing to the preferential secretion of T_3 by the hyperthyroid gland.[89] There is little correlation between the degree of elevation of thyroid hormones and the presentation of thyroid storm. Serum TSH concentrations are typically undetectable; however, because of the influence of nonthyroidal illness on TSH secretion (see earlier), a low TSH by itself is insufficient to make a diagnosis of thyroid storm. Serum T_4 and T_3 concentrations in the normal range, regardless of the TSH concentration, effectively eliminate thyroid storm as a tenable diagnosis.

In thyroid storm, abnormal serum liver function tests are common. Hypocalcemia may be observed secondary to increased osteoclast-mediated bone resorption in the hyperthyroid patient. Hematocrit concentrations may be elevated because of volume contraction, and leukocytosis is common even in the absence of infection.

The differential diagnosis of thyroid storm includes sepsis, neuroleptic malignant syndrome, malignant hyperthermia, and acute mania with lethal catatonia, all of which can precipitate thyroid storm in the appropriate setting. Clues to the diagnosis of thyroid storm are a history of thyroid disease, history of iodine ingestion, and the presence of a goiter or stigmata of Graves disease. The physician must have a high clinical index of suspicion for thyroid storm, as therapy must be instituted before the availability of thyroid function test results in most cases.

Treatment

It should be emphasized that a thyroid storm is an important medical emergency that must be treated in an ICU.[89] Therapy can be divided into two major categories (Box 137.5): (1) *thyroid-directed treatment* aimed at decreasing thyroid hormone production, conversion, and secretion and blocking the peripheral manifestations of thyroid hormone and (2) *supportive treatment* aimed at controlling the fever, stabilizing the cardiovascular system, and managing the precipitating cause.

Thyroid-Directed Treatment

Prompt inhibition of thyroid hormone synthesis and secretion is essential. Antithyroid drugs are given in large doses to both inhibit synthesis of thyroid hormones and block the uptake of iodine. Propylthiouracil (PTU) is preferred over methimazole, given its greater efficacy when used in large doses, in reducing T_3 levels during severe hyperthyroidism (by inhibition of type 1 deiodinase) and impairing peripheral conversion of T_4 to T_3.[110] However, because other, more powerful inhibitors of type 1 deiodinase are usually part of the therapeutic

BOX 137.5 Treatment of Thyroid Storm

Thyroid-Directed Therapy

Direct Inhibition of Thyroid Hormone Synthesis

Propylthiouracil: 800 mg PO/PR first dose, then 200–300 mg PO/PR q8h, *or*
Methimazole: 80 mg PO/PR first dose, then 40–80 mg PO/PR q12h

Block Release of Thyroid Hormones From the Gland

Telepaque (iopanoic acid): 1 g PO once daily (if available), *or*
SSKI: 5 drops PO q8h, *or*
Lugol solution: 10 drops PO q8h, *or*
Lithium: 800–1200 mg PO once daily; achieve serum lithium levels 0.5–1.5 mEq/L

Adjunctive

Block T_4-to-T_3 Conversion

Telepaque (iopanoic acid)
Corticosteroids: dexamethasone 1–2 mg PO/IV q6h
Propylthiouracil
Most beta-blockers: propranolol 40–80 mg PO q6h

Remove Thyroid Hormones From Circulation

Cholestyramine: 4 g PO q6h, *or*
Colestipol: 20–30 mg PO once daily, *or*
Plasmapheresis, *or*
Peritoneal dialysis

Supportive Therapy

Hyperthermia

IV fluids
Antipyretics
Cooling blanket

Hemodynamic

Beta-adrenergic blocking drugs:
- Propranolol: 1 mg IV/min to a total dose of 10 mg, then 40–80 mg PO q6h, *or*
- Esmolol: 500 mg/kg/min IV, then 50–100 mg/kg/min, *or*
- Metoprolol: 100–400 mg PO q12h, *or*
- Atenolol: 50–100 mg PO daily

Other

Vasopressors
Digoxin

Etiologic

Treatment of underlying illness(es)

Other

Anxiolytics (once mental status clears)

IV, Intravenous; *PO,* orally; *PR,* rectally.

regimen in thyroid storm, the main beneficial effects of PTU are its inhibition of iodide uptake and hormone synthesis. PTU and methimazole can be administered by nasogastric tube or rectally, if necessary.[111] Neither of these preparations is available for parenteral administration, although a protocol has been reported for the reconstitution of methimazole to be given IV.[112]

Iodides, the most effective drugs to block release of thyroid hormone from the thyroid gland, should be used only after antithyroid drugs have been administered. Monotherapy with iodides will actually increase the synthesis of new thyroid hormones and markedly worsen the hyperthyroidism when the gland escapes from the initial iodide-induced blockade of hormone secretion (the acute Wolff-Chaikoff effect).[113] Previously, the iodide preparation of choice was the radiographic contrast dye, iopanoic acid, because of its high iodine content (0.6 mg iodine/g dose) and the ability for the drug to directly inhibit type 1 deiodinase and thus block T_4-to-T_3 conversion; however, this drug is largely unavailable worldwide. Thus Lugol solution and saturated solution of potassium iodide (SSKI) are currently the main sources of therapeutic iodides.[114] It is important to realize that use of iodides precludes the use of radioactive iodine as a definitive therapy for hyperthyroidism for several months. Lithium has also been reported to be effective in inhibiting thyroid hormone release to a similar degree as iodides.[115]

High-dose dexamethasone is recommended as supportive therapy, both as an inhibitor of T_4-to-T_3 conversion and as management of possible coexistent adrenal insufficiency. Beta-adrenergic blockers, specifically propranolol, are also weak inhibitors of T_4-to-T_3 conversion, although their main beneficial effect is on heart rate control.[116] Orally administered ion-exchange resin (colestipol or cholestyramine) can trap hormone in the intestine and prevent recirculation.[117] Plasmapheresis, peritoneal dialysis, and charcoal hemoperfusion have also been used in severe cases.[118]

Supportive Treatment

Simultaneously with antithyroid-directed therapy, treatments aimed at cooling the patient down to a reasonable temperature and providing hemodynamic support should be instituted. IV fluids, antipyretics, and cooling blankets are all effective. Beta-adrenergic blockers such as propranolol (oral or IV) and esmolol (IV) are given for heart rate control. Calcium channel blockers may be used to control tachyarrhythmias. Anxiolytics are frequently helpful once the patient's mental status improves. Finally, treatment of the underlying precipitating illness is essential to survival in thyroid storm.

Long-Term Therapy

Once the acute phase of thyroid storm is controlled, antithyroid drug therapy should be continued until euthyroidism is achieved, and the adjunctive therapy can be discontinued. Definitive therapeutic options for hyperthyroidism include radioactive iodine (after a few months to allow excretion of the excess iodides used during acute management of thyroid storm) and surgery.[119] Treatment with antithyroid drugs for 18–24 months in the hopes of achieving a remission is recommended for patients with Graves disease,[119] and there are emerging data that even a much longer period of antithyroid drugs may be an option.[120]

MYXEDEMA COMA

Myxedema coma is a rare syndrome that represents the extreme expression of severe long-standing hypothyroidism.[121–123] It is a medical emergency, and even with early diagnosis and treatment, the mortality can be as high as 60%.[124] The name is somewhat of a misnomer, as actual coma is rare. The syndrome includes decompensated hypothyroidism, central nervous system impairment, and cardiovascular compromise. Myxedema coma occurs most often in the elderly and during the cold months; in one series in India, 15 of 23 cases of myxedema coma were admitted in the winter.[125] As with thyroid storm, myxedema coma is usually caused by a precipitating event in untreated or partially treated hypothyroid patients.

Clinical Manifestations

The cardinal features of myxedema coma are (1) hypothermia, which can be profound; (2) altered mental status; (3) cardiovascular depression; and (4) a precipitating cause (Box 137.6). Severely hypothyroid patients essentially become poikilothermic because of disordered thermoregulation.

BOX 137.6 Clinical Features of Myxedema Coma

- Mental obtundation
- Hypothermia
- Bradycardia
- Hypotension
- Coarse, dry skin
- Myxedema facies
- Hypoglycemia
- Atonic gastrointestinal tract
- Atonic bladder
- Pleural, pericardial, and peritoneal effusions

BOX 137.7 Precipitating Factors of Myxedema Coma

- Cold stress
- Infection
  - Pneumonia
  - Urinary tract
  - Other
- Stroke
- Congestive heart failure
- Trauma
- Burns
- Surgery
- Intravascular volume contraction
  - Gastrointestinal blood loss
  - Diuretic use
- CNS-active drugs
  - Analgesics/narcotics
  - Sedatives/hypnotics
  - Tranquilizers
  - Anesthetic agents

CNS, Central nervous system.

This is the reason many cases occur in the winter months. Body temperatures as low as 23.3°C have been reported; thus rectal temperatures are essential in making the diagnosis. Excessive lethargy and sleepiness may have been present for weeks to months, often interfering with meals, and patients may even present obtunded.[125] Decreased consciousness has been found to be an important adverse prognostic indicator for mortality.[126] Rarely, psychosis and delirium have been reported. Bradycardia and hypotension may be profound, and the respiratory rate is often depressed. Because intrinsic hypothyroidism by itself is insufficient to produce the clinical syndrome of myxedema coma, a precipitating cause must be assumed to be present.

Most patients have the physical features of severe hypothyroidism, including macroglossia; delayed reflexes; dry, rough skin; and myxedematous facies, which results from periorbital edema, pallor, hypercarotenemia, and patchy hair loss. Hypotonia of the gastrointestinal tract is common and often so severe as to suggest an obstructive lesion.[127] Urinary retention caused by a hypotonic bladder is related but less frequent. Cardiac manifestations such as pleural, pericardial, and peritoneal effusions; cardiac tamponade; and heart failure may be present.[128] Severe airway obstruction has been reported.[129]

Precipitating Factors

The stress of severely cold temperatures is a common precipitant to myxedema coma (Box 137.7). Other common precipitating factors include pulmonary and urinary tract infections, cerebrovascular accidents, trauma, surgery, congestive heart failure, and intravascular volume loss from acute or chronic gastrointestinal bleeding or overuse of diuretics.[121–123] The clinical course of lethargy proceeding to stupor and then coma is often hastened by drugs, especially sedatives, narcotics, antidepressants, and tranquilizers.[130] Amiodarone, because of its high iodine content,[113] has been reported to induce both thyroid storm[131] and myxedema coma.[132] Similar to the association of tyrosine kinase inhibitors and thyroid storm, agents such as sunitinib have also been reported to induce severe hypothyroidism.[133] Many cases of myxedema coma have occurred in undiagnosed hypothyroid patients who present for other medical problems.[134]

Diagnosis

Like the diagnosis of thyroid storm, myxedema coma is a clinical diagnosis, and similar to thyroid storm, a scoring system by Wartofsky and colleagues has been proposed.[135] Elderly patients may present with particularly subtle findings. Even though it is rare, the diagnosis of myxedema coma should be considered in hypothermic, obtunded patients. Medical histories of these patients, including a prior history of hypothyroidism, may only be able to be confirmed from other sources. Friends, relatives, and acquaintances might have noted increasing lethargy, complaints of cold intolerance, sluggishness, and despondency. Clues to the diagnosis include an outdated container of L-T_4 (levothyroxine) discovered with the patient's belongings, which suggests that the patient has been noncompliant in taking thyroid hormone replacement medication. The medical record may also indicate prescribed thyroid hormone use, previous referral to treatment with radioactive iodine, or a history of thyroidectomy. Finally, the physical examination finding of a thyroidectomy scar should raise suspicion as to the diagnosis.

Because the vast majority of myxedema coma cases are a result of primary hypothyroidism,[129] the laboratory findings include an elevated serum TSH and low or undetectable total and free serum T_4 concentrations. These thyroid hormone abnormalities are similar to those in uncomplicated overt hypothyroidism. In patients with central hypothyroidism, the diagnosis of myxedema coma may be very difficult, as serum TSH concentrations will be normal or low. However, other symptoms of pituitary dysfunction are usually present in these rare patients.

Dilutional hyponatremia is common and may be severe. Elevated creatine kinase concentrations, sometimes markedly so, are encountered frequently and may misdirect the clinical picture toward cardiac ischemia.[136] However, the MB fraction in most of these cases is normal, and an electrocardiogram (ECG) often demonstrates low voltage and loss of T waves that are characteristic of severe hypothyroidism. Elevated lactate dehydrogenase (LDH) concentrations, acidosis, and anemia are common findings. Lumbar puncture reveals increased opening pressure and high protein content in the cerebrospinal fluid.

Few of the signs and symptoms discussed are unique to myxedema coma. Protein-calorie malnutrition, sepsis, hypoglycemia, and exposure to certain drugs and toxins, in addition to cold exposure, can cause severe hypothermia. Hypotension and hypoventilation, other cardinal features of myxedema coma, occur in other disease states. Furthermore, low thyroid hormone concentrations may be seen in critically ill patients with nonthyroidal illness (see earlier). As with thyroid storm, the physician must have a high clinical index of suspicion for myxedema coma, as therapy must be instituted before the availability of thyroid function test results in most cases.

Treatment

Treatment of myxedema coma is a medical emergency and should be managed in an ICU setting.[129] The mainstays of therapy are supportive care with ventilatory and hemodynamic support, rewarming, correction of hyponatremia and hypoglycemia, treatment of the precipitating incident, and administration of thyroid hormone (Box 137.8).[121,129] Sedatives, hypnotics, narcotics, and anesthetics must be minimized or avoided altogether because of their extended duration of action and exacerbation of obtundation in hypothyroid patients.

Hypothermia is one of the hallmarks of myxedema coma, and its severity may be underestimated if the thermometer used does not register below 30°C. At core temperatures below 28°C, ventricular fibrillation is a significant life-threatening risk. Despite its gravity, the management of the hypothermia of myxedema coma differs from the treatment of exposure-induced hypothermia in euthyroid subjects. In myxedema coma, patients should be kept in a warm room and covered with blankets. Active heating should be avoided, because it increases oxygen consumption and promotes peripheral vasodilation and circulatory collapse. Active heating is recommended only for situations of severe hypothermia where ventricular fibrillation is an immediate threat. In these cases, the rate of rewarming should not exceed 0.5°C per hour, and the core temperature should be raised to approximately 31°C.

Because of the possibility of coexisting adrenal insufficiency in patients with myxedema coma, IV steroids (i.e., hydrocortisone 100 mg IV every 8 hours) are indicated before initiating L-T_4 therapy. Parenteral administration of thyroid hormone is necessary because of uncertain absorption through the gut.[137] A reasonable approach is an initial IV loading dose of 200–300 μg of L-T_4. If there is inadequate improvement in the state of consciousness, blood pressure, or core temperature during the first 6–12 hours after administration, another dose of L-T_4 should be given to bring the total dose during the first 24 hours to 0.5 mg. This should be followed by 50–100 μg IV every 24 hours until the patient is stabilized. Alternatively, in the most severe cases, some clinicians recommend using L-T_3 at a dosage of 12.5–25 μg IV every 6 hours until the patient is stable and conscious. Caution must be used to avoid overstimulation of the cardiovascular system. Once stable, the patient should be switched to L-T_4. The dose of thyroid hormone should be adjusted on the basis of hemodynamic stability, the presence of coexisting cardiac disease, and the degree of electrolyte imbalance.

Although myxedema coma is associated with a high mortality, survival can be maximized by correcting the secondary metabolic disturbances and reversing the hypothyroid state in a sustained but gradual fashion. Efforts to correct hypothyroidism too rapidly may completely negate the beneficial effects of the initial treatment.

BOX 137.8 Treatment of Myxedema Coma

Supportive

Assisted ventilation
Hemodynamic support
Passive rewarming for hypothermia
Intravenous glucose for hypoglycemia
Water restriction or hypertonic saline for severe hyponatremia
Hydrocortisone IV (100 mg q8h)
Treatment of precipitating factor(s)
Avoidance of all CNS-acting medications

Thyroid Hormone Replacement

L-T_4: 200- to 300-μg loading dose IV, up to 500 μg IV in the first 24 h *and/or*
L-T_3: 12.5 μg IV q6h

CNS, Central nervous system; *IV,* intravenous.

Long-Term Therapy

Once the patient with myxedema coma is clinically stable, thyroid hormone replacement can be switched to oral L-T_4. The dose of L-T_4 should be adjusted over the ensuing weeks and months to achieve serum T_4 and TSH concentrations in the normal range.

KEY POINTS

- Critical illness can result in multiple nonspecific alterations in serum thyroid function tests that relate to the severity of the illness.
- The interpretation of thyroid function tests in the ICU patient can be challenging.
- In the ICU, identifying those patients with intrinsic thyroid dysfunction must take into consideration both the clinical assessment of the patient and the duration and severity of the illness. Whenever possible, it is best to defer evaluation of thyroid function until the patient has fully recovered from the critical illness.
- The benefits of treating nonthyroidal illness, including use of thyroid hormone, in various populations remain controversial and incompletely understood.
- Thyroid storm and myxedema coma are medical emergencies that are associated with high mortality rates. Recognition of their clinical presentation and rapid initiation of treatment are critical.

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Diabetes Insipidus

Serge Brimioulle

Diabetes insipidus is a disorder of water metabolism associated with polyuria, urine hypotonicity, and hypernatremia.[1,2] The quantitative criteria include urine output greater than 200 mL/hr or 3 mL/kg/hr, urine osmolality less than 150 mOsm/kg, and plasma sodium greater than 145 mEq/L. If urine osmolality measurement is not available, hypotonicity can be assessed from a urine specific gravity less than 1.005.

CENTRAL DIABETES INSIPIDUS

Neurogenic or central diabetes insipidus is characterized by a lack of antidiuretic hormone (ADH) that may result from any injury to the anterior hypothalamus, pituitary stalk, or posterior pituitary gland.[3] In acute critically ill patients, the most common causes of diabetes insipidus are surgery for pituitary tumors, cerebral trauma, intracranial hypertension, and brain death (Table 138.1). Diabetes insipidus also may occur as a complication of bacterial meningitis or encephalitis, vascular aneurysm or thrombosis, drug administration, or alcohol intoxication. Injuries to the hypothalamus most often yield permanent diabetes insipidus because ADH is synthesized in the hypothalamus itself. Injuries to the pituitary stalk and neurohypophysis more commonly cause transient diabetes insipidus because hypothalamic ADH secretion can be effective even in the absence of anatomic pathways to the normal site of release. Chronic diabetes insipidus in critically ill patients generally results from tumors of the pituitary region and from the sequelae of cerebral trauma.

CLINICAL PICTURE

In complete hypothalamic or pituitary injuries, diabetes insipidus generally develops 6–24 hours after the injury because previously released ADH remains circulating this long. Patients with untreated diabetes insipidus usually develop urine outputs of 10–15 L/day. When the thirst mechanism is preserved, it is activated as soon as osmolality or volemia decreases. If the patient remains conscious and is given free access to water, he or she may be able to drink large amounts and compensate for the urine losses. In other cases, the large amounts of dilute urine rapidly result in dehydration, with hypovolemia and hypotension, and in hypernatremia, with neurologic deterioration. It is important that diabetes insipidus be recognized and treated rapidly, especially in comatose or noncommunicative patients. In patients with partial diabetes insipidus, the onset of polyuria may be delayed and the volume of urine may be lower. Nevertheless, if urine is hypo-osmolar and the diabetes insipidus is not treated, dehydration and hypernatremia finally occur and cause symptoms.

Clinical signs of hypernatremia usually appear only when the plasma sodium concentration increases to greater than 155–160 mEq/L or plasma osmolality increases to greater than 330 mOsm/kg.[1–3] Signs may appear sooner if hypernatremia is associated with other metabolic disorders, particularly with disorders that also increase plasma osmolality. Symptoms mainly include confusion and lethargy. Severe hypernatremia results in coma and sometimes seizures. Acute and severe dehydration and hypernatremia may lead to cerebral shrinkage, sometimes associated with subdural or intraparenchymal hemorrhages.

Clinical signs of dehydration include blood volume depletion and hypotension in the most severe cases. Biologic markers of dehydration are usually absent in ICU patients with central diabetes insipidus because the urine loss begins abruptly and commonly reaches more than 1 L/hr. The free water deficit can be estimated by the following formula:

$$\text{Deficit (L)} = \text{body weight (kg)} \times 0.6 \times (Na^+ - 140)/Na^+$$

The formula assumes that only free water has been lost and that sodium stores are normal. Most often, some sodium has been lost together with additional water, and the total water deficit is even higher than that estimated from the formula. A moderate level of hypernatremia (e.g., 155 mEq) already is associated with a free water deficit of more than 4 L and a total water deficit that may be much higher if sodium has been lost.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of polyuria includes the intake of diuretic drugs, hyperglycemia, fluid overload, and fluid mobilization. The search for diuretic administration should include not only conventional diuretics but also mannitol and iodinated contrast agents. The administration of diuretics may not be evident when these substances have been given before admission to the intensive care unit (ICU) (e.g., in another hospital before patient transfer; in an ambulance during transfer; or in the operating room during neurosurgery, trauma surgery, or vascular surgery). Preventive administration of furosemide and mannitol is given routinely in some neurosurgical procedures and may result in marked polyuria during and after the operation. Hyperglycemia-induced osmotic diuresis is common, can be suspected from polyuria or from hyperglycemia, and is confirmed or ruled out by the presence or absence of glucosuria. Hypervolemia, resulting from fluid overload or unmasked by discontinuation of sustained positive-pressure ventilation, may increase urine output to greater than 5 L/day for several days in patients with normal renal function. Mobilization of edema, at the time of recovery from disease or from surgery, also can result in sustained polyuria. In all these conditions, however, the urine remains close to isotonic (osmolality about 300 mOsm/kg). Abundant intake of hypotonic fluid can cause polyuria and urine hypotonicity but does not result in hypernatremia if renal function is normal. The observation of decreased urine output after ADH administration is

TABLE 138.1 Causes of Diabetes Insipidus

Central
Congenital anomalies: corpus callosum agenesis, cleft palate
Granulomatous disease: sarcoidosis, tuberculosis, Wegener disease
Histiocytosis
Sickle cell disease
Idiopathic: autoimmune
Tumors: suprasellar, infrasellar, aneurysms
Infection: meningitis, encephalitis
Head trauma, neurosurgery, brain death
Nephrogenic
Congenital disease
Renal disease: obstructive uropathy, reflux nephropathy, cystic disease, electrolyte disorders
Renal involvement in systemic disease: sarcoidosis, amyloidosis, sickle cell disease
Drugs: phenytoin, aminoglycosides, amphotericin, antivirals, demeclocycline, lithium

TABLE 138.2 Management of Diabetes Insipidus

Control polyuria with DDAVP or vasopressin
Calculate and replace free water loss
Monitor and replace urine losses hourly
Monitor plasma electrolytes and adapt therapy every 4 hours

DDAVP, 1-deamino-8-D-arginine vasopressin.

not diagnostic of diabetes insipidus because ADH is able to reduce urine output and to increase urine osmolality in all conditions except nephrogenic diabetes insipidus.

Copeptin has been recently reported useful in the diagnosis of diabetes insipidus.[4,5] ADH and copeptin are released together and in a 1:1 proportion during the breakdown of the VP-NPII precursor. Whereas ADH levels are difficult to measure because of technical reasons, copeptin has been reported as a sensitive and simple marker of ADH release.[4,5] Copeptin is therefore interesting to differentiate primary polydipsia and the two forms of diabetes insipidus. It has been reported useful in chronic states of hypotonic polyuria and during diagnostic tests.[6,7] Copeptin is less contributive in critically ill patients, in whom the symptom clarity and the recent history are often sufficient to yield the diagnosis.

TREATMENT

The management of diabetes insipidus includes two components (Table 138.2): (1) reduction of excessive urine output and (2) correction of water deficit. The polyuria of central diabetes insipidus is treated effectively by vasopressin (ADH) or by its synthetic analog desmopressin acetate (DDAVP [1-deamino-8-D-arginine vasopressin]).[8,9] As indicated by its multiple names, vasopressin not only has antidiuretic but also vasoconstrictive and oxytocic effects, whereas desmopressin essentially retains the antidiuretic action. The effects of aqueous vasopressin (4–10 U subcutaneously or intramuscularly) on diuresis begin rapidly but last for only a few hours. Vasopressin must be repeated every 4–6 hours, and it has been recommended only for diagnostic purposes or in acute conditions (e.g., trauma) in which the diabetes insipidus might be transient. The effects of vasopressin tannate in oil emulsion (2–5 U intramuscularly) last 48–96 hours, but the preparation requires close attention to warming and mixing the suspension before injection. Vasopressin tannate previously used to be the standard therapy in patients with central diabetes insipidus, but it has now been abandoned in favor of desmopressin. Vasopressin tannate, where available, still may be used in patients who are refractory to desmopressin or who experience significant side effects. Desmopressin has prolonged effects (8–20 hours) and is appropriate for intravenous, subcutaneous, and intranasal routes. Lypressin is another ADH analog that is appropriate for intranasal use, but its effectiveness is limited by its duration of action of only 4–6 hours. Desmopressin is known to increase factor VIII and von Willebrand factor levels and is sometimes used for this purpose in patients with coagulation disorders and in surgical procedures associated with significant bleeding. In the ICU and acute central diabetes insipidus, desmopressin is initially given as 10–20 μg intranasally and repeated every 30–60 minutes until urine output is reduced to less than 100 mL/hr. The initial dose required to maintain a normal urine volume ranges from 10 to 60 μg in most patients. The total appropriate dose is given again when the urine output increases again to greater than 200 mL/hr (i.e., after 8–24 hours). The dosage must be reduced if urine output is excessively decreased. Systematic administration is not recommended because most cases of diabetes insipidus seen in ICUs are associated with acute events and may be incomplete or intermittent or both. The subcutaneous route is seldom used because absorption may be erratic in vasoconstricted patients and because an intravenous line is virtually always available in ICU patients. Desmopressin is injected intravenously when the intranasal route is not available (i.e., in cases of rhinorrhea and facial trauma). The required initial dose ranges from 2 to 20 μg and is given as repeated 2- to 4-μg boluses.

Vasopressin therapy can be associated with arterial hypertension, myocardial infarction, mesenteric infarction, peripheral ischemia, and uterine cramps. Vasopressin tannate may cause allergic reactions, ranging from urticaria to anaphylaxis, and sterile abscesses at sites of injection. Desmopressin may interfere with anticoagulant drugs and cause hypercoagulability. When given in excess, all these antidiuretic agents can result in oliguria, hyponatremia, and water intoxication. The severity of diabetes insipidus may vary over time, even in patients with chronic diabetes insipidus, and some patients with chronic diabetes insipidus who are used to drinking large amounts of water may continue to do so even if urine output is limited by a diuretic drug.

Patients with acute diabetes insipidus should receive a sufficient amount of water to match urine output until the polyuria is controlled and to correct the deficit of free water that already exists at the time of diagnosis. If the gastrointestinal system is functional, water can be infused at rates of 1–2 L/hr through a gastric tube. Otherwise, isotonic dextrose should be infused intravenously in appropriate amounts (hypotonic dextrose administration can be obtained by infusing equal amounts of water and isotonic dextrose in a central vein, but this procedure has been associated with vascular injuries). Practically, the dedicated gastric or intravenous infusion rate is adjusted at least hourly to match the urine output of the last equivalent period. Additional water is provided to correct the initial water deficit over a few hours. Plasma electrolytes should be monitored every 4 hours until a normal natremia is restored and stabilized. Blood glucose must be monitored closely and hyperglycemia treated aggressively using intravenous insulin. Failure to control hyperglycemia may be associated with osmotic diuresis caused by glucosuria and superimpose an equivalent of diabetes mellitus on the already present diabetes insipidus.

NEPHROGENIC DIABETES INSIPIDUS

Nephrogenic diabetes insipidus is characterized by the inability of the renal parenchyma to concentrate urine in response to ADH.[10] The disorder is seldom diagnosed in the ICU and is usually more severe

when it is congenital. Hereditary forms generally result from mutations to the AVP-2 receptors or AQP-2 water channels. Acquired forms are the result of vasopressin resistance of the distal tubule and collecting duct or of markedly reduced renal concentrating capacity. Most of them are attributed to electrolyte disturbances and to lithium therapy, but many other drugs have been implicated. Nephrogenic diabetes insipidus may be treated with a low-sodium, low-protein regimen that reduces the solute load, with thiazide diuretics that induce a mild volume depletion and help reduce the urine volume to acceptable values, and with nonsteroidal antiinflammatory drugs such as indomethacin that inhibit prostaglandin synthesis.

KEY POINTS

- Diabetes insipidus is characterized by polyuria, urine hypotonicity, and hypernatremia.
- Central diabetes insipidus results from a lack of ADH; nephrogenic diabetes insipidus results from renal insensitivity to ADH.
- In the ICU, diabetes insipidus is caused mainly by pituitary surgery, trauma, and brain death.
- Clinical signs are related to dehydration and hypernatremia.
- ICU patients generally are unable to compensate for excessive urine losses by drinking.
- Differential diagnosis includes administration of diuretics, mannitol, and iodinated agents.
- Polyuria is controlled with desmopressin 10–20 μg intranasally or 2–4 μg intravenously.
- Water deficit is corrected with enteral water or intravenous 5% dextrose in water.
- Diuresis should be monitored hourly, and ongoing urinary losses should be compensated for.

References for this chapter can be found at expertconsult.com.

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139

General Principles of Pharmacokinetics and Pharmacodynamics

Mitch A. Phelps and Henry J. Mann

Critically ill patients suffer from a variety of physiologic insults that result in a rapidly changing physiologic status, thus making appropriate drug dosing a challenging problem. Understanding how these changes affect pharmacokinetics and pharmacodynamics can result in improved dosing decisions. This chapter reviews the basic principles of pharmacokinetics and pharmacodynamics and how they may be affected by critical illness.

The terms *pharmacokinetics* and *pharmacodynamics* describe the amount of drug in the body at a given time and the pharmacologic effects caused by the drug.[1] Pharmacokinetics describes the movement of a drug into, within, and out of the body over time, whereas pharmacodynamics explains the effects the drug has on the body. How a patient responds to therapy is a function of both the physiologic processes that dictate drug exposure (the changes in drug concentration over time) and the processes that govern how that exposure translates into pharmacodynamic effects. Understanding the pharmacokinetic parameters of clearance, volume of distribution, half-life, steady state, and absorption, along with pharmacodynamic principles such as receptor theory, potency, affinity, tolerance, and minimum effective concentration can enhance the treatment of critically ill patients.

GENERAL PRINCIPLES OF PHARMACOKINETICS

Clearance, volume of distribution, half-life, and bioavailability are four pharmacokinetic parameters that allow the clinician to better estimate dosing requirements. If the concentration of a drug in a sampled fluid (e.g., plasma, urine, saliva) correlates well with its pharmacologic response (therapeutic or toxic), then the application of pharmacokinetics is likely to be beneficial (Fig. 139.1). This is especially true for drugs where lack of efficacy because of low exposure or toxicity because of high exposure pose significant risks to the patient.

Measurement of the relationship between drug concentration and therapeutic or toxic response in a large number of patients enables the development of a therapeutic range or target concentration for that drug (Fig. 139.2).[2,3] A multitude of host factors (e.g., hemodynamic status, decreased organ function, nutritional status, concurrent disease states) increase the likelihood that drug dosing based on individualized pharmacokinetic assessment will be beneficial.[4,5] Gender-related differences can occur in both pharmacokinetic and pharmacodynamic responses.[6] Individual chapters in this text are devoted to many of these agents and their adjustments for dosage in patients with renal or hepatic failure.

PHARMACOKINETIC MODELS

The pharmacokinetic concepts of clearance, volume of distribution, half-life, and bioavailability are based on enormously complex physiologic principles and use mathematical models that make many assumptions. Most clinically useful pharmacokinetic equations assume one- or two-compartment models (see Fig. 139.2).

When the drug enters the one-compartment model, it is assumed to be instantaneously and completely mixed in a given volume of distribution, resulting in a uniform concentration throughout the compartment. The rate constant *K* reflects the usual situation of elimination by a first-order, linear process. The drug is assumed to enter the compartment instantaneously in the case of an intravenous bolus dose. If the dosage is administered through oral or intramuscular routes, entry into the compartment is assumed to occur at a rate defined by a first-order absorption rate constant (Ka), whereas entry into the compartment is assumed to occur at a constant rate described by a zero-order rate constant (Ro) if the drug is administered by intravenous infusion. *Bioavailability* (F) is defined as the fraction of the administered dose that reaches the systemic circulation.

Clearance (CL) is a primary parameter that can be physiologically associated with a particular organ in the body such as the liver or kidney. Clearance is often expressed by the equation $CL = K \times V$, leading to the impression that CL is a function of the parameters K and V. However, this arrangement of the equation is not correct from a physiologic point of view. CL and V are both primary parameters, and K is a secondary parameter. The first-order rate is determined by changes in either CL or V, and the equation is correctly written as $K = CL/V$.

Half-life ($t_{1/2}$) is a useful measure of how quickly a drug is eliminated from the body and is related to the first-order elimination rate constant:

$$t_{1/2} = \frac{\ln(2)}{K} = \frac{0.693}{K} \qquad \text{(Equation 1)}$$

Specifically, $t_{1/2}$ defines the time taken for the drug concentration to decrease by one-half. In a linear pharmacokinetic system with first-order elimination, $t_{1/2}$ is constant, and it takes the same amount of time for the concentration to fall from 100 to 50 (arbitrary units) as it does to decline from 50 to 25 (Fig. 139.3).

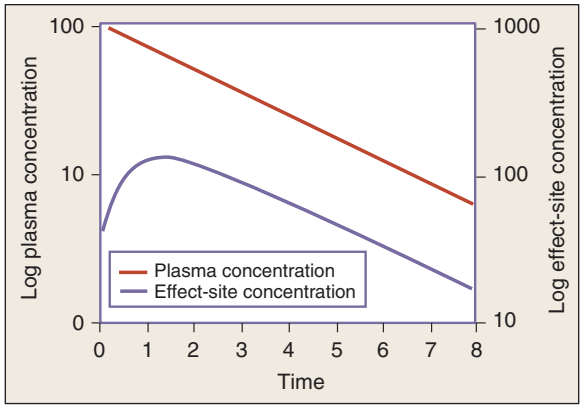

Fig. 139.1 For concentration monitoring to be useful, there must be a strong relationship between concentration of the drug measured in an easily accessible fluid and concentration at the effect site.

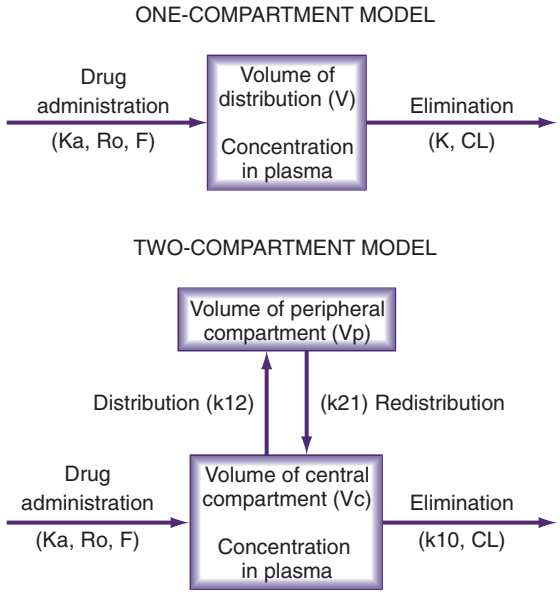

Fig. 139.2 Pharmacokinetic models simplify complex physiologic process. Concentrations may behave as if the body were a single rapidly equilibrating compartment or follow a more complicated two-compartment model in which a slower distribution phase into tissues is observed. See text for explanation of terms.

The one-compartment model allows concentrations at any point in time to be calculated:

$$C2 = C1 \times \exp^{-K \times \Delta t} \qquad \text{(Equation 2)}$$

where Δt is the time between measurements C1 and C2. The monoexponentially decreasing concentration-time curve appears linear when plotted on semi-log coordinates.

Sometimes a drug does not instantly equilibrate with all tissues in the body. This can often be adequately described by a two-compartment model, which is characterized by a rapidly distributing central compartment and a more slowly equilibrating peripheral compartment (Fig. 139.4). The equation describing the concentration-time profile for the two-compartment model is:

$$C = A \times \exp^{-\alpha \times t} + B \times \exp^{-\beta \times t} \qquad \text{(Equation 3)}$$

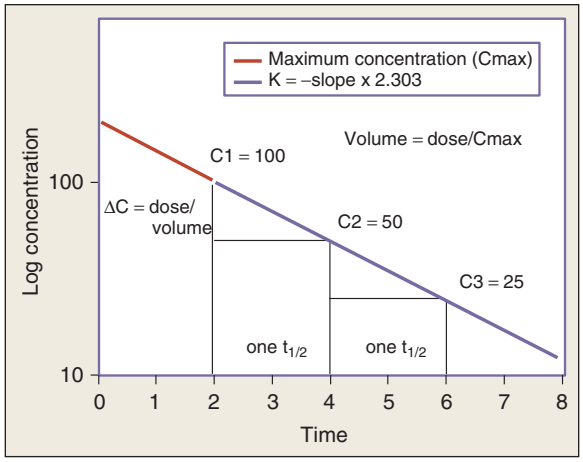

Fig. 139.3 Log concentration-time curve for a one-compartment model after intravenous administration, illustrating volume of distribution, elimination rate constant, and half-life.

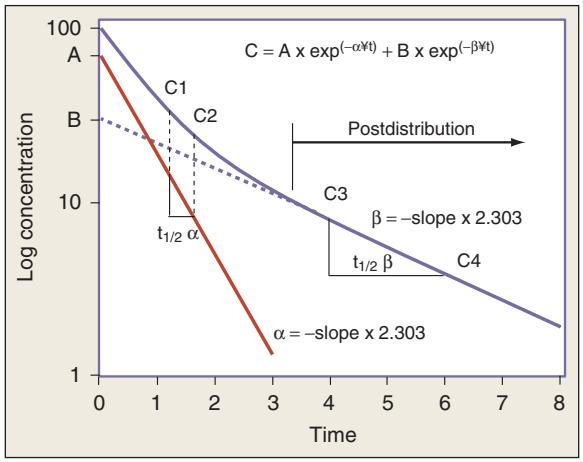

Fig. 139.4 Log concentration-time curve for a two-compartment model after intravenous administration, illustrating a distribution period (α) and postdistribution period (β). Concentrations C1 and C2 reflect both distribution and elimination processes, whereas concentrations C3 and C4 reflect postdistribution elimination processes.

The distinguishing feature of this biexponential equation is that when plotted on semi-log coordinates, the concentrations are the sum of two distinct straight lines representing two half-lives. One is the *terminal* or β half-life, and the other is the *rapid distribution* or α half-life. As the rapid distribution exponential becomes negligible in the equation, the slower exponential term dominates, and the concentration-time profile resembles that of a single-compartment drug. Consequently, the equation:

$$C2 = C1 \times \exp^{-\beta \times \Delta t} \qquad \text{(Equation 4)}$$

in which β replaces K, can still be used to predict concentrations, as long as both C1 and C2 are in the postdistributive phase. This sum-of-exponentials approach can be extended to three-compartment or even more complex models, but it is difficult to obtain all the concentrations needed to characterize each exponent.

Clearance

CL is a primary pharmacokinetic parameter that measures the ability of the body to eliminate a drug. It is often stated that clearance is the

volume of blood (plasma) that is completely cleared of drug per unit time. Although this is one way to define clearance, it does not capture the relationship between drug clearance (mL/min) and the rate of drug elimination (mg/hr). In pharmacokinetics, the general concept of clearance is also the rate of elimination relative to the concentration. In a first-order pharmacokinetic system, the rate of elimination is proportional to the drug concentration; clearance is this proportionality constant:

$$\text{Rate of elimination} = CL \times \text{concentration} \qquad \text{(Equation 5)}$$

Clearance is clinically useful because it can be directly related to the organ of elimination. We can talk about renal clearance, hepatic clearance, or biliary clearance, and the sum of each of the individual clearances is the total body clearance. This allows us to adjust doses in response to changes in organ function. A patient with developing renal failure is likely to require a reduction of the dose of a drug that is eliminated by the kidney but not necessarily a dose reduction of a drug that is eliminated by the liver. For example, if the clearance of a drug is known to be 50% renal and 50% hepatic and renal function is decreased by 50%, it is necessary to reduce the dose by only 25% to maintain the same concentration.

The area under the curve (AUC) is a useful measure of drug exposure and results from dose and CL:

$$AUC = \frac{Dose}{CL} \qquad \text{(Equation 6)}$$

This concept is similar to a steady-state concentration (Css) being considered as the measure of drug exposure during a continuous intravenous infusion. The Css is solely a function of the infusion rate (Ro) and CL:

$$Css = \frac{Ro}{CL} \qquad \text{(Equation 7)}$$

Notice that Css is not a function of the volume of distribution. Though counterintuitive, doubling the volume of distribution will not result in a halving of Css. The important point is that the equation is predicting the concentration at a steady state. During a constant infusion, rapidly doubling the volume of distribution will only transiently halve the concentration. If clearance remains unchanged, the concentration will return to the same Css.

With intermittent dosing, drug concentrations go up and come down during each dosing interval. The average Css (Css,avg) is a time-averaged concentration (i.e., the mean of all concentrations during the dosing interval); it is also a function of clearance and the dosing rate. In the case of oral administration, the dosing rate is a function of the dose administered (D), dosing interval (τ), and F:

$$Css,avg = \frac{F \times D/\tau}{CL} \qquad \text{(Equation 8)}$$

As before, the overall drug exposure is not influenced by the volume of distribution, but it does change in proportion to changes in clearance or the dosing rate through changes in F, D, or τ.

Volume of Distribution

The volume of distribution (V) is another primary pharmacokinetic parameter and is useful for determining the change in drug concentration for a given dose. After an intravenous bolus dose in a one-compartment pharmacokinetic model, the change in concentration (ΔC) between the maximum concentration (Cmax) and the concentration immediately before the dose is administered is a function of the dose (D) and the V:

$$\Delta C = \frac{D}{V} \qquad \text{(Equation 9)}$$

This equation is useful for predicting both the concentration after a first bolus dose and the increase in concentration at any point in time after a bolus dose. If a concentration before a bolus dose is known, the equation can be used to predict the increase in concentration after the dose is administered (see Fig. 139.3). This equation is also useful for estimating the dose needed to reach a given concentration. If it is known that the volume of distribution is 0.45 L/kg and a Cmax of 10 mg/L is desired after the loading dose, the dose is estimated to be 10 mg/L $\times$ 0.45 L/kg = 4.5 mg/kg. This equation only predicts loading doses and not maintenance doses. A steady-state condition is not necessary, which is common in critical care.

The value for the volume of distribution does not necessarily coincide with any particular physiologic space. The veracity of this statement becomes readily apparent when one considers a drug such as digoxin, which has a volume of distribution of approximately 440 L. Clearly, a volume of distribution of that magnitude cannot have a relationship to any physiologic space in an average-sized human. Therefore the term *apparent volume of distribution* is often used.

The concept of the volume of distribution gets more complex when more than one compartment is needed to describe the pharmacokinetics of a drug. Mathematically, the volume of distribution is a hypothetical volume that is needed to relate the amount of drug in the body to a measured concentration in a fluid (plasma). Unlike the one-compartment model, wherein the entire drug in the body is regarded as being in a single compartment until it is eliminated, drug also circulates through additional compartments in a multicompartment model. In this situation, the volume of distribution must increase as drug distributes to other compartments until distribution equilibrium among all compartments is reached. Technically, an infinite number of volumes of distribution are observed as this equilibration process occurs, but only three are commonly defined. The *volume of distribution of the central compartment* (Vc) is the volume of the usual sampling compartment; it is always the smallest volume term. Immediately after the administration of an intravenous bolus, all added drug is in the central compartment, and Vc can be used to calculate a change in concentration.

The volume of distribution increases over time until a *distribution equilibrium* is reached among all compartments. This is the largest value for the volume of distribution. The fact that the distribution equilibrium has occurred can be discerned from a log concentration versus time plot (see Fig. 139.4). The curve becomes log linear when the rate of drug entry into each peripheral compartment equals the rate of return from each compartment. Because it is often calculated using the clearance and β or terminal elimination half-life, this volume is often called V_β:

$$V_\beta = \frac{CL}{\beta} \qquad \text{(Equation 10)}$$

The *steady-state volume of distribution* (Vss) is the sum of the volumes of all the compartments in the model. If a drug were infused to steady state, Vss would be the proportionality constant relating Css to the total amount of drug in the body.

Half-Life

Half-life ($t_{1/2}$) is defined as the time taken to reduce the drug concentration by half (see Fig. 139.3). Half-life is referred to as a *secondary parameter* because it is a function of two primary parameters, clearance and volume of distribution:

$$t_{1/2} = \frac{\ln(2) \times V}{CL} = \frac{0.693 \times V}{CL} \qquad \text{(Equation 11)}$$

A change in either clearance or volume of distribution results in a proportional change in half-life.

Because the half-life characterizes how rapidly concentrations decrease over time, it is used to determine how frequently a drug needs to be dosed. Drugs with rapid half-lives need to be dosed more frequently than drugs with longer half-lives. For example, the half-life for an aminoglycoside is relatively short in patients with good renal function, and the drug may require dosing every 6 hours. In patients with poor renal function, the half-life is longer, and dosing may be prolonged to 24-hour intervals to maintain appropriate peak and trough concentrations. In the critical care patient, the development of renal failure can significantly change aminoglycoside clearance, and the accompanying change in drug half-life will necessitate a change in dosing interval.

In a one-compartment system with constant clearance and volume of distribution, drug half-life is also constant. However, in a multicompartment model, the volume of distribution increases over time as drug equilibrates into tissue compartments until V_β is reached. According to the previous equation, the half-life also increases over time and eventually reaches a maximum at $t_{1/2\beta}$ (see Fig. 139.4).

In multicompartment models, there is usually one half-life of interest for each compartment. These half-lives are derived from the hybrid time constants associated with each compartment. In a two-compartment model, these two exponentials are typically called α and β and are arbitrarily termed the *rapid* and *slow exponents,* respectively. These time constants give rise to the distribution $t_{1/2}\alpha$ and the slower or terminal $t_{1/2}\beta$. One useful way to think about distribution half-lives is analogous to the standard way of thinking about any half-life. In the one-compartment model, it takes five half-lives for 97% of the drug to be eliminated from the body. The situation is similar for each exponent, but the interpretation is that it takes five distribution half-lives for that exponent to become negligible in the sum of exponentials equation—that is, for the rapid distribution phase to reach equilibrium.

Most drugs have a rapid distribution phase that could be detected if concentrations were measured frequently enough. Aminoglycosides are again an illustrative example of this concept because they have a rapid, although not instantaneous, distribution phase (Fig. 139.5).

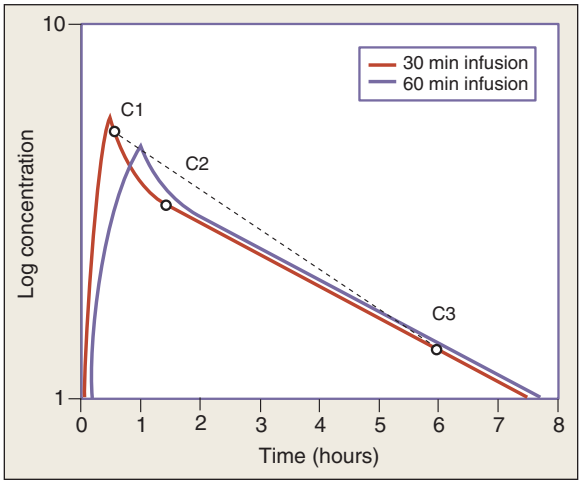

Fig. 139.5 If an aminoglycoside (tobramycin) is administered by intravenous infusion over 30 minutes, the peak concentration will be higher than with infusion over 60 minutes, but the total area under the curve will be the same. In therapeutic drug monitoring, if sample C1 is obtained during the distribution phase and paired with C3, the calculated half-life will be shorter than if two postdistribution concentrations (C2 and C3) are paired together.

With a distribution phase half-life of 5–10 minutes, it would take approximately 25–50 minutes before the log-linear elimination phase could be observed. This results in the recommendation to wait approximately 1 hour after the end of an infusion before sampling blood to measure an aminoglycoside concentration. If a blood sample is obtained before this time, the drug will still be in the distribution phase, and the concentration measured will lead to underestimation of the drug half-life. In addition, slowly equilibrating compartments have been demonstrated when aminoglycoside concentrations are measured during washout.[7] Aminoglycosides are usually dosed frequently enough so that the slowly equilibrating compartment is not detected.

Bioavailability

The extent of drug absorption, termed *bioavailability* (F), is generally a reference to the exposure when the drug is intravenously administered. This parameter is determined by comparing the AUC of the drug intravenously administered to that of the same drug administered via another route. The bioavailability of a drug intravenously administered is regarded as being 100% (i.e., F = 1.0), and other routes of administration (e.g., oral dosing, intramuscular injection) often have a reduced bioavailability (e.g., F = 0.8, or 80% bioavailability). Bioavailability is a function of the extent of absorption and the amount of drug metabolized before entering the systemic circulation (first-pass effect). Drugs with low bioavailability either cannot be administered by any route other than the intravenous one (e.g., sodium nitroprusside, dobutamine) or require higher doses when administered via the oral route compared with the intravenous route (e.g., furosemide, morphine, propranolol). Alternative routes of administration (e.g., rectal, topical, subcutaneous injection, intramuscular injection) are occasionally used in critically ill patients, owing to poor oral bioavailability. These routes all suffer from problems with delayed or poorly predictable serum concentrations. Vasoconstriction, hypoperfusion, edema, gastric suctioning, ileus, diarrhea, and enhanced gastrointestinal motility are all common problems in critically ill patients that can adversely affect bioavailability.

The *first-pass effect* limits drug absorption in three ways. As some drugs enter the gut wall, they are susceptible to transport proteins (primarily P-glycoprotein) that actively pump the molecules back into the lumen of the gastrointestinal tract.[8] Molecules that escape this process are then subjected to metabolism by enzymes in the gut wall. Those that escape gut metabolism enter the hepatic circulation and are subjected to metabolism in the liver before their first opportunity to be presented to the systemic circulation.[9] Drugs that have a high hepatic extraction ratio (i.e., are very efficiently removed by the liver) are most likely to show decreased bioavailability because of this first-pass effect; conversely, the bioavailability of these drugs increases if liver dysfunction decreases the hepatic extraction ratio.

Steady State

After an infusion is started, drug concentrations increase and eventually reach a concentration that does not change over time. At this point, the rate of drug entering the body is equal to the rate leaving it, and steady-state conditions apply. During intermittent dosing, drug concentrations accumulate over time, and eventually a steady state is attained when the concentration profile over each interval resembles all other steady-state profiles (Fig. 139.6). In the clinical setting, the measurement of drug concentration is often delayed for a period equal to five half-lives because at that point the concentration will reflect 97% of the final Css.

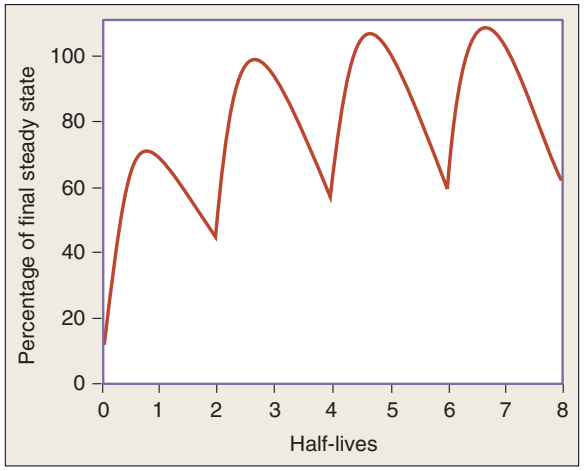

Fig. 139.6 With intermittent dosing, concentration profiles also approach steady state wherein peak and trough concentrations during one cycle are reproducible in the next cycle.

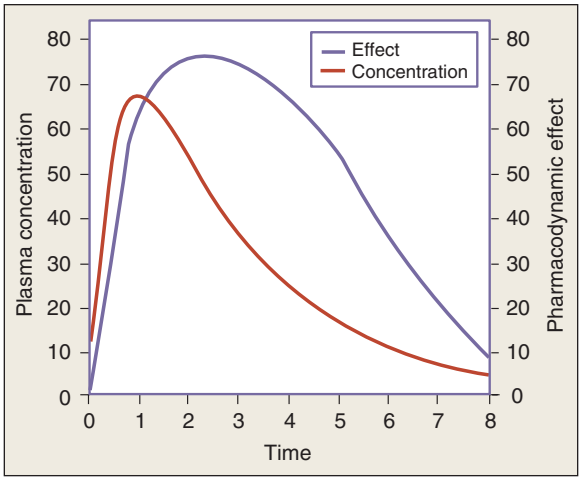

Fig. 139.8 Pharmacodynamic effects often lag behind the matching pharmacokinetic model. In this instance, maximum concentration in blood occurs at 1 hour, whereas maximal drug effect occurs between 2 and 3 hours.

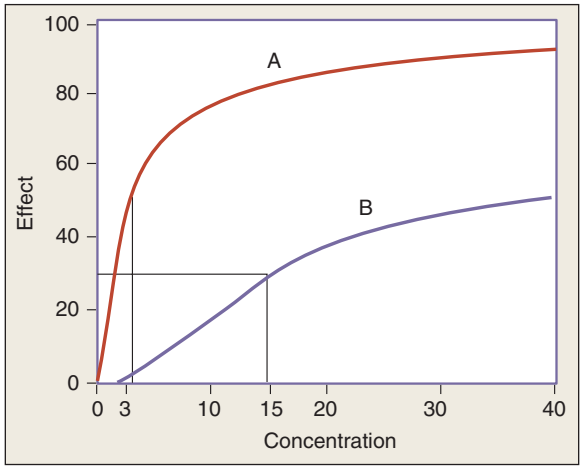

Fig. 139.7 The Emax pharmacodynamic model illustrates that as drug concentrations continue to increase, the increases in drug effect become progressively smaller. Drug A has a lower EC50 (3) than drug B (15) and is said to be more potent than drug B.

PHARMACODYNAMICS

Pharmacodynamics is the study of the relationship between the concentration or exposure of a drug and its pharmacologic effect. Complex pharmacodynamic models with many linked submodels are routinely employed during drug development to determine drug-dosing regimens. In clinical practice, the relatively simple Emax model is often adequate[10]:

$$\text{Effect} = \frac{\text{Emax} \times \text{concentration}}{\text{EC50} + \text{concentration}} \qquad \text{(Equation 12)}$$

Graphically, this equation has a hyperbolic shape (Fig. 139.7) with parameters Emax and EC50. Emax represents the maximal effect attainable because of the drug. The EC50 is the concentration at which half the maximal effect is observed; it is thus a measure of drug potency. The model dictates that increasing doses of the drug do not proportionately increase its effect; eventually, the effect of the drug begins to reach a plateau. If the drug concentration is expected to be less than EC50, increasing the dose will produce a nearly proportional increase in effect. However, as concentrations exceed the EC50, an increase in dose may not be warranted. The increased concentrations will produce a lesser increase in desired effect and may place the patient at risk for development of adverse drug-related effects.

Time does not appear in the Emax model, and concentrations are explicitly defined as Css so that the effect resulting from a given concentration is considered to be a steady-state effect. This model applies when drug in the plasma rapidly equilibrates with drug at the site of action, and there is no indirect mechanism between the concentration at the site of effect and the effect itself. The more common situation is that the effect lags somewhat behind the concentration (Fig. 139.8). If concentrations are going up and coming down over time, as would be expected with an intermittent intravenous or oral dosing schedule, the effect is also expected to go up and down over time, but the time frames may not coincide exactly. For example, the plasma concentration might peak at 1 hour and the effect might peak several hours later. There is a mismatch or disequilibrium between concentration and effect, and a plot of effect versus concentration—with the points connected in time order—yields a hysteresis loop. For any given concentration, there are two effects: one on the upswing of the concentration-time curve and another on the downswing.

The pharmacodynamic effects noted with a given drug result from the drug's interaction with receptors and the resultant activation or inhibition of effects mediated by that receptor. These effects may be either the desired therapeutic action or an unwanted toxic effect. Generally, it is assumed that the intensity of effect produced by the drug is a function of the quantity of drug at the receptor site, whereas relative potency results from varying degrees of selectivity for the receptor and the receptor's affinity for binding the drug. More potent drugs elicit a given effect at lower concentrations than less potent drugs.

Drugs that stimulate a response from the receptor are *agonists,* and those that inhibit a response from the receptor are *antagonists*. Because antagonists have no effect of their own at the receptor, the net effect depends on both the concentration of the antagonist and the agonist being blocked. The relative concentration of the agonist compared with the antagonist primarily determines the effect observed when an antagonist is competing for the same binding site as the molecule or drug that stimulates the receptor. Irreversible antagonists, however, either bind with very strong affinity to the receptor so they cannot be displaced or bind to another site on the substrate that interferes with

binding at the receptor. The effect of irreversible antagonists is independent of the agonist's concentration and results in a decrease in the maximal effect of the agonist. The duration of effect for irreversible antagonists is determined by the rate of turnover for the receptor.

Tolerance to a drug is seen when the response at a given dose decreases. This may be a result of receptor down-regulation (decreased number or sensitivity of receptors) or enzyme induction (increased metabolism). Cross-tolerance, as is commonly seen with opioids, occurs when similar drugs act on the same receptor.

PROTEIN BINDING

Many drugs are bound to plasma proteins, most commonly albumin and alpha-1 acid glycoprotein (AAG), which are highly abundant at concentrations in the ranges of ~3.5–5 g/dL and ~0.04–0.1 g/dL, respectively, in healthy individuals.[11] In general, drug bound to plasma proteins neither can be cleared through metabolism or excretion, nor can it bind to its target to impart its therapeutic (or toxic) effect. Therefore clearance processes act only on unbound drug, which dictates the pharmacodynamic effects. The terms *bound drug concentration* (Cb), *unbound* (or free) *drug concentration* (Cu), *total* (bound plus unbound) *drug concentration* (Ctot), and *unbound* (or free) *fraction* (fu) are frequently used:

$$\text{Ctot} = \text{Cu} + \text{Cb}$$

$$\text{Fu} = \frac{\text{Cu}}{\text{Ctot}} \qquad \text{(Equation 13)}$$

Similarly,

$$\text{AUCu} = \text{fu} \times \text{AUCtot} = \text{fu} \times \text{F} \times \frac{\text{Dose}}{\text{CL}} \qquad \text{(Equation 14)}$$

where AUCu is the unbound drug exposure, fu is the fraction unbound, AUCtot is the total exposure (total AUC), F is the bioavailability, and CL is the clearance.

The clinical relevance of protein binding and of changes in protein binding during therapy have been previously debated. Based on a review in 2002 by Benet and Hoener, changes in plasma protein may be clinically relevant and result in significant changes to steady-state unbound concentration only for drugs with low fu (<30%), high extraction ratio, and either administered intravenously or when administered orally but where nonhepatic clearance is the primary route of elimination.[12]

Benet and Hoener reviewed pharmacokinetic data on 456 drugs from the literature. No orally administered drug with a high extraction ratio and nonhepatic clearance met the criterion for low fu (<30%). Only 25 (5%) of the 456 drugs had high extraction ratios, were not administered by the oral route, and met the criterion for which protein binding may influence drug exposure. However, many of these 25 agents are routinely used in critical care (Table 139.1).

Other analyses have been presented more recently, and these highlight additional complexities that may not have been considered fully in previous reports. Schmidt and colleagues suggest generalized recommendations may be incomplete, and clinical relevance of protein binding depends on each drug's distinct properties, such as mechanism of action, affinity for plasma proteins and the drug target, biodistribution and local concentrations at the site of action, or incorrect assumptions such as the reliance on estimated instead of measured fu.[11]

In critically ill patients, protein concentrations can change quickly. This is particularly true of the acute-phase reactant, AAG. Given the relatively low blood levels of AAG compared with albumin, fu could increase dramatically as a result of rapidly declining AAG levels.[11] In addition, some patients (e.g., those undergoing dialysis or those with cachexia) have altered protein binding.[13] The extent of protein binding, route of administration, route of elimination, and extraction ratio of the drug all should be considered when determining whether a change in binding is likely to result in a change in effect.

TABLE 139.1 Drugs for Which Changes in Protein Binding May Influence Clinical Drug Exposure After Intravenous or Intramuscular Administration*

Alfentanil	Itraconazole
Amitriptyline	Lidocaine
Buprenorphine	Methylprednisolone
Chlorpromazine	Midazolam
Cocaine	Milrinone
Diltiazem	Nicardipine
Diphenhydramine	Pentamidine
Doxorubicin	Propofol
Erythromycin	Propranolol
Fentanyl	Remifentanil
Gold sodium thiomalate	Sufentanil
Haloperidol	Verapamil
Idarubicin	

*Criteria for selection included >70% protein binding and hepatic clearance >6.0 mL/min/kg or nonhepatic extraction ratio clearance ≥0.28 × renal blood flow (>4.8 mL/min/kg).
Modified from Benet LZ, Hoener BA. Changes in plasma protein binding have little clinical relevance. Clin Pharmacol Ther. 2002;71:115–121.

As a final note on protein binding, care must be taken when evaluating total drug concentrations in patients with altered protein binding. Consider the case of phenytoin. The percentage of unbound drug is typically 10% but is approximately doubled in patients receiving hemodialysis (Table 139.2). If phenytoin were administered as a standard dose to all patients, there would be no problem; phenytoin is a low-clearance drug, and protein binding should not influence overall unbound exposure whether the drug is administered orally or intravenously. However, phenytoin concentrations are often obtained for the purposes of therapeutic drug monitoring, and efforts are made to achieve circulating levels within the commonly accepted therapeutic range of 10–20 mg/L. In patients with normal protein binding, this exposure equates to an unbound therapeutic range of 1–2 mg/L. In patients with 20% unbound drug, the desired unbound range is still 1–2 mg/L, but the range based on total concentration is approximately halved. In cases of higher fu, if phenytoin dosing is increased to achieve 10–20 mg/L, toxicities may be observed because the unbound concentration will be twice the desired value.

NONLINEAR PHARMACOKINETICS

The application of pharmacokinetics to therapeutic drug monitoring becomes considerably more difficult with drugs that exhibit nonlinearities. With linear pharmacokinetics, parameters are stable over time and across concentrations and dose levels. Doubling of the dose results in doubling of the concentration, and a given dose provides the same AUC regardless of the dosing history. *Nonlinear pharmacokinetics* is a term used when these principles of superposition no longer hold. An increase in dose may result in an increase in concentration that is more than or less than proportional, or it may result in clearance changes

TABLE 139.2 Effect of Decreased Protein Binding on Bound and Unbound Concentrations of Phenytoin

	CONCENTRATIONS OF PHENYTOIN AT THERAPEUTIC RANGE (MG/L)		
Concentration	Typical Patient	Patient With Protein Binding Decreased By 50%	Result of Erroneous Increase in Phenytoin Dose in Patient With Decreased Protein Binding*
Total (Ctot)	20	10	20
Unbound (Cu)	2 (10%)	2 (20%)	4 (20%)
Bound (Cb)	18	8	16

*Because of the altered protein binding, Ctot is less when Cu is in the therapeutic range (i.e., 2 mg/L). During therapeutic drug monitoring, it is the Ctot that is measured. If the decreased protein binding is not taken into account and the phenytoin dose is increased to achieve a Ctot of 20 mg/L, the actual Cu will double and toxic effects could ensue.

over time. Several common types of nonlinearities occur in the clinical setting.

Phenytoin is the classic example for nonlinear elimination. Increases in a phenytoin dose can result in greater-than-proportional increases in concentration. In any pharmacokinetic system, clearance is defined as the rate of elimination relative to the concentration. Hence, an instantaneous rate of elimination can be defined as follows:

$$\text{Rate of elemination} = CL \times C \qquad \text{(Equation 15)}$$

In a linear elimination process, clearance is constant, and doubling the concentration doubles the rate of elimination. In the case of phenytoin with nonlinear elimination, clearance is not constant. Nonlinear elimination occurs because the metabolic pathway responsible for the elimination of the drug is saturable. The enzyme system has a maximum rate of metabolism that can be approached at therapeutic concentrations of phenytoin. These principles can be better understood by considering the rate of elimination described by the Michaelis-Menten equation (Fig. 139.9). It has two parameters, the *maximum rate of elimination* (Vmax) and the *concentration that results in one-half the maximum rate* (Km):

$$\text{Rate of elemination} = \frac{V\text{max} \times C}{Km + C} \qquad \text{(Equation 16)}$$

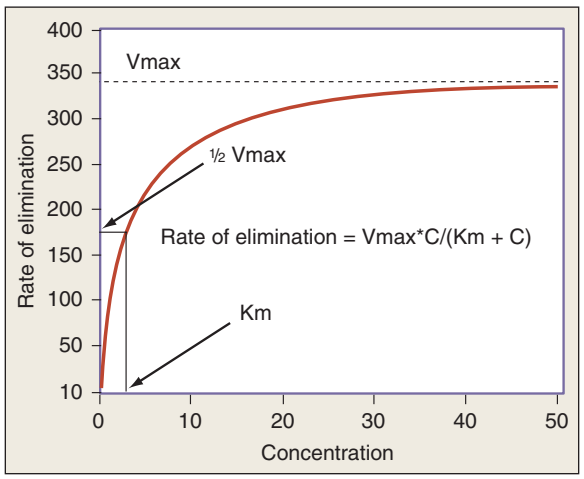

Fig. 139.9 The Michaelis-Menten model demonstrates elimination as a nonlinear function of concentration, with characteristics including a maximum rate of elimination (Vmax) and a concentration at which one-half of the maximum rate of elimination occurs (Km).

Although the parameters Vmax and Km are constant, it can be seen that clearance is a function of concentration (C). The clearance of a drug decreases as the concentration increases:

$$CL = \frac{\text{Rate of elemination}}{C} = \frac{V\text{max}}{Km + C} \qquad \text{(Equation 17)}$$

Although enzyme systems do have maximal rates, the usual drug concentrations attained in the clinical setting are considerably lower than Km, the quantity Vmax/(Km + C) is minimally influenced by concentration, and clearance becomes constant. Therefore even though many drugs are metabolized by hepatic enzymes, few drugs of clinical interest display detectable nonlinear elimination.

At steady state, the amount of drug eliminated every day must equal the dose taken, and the elimination rate equals the dosing rate. After rearranging the equation for the Css:

$$Css = \frac{\text{Dosing rate} \times Km}{V\text{max} - \text{Dosing rate}} \qquad \text{(Equation 18)}$$

This equation shows that an increase in dosing rate produces a greater-than-proportional increase in the Css. Furthermore, if the dosing rate exceeds Vmax, a Css will never be attained.

Another type of nonlinearity is time-dependent pharmacokinetics, as demonstrated by carbamazepine inducing its own metabolism.[14] This autoinduction causes the clearance of carbamazepine to increase over time. It is important to gradually increase the dose of carbamazepine during the first few weeks of therapy up to the expected maintenance dose to avoid toxicities related to elevated concentrations.

Protein binding also can become saturable with some drugs. Intuitively, one might think that saturation of protein binding would result in higher unbound drug concentrations available to exert desirable effects and toxicities, but it must be kept in mind that the organs responsible for drug clearance are eliminating unbound drug. Therefore unless the clearance of a drug also changes, the steady-state unbound concentration will remain constant in the face of saturable protein binding. The total concentration is a function of the unbound concentration and the fraction unbound:

$$Ctot = \frac{Cu}{fu} \qquad \text{(Equation 19)}$$

If the fraction unbound increases at higher unbound concentrations, total concentrations do not increase in proportion to unbound concentrations. This can be perplexing in therapeutic drug monitoring situations. Increases in dose produce less-than-expected increases in

total concentration. As the dose is pushed higher to reach desired total concentrations, toxicities may be observed because saturable binding causes the unbound concentration to be greater than expected.

LARGE-MOLECULE THERAPEUTICS

Historically, large-molecule drugs have not been a major concern in the critical care setting. However, given the successes of protein therapies, namely monoclonal antibody (mAb) drugs, there has been a dramatic increase in the clinical use of these protein therapies as standard of care for a variety of immune disorders, cancers, and other diseases.[15] Recent studies are also evaluating mAb immunotherapies for sepsis and drug-resistant infections.[16,17] Although the principles discussed earlier apply to both small-molecule and large-molecule therapies, there are a few aspects of large-molecule and mAb drug pharmacology that are distinctly different from small molecules and are worth noting here.

Because of their large size and inability to diffuse across biologic membranes, and despite decades of ongoing research to develop delivery strategies via other routes, intravenous infusion remains the primary route of administration for mAb therapies, though some can achieve therapeutic systemic concentrations via subcutaneous or intramuscular injection as well.[18,19] As mAbs do not diffuse across membranes, central volumes of distribution for mAbs tend to be small and on the order of ~2–3 L equating to plasma water volume, and tissue distribution may add another ~5–15 L.[20] Also because of their large size, mAbs are not cleared through renal filtration. Instead, the primary pathway for clearance of mAb therapies is lysosomal degradation via pinocytosis and endocytic uptake in epithelial cells. This tends to be a slow process, and mAb therapies often have half-lives of days or weeks. The long half-life is enhanced by the neonatal Fc receptor, FcRn, which binds to the Fc region of the mAb structure in a pH-dependent manner and recycles the endocytosed mAb away from the lysosomal pathway back to the cell surface, where it is released back into circulation.[20] Though this process is generally linear, mAb therapies may have nonlinear pharmacokinetics because of concentration-dependent and time-dependent clearance mechanisms. For example, mAb therapies are sometimes immunogenic and induce the production of antidrug antibodies (ADAs).[21] In other words, the patient receiving the mAb therapy may develop antibodies to the mAb therapy. This typically results in immune-mediated clearance that increases over time.

Similar to the time-dependent changes in mAb clearance from ADA, the high specificity and high affinity binding of mAbs to their therapeutic targets can also contribute to nonlinear disposition of mAb therapies through target-mediated drug disposition (TMDD).[20] Because mAb binding is with high specificity and high affinity to the target, the law of mass action drives the equilibrium toward the drug-target complex:

$$[D] + [T] \rightleftharpoons [D \cdot T] \longrightarrow Effect \qquad \text{(Equation 20)}$$

where *[D]* is drug concentration, *[T]* is target concentration, and *[D·T]* is drug-target complex concentration. For high-affinity drugs, such as mAbs, when the quantity of target receptors expressed is similar to the quantity of mAb drug molecules in the body, a significant portion of the mAb may be effectively removed from circulation through the high-affinity binding to the target. In some cases, this binding leads to target-mediated clearance of the mAb through internalization and degradation of the mAb-target complex. In other cases, the mAb may slowly release from the target over time, which does not result in clearance, but rather contributes to a higher apparent volume of distribution because the bound mAb is effectively removed from circulation temporarily as if it had distributed to a separate extravascular compartment. In either case, the pharmacokinetics would be nonlinear because they would depend on the concentration of mAb relative to target. Furthermore, as the expression of the target changes over time, either as a direct result of the mAb therapy or as a result of changing disease status, the impact of TMDD will also change over time. This can be overcome by administering the mAb therapy at high enough doses or at short enough intervals to ensure mAb concentrations far exceed the target concentrations. In this scenario, the target is continuously saturated with excess mAb, and the contribution of TMDD is minimal relative to total other processes governing mAb distribution and clearance. Based on the law of mass action, we can determine the target engagement, or fraction of total target that is bound by the mAb drug:

$$\frac{[D \cdot T]}{[T_t]} = \frac{[D]}{[D] + K_d} \qquad \text{(Equation 21)}$$

where *[D]* is the drug concentration, $[T_t]$ is the total target concentration, and K_d is the dissociation constant of the drug-target complex, *[D·T]*. This fraction is often expressed as a percentage of receptor occupancy (RO%). Therapeutically, we generally aim to ensure a minimum RO% is maintained (e.g., >95% or >99%) throughout the dosing interval. This ensures maximal and prolonged pharmacodynamic drug effect, and it has the added benefit of ensuring TMDD will have a minimal impact on overall drug disposition.

KEY POINTS

- Modification of a drug dosing regimen, or even modification in the choice of therapy, may be necessary in the critically ill patient because of changes in physiologic processes that alter drug pharmacokinetics; this is especially true for drugs where clear dose-response or exposure-response relationships have been established and where lack of efficacy because of low exposure or toxicity because of high exposure pose significant risks to the patient.
- Clearance (CL) is a primary or fundamental pharmacokinetic parameter that describes the efficiency of the body in eliminating a drug and is defined by the volume of a particular compartment (blood or tissue) completely cleared of drug per unit time; volume of distribution (V), another fundamental pharmacokinetic parameter, reflects the theoretical volume into which a drug distributes and is not necessarily associated with an actual, physiologic space.
- Secondary pharmacokinetic parameters include drug half-life ($t_{1/2}$), the measure of how quickly a drug is eliminated from the body and described as $t_{1/2} = 0.693/Kel$ or $0.693 \times V/CL$; the area under the concentration- time curve (AUC), which is a measure of drug exposure and is defined by AUC = Dose/CL; and the extent of drug absorption or bioavailability (F), which is the ratio of dose-normalized AUCs for extravascular to intravascular routes of administration, where $F = (AUCEV/Dose_{EV})/(AUCIV/Dose_{IV})$.
- After five half-lives of either α (the distribution $t_{1/2}$) or β (the elimination $t_{1/2}$), a drug will be 97% distributed throughout the body or eliminated from the body, respectively.
- The first-pass effect refers to the elimination of drug that is absorbed orally but then metabolized and/or secreted in either the liver or the gut wall before reaching the systemic circulation.
- The typically observed hyperbolic relationship between effect and dose that results in less-than-proportional increases in response as concentrations increase is often described by the Emax pharmacodynamic model; observed pharmacologic effects often lag behind the serum concentration eliciting the effect and can be observed as a hysteresis loop when effect-concentration pairs are connected in time order.

- Antagonists may inhibit an effect at a receptor through concentration-dependent competitive blocking or by binding irreversibly to the receptor.
- Most small-molecule drugs are bound to some extent by plasma proteins, and it is the unbound concentration of drug that determines the pharmacodynamic effect; changes in protein binding that may occur in the critically ill patient may affect drug exposure or pharmacodynamic effects depending on several factors, although these changes do not affect clinical outcomes from therapy for a majority of drugs.
- Nonlinear pharmacokinetics occurs when clearance or volume changes as a function of dose, drug concentration, or time; the Michaelis-Menten equation, $CL = Vmax/(Km + C)$, where Vmax is the maximum rate of elimination, Km is the concentration of drug that results in one-half the maximum rate, and C is the concentration of drug, is often used to describe nonlinear clearance processes.
- Because of their large size and relatively slow rates of clearance through catabolic or nonlinear, target-mediated pathways, mAb therapies have low volumes of distribution and typical half-lives of days or weeks; just as with small-molecule drugs, changes in physiologic processes in the critically ill patient can alter the pharmacokinetics of mAb therapies.

References for this chapter can be found at expertconsult.com.

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Poisoning: Overview of Approaches for Evaluation and Treatment

Brenna Farmer

Patients presenting to the hospital with overdoses and poisonings should undergo an initial evaluation to determine whether a specific poisoning can be detected that would lead to specific management options. History and physical examination are key to determine what poisoning, such as a toxidrome—a syndrome related to a toxic exposure (cholinergic, anticholinergic, sympathomimetic, opioid, sedative-hypnotic, or withdrawal syndromes)—could be causing a patient's presentation. Once a poisoning or overdose has been identified, management can be determined. Management options can include gastrointestinal decontamination, enhancing elimination, and/or use of antidotes. Additionally, some poisonings and overdoses only require supportive care.

HISTORY

A thorough poison history should be obtained. Route of exposure should be obtained. Necessary elements for a suspected ingestion include suspected substance, amount ingested, time of ingestion, and any possible coingestants. Other important elements include past medical history, medication history, social history, and family history. Access to other medications in the home, including dietary and herbal supplements and over-the-counter medications, must be determined. Review of symptoms, including if vomiting was present, will also be important when determining if gastrointestinal decontamination would be useful.

PHYSICAL EXAMINATION

Poisoned patients should undergo a thorough physical examination to determine if a toxidrome is present. Specific elements of the examination that allow for this determination include mental status; pupil size and reactivity; mucous membrane evaluation; cardiac and pulmonary examinations; abdominal examination for bowel sounds and presence of palpable bladder; skin examination for temperature, flushing, and perspiration; muscle tone; and neurologic examination for the presence of tremors, clonus, and reflexes. See Table 140.1 for toxidrome physical examination findings.

LABORATORY ANALYSIS

While determining whether a poisoning has occurred or trying to determine the cause of an undifferentiated poisoning, some laboratory values can be helpful. Common laboratory studies to obtain include basic metabolic panel for electrolytes and to determine anion gap; ethanol, acetaminophen (paracetamol), and salicylate concentrations; liver function tests for transaminases; serum osmolarity if toxic alcohol is suspected; and blood gas for pH. These laboratories can aid in narrowing the differential diagnosis when a patient has overdosed or make the diagnosis in acetaminophen or salicylate poisoning.

TOXICOLOGY LABORATORY

Urine drug screens are usually obtained in poisoned patients; however, there is no standardized screen. The interpretation of these tests depends on the clinician's knowledge of which toxins have been screened and whether confirmatory testing (ideally performed by a different analytic method) will follow.[1] The length of time required to receive results varies among hospitals. Quantitative serum drug testing is done when quantitation of a toxin is clinically relevant, as is the case for acetaminophen, anticonvulsant agents, salicylates, digoxin, ethanol, ethylene glycol, methanol, iron, lithium, and theophylline. The clinician caring for the poisoned patient should discuss drug testing with the analytic toxicologist so that the results of testing can be appropriately interpreted. The clinical value of analytic toxicology testing depends on the clinician's ability to understand and interpret the results because of limitations of the screening and other tests.[1]

Once a poisoning has been identified, specific management options may be necessary, from gastrointestinal decontamination and enhancing elimination, to use of specific antidotes.

GASTROINTESTINAL DECONTAMINATION

The theory of gastric decontamination is that removal of toxins is done first from the stomach (where absorption is poor) before moving to the small intestine (where absorption is more rapid) so as to decrease the toxicity of the poisoning. Because of controversies regarding the role of gastrointestinal decontamination (GID), senior toxicologists from the American Academy of Clinical Toxicology and the European Association of Poison Centres and Clinical Toxicologists (EAPCCT) agreed to collaborate on the production of position statements on GID treatments. These statements, published in 1997, are systematically developed guidelines founded on a criteria-based critical review of all relevant scientific literature.[2] All position statements were updated in 2004, with some getting new updates in 2014 (Table 140.2). GID included ipecac, gastric lavage, single-dose activated charcoal, cathartics, and whole-bowel irrigation.

Ipecac

Ipecac, a prepared form of the *Cephaelis acuminata* or *Cephaelis ipecacuanha* plant, is no longer recommended for routine use in the management of poisoned patients, as there is no evidence that it improves outcomes.[3] Vomiting within 30 minutes after administration is caused

TABLE 140.1 Toxidrome Physical Examination Findings

Toxidrome Physical Examination	Cholinergic	Anticholinergic	Sympathomimetic	Opioid	Opioid Withdrawal	Sedative-Hypnotic	Sedative-Hypnotic Withdrawal
Mental status	Awake	Obtunded or delirious	Awake	Depressed	Awake	Depressed	Agitated, awake, delirious
Pupils	Pinpoint Reactive	Dilated Unreactive	Dilated Reactive	Pinpoint Reactive	Dilated Reactive	Normal	Dilated Reactive
Mucous membranes	Wet	Dry	Normal	Normal	Normal	Normal	Normal
Cardiovascular	↓ Heart rate	↑ Heart rate	↑ Heart rate	Normal	Normal	Normal	↑ Heart rate
Pulmonary	Wheeze, rhonchi ↑ Respiratory rate	Normal	Normal	↓ Respiratory rate ↓ Depth of breathing	Normal	Normal	Normal
Bowel sounds	↑	↓	Normal	↓	↑	Normal	Normal
Bladder	Not palpable	Palpable	Normal	May be palpable	Normal	Normal	Normal
Skin temperature	↓	↑	↑	Normal	Normal	Normal	↑
Skin color	Normal	Flushed	Flushed	Normal or cyanotic	Normal	Normal	Normal
Perspiration	Present	Absent	Present				Present
Antidote	Atropine						
Pralidoxime	Physostigmine	Benzo-diazepines	Naloxone			Benzodiazepines	

TABLE 140.2 Position Statement Summaries on Gastrointestinal Decontamination Treatments

Management	Recommendation
Gastric Decontamination	
Ipecac	Syrup of ipecac should not be administered routinely for the management of poisoned patients.[3]
Gastric lavage	Gastric lavage should not be employed routinely in the management of poisoned patients.[4]
Single-dose activated charcoal	Single-dose activated charcoal should not be administered routinely in the management of poisoned patients.[5]
Cathartic	Administration of a cathartic alone has no role in the management of poisoned patients. Routine use of a cathartic in combination with activated charcoal is not endorsed.[6]
Whole-bowel irrigation	Whole-bowel irrigation should not be used routinely in the poisoned patient.[7]
Enhance Elimination	
Multiple-dose activated charcoal	Multiple-dose activated charcoal should be considered if a patient has ingested a life-threatening amount of carbamazepine, dapsone, phenobarbital, quinine, or theophylline.[8]
Urinary alkalinization	Urinary alkalinization should be considered as first-line treatment in patients with moderately severe salicylate poisoning who do not meet the criteria for hemodialysis. Urinary alkalinization also should be considered for patients with severe poisoning caused by 2,4-dichlorophenoxyacetic acid or mecoprop (MCPP) poisoning. Urinary alkalinization is not recommended as first-line treatment for cases of phenobarbital poisoning, because multiple-dose activated charcoal is superior.[9]

by local irritation of the gastric mucosa, and after 30 minutes vomiting is centrally induced.[10] In experimental studies, the amount of marker removed by ipecac treatment was highly variable and diminished with time.[3]

Gastric Lavage

Gastric lavage should not be employed routinely in the management of poisoned patients, as there is little clinical evidence of benefit and no controlled trials showing benefit.[4] If performed because of a potentially life-threatening poison ingestion, an experienced provider should perform the lavage based on the complications that can occur.[4] Gastric lavage involves a large-bore (36F–40F) orogastric tube passed into the stomach, after which small volumes (200–300 mL) of liquid are alternately administered and aspirated. Comatose patients and those with loss of their protective airway reflexes should have an endotracheal tube placed before this procedure. An oral airway prevents biting of the tube. The amount of stomach contents removed via this procedure is highly variable and decreases with time.[11–13] The procedure can actually push stomach contents into the intestine.[14] Contraindications include loss of protective airway reflexes (unless the patient is endotracheally intubated),

ingestion of a corrosive substance or a hydrocarbon, gastrointestinal pathology, and other medical conditions that could be worsened by the use of lavage. Complications of the procedure include aspiration, laryngospasm, hypoxia, hypercapnia, mechanical injury, and fluid and electrolyte imbalances in children.[15]

Single-Dose Activated Charcoal

Activated charcoal is made when coconut shells, peat, wood, or other materials undergo controlled pyrolysis and are subsequently activated by heating in steam or air at high temperatures. Activation creates multiple internal pores and the small particle size necessary for adsorption. The particles have a large surface area and are capable of adsorbing poisons with varying affinities. Although in vitro studies demonstrate adsorption of many drugs to activated charcoal, animal studies reveal variable reductions in the systemic uptake of marker substances.[16] Volunteer and clinical studies have not demonstrated that single-dose administration of activated charcoal improves outcome. Therefore single-dose activated charcoal should not be administered routinely in the management of poisoned patients. Administration of activated charcoal may be considered if a patient has ingested a potentially toxic amount of poison that is known to be adsorbed to charcoal not longer than 1 hour before treatment, as its effectiveness decreases over time. There is no evidence that the administration of activated charcoal improves outcome.[5,17]

Contraindications to the administration of activated charcoal include decreased level of consciousness and unprotected airway, ingestion of caustic substances or hydrocarbons, gastrointestinal pathology, and medical conditions that could be further compromised by the administration of activated charcoal. Complications include aspiration and direct administration of charcoal into the lung.[5]

Because activated charcoal is an inert substance, it is thought that lung injury after aspiration of activated charcoal is caused by gastric contents. Aspiration of gastric contents causes neutrophils to release neutrophil elastase, which increases pulmonary vascular permeability.[18] In comparison, intratracheal administration of activated charcoal does not increase elastase in the bronchoalveolar fluid.[19] Activated charcoal can activate alveolar macrophages, which are a potent source of oxygen radicals, proteases, and other inflammatory mediators. Charcoal also causes obstruction of small distal airways. Overdistention of alveolar segments in areas not occluded by charcoal leads to volutrauma in those areas, which increases microvascular permeability.[20] Although case reports reveal long-term pulmonary pathology after aspiration or instillation of activated charcoal,[21,22] the true incidence of chronic problems after charcoal aspiration is unknown.

Cathartics

Administration of a cathartic alone has no role in the management of poisoned patients. Routine use of a cathartic in combination with activated charcoal is not endorsed.[6]

Whole-Bowel Irrigation

Whole-bowel irrigation consists of administration through a nasogastric tube of an osmotically balanced, polyethylene glycol–based electrolyte solution to decontaminate the entire gastrointestinal tract by physically expelling intraluminal contents. As much as 1500–2000 mL/hr can be administered to an "awake" adult patient. Negotiation to let the patient attempt to drink the solution only causes delay, because patients are unable to drink at a constant rate. Whole-bowel irrigation should not be used routinely in the poisoned patient. However, it can be considered for potentially toxic ingestions of sustained-release or enteric-coated drugs and for drugs not likely to be adsorbed to activated charcoal (iron, lithium, potassium) and for the removal of illicit drug packets.[7] Contraindications include bowel pathology, unprotected or compromised airway, hemodynamic instability, and intractable vomiting. Complications are nausea, vomiting, and abdominal cramps.[7]

Clinical Implications of Gastrointestinal Decontamination

There is no role for syrup of ipecac in the hospital setting. Gastric lavage may be considered for obtunded patients if it can be instituted within 1 hour after the ingestion. Single-dose activated charcoal should not be routinely administered to patients with mild to moderate degrees of poisoning. Whole-bowel irrigation should be considered for awake patients within the first hours after ingestion of a sustained-release preparation, ionic compounds (e.g., lithium), or packets of illicit drugs.

These guidelines refer to the routine management of poisoned patients. Cellular toxins require special consideration. The physician should always call the Poison Center (1-800-222-1222 in the United States) to discuss a patient with an ingestion and to seek further guidance on management.

ENHANCED ELIMINATION

Multiple-Dose Activated Charcoal

Multiple-dose activated charcoal is the repeated oral administration of activated charcoal, without sorbitol, to enhance drug elimination. If the drug concentration in the gut is lower than that in the blood, the drug will passively diffuse back into the gut. The concentration gradient, intestinal surface area, permeability, and blood flow determine the degree of passive diffusion. As the drug passes continuously into the gut, it is adsorbed onto the charcoal particles, a process called *gastrointestinal dialysis*. Multiple-dose activated charcoal also interrupts the enterohepatic and enterogastric circulation of drugs. Drugs with a prolonged elimination half-life, a small volume of distribution (less than 1 L/kg), and little protein binding are the most amenable to this sort of management.[8] Multiple-dose activated charcoal should be considered if a patient has ingested a life-threatening amount of carbamazepine, dapsone, phenobarbital, quinine, or theophylline. With all of these drugs, data confirm enhanced elimination, although no controlled studies have demonstrated clinical benefit.[8] Other ingestions may benefit from multiple-dose activated charcoal, but there are insufficient clinical data to routinely recommend its use.

The initial dose of charcoal is 50–100 g, and this treatment is followed every 1, 2, or 4 hours by a dose equivalent to 12.5 g/hr. More frequent, smaller doses may prevent vomiting. Multiple-dose activated charcoal can be continued until the patient improves clinically. Contraindications include an unprotected airway, intestinal obstruction, and an anatomically abnormal gastrointestinal tract. Complications include bowel obstruction and vomiting with subsequent aspiration.[8]

Urinary Alkalinization

Urinary alkalinization is the administration of intravenous (IV) sodium bicarbonate to produce urine with a pH $\geq$7.5. The objective of treatment is pH manipulation, not forced diuresis. Hypokalemia is the most common complication. Alkalemia also can occur.[9] Urinary alkalinization should be considered as first-line treatment in patients with moderately severe salicylate poisoning who do not meet the criteria for hemodialysis. Urinary alkalinization also should be considered for patients with severe poisoning caused by 2,4-dichlorophenoxyacetic acid or mecoprop (MCPP) poisoning. Urinary alkalinization is not recommended as first-line treatment for cases of phenobarbital poisoning, because multiple-dose activated charcoal is superior.[9]

SELECTED ANTIDOTES

Stabilization of the patient always should precede administration of antidotes. The effects of the toxin can outlast the effects of the administered antidote. Patients receiving antidotes should be observed in a critical care setting.

Dextrose

Up to 8% of patients with altered mental status are hypoglycemic.[23] Hypoglycemia can be a result of drug or toxin exposure, nutritional deprivation, or a medical complication (e.g., sepsis, hyperthermia). Glucose should be checked at the bedside for all patients with altered mental status.

Naloxone

Endogenous and exogenous opiates produce their effects by binding at one or more opiate receptors. Naloxone, nalmefene, and naltrexone are competitive opioid antagonists that bind at the mu, kappa, and delta receptors and competitively prevent the binding of endogenous and exogenous opiates at these receptors. The duration of action of naloxone is 15–90 minutes. Its clinical effects depend on the dose and route of naloxone administration and the dose and rate of elimination of the opiate agonist. Naloxone can be administered by IV, intramuscular, intratracheal, or sublingual routes. After IV administration, naloxone rapidly enters the central nervous system (CNS). In patients with opioid poisoning, respiration improves within 1–2 minutes, and consciousness may be restored. The goal of naloxone administration is to restore respiratory function. Miosis, inhibition of baroreceptor reflexes, laryngospasm, and decreased gastrointestinal motility are also reversed.[24,25]

Naloxone should be administered to all patients presenting with respiratory depression (slowed respiratory rate and/or decreased depth of breathing) or respiratory failure and altered mental status or coma of unknown cause. Opioid-dependent patients should receive only small doses in an effort to restore respiratory function and prevent rapid withdrawal. If a patient is not opioid dependent, a reasonable starting dose is 0.4 mg, increasing to 10 mg (in increments) if there is no response. Large doses of naloxone may be necessary to reverse the effects of drugs with high affinity for the delta and kappa opiate receptors.[24,25]

If respiratory depression returns, the initial dose of naloxone may have to be repeated or a constant infusion of naloxone initiated. The starting dose for a constant infusion of naloxone is hourly administration of about one-half to two-thirds of the bolus dose that reversed the opioid effects. If withdrawal is precipitated, it is short lived and not life-threatening. Complications of naloxone administration are very rare.[24,25] Naloxone is not indicated for patients once they are intubated and receiving mechanical ventilation, as these procedures reverse respiratory depression.

Flumazenil

Flumazenil competitively antagonizes the pharmacologic effects of drugs that act on the benzodiazepine receptor of the gamma-aminobutyric acid A ($GABA_A$) receptor (e.g., all drugs in the benzodiazepine class).[26] Receptor occupancy follows the law of mass action, and antagonism is dose dependent. The duration of action of flumazenil is variable and depends on the type of benzodiazepine ingested, relative doses of agonist and antagonist, presence of ongoing benzodiazepine absorption, and relative receptor binding affinities. Flumazenil also antagonizes the sedative effects of drugs other than benzodiazepines, such as zolpidem (Ambien), cannabis, ethanol, promethazine, chlorzoxazone, and carisoprodol. These drugs may have differing affinities for the $GABA_A$ receptor, implying that the dose of flumazenil required to reverse the effects depends on the affinity of the specific drug for the receptor.[27]

Flumazenil is safe and effective for reversing conscious sedation after short procedures such as endoscopy. This safety has been generalized to imply that flumazenil also is safe for patients with a multidrug overdose and that reversal of benzodiazepine-induced sedation prevents morbidity from procedures such as endotracheal intubation or computed tomography. However, many patients have experienced single or multiple seizures after flumazenil administration. Status epilepticus has been precipitated, leading to death. The data are insufficient to determine whether morbidity or mortality is increased as a result of flumazenil-precipitated seizures.[28,29]

Flumazenil administration can precipitate seizures in patients with an overdose who have ingested both a benzodiazepine and a proconvulsant drug or just a proconvulsant drug. Flumazenil also can precipitate seizures in patients who have a history of seizures, chronic benzodiazepine ingestion, or head injury. Identification of patients at risk for seizures is difficult.[30] Before administering flumazenil to a patient with a benzodiazepine ingestion, it is reasonable to first obtain an electrocardiogram to rule out exposure to proconvulsant tricyclic antidepressants. Resedation occurs after 18–120 minutes in approximately half of patients awakened by flumazenil. Therefore either continuous IV infusion or observation for a number of hours is required.[31]

Administration of flumazenil to patients with an overdose should not be routine. It should be limited to the following situations: iatrogenic overdose with known patient history, obtundation in a toddler secondary to ingestion of benzodiazepine, and reversal of a paradoxical response to benzodiazepine.

Physostigmine

Physostigmine inhibits acetylcholinesterase, the enzyme responsible for the metabolism of acetylcholine (ACH). ACH is an endogenous neurotransmitter that mediates action by binding to muscarinic and nicotinic receptors. Accumulation of ACH stimulates cholinergic nerve endings. In the poisoned patient, physostigmine is most frequently administered to treat anticholinergic toxicity. Clinical signs of anticholinergic toxicity are recognized by the mnemonic, "Blind as a bat, Red as a beet, Hot as a hare, Dry as a bone, Mad as a hatter" (see Table 140.1). Physostigmine administration should be considered if life-threatening clinical signs of anticholinergic peripheral effects (hypertension, tachycardia, and seizures) or central effects (painful psychosis, delirium) are present. Physostigmine is superior for delirium control from anticholinergics compared with other treatments for anticholinergic toxicity.[32] Complications of cholinergic crises caused by excessive doses of physostigmine include hypertension, dysrhythmia, asystole, bronchorrhea, bronchoconstriction, seizures, and status epilepticus. Contraindications to physostigmine administration include bradycardia and conduction delays, reactive airway disease, peripheral vascular disease, intestinal or bladder obstruction, and treatment with a depolarizing neuromuscular blocking agent (e.g., succinylcholine). An acceptable dose of physostigmine is 1–2 mg IV over 10 minutes. This drug should be administered in the presence of a physician because of the potential for precipitation of life-threatening cholinergic effects.[33]

HYPOTENSION IN THE POISONED PATIENT

Hypotension in the poisoned patient is most frequently caused by receptor blockade, drug-induced myocardial depression, or drug-induced vasodilatation. Clinicians reflexively initially treat hypotension by infusing IV fluids; however, unless the poisoned patient is hypovolemic, large volumes of fluid can predispose patients to the development of acute respiratory failure.

Catecholamines are the pressors of choice for treatment of hypotension in most intensive care unit (ICU) patients who are older, chronically ill, or acutely ill from an infectious process. The causative factors in sepsis-induced vasodilation and myocardial depression/ischemia are different from the factors that cause drug-induced vasodilation, myocardial depression, or ischemia. Treatment approaches must address the cause of the hypotension and not assume that all hypotensive patients should be treated in a similar manner.

Poisoned patients who are young and healthy respond to hypotension with an outpouring of endogenous catecholamines. Adrenergic receptors are sensitive in young patients. Administration of exogenous catecholamines is unlikely to be of much benefit because catecholamine receptors are already maximally stimulated by endogenous catecholamines. Agents that must be considered for the treatment of hypotension in the poisoned patient are sodium bicarbonate (for a sodium channel–blocking agent), glucagon, and insulin/glucose.

Glucagon

The cardiovascular effects of glucagon are mediated by myocardial glucagon receptors that are catecholamine independent. Stimulation activates adenylate cyclase, leading to increased intracellular levels of the second messenger, cyclic adenosine monophosphate (cAMP). This cyclic nucleotide increases myocardial calcium uptake. Both the slope of phase zero of the action potential and the conduction velocity through the atrioventricular node are increased. Glucagon increases heart rate and stroke volume, thereby increasing cardiac output. After IV administration, augmented inotropy is seen within 1–3 minutes, with a peak effect in 5–7 minutes.[34]

Glucagon should be considered early in the treatment of hypotensive poisoned patients, especially those patients with beta-adrenergic antagonist toxicity. Treatment regimens vary. An acceptable regimen is 10 mg of glucagon given over 10 minutes (rapid administration causes vomiting), followed by 1–3 mg/hr. If the patient wretches, the hourly dose of glucagon should be decreased. Elderly patients may be more sensitive to the emetic effects of the drug. Tachyphylaxis can occur with glucagon. Therefore additional therapies may be needed.

Insulin and Glucose

Insulin improves contractility in anoxic rat hearts and improves cardiac index after cardiopulmonary bypass surgery. During drug-induced shock, insulin shifts myocardial fatty acid oxidation to carbohydrate oxidation, which increases contractility, left ventricular pressure, and rate of change of developed pressure. Enhanced fatty acid oxidation, such as occurs after epinephrine administration, transiently increases contractility at the expense of increased myocardial oxygen consumption.[35]

Insulin and glucose treatment in poisoned patients is commonly referred to as *high-dose insulin-euglycemia therapy* (HIET). Insulin can be bolused at 0.5–1 U/kg, followed by an infusion at 0.5–1 U/kg/hr.[36] The infusion can be titrated up to improve inotropy and contractility and to increase blood pressure. Case reports have had safe outcomes with large bolus and infusion doses.[36] Concurrent administration of glucose is used to maintain euglycemia. Hourly serum glucose checks are mandatory because hypoglycemia occurs frequently. Potassium should also be monitored because of intracellular shift.

CARDIAC ARRHYTHMIAS

ICU treatment regimens assume that a diseased heart is the cause of most cardiac arrhythmias. This assumption is invalid in poisoned patients. Treatment of the arrhythmia must take into consideration the pharmacology of the toxin causing the arrhythmia.

ACUTE RENAL FAILURE

In poisoned patients, acute renal failure (ARF) is most frequently the result of a decrease in extracellular fluid volume and renal hypoperfusion caused by drug- or chemical-induced vasodilation, drug-induced myocardial depression, or rhabdomyolysis. Attempts to prevent ARF are important because there is no specific therapy once ARF is established. Studies evaluating the efficacy of low-dose dopamine (0.5–3.0 mg/kg/min) in preventing ARF have not demonstrated any benefit, but the patient populations in these studies consisted of critically ill patients with established ARF or at high risk for developing ARF.[37] The efficacy of administration of low-dose dopamine after periods of hypotension in poisoned patients who typically are younger and without chronic disease has not been evaluated. When dopamine is administered to normal human subjects, there is a dose-dependent increase in renal blood flow, sodium excretion, and glomerular filtration rate.[38] Low-dose dopamine also limits adenosine triphosphate (ATP) use and oxygen requirements in nephron segments at risk for ischemia.[39] Although there are no studies regarding the efficacy of low-dose dopamine in cases of drug-induced hypotension, one may consider administration in previously healthy poisoned patients who have adequate vascular volume and remain oliguric or anuric despite maximal diuretic therapy.

SEIZURES

Blood pH can be as low as 7.17 at 30 minutes and 7.20 at 60 minutes after resolution of a 30- to 60-second seizure.[40] Acidosis decreases cardiac output, oxygen extraction, and left ventricular end-diastolic pressure and impairs myocardial contractility. If a patient has ingested a cardiotoxic drug (e.g., a tricyclic antidepressant) that causes significant myocardial depression, the consequences of acidosis can increase the toxicity of the drug. Ictal increases in plasma epinephrine levels can add to the potential risk for cardiac arrhythmias. Additionally, airway reflexes are inhibited postictally, which adds to the potential for aspiration.[41]

Whether seizures increase morbidity and mortality in poisoned patients is difficult to ascertain. Deaths of poisoned patients who sustain seizures are usually attributed to the toxicity of the drug. Because of the number of variables, it is impossible to know whether the risk for mortality is influenced by the presence of convulsions. Accordingly, the physician should take an aggressive approach toward terminating seizures in poisoned patients. Benzodiazepines are the drugs of choice to quickly terminate seizures because they are lipophilic and rapidly enter the CNS.

MECHANICAL VENTILATION AND EXTUBATION

Endotracheal intubation is commonly indicated for the management of poisoned patients on the basis of respiratory depression or impaired protective airway reflexes or both. As the drug is metabolized, its effects abate, and the patient's sensorium improves, the patient may become alert slowly or very suddenly. The patient should be extubated if ability to protect the airway is evident and ventilation is adequate for 15–60 minutes with minimal respiratory support (e.g., 5 cm H_2O positive end-expiratory pressure and 5 cm H_2O pressure support). Unnecessary or excessive administration of sedatives or anxiolytics in an attempt to make the patient more comfortable can delay weaning from mechanical ventilation and extubation and increase the risk for complications.

KEY POINTS

- The theory of gastric decontamination is that removal of toxins from the stomach (where absorption is poor) before they move into the small intestine (where absorption is more rapid) decreases the toxicity of the poisoning.
- Stabilization of the patient should always precede administration of antidotes. The effects of the toxin can outlast the effects of the administered antidote. Patients receiving antidotes should be observed in a critical care setting.
- Treating hypotensive, poisoned patients with large volumes of IV fluids can increase the risk for acute respiratory failure.
- Efforts to prevent development of ARF in the poisoned patient are important because there is no specific therapy once ARF is established.
- An aggressive approach should be taken toward terminating seizures in the poisoned patient. Benzodiazepines are the drugs of choice to quickly terminate seizures, because they are lipophilic and rapidly enter the CNS.
- The clinical value of analytic toxicology testing depends on the clinician's ability to understand and interpret the results.

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Resuscitation of Hypovolemic Shock

S. Ariane Christie and Juan Carlos Puyana

Alfred Blalock demonstrated that injury precipitates local and regional fluid loss, the effects of which can be ameliorated by vigorous restoration of intravascular volume. This concept is foundational to understanding the pathophysiology of shock and provides the rationale underlying intravenous (IV) therapy for hemorrhage and hypovolemia.[1]

Severe hypovolemia consists of loss of intravascular or total body fluid volume necessary to cause insufficient tissue perfusion at the local and cellular level. If not rapidly corrected, hypovolemic shock leads to refractory end-organ damage, multisystem organ failure, and death. Broadly, hypovolemic shock can be divided into two etiologies with concomitant differences in treatment (Fig. 141.1). Nonhemorrhagic hypovolemic shock consists of body fluid loss and is treated primarily with fluid replacement to restore intravascular volume. Hemorrhagic shock results from blood loss and is treated with hemorrhage control, replacement of whole blood or its components, and avoidance or correction of coagulopathy.

NONHEMORRHAGIC HYPOVOLEMIC SHOCK

Management of nonhemorrhagic hypovolemic shock centers around rapid replacement of intravascular volume and subsequent restoration of tissue perfusion. Additional priorities include management of concomitant electrolyte and acid/base abnormalities and diagnosis and treatment of the etiology of the patient's underlying fluid loss.

Fluid Resuscitation Principles

For the majority of patients with hypovolemia, resuscitation should consist of rapid bolus infusion of isotonic crystalloid solution with ongoing monitoring of physiologic and laboratory data to evaluate response and dictate termination of therapy. Potential resuscitation products to treat hypovolemia include crystalloid solutions (0.9% normal saline and buffered solutions), colloid solutions (albumin, dextran, hyperoncotic starch) and blood products (fresh frozen plasma [FFP], packed red blood cells [PRBCs], platelets). Multiple large, randomized control trials (SAFE,[2] CRISTAL[3]) and subsequent meta-analyses comparing outcomes with crystalloid versus colloid solutions have demonstrated no significant advantage to colloid resuscitation in terms of 28-day mortality. Data on secondary outcomes, including renal replacement and intensive care unit (ICU) and hospital length of stay have been mixed, but no clear benefit to colloid resuscitation has been demonstrated. Notably, in subgroup analysis of the SAFE trial, resuscitation with albumin was associated with higher mortality among patients with head injuries. Because of a lack of demonstrable benefit and higher cost of colloid, crystalloid resuscitation should be used as the first-line resuscitation fluid for severe hypovolemia in critically ill patients. Despite a paucity of data favoring colloid use, albumin may be an appropriate resuscitation adjunct in cases of refractory hypovolemia thought to be secondary to low oncotic pressure. Other colloid solutions, including hyperoncotic starch, have been associated in large, randomized trials with increased risk of renal failure and death and should not be used to treat hypovolemia.[4,5]

There is ongoing debate regarding the most appropriate crystalloid product for resuscitation for hypovolemia. Normal saline contains high levels of sodium and chloride compared with plasma (154 mEq/L each of Na and Cl), raising concerns that particularly large volume resuscitations of 0.9% normal saline may precipitate hyperchloremic metabolic acidosis. Buffered isotonic solutions, including PlasmaLyte-A and lactated Ringer's, have been suggested as potential first-line alternatives in resuscitation. The 2018 Balanced Crystalloids versus Saline in Critically Ill Adults (SMART) trial randomized over 15,000 critically ill patients to either 0.9% normal saline or buffered crystalloids. The authors reported a lower composite rate of 30- day all-cause mortality, new need for renal replacement therapy, or renal dysfunction among patients resuscitated with buffered solutions compared with 0.9% normal saline (odds ratio [OR] 0.91, $P = .04$).[6] However, a 2019 Cochrane database meta-analysis of 21 randomized controlled trials and 20,000 patients failed to find an advantage of buffered solutions over 0.9% normal saline with regard to hospital mortality or renal failure.[7] Overall, data suggest that infusion of buffered isotonic crystalloids is likely a reasonable first-line approach for resuscitation of hypovolemic shock among critically ill patients, although specific fluid choice should continue to be tailored to each patient's specific metabolic and physiologic parameters.

Electrolyte and Acid/Base Disturbances

Nonhemorrhagic hypovolemic shock often occurs concomitantly with or results in metabolic disturbances, including critical excesses or deficiencies of electrolytes such as sodium, potassium, magnesium, chloride, bicarbonate, and disordered acid/base balance. Although the detailed discussion of the management of electrolyte abnormalities is addressed elsewhere in this text, it is important to rapidly identify and correct these disturbances to restore physiologic homeostasis to the patient in hypovolemic shock.

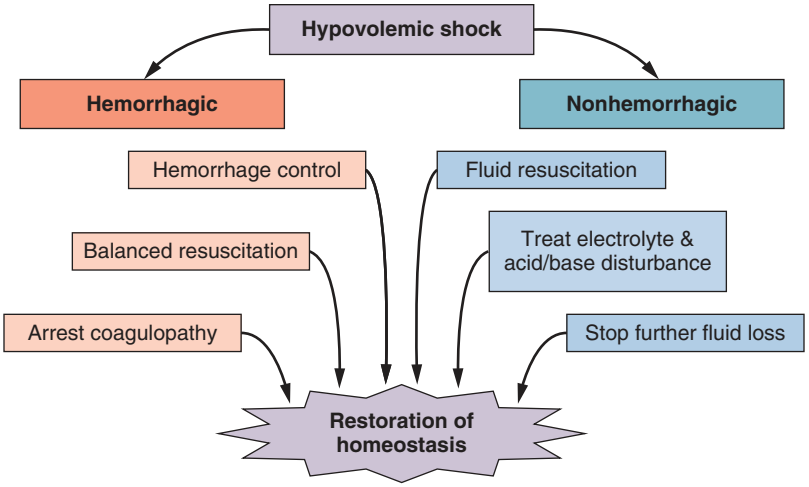

Fig. 141.1 Etiology and Treatment of Hypovolemic Shock.

Etiologies of Nonhemorrhagic Hypovolemic Shock

Although the cornerstone of managing nonhemorrhagic hypovolemic shock is rapid fluid replacement, identification and treatment of the underlying cause of fluid loss is necessary to avoid further hypovolemia and tailor resuscitation strategy. Etiologies of hypovolemic shock include inadequate fluid intake (often in hospitalized, elderly, debilitated, or restrained patients) or losses of fluid from the skin or soft tissue (exertional and insensible losses during strenuous activity, burns and desquamating conditions, open wound and abdomens), the gastrointestinal tract (vomiting, diarrhea, nasoenteric tube, biliary drain, or ostomy losses), third-spacing conditions (sepsis, small bowel obstruction, cirrhosis, heart failure, pancreatitis), and renal conditions in which resorption of electrolytes or water is impaired (diabetes insipidus, cerebral salt wasting, diuretic overuse). Clinical work-up, laboratory, and imaging studies should focus on diagnosis of these conditions.

HEMORRHAGIC SHOCK

Hemorrhagic shock is the most common cause of preventable trauma death,[8] but also can occur as a result of surgical bleeding, aneurysm rupture, massive gastrointestinal hemorrhage, or refractory coagulopathy. Prompt and definitive control of hemorrhage, replacement of whole blood or its components to restore tissue perfusion and prevention, and treatment of coagulopathy are the cornerstones of treatment (Fig. 141.2).[9,10] To facilitate these goals a systematic approach to resuscitation must include rapid scene-to-hospital transport; expedient

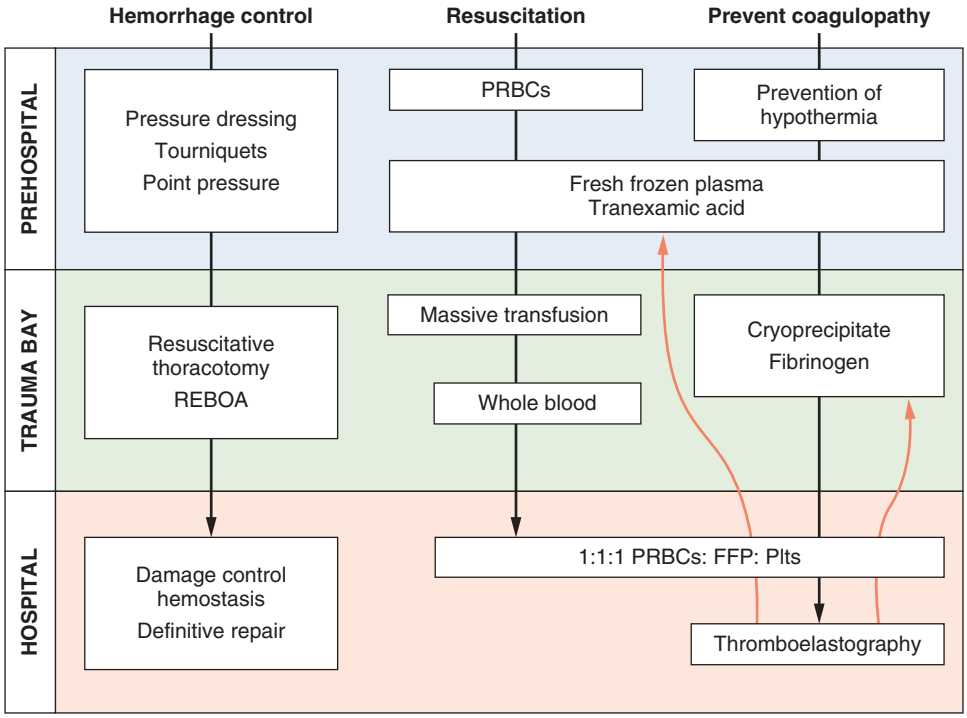

Fig. 141.2 Management Diagram of Hemorrhagic Shock Resuscitation. *FFP,* Fresh frozen plasma; *Plts,* platelets; *PRBCs,* packed red blood cells; *REBOA,* resuscitative endovascular balloon occlusion of the aorta.

surgical intervention; interventional radiology (IR)-guided angioembolization; and balloon occlusive techniques such as resuscitative endovascular balloon occlusion of the aorta (REBOA[11]), early management with balanced blood product transfusions, and avoidance of excessive crystalloid resuscitation. Trauma centers of all levels benefit from standardizing protocols for resuscitation and the diagnosis and treatment of trauma-induced coagulopathy.

Vascular Access for Patients With Severe Hemorrhage

In the trauma patient presenting with multiple serious injuries and hemorrhagic shock, obtaining prompt vascular access is essential to facilitate resuscitation. Advanced trauma life support (ATLS) guidelines recommend placement of two large-bore (16 gauge or larger) IV catheters to allow rapid infusion though a short-length, large-diameter canula. The most suitable veins are at the wrist, dorsum of the hand, antecubital fossa in the arm, and the saphenous vein in the leg.

If peripheral IV catheters cannot be placed, two additional options for rapid access include central venous and intraosseous access. The femoral vein is the most frequent central vein cannulated in trauma resuscitations. Femoral venous access can be placed using anatomic landmarks or ultrasound guidance, and the site is readily compressible against the femur. Femoral vein cutdown under direct vision may be used to obtain rapid access in pulseless patients. Subclavian venous access is another central venous alternative and can be placed safely in experienced hands. The internal jugular vein is rarely used in trauma patients because of the possibility of cervical spine injuries and the concomitant need for cervical collar immobilization.

Intraosseous (IO) needles are increasingly used in the emergency department and prehospital settings to obtain rapid access for medication administration or, if necessary, product resuscitation.[12,13] The technique is particularly useful in challenging or dynamic environments such as in a moving vehicle or in unstable patients where hypovolemia makes venous cannulation difficult. IO needle placement is easy to learn, and prehospital responders are trained in application in many trauma systems.

Importantly, regardless of access type, access should never be initiated on an injured limb. When thoracoabdominal injury is suspected, it is prudent to obtain infradiaphragmatic and supradiaphragmatic access.

Resuscitative Strategies in Hemorrhagic Shock: Red Cells, Platelets, and Plasma—the Ideal Ratio and Whole-Blood Resuscitation

The worldwide experience in severe traumatic injury during military conflicts provided the background and much of the data underlying product resuscitation. The introduction of whole-blood transfusion during World Wars I and II dramatically changed patient outcomes in cases of severe hemorrhage. However, because of lack of knowledge about how infusates disperse and are eliminated after trauma, fluid overload was a common and lethal side effect of resuscitation through the Korean War. Between the Korean and Vietnam Wars, Shires and colleagues described how fluid and electrolytes shift into cells after severe hemorrhagic shock.[14] Subsequent changes in resuscitation practice resulted in better outcomes and lower incidence of acute renal failure during the Vietnam War. The 1970s brought about the separation of blood components.[15] It has taken nearly three decades and the two Middle Eastern conflicts of the 2000s for clinical practice to return to the basic concept that hemorrhagic losses should ideally be replaced with whole blood or, at least, a physiologic ratio of whole blood's main components: plasma, platelets, and red cells,[16,17] an approach referred to as balanced or *whole blood–like* resuscitation.[18,19]

Use of whole blood continues to increase across trauma centers in the United States, and whole blood is now readily available directly in many trauma bays for immediate resuscitation. Whole blood innately provides the bleeding patient the correct ratios of lost components while maximizing the resuscitative and hemostatic effects of product transfusion.[20,21] Additional benefits include minimization of donor exposures, as the lower shelf-life capacity of whole-blood storage results in "fresher" transfusions compared with transfusion of balanced components, which can be stored longer.

Blood options include type O negative, type specific, typed and screened, or typed and crossmatched whole blood or PRBCs. The initial choice depends on the degree of hemodynamic instability. A type and screen identify the patient's blood group and evaluate the serum for major blood group antibodies. Obtaining type-specific red cells requires 5–10 minutes in most institutions. A full crossmatch involves mixing donor cells with recipient serum to rule out antigen/antibody reactions and generally requires about 45 minutes.

Type O negative red cells have no major antigens and can be used safely for patients with any blood type. Unfortunately, only 8% of the population has O-negative blood, and stored O-negative blood availability is chronically limited. O-positive blood can be used empirically in male patients but should be avoided in female patients of childbearing age. Importantly, if 50%–75% of the patient's blood volume has already been replaced with type O blood, type O should continue to be used throughout the resuscitation, as the patient may have received enough anti-A or anti-B antibodies to precipitate hemolysis if A, B, or AB units are subsequently given.

Massive transfusion protocols are a critical part of hemorrhage control in major trauma centers. Activating the massive transfusion protocol hastens the preparation, allocation, and delivery of a fixed ratio of red cells to plasma to platelets.

If component products are to be used, clinicians should employ a balanced 1 PRBCs:1 FFP:1 platelets resuscitation strategy. Multiple military and civilian retrospective studies demonstrated increased survival when PRBC transfusions were accompanied by high plasma- and platelet-to–red cell ratios.[22,23] The Prospective Observational Multicenter Major Trauma Transfusion (PROMMTT) trial found early product administration in a 1:1:1 or 1:1:2 ratio was associated with improved 6-hour survival after admission.[24,25] In 2015 a multicenter, randomized clinical trial was completed in order to address the effectiveness and safety of a 1:1:1 transfusion ratio compared with a 1:1:2 transfusion ratio in patients with trauma who were predicted to receive a massive transfusion. The Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial showed that in patients with severe trauma and major bleeding, early administration of plasma, platelets, and RBCs in a 1:1:1 ratio compared with a 1:1:2 ratio did not result in significant differences in mortality at 24 hours or at 30 days. However, more patients in the 1:1:1 group achieved hemostasis and fewer experienced death resulting from exsanguination by 24 hours. As expected, though, there was an increased use of plasma and platelets transfused in the 1:1:1 group, but no other safety differences were identified between the two groups.[26]

Trauma-Induced Coagulopathy and Viscoelastic-Directed Component Resuscitation

In addition to prompt hemorrhage control and balanced product resuscitation, treatment of hemorrhagic shock requires prevention and rapid reversal of coagulopathy. Coagulopathy develops in approximately one-third of all injured patients and is associated with increased transfusion-related multiorgan system failure and death.

Until recently, trauma-induced coagulopathy (TIC) was thought to be a secondary phenomenon resulting from dilutional loss of coagulation factors during hemorrhage and fluid resuscitation. In 2003 two independent investigators identified early prothrombin time (PT) and

TABLE 141.1 Cutoffs for Conventional Coagulation Assays in Trauma-Induced Coagulopathy

Assay	Reported Cutoff		
Partial thromboplastin time (PTT)	>34–60 seconds	or	>1.5× institutional reference range
Prothrombin time (PT)	>18 seconds		
International normalized ratio (INR)	>1.2–1.5		

partial thromboplastin time (PTT) abnormalities in severely injured patients before resuscitation, identifying an independent pathology now referred to as TIC.[27,28] Several highly integrated coagulation and inflammatory pathways have since been implicated in the pathophysiology of TIC and are the subject of ongoing research. Known mediators include activated protein C, disordered fibrinolysis, and posttraumatic platelet and endothelial dysfunction.[29–37]

To adequately attenuate and prevent TIC, clinicians should be aggressive with providing up-front balanced product resuscitation to critically injured patients according to the principles outlined earlier and without waiting for serum coagulation tests. As resuscitation proceeds, we advocate routine use of thromboelastography (TEG) to help tailor product management. Although TIC was initially defined by prolongation of the standard coagulation assays (PTT and international normalized ratio [INR]) different cutoffs have been described in the trauma literature (Table 141.1), and there has been increased interest and use of point-of-care functional viscoelastic tests such as TEG and rotational thromboelastometry (ROTEM) for the diagnosis and management of patients with TIC.[38] TEG is a well-validated point-of-care assay of clot generation, integrity, and breakdown providing rapid assessment of TIC in the acute setting.[39,40] It allows providers to target specific resuscitation products (cryoprecipitate, FFP, platelets, fibrinogen) to the patient's individual needs and has become standard of care in trauma resuscitations in high-volume trauma centers. Prospective randomized data have demonstrated a mortality benefit for patients undergoing TEG-guided massive transfusion compared with conventional coagulation assays, and viscoelastic assays should be used routinely as part of trauma resuscitation and massive transfusion algorithms.[41]

Fibrinogen deficit and hyperfibrinolysis are known to contribute to the pathophysiology of TIC. FFP does not contain sufficient amounts of fibrinogen for adequate replacement, and in the United States cryoprecipitate is often used to replace fibrinogen stores.[42] In Europe, retrospective studies have reported good efficacy of fibrinogen concentrate in correcting functional deficits after trauma, and emerging data suggest that this approach may demonstrate promise in reducing blood requirements after injury.[43,44]

Platelet Dysfunction After Injury

Platelet dysfunction likely plays a particularly important role in disordered clotting after injury. Endothelial cell injury (leading to extensive adenosine diphosphate [ADP] metabolism) and overwhelming immediate platelet activation (leading to "platelet exhaustion") may both contribute to platelet dysfunction in early trauma. A prolonged refractory state after initial injury could explain why platelets may be qualitatively dysfunctional even without thrombocytopenia.

Disturbances in platelet function are common after injury and portend poor outcomes. Multicenter observational data suggest that platelets are inhibited in 86.1% of trauma patients compared with 4.2% in healthy volunteers with worse base deficit (a marker of injury severity) correlating to greater platelet dysfunction.[45] Another prospective observational study found nearly half of critically injured patients had evidence of platelet hypofunction upon admission. Platelet hypofunction was associated with up to a 10-fold increase in 24-hour mortality (20.0% vs. 2.1%, $P = .009$).[46]

Hyperfibrinolysis and Tranexamic Acid for Trauma Patients

Evidence of hyperfibrinolysis as underlying TIC has led to interest in antifibrinolytic agents as potential adjuncts for the resuscitation of injured patients. The CRASH-2 (Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage 2) trial was a placebo-controlled trial performed in 274 hospitals in 40 countries. Adult trauma patients were included if they presented within 8 hours of blunt or penetrating injury, were at risk of significant hemorrhage, or presented with systolic blood pressure <90 mm Hg or heart rate >110 beats per minute. The authors found that patients randomized to 1 g tranexamic acid (TXA) had a lower relative risk (RR) of mortality compared with placebo (RR 0.91, $P = .0035$), and the risk of bleeding (RR 0.85, $P = .0077$) and vascular occlusion (RR 0.69, $P = .096$) were also decreased. This study was performed in a rigorous manner that reflected real-world clinical practice across a variety of settings ranging from austere environments to tertiary medical centers. The CRASH-2 trial provides level I evidence supporting TXA, and TXA is now widely administered in trauma centers to improve outcomes in patients at risk of hemorrhagic shock. Notably, outcomes are best when TXA is administered early, ideally within the first 3 hours of injury.[47]

Prehospital Resuscitation

Ideal resuscitation starts as early as possible after injury. Recent research efforts have evaluated strategies and effectiveness of prehospital transfusion of plasma, PRBCs, and whole blood. Prehospital PRBC administration has been independently associated with a lower risk of 24-hour mortality, 30-day mortality, and TIC in patients with severe blunt traumatic injury.[48] Additionally, initiating PRBC transfusion during patient transport to the trauma center was independently associated with improved outcomes. Similarly, the Prehospital Air Medical Plasma (PAMPer) trial was a multicenter cluster-randomized clinical trial that compared the administration of thawed plasma with standard-care resuscitation during air medical transport among 501 injured patients at risk for hemorrhagic shock. Patients randomized to receive prehospital plasma had significantly lower 30-day mortality compared with the standard-care group (23.2% vs. 33.0%, $P = .03$). Mean PT ratios were lower in the plasma group vs. standard-care group (1.2 vs. 1.3, $P < .001$).[49]

The Control of Major Bleeding after Trauma (COMBAT) trial sought to assess the effect of ground ambulance plasma administration but found no difference in overall mortality among patients receiving plasma compared with their standard-care counterparts.[50] Post hoc pooled analysis of PAMPer and COMBAT participants indicated prehospital plasma was associated with a survival benefit in patients with hemorrhagic shock among patients with transit times exceeding 20 minutes.[51]

The safety and efficacy of prehospital TXA administration has also been the subject of considerable interest and study. A recent multicenter, randomized controlled trial failed to find significant differences in 30-day mortality between patients receiving prehospital TXA versus placebo.[52] However, among a severely hypotensive subgroup of patients (systolic blood pressure [SBP] ≤70 mm Hg), TXA was associated with significantly increased survival (18.5% vs. 35.5%; difference, $P < .003$), suggesting that TXA is likely a useful and safe prehospital adjunct particularly in critically ill patients. Notably,

survival benefit was seen when TXA was administered within the first hour of injury.

Prediction of Coagulopathy

Multiple algorithms have been developed to attempt to predict patients at risk for TIC. Notable prediction tools include the Assessment of Blood Consumption (ABC) score and the Clinical Coagulopathy Score (created by the Trans-Agency Consortium for Trauma-Induced Coagulopathy [TACTIC]). The ABC score includes four dichotomous variables: penetrating mechanism, SBP ≤90 mm Hg, emergency department heart rate ≥120 beats/minute, and positive fluid on abdominal ultrasonography. In a multicenter study the ABC score yielded a negative predictive value of 97%, and less than 5% of patients who require massive transfusion will be missed using the ABC score.[22] The TACTIC clinical coagulopathy score for TIC helps define postinjury mortality caused by coagulopathy, offering standardized clinical scoring and mortality criteria in patients with TIC. However, none of these scoring systems have become widely accepted in the diagnosis of TIC. Retrospective data comparing various scoring systems failed to demonstrate a difference between their capacity to predict massive transfusion.[23]

Putting It All Together: A Comprehensive Approach for Management of Shock and Severe Bleeding

Resuscitation management should start at the scene. Emergency medical technician (EMT) personnel should be trained in hemostasis, and tourniquets should be liberally applied. Prehospital product, plasma, and TXA should be used in severely injured patients as part of early resuscitation.

Trauma centers should have systems in place for whole blood or (if not yet available) balanced product resuscitation.

Once the patient arrives to the trauma center, TEG, hemoglobin, and a venous blood gas should be immediately obtained and used to tailor resuscitation. Massive transfusion and TXA protocols should be activated early for patients presenting with critical injury or hemorrhagic shock.

Emergency department, interventional radiology, and surgical interventions for hemorrhage control should be implemented rapidly. Damage control and staged procedures must be carefully planned, and multidisciplinary communication with the ICU team and other consultants is key to maintain the proper order of priorities and to implement ancillary care. Throughout resuscitation, serial TEG should be used to guide resuscitation.

KEY POINTS

- Hypovolemic shock can be divided into two etiologies with concomitant differences in treatment. Nonhemorrhagic hypovolemic shock consists of body fluid loss and is treated primarily with fluid replacement to restore intravascular volume. Hemorrhagic shock results from blood loss and is treated with hemorrhage control, replacement of whole blood or its components, and avoidance or correction of coagulopathy.
- Nonhemorrhagic hypovolemia should be treated with rapid bolus infusion of isotonic crystalloid with ongoing monitoring of physiologic and laboratory data to evaluate response and dictate termination of therapy. We prefer use of buffered isotonic solutions for critically ill patients, particularly in large-volume resuscitations.
- Hemorrhagic shock is the most common cause of preventable trauma death.
- Trauma resuscitation should be systematic and include rapid scene-to-hospital transport and expedient prehospital, emergency department, surgical, and IR-guided techniques for hemorrhage control.
- Patients with severe injuries should receive early management with whole blood or balanced blood product transfusions in a 1:1:1 ratio of PRBCs:FFP:platelets. Excessive crystalloid resuscitation should be avoided.
- TEG should be promptly obtained and used to further tailor resuscitation.
- Trauma centers of all levels benefit from standardizing protocols for resuscitation and the diagnosis and treatment of TIC.

References for this chapter can be found at expertconsult.com.

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Mediastinitis

Eric I. Jeng, Giovanni Piovesana, and Thomas M. Beaver

The mediastinum is the thoracic space confined by the sternum anteriorly, the spine posteriorly, the pleural laterally, the diaphragm inferiorly, and the thoracic outlet superiorly. It can be divided anatomically into superior and inferior compartments by the sternal angle. The inferior compartment is further divided into the anterior (between the posterior sternum and the anterior pericardium), middle (the intrapericardial contents), and posterior (bounded anteriorly by the posterior pericardium and posteriorly by the spine) mediastinum (Fig. 142.1).

Mediastinitis is defined as inflammation of the mediastinum, and the diagnosis, treatment, and prognosis are determined by location and etiology. Primary mediastinitis arises without prior intervention, whereas secondary mediastinitis occurs postintervention. Clinically, mediastinitis of the anterior and middle mediastinum occurs most frequently as a postoperative complication of a cardiothoracic procedure. Esophageal pathology accounts for the overwhelming majority of the mediastinal infections of the posterior compartment.

Other more unusual forms of mediastinal infections or inflammation include those that migrate into the mediastinum from adjacent contiguous spaces and those that are more indolent than acute and are characterized by chronic inflammation and fibrosis.

Accordingly, this presentation follows these anatomic and etiologic distinctions: acute anterior mediastinitis, acute posterior mediastinitis, and migratory and chronic mediastinal inflammation.

ACUTE ANTERIOR MEDIASTINITIS

The most common form of acute anterior mediastinitis occurs after sternotomy for a cardiothoracic operation. It may also occur after traumatic sternal fracture[1]; descending cervical infections; and/or teratomatous, thymic, and thyroid infections/inflammation.

The term *mediastinitis* after cardiothoracic surgery refers to an infection involving the space deep to the sternum. Other forms of postoperative infection can be identified as superficial sternal wound infection (SWI; above the fascia without sternal involvement) and sternal osteomyelitis (without deeper infection).

Clinically, it is sometimes unclear as to whether one is dealing with a superficial problem above the level of the fascia, a sterile dehiscence, or a deeper infection. As no impervious anatomic barrier exists between the posterior cortex of the sternum and the space behind it, any infection posterior to the sternum is considered an infection of the anterior mediastinum. More than a small amount of drainage, any sternal instability, or evidence of separation suggest at least a sterile dehiscence and the need for re-exploration, deep cultures, and appropriate reclosure.

Incidence, Pathology, and Prevention

The reported incidence of mediastinitis ranges from 0.24% to 4% postcardiotomy.[2–4] Comorbidities that increase the risk of postoperative mediastinitis include diabetes, elevated body mass index, older age, renal failure, prolonged preoperative hospitalization, immunosuppression, chronic obstructive pulmonary disease, cigarette smoking, reoperation, and preoperative atrial fibrillation.[3,5–7]

Intraoperative factors have also been shown to play a role in postcardiotomy infection. Bilateral internal mammary use for coronary bypass grafting has about a 5% risk of sternal dehiscence as compared with 1% in single internal mammary usage. In addition, off-midline sternotomy, prolonged operative time, and the use of an intraaortic balloon pump[7] have also been shown to increase risks of mediastinitis.

Multiple studies have cited bone healing is significantly impaired by using bone wax for sternal hemostasis as compared with water-soluble polymer wax, suggesting the use of the latter as a useful alternative, because bone healing immediately postoperatively is the most critical time frame for the prevention of sternal nonunion and infection.[8]

In high-risk patients, sternal closure with rigid plate fixation may decrease the incidence of postoperative mediastinitis[9] as compared with a similar population of patients whose sterna were closed with traditional wire alone. Some have shown that the use of cyanoacrylate glue can decrease the infection rates of superficial and deep surgical sites in patients who have sternal detachment and/or are at high risk for developing infection.[10] For those advocating minimally invasive and alternative approaches to cardiac procedures, all together avoiding the sternotomy appears to also reduce the risk of mediastinal infection after cardiac operations.[7]

Postoperatively, increased glucose levels (>200 mg/dL),[11,12] re-exploration, and prolonged ventilator use are associated with a higher incidence of deep sternal infection.[7] As such, many quality metrics postcardiotomy are related to glucose control and time to extubation. In patients requiring complex cardiac repair, postoperative tracheostomy is frequently required. Despite the close proximity to the sternal incision, early tracheostomy for patients with ventilator dependence has not been shown to be associated with an increased incidence of mediastinitis.[13] Tracheostomy per se is not a risk factor for sternal breakdown, but rather serves as a surrogate for respiratory failure.[14,15] As many ICUs have moved toward percutaneous tracheostomy, Hubner and colleagues evaluated the technique of percutaneous tracheostomy specifically and found that it has not been associated with a subsequent increase in mediastinal infection.[16]

Staphylococcal species are the most common organisms seen in patients with poststernotomy deep wound infection, and these are increasingly methicillin resistant.[17] Coagulase-negative resistant organisms are more common in patients who have prolonged hospitalizations.[18] Gram-negative organisms may be cultured, particularly from patients with diabetes, in patients with gram-negative pneumonia before operation, or in those who require re-exploration.[1] Given the most common organisms causing these infections, a second-generation cephalosporin is still the most accepted preoperative prophylaxis. Vancomycin is substituted in patients with penicillin allergy, and the

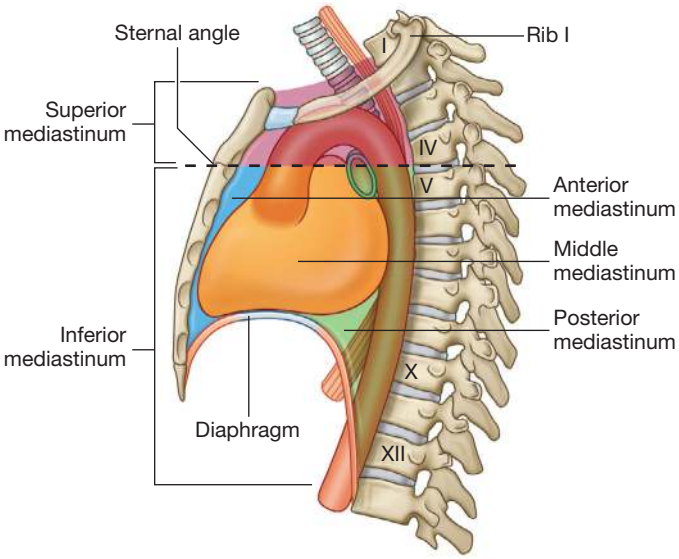

Fig. 142.1 With respect to etiology, mediastinitis may be either primary, arising without prior intervention, or secondary, occurring postintervention. Clinically, the anatomic anterior and middle compartments can be considered together, as mediastinitis occurs most commonly in these combined spaces secondarily as a postoperative complication of cardiac operations. Esophageal pathology accounts for the overwhelming majority of mediastinal infections of the posterior compartment. (From Drake RL, Vogl AW, Mitchell AW. *Gray's Anatomy for Students*, 2nd ed. Philadelphia, PA: Churchill Livingstone; 2009: Fig 3-5.)

addition of preoperative gram-negative coverage is appropriate in such cases, given vancomycin's poor coverage of such organisms.[19] Topical vancomycin has been shown to be effective in decreasing the incidence of sternal infections, and it is used routinely in some practices.[20] Evidence-based guidelines from the Society of Thoracic Surgeons recommends gram-positive prophylaxis for no more than 48 hours in addition to preoperative nasal mupirocin.[17,19]

Diagnosis

Patients with mediastinitis after sternotomy generally have clinical signs of wound drainage and sternal instability, but neither may be initially present. Fever and leukocytosis are common symptoms. Some patients manifest signs of sepsis, with mental status changes and hemodynamic compromise. Mediastinitis can appear as early as 1 day after the index operation or as remotely as months after an operation. The variable diagnostic accuracy of imaging techniques for the diagnosis of mediastinitis permits them to be supportive,[21] but rarely, if ever, definitive. This is especially true during the early time frame (<30 days), when the vast majority of patients present. During this time, fluid collections and mediastinal soft tissue changes are common, if not universal, with both being nonspecific for infection.[22]

Computed tomography (CT), magnetic resonance imaging (MRI), and technetium-99m leukocyte imaging can identify patients who have deep sternal wound infection (DSWI) and require surgical débridement.[23] Cooper and colleagues showed that the patterns of intense uptake at 4 and 20 hours or increasing uptake between 4 and 20 hours were 100% sensitive and 89% specific for the detection of DSWI. It is useful in patients with suspected DSWI when clinical examination fails to confirm a diagnosis or when deep sternal aspirates of the superficial SWIs are equivocal. Leukocyte imaging is not useful for detecting superficial SWIs.[24] Given the speed and efficiency, CT scan is favored in localizing the site of pathology and can give a better picture of the overall patient condition.

A profile of abnormal cytokine levels has been characterized,[25] with the terminal SC5b-9 complement complex concentration being substantially higher in patients with mediastinitis and having no overlap with the values in non-mediastinitis, post–cardiac surgery controls. In difficult-to-diagnose cases, blind retrosternal, subxiphoid needle aspiration and culture have been variably employed, and aspiration with ultrasound guidance has been reported after cardiac transplantation.[26] A recent small series suggested diagnostic success in patients without classic signs of infection by anteriorly inserting a 22-gauge needle percutaneously and aspirating between the recently closed sternal edges. Cultures and Gram stains were used to establish the presence of infection, with a high degree of specificity and sensitivity.[27]

Treatment

The different technical approaches to treat anterior mediastinitis are related to the temporal interval from the antecedent operation, the depth and extent of the infection, and the acuity of the patient.[28] The classification by Pairolero and Arnold[29] is based on clinical features and can be used to practically approach the various types of clinical entities.

There are three major types of sternomediastinitis in this system.

Type I sternomediastinitis manifests with serosanguineous drainage within a few days after sternotomy. Purulence, osteomyelitis, and chondritis are notably absent. Mediastinal tissues are still soft and pliable. Bacterial cultures are initially negative or yield staphylococci. In such cases, the sternotomy is reopened, all blind pockets are eliminated, and the mediastinum is irrigated. This type of infection is best managed by the reinsertion of drainage tubes and reclosure of the sternum with either a variation of the Robicsek[30] weave or a commercially available plate fixation device. Aggressive intravenous and topical antibiotic treatment should be used in these cases.

Type II sternomediastinitis is a fulminant process that occurs 1–3 weeks after surgery. In addition to reopening, drainage, and irrigation, these patients require débridement of the necrotic soft tissue, bone, and cartilage. This may be performed initially, when the wound is reopened, but may be delayed if the patient is septic or if their general condition is too critical to allow a major intervention. An effort should be made to remove all foreign materials such as felt pledgets and pacing wires. Exposed suture lines can be reinforced with autologous tissue, such as fascia lata, omentum, and/or covered with muscle flaps. The wound is then kept open and treated with daily dressing.

Type III sternomediastinitis occurs 1 month to 1 year after surgery. The patient typically presents with chronic draining sinus tracts that lead to the infected sternum, cartilages, or retained foreign bodies. Repair requires wide exposure, extensive débridement, often total sternectomy, and/or muscle/omental flap coverage using autologous tissues.

Diluted antibiotic, povidone-iodine, and aqueous acid solutions have been reported as irrigation protocols.[28,31] The duration of irrigation has varied from 3 days to 1 week, while systemic antibiotics are continued, as would be the case for other adult bone infections.[32] The cultures obtained at operation dictate the systemic antibiotics that will ultimately be used, but initial coverage may include a second-generation cephalosporin and gram-negative coverage until a Gram stain or the culture results are definitive.

If a multiple-stage approach is indicated, the approach involves an interval during which the sternum and skin are left open and a negative-pressure wound vacuum device is used.[33,34] It should be cautioned that the management of open sternal wounds can be associated with a risk of sudden cardiac hemorrhage from the exposed grafts, the aorta, and/or the right ventricle. The risk of death in such patients is >50%,[35–37] but this may be the result of the underlying etiology requiring open

chest management. Given the added risks of an unapproximated sternum, most recommend close attention be paid to the proximity of the sternal edges and the right ventricle. A custom fashioned plastic 60-cc syringe to mechanically prop open the sternum, in theory, can be used to prevent both tamponade in an already edematous heart and mechanical shearing of the right ventricle against the sternal edge. Postoperative management includes sedation, possible muscle paralysis, and mechanical ventilation until complete coverage can be achieved.

Whether used as an initial single-stage procedure or as a secondary procedure, tissue transposition into the anterior mediastinum has dramatically changed the prognosis of this once often fatal complication.[38]

The use of omentum versus any specific muscle flap is dictated by availability, but when the option exists, the use of omentum has been touted as advantageous over muscle flaps.[39] Omentum has also been successfully employed in infections after ascending aortic replacement for its properties of improving oxygen supply, enhancing antibiotic delivery, and enhancing the immunologic response while absorbing secretions that can lead to bacterial proliferation.[40] Skin coverage over a transposed flap may be accomplished by primary presternal skin reapproximation or split-thickness skin grafting, or, with the rectus muscle, a skin paddle may be transposed as well.

Prognosis

Although the mortality of mediastinitis has improved dramatically over the past three decades, the likelihood of death remains high (13%–47%) and most often from associated comorbidities or complications.[41] Early detection with expeditious operative débridement and tissue coverage are the major advances that have enabled improvement of short-term mortality. It should be noted that despite these improvements, there are still long-term consequences of mediastinitis past the acute phase. The Northern New England Cardiovascular Disease Study Group found that the 4-year mortality for patients with a postoperative deep sternal infection was three times greater than that for patients without this complication, and this increased all-cause mortality rate persisted with up to 10 years of follow-up. For patients surviving for longer than 6 months after a cardiac operation, the incidence of death was 70% higher than the rate among patients who did not have a mediastinal infection.[42]

POSTERIOR MEDIASTINITIS

Acute infections that arise in the posterior mediastinum generally result from primary disease of the esophagus or, more frequently, iatrogenic complications from esophageal intervention.[43]

In general, esophagitis (eosinophilic, fungal, or other pathogenic organisms) that extends through the esophagus results in mediastinitis. This can lead to periesophageal abscess formation caused by micro/macro perforations. Other common causes of esophageal perforation include Boerhaave syndrome and corrosive or foreign body ingestion. Periesophageal pathology may additionally be secondary to esophageal operations. The source of an infection may be anastomotic disruption, with esophageal leaks occurring in 4.3%–8.7% of patients who underwent an intrathoracic esophagogastric anastomosis.[44] Traumatic injuries to the trachea, proximal bronchi, or esophagus obviously may also result in the contamination of this space. More rarely, the erosion of a broncholith from a partially or completely obstructed bronchus can also cause posterior mediastinistis.[45]

Diagnosis

With a relevant history, the presence of cervical pain and/or chest pain with a high fever would strongly suggest the diagnosis. Supraclavicular crepitus may be identified in patients with upper mediastinal pathology, but is generally absent initially in those with middle or lower esophageal disease. Leukocytosis may be the singular early laboratory abnormality. Furthermore, sepsis with altered mental status and hypotension may occur. Certainly, in some of these patients, plain chest film may reveal a pleural effusion, and more rarely, air may be seen in the retropharyngeal space or other abnormal locations along the length of the mediastinum posterior to the pericardium. Fluoroscopic esophagogram and CT scan with oral contrast are the mainstays for diagnosis and localization. CT can demonstrate abnormal air or fluid collections along the esophagus or esophagogastric junction in the thoracic, abdominal, and pelvic spaces. Direct visualization via endoscopy can aid in diagnosis and repair strategy. In addition, transesophageal ultrasonography and fine-needle aspiration have been jointly used to diagnose a variety of periesophageal infections.[46]

Treatment

A contained esophageal disruption (extravasation of contrast that drains rather promptly back into the lumen) may be managed successfully in stable patients by serial clinical evaluation, limited oral intake, antibiotic therapy, and repeat imaging.[47] This may be particularly true in young children.[48]

In patients with more frank mediastinal contamination not confined to the local perforation but identified within the first 24 hours, operation with primary repair and drainage is often indicated.[49,50] If the length of time since the perforation is sufficiently short and the injury is sufficiently small so that local inflammation is limited, primary repair of a disruption—preferably with viable vascularized tissue buttressing—has been successfully employed,[50] even after 24 hours.[51] Success has also been recently reported with the use of covered self-expanding esophageal stents.[52] Image-guided nonoperative drainage with antibiotics has been successfully employed in selected cases where a defined collection or abscess could be identified.

In a case series reported by Ben-David and colleagues, uncontained acute (less than 24 hours) esophageal perforations in the chest greater than 2 cm in size were successfully treated with a combination of endoscopically placed stent, minimally invasive laparoscopic/thoracoscopic mediastinal drainage, and a laparoscopically placed gastrostomy or jejunostomy tube. By adopting this treatment algorithm, control of the esophageal leak was confirmed in all patients within 24 hours of the esophageal stent placement, and 73% of the patients were able to begin a diet 48 hours after their esophagogram confirmed no further extravasation of contrast.[53,54]

In patients with more extensive local inflammation, such as those diagnosed more than 24 hours after perforation and those who are more systemically ill, drainage with or without some esophageal diversion may be employed. Continued sepsis and multiple organ failure are the most common causes of death among these patients, and multiple operations to excise necrotic tissue and drain the space are sometimes required before definitive reconstruction.

MIGRATORY AND CHRONIC MEDIASTINAL INFLAMMATION

The mediastinum may be infected secondarily from contiguous acute infections involving adjacent anatomic spaces such as the pleurae, lungs, spine, intraabdominal processes, and retroperitoneum.[55]

Perhaps the most dramatic and well described of the migratory mediastinal infections are those that descend from the neck, which is known as *descending necrotizing mediastinitis*. These include those infections that arise as classic Ludwig angina (odontogenic or nonodontogenic) or from cervical puncture wounds. Gravity and the negative

pressure of the thoracic cavity have been cited as reasons for this descent through the pretracheal space into the upper posterior mediastinum. These patients are often young and may have a history of a dental infection. Cervical pain, cellulitis, necrosis, and abscess formation may occur, and a high index of suspicion leading to CT imaging can be diagnostic. Broad-spectrum antibiotics are essential and must be accompanied by cervical and mediastinal drainage directed by the clinical and radiologic findings.[56,57] Drainage may be accomplished in a variety of ways, including right thoracotomy, left-sided video-assisted thoracoscopy, or an anterior clamshell incision. The mortality of this condition has historically ranged from 20% to 40% and increases directly with the interval between the onset of symptoms and diagnosis.

Oropharyngeal cervical infections descending into the mediastinum have been successfully managed with antibiotics and a combination of percutaneous drains and/or videoscopic débridement.[55,58] In any case, aggressive imaging surveillance and a commitment to achieving and maintaining adequate drainage (multiple varied procedures) are necessary to successfully manage this relatively rare life-threatening disorder.[59]

Mediastinal fibrosis is a chronic condition that may present precipitously when the process constricts a mediastinal structure, compromising its lumen. Pulmonary vein, pulmonary artery,[60] vena cava,[61] and tracheal stenoses are the most commonly seen. The diagnosis is generally established by CT or MRI, which reveals a diffusely infiltrating, sometimes calcified, mass. Bronchoscopy may contribute to the diagnosis.[62] The fibrosis is a benign, acellular proliferation of fibrous collagenous tissue that is idiopathic or may be an immunologic sequela of an intervention (e.g., radiofrequency ablation) or infection (mycotic, specifically, and most commonly, *Histoplasma*).[63,64] Treatment may include steroid therapy[65] and local dilation of the stenotic lumen with stents or operation.[66]

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KEY POINTS

- The mediastinum can be separated into the superior, anterior, middle, and posterior mediastinal spaces.
- Diagnosis and early treatment of acute anterior mediastinitis can improve short-term mortality.
- Etiology of mediastinitis defines treatment and diagnostic options.
- Preoperative, intraoperative, and postoperative factors can contribute to mediastinitis.
- CT, MRI, and technetium-99m leukocyte imaging can aid in the diagnosis and treatment of mediastinitis.
- Mediastinitis worsens short- and long-term morbidity and mortality.

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Epistaxis

Rohit Pravin Patel

Epistaxis is an acute hemorrhage from within the nasal cavity, including the nasopharynx, and accounts for 0.5% of all U.S. emergency department visits. Approximately 60% of individuals experience epistaxis at least once in their lifetime, although only 6% of cases require medical treatment.[1,2] The peak incidence of epistaxis in adults is in the 45- to 65-year-old age group, and the incidence of severe posterior bleeding is greater.[3] Special aspects regarding the care of critically ill patients with epistaxis, including prevention, diagnosis, and management options, will be discussed in this chapter. An algorithm for the management of epistaxis by the American Academy of Otolaryngology Head and Neck Surgery is included to assist in clinical decision support (Fig. 143.1).

ANATOMY

The vascular supply of the nasal cavity forms from the terminal branches of the internal and external carotid arteries. The majority of epistaxis (90%–95%) occurs on the anterior nasal septum at a region called *Little area*. This area is supplied by Kiesselbach plexus, a network of vessels from three large thin-walled arteries (sphenopalatine artery, anterior ethmoidal artery, and superior labial artery).[4] Epistaxis is classified as anterior or posterior, although no clear landmarks separate the two.[1,5] Melia and McGarry proposed that anterior bleeding is from a source anterior to the plane of the pyriform aperture (the anterior bony nasal aperture), which includes bleeding from the anterior septum and from the vestibular skin and mucocutaneous junction. Posterior bleeding is from a vessel situated posterior to the piriform aperture and allows for further division into the lateral wall, septal, and nasal floor bleeding.[6] The two primary sites of posterior epistaxis include the posterior lateral nasal wall and the posterior nasal septum, with the most common artery involved being the sphenopalatine artery. Epistaxis from the anterior ethmoidal artery is less common and is typically associated with midface trauma or iatrogenic injury during endoscopic sinus surgery.[7,8]

DIAGNOSIS

It is important that the clinician wear appropriate safety clothing and equipment (disposable apron, gloves, surgical face mask, suction, and headlight). It is also important to gather details of the initial presentation, previous bleeding episodes, comorbid conditions, and current medications. Coagulation screening is only indicated when the clinical history suggests coagulopathy of a known use of anticoagulants.[9] Warfarin is a commonly prescribed anticoagulant, and patients with epistaxis on warfarin are older, have longer mean hospital stays, and show trends that they require more aggressive treatment to control. In a review of patients taking warfarin with epistaxis, it was found that more than 75% of the patients were over-anticoagulated at the time of admission.[10] Critically ill patients are frequently supine, with decreased alertness, and blood may drain into the nasopharynx and, subsequently, the stomach, making it difficult to differentiate from gastrointestinal bleeding. An anterior speculum examination with a good light source usually allows the identification of focal anterior bleeding. Generalized mucosal ooze in a patient with systemic coagulopathy and large amounts of bleeding that obscures visualization can make identification of the source difficult. In addition to the anterior/posterior classification system discussed earlier, bleeding can be classified as venous/arterial or high/low flow based on the rate of bleeding. Venous bleeding can involve low flow, such as mucosal oozing, or it can be high flow from structures such as the cavernous sinus. Arterial bleeding can be low flow from oozing from small perforating vessels, or it can be high flow in carotid artery injuries.[11] Epistaxis can also be classified as primary or secondary when there is an underlying coagulopathy associated with anticoagulant/antiplatelet medications.[6] For patients in which anterior bleeding is not easily identifiable, nasal endoscopy has been shown to identify over 80% of bleeding sites not otherwise seen and reduce the duration of hospital admission. Chiu and McGarry reported positive identification of 94% of posterior bleeding sites in 50 consecutive patients, while Supriya and colleagues identified 38 of 47 posterior bleeding sites in a series of 100 patients, with an overall positive identification rate of 91%.[8,12]

TREATMENT

General management includes protection of the airway, addressing hemodynamic compromise, and controlling active hemorrhage. Patients with a reduced level of consciousness or head injury are at risk of aspiration and should require consideration of airway protection with endotracheal intubation. Intravenous access and fluid resuscitation should be addressed quickly, as patients can become unstable. The first priority is to control or slow the active hemorrhage with some form of temporizing packing. Commercially available anterior or posterior balloon combination packs can be used with the goal of slowing the rate of blood loss while the setup of anticipated equipment is established. Before insertion of these packing materials, an attempt can be made by simply applying pressure to the nose while the patient is positioned upright and leaning forward for 20 minutes. The goal here is to slow the blood loss rate by collapsing the bleeding vessels and forming a clot.

Treatment: Anterior Bleeding

Cautery of an identified bleeding point is the optimal method of management in adult epistaxis and can successfully control anterior bleeding, with silver nitrate and electrocautery as options. Silver nitrate is applied by rolling the applicator stick between your thumb and first finger while gently applying the tip to the area you wish to cauterize for

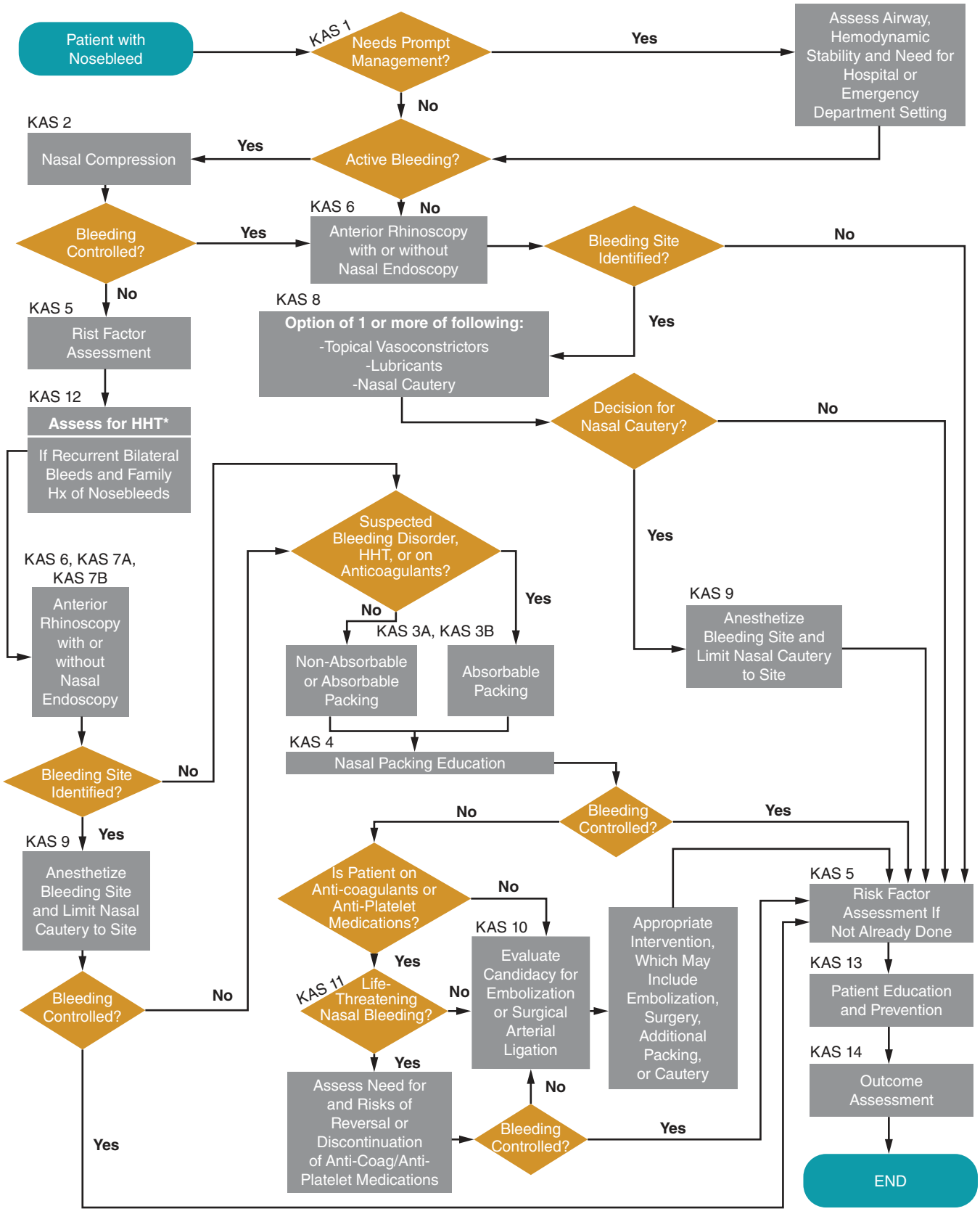

Fig. 143.1 Epistaxis guideline key action statements: Diagnostic and treatment algorithm. *HHT,* Hereditary hemorrhagic telangiectasia; *Hx,* history; *KAS,* key action statement. (From Tunkel DE, Anne S, Payne SC, et al. Clinical practice guideline: Nosebleed (epistaxis). *Otolaryngol Head Neck Surg.* 2020;162[Suppl. 1]: S1–S38, Figure 6.)

about 5–10 seconds. Care should be taken not to burn the nasal skin as you enter the nose or aggressively use it on the septum. Start adjacent to the vessel, making an orbit around the vessel before rolling the tip in to the center, as rebleeding is common when going straight for the site. Shargorodsky and colleagues found that cautery had a significantly lower treatment failure rate (defined as a rebleed requiring intervention by a physician within 7 days) and a lower mean number of interventions required to achieve lasting hemostasis with nondissolvable packing. Among the patients who required admission, those who underwent directed vascular control had fewer inpatient days.[13] If cautery does not control the bleeding, a nasal pack will be required. Nasal packs should be introduced into the nose directly front-to-back following the floor of the nose. Never place it upward, as this does not work, is painful, and increases the risk of complications. Commercially available packs are available and consist of balloon/hydrocolloid fabrics that expand after placement into the nasopharynx. Most of these have a string or tubing that should be taped to the patient's cheek to secure it.

Treatment: Posterior Bleeding

Severe idiopathic nontraumatic posterior bleeding typically occurs in the elderly, who often have underlying cardiac and respiratory comorbidities. It should be suspected after appropriate anterior control measures have been taken and bleeding continues. Typically, a 12 French Foley catheter or similar item is used in conjunction with a ½-inch ribbon gauze or commercially available anterior packing supplies. The catheter balloon should be tested with saline before use. A nasal decongestant and topical local anesthetic solution should be administered to the nasal cavity and on the ribbon gauze. The catheter is lubricated and advanced into the nose until the tip can just be seen passing the soft palate in the mouth. At this point, the catheter needs to be pulled back 1 cm as the balloon inflates in the nasopharynx. Between 5 and 10 mL of saline is used to inflate the balloon, and once inflated, the catheter is pulled taut so that the balloon is effectively occluding the posterior nasopharynx at the back of the nasal cavity. Anterior packing is then performed by folding layers of the ribbon. These patients are at risk for adverse events such as rebleeding and hypoxia, likely the result of comorbidities such as cardiovascular disease, pulmonary disease, renal disease, obesity, and obstructive sleep apnea.[14,15] For continued bleeding, surgery or embolization is an option. Moshaver and colleagues showed that compared with surgical intervention, posterior nasal packing resulted in a significantly shorter mean hospital stay and reduced healthcare costs. The overall success rate was 89%, and no difference was found in the complication rates between the two treatment options.[16] Arterial embolization appears similar to surgery in terms of its success in controlling intractable epistaxis, with several recent studies showing success rates of 80%–90%.[17–21] The advantage of surgery is a lower risk for major complications such as stroke, blindness, and soft tissue ischemia. The advantage of embolization is the ability to perform the procedure under local anesthesia, thus avoiding general anesthesia in patients with comorbidities, in addition to the improved diagnosis of vascular abnormalities such as malformations and pseudoaneurysms. Marin and colleagues showed that 90.6% of episodes requiring vascular intervention had a posterior source. The most performed surgical technique was endoscopic sphenopalatine artery ligation (ESPAL) (69.4%), followed by cautery of mucosal bleeding (24.2%), cautery of the ethmoidal artery (24.2%), argon plasma coagulation (8.1%), and endoscopic clipping/ligation of maxillary artery (3.2%).[22] There is a growing body of support for early intervention in epistaxis with ESPAL, with the increased use of endoscopic sinus surgery and greater understanding of local regional anatomy, with improved patient satisfaction and cost reduction compared with traditional packing techniques.

Treatment: After Packing the Nose

The packing is usually kept in for 5 days, but this is usually physician and institution dependent. Patients do not tolerate nasal packing well. Shargorodsky and colleagues examined whether the duration of packing was associated with the recurrence of epistaxis after removal and did not demonstrate a significant difference between the recurrence rate and the number of pack days, showing no evidence that removing the packing after fewer than 5 days was associated with increased recurrence of epistaxis.[13] Furthermore, good results have been shown in packing durations of 1–3 days, with the control of bleeding as high as 85% for anterior epistaxis.[23] Nasal packing of all types requires gram-positive coverage for prophylaxis against toxic shock syndrome. *Staphylococcus aureus* can be isolated from the nasal cavity in one-third of these patients, of whom 30% produce the exotoxin responsible for toxic shock syndrome.[24] Other complications include pressure necrosis of the palate, alar, or skin and displacement with airway obstruction.

MEDICOLEGAL THOUGHTS

The absence of a defined management algorithm, wide therapeutic options, and the potential for severe complications all contribute to epistaxis as a target for medicolegal cases. Understanding the variables will assist in advancing strategies and enhancing patient care. The most common reason has been the alleged failure of the treating physician to recognize complications in a timely manner and delays in the subsequent diagnosis, such as cancer and retained foreign bodies.[25–27] It is important to realize that epistaxis is a sign, not a diagnosis. Other cases have been related to a failure in recognizing anatomic variations, which led to blindness and stroke caused by inadvertent embolization.[5,28] This shows the importance of preinterventional imaging. Last, malposition or inadequate nasal packing with complications such as aspiration and dislodgment have been found throughout the hospital stay.[29]

SPECIFIC INTENSIVE CARE UNIT SITUATIONS: NASAL INTUBATION

Nasotracheal intubation commonly causes epistaxis from injury to the nasal mucosa or turbinate. Good mucosal preparation for nasotracheal intubation should include adequate lubrication, topical local anesthetics, and vasoconstrictors. Moreover, if resistance is met, the tube should be slightly rotated to allow better passage, or the other nare should be attempted.[30,31] The inferior turbinate and the adjacent septum are the most common sites of nasal damage.[32,33] Placement into intracranial compartments has occurred in the setting of skull base trauma. Blind placement in these situations may be associated with severe complications. Although posterior nasal packing should not be performed in the presence of nasal bone fractures, severe epistaxis may necessitate nasal packing with the use of balloon systems or arterial embolization ligation.[34,35] Cribriform plate fractures are the most common site for intracranial catheter placement and can occur with even small amounts of pressure.

SPECIFIC INTENSIVE CARE UNIT SITUATIONS: POSTOPERATIVE EPISTAXIS

Sellar and parasellar lesions are typically approached through transsphenoidal surgery, and postoperative bleeding originates from the external carotid system. Redundant mucosa, highly vascular and friable mucosa, large septal deviations, septal spurs, and complex sphenoid septations can make endoscopic transsphenoidal surgery difficult and

increase the risk for epistaxis.[36] Management of bleeding immediately postoperatively involves nasal packing and re-exploration in the operating room if the packing is not successful. In delayed bleeding, otorhinolaryngologic services typically perform endoscopic packing, balloon tamponade, silver nitrate application, and/or electrocautery. If these measures do not stop the bleeding, angiography followed by embolization can be performed.[37] Postoperative hypertension is generally viewed as a risk factor for epistaxis and is also an independent risk factor for persistent spontaneous epistaxis.[38]

SPECIFIC INTENSIVE CARE UNIT SITUATIONS: MASSIVE FACIAL TRAUMA

Traumatic pseudoaneurysms of the internal carotid artery are rare but can be a fatal cause of epistaxis, with a mortality rate as high as 50%.[39,40] Pseudoaneurysms or localized arterial disruptions are caused by blunt or penetrating trauma. Shearing forces and hemorrhages in the arterial wall weaken the artery and allow formation, and the continued pulsatile forces cause erosion on the thin bone layer.[41,42] The Maurer triad, which consists of unilateral blindness, orbital fracture, and massive epistaxis, is considered pathognomonic for internal carotid artery pseudoaneurysms.[43] The diagnosis is often delayed because of a latency period between the trauma and the bleeding, which averages 3 weeks in 88% of cases.[44,45] Angiographic imaging is the gold standard, with endovascular techniques being the preferred therapeutic approach.

NOVEL AND ADJUNCTIVE THERAPIES

Vasoconstrictors, hot water irrigation, and topical hemostatic compounds have all been used as adjunctive therapies to the previously mentioned procedures for the control of bleeding. Hot water irrigation via a balloon placed in the nasopharynx for approximately 3 minutes at 50°C to induce mucosal edema (and occlude the bleeding vessel) has been shown to control posterior epistaxis.[46,47] Topical hemostatic compounds are now available, consisting of gelatin granules and human thrombin. Studies show higher effectiveness, ease of application, and lower discomfort scores for their insertion and removal.[48]

MORTALITY

A number of risk factors are associated with increased mortality after admission with epistaxis, and this information could help with risk stratification. Factors include increased age and comorbidity scores, low admission albumin, low admission hemoglobin, an abnormal clotting screen, and an admission time of more than 2 days. Use of anticoagulation medications did not affect the mortality rate. Pneumonia and malignancy were the two most common causes of death.[49]

ALGORITHM[50]

Consistent with previous discussion, the American Academy of Otolaryngology Head and Neck Surgery have provided clinicians with an algorithm based on action statements produced from its clinical practice guideline supplement (see Fig. 143.1).[50]

KEY POINTS

- In the critically ill patient, diagnosis of epistaxis may be more difficult because of supine positioning and decreased alertness and is often confused with upper gastrointestinal bleeding.
- Epistaxis is a sign and not a diagnosis; once bleeding is controlled, the search for the etiology should be conducted. Coagulation studies should be performed in those on anticoagulant/antiplatelet medications, with consideration of correction.
- For intractable epistaxis, options should include surgery or embolization. Surgery has the advantages of decreased complication rates of stroke and blindness, and embolization has the advantage of avoiding general anesthesia in patients with nasopharyngeal bleeding.
- Aspiration, hypoxia, and dislodgment complications with nasal packing must be continuously evaluated for, especially in patients with severe comorbidities.
- In the absence of life-threatening bleeding, the clinician should initiate first-line treatments (nasal compression, vasoconstrictors, moisturizing or lubricating agents, nasal cautery/packing) before transfusion, reversal of anticoagulants, or withdrawal of anticoagulation/antiplatelet agents.
- Factors that increase the risk of mortality should be considered when making a treatment plan.
- Use of an algorithm for management of epistaxis may improve patient outcomes, decrease length of stay, and decrease costs.

References for this chapter can be found at expertconsult.com.

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Management of the Postoperative Cardiac Surgical Patient

Shailesh Bihari

Intensive care may account for more than one-third of the total hospital costs for cardiac surgery patients, and much of the short-term morbidity and mortality are based on perioperative events. The overall mortality after cardiac surgery is low. However, this ranges from less than 1% for elective coronary artery bypass grafting to more than 30% for more complex surgery in patients with significant myocardial dysfunction and significant comorbidities. Hence a comprehensive understanding of cardiovascular physiology and surgery is essential for a modern-day intensivist.

The initial days of care for a cardiac surgery patient present multiple challenges for an intensivist. The intensive care unit (ICU) stay for most patients lasts for 24–48 hours, but during this critical period, life-threatening problems such as low cardiac output (CO), arrhythmias, and coagulopathy may occur. After 48 hours, the problems encountered tend to become more like those experienced by other groups of critically ill patients.

CARDIAC SURGERY PATIENTS IN THE INTENSIVE CARE UNIT

History of Cardiac Surgery Linked to the History of Intensive Care

The development of modern cardiac surgery is intimately related to the development of the ICU. Until the 1950s, cardiac surgery was limited to the control of traumatic injuries and the closed repair of valves. The development of the extracorporeal pump oxygenator in 1953 ushered in the era of open heart surgery.[1] Heart valve replacement then became possible, and subsequently in the 1960s, coronary artery bypass grafting (CABG) for ischemic heart disease was developed and rapidly popularized.[2]

Several studies have demonstrated that risk-adjusted mortality rates after CABG vary significantly among surgeons and hospitals and that mortality is related both to the number of surgeries performed by each surgeon and the total volume of procedures performed at the hospital.[3–6] For high-risk surgical patients, survival is also related to the characteristics of the ICU care.[7]

Changing Epidemiology of Cardiac Surgery

Over the past decade, the population of patients treated with cardiac surgery has changed dramatically. Advances in cardiology, including reperfusion therapy, angioplasty, stenting, and drug-eluting stents, have obviated the need for surgical approaches to treatment except for particularly complex problems or after failure of other, less invasive modalities. In the year 2000, 561,000 patients in the United States underwent percutaneous transluminal coronary angioplasty (PTCA), an increase of 262% relative to 1987. In the same year, 314,000 patients underwent CABG. Multiyear trends, represented in Fig. 144.1, show a leveling off and subsequent decrease in the overall number of patients undergoing CABG.[8] Studies comparing the use of stents versus CABG for left main disease have found no significant difference in rates of death, Q-wave infarction, or stroke; however, stenting was associated with higher rates of target vessel revascularization than was CABG.[9]

Even as younger patients are being treated with interventional techniques, the elderly are increasingly referred for operation. As the population ages and care becomes more sophisticated, cardiac surgery is being performed on older, sicker, and more complicated patients. Although these operations are successful even in most octogenarians, they are associated with increased hospital mortality and longer ICU and hospital stays. It is clear, however, that good results in terms of long-term survival and quality of life are achievable.

There has been significant research into organizational factors in general ICU; however, there is less supporting information around issues such as open versus closed ICU and surgeon-led care versus intensivist-led care in the cardiac arena.

Alternative Techniques for Cardiac Surgery

The increasing age of patients undergoing cardiac surgery and the relatively high incidence of adverse effects related to cardiopulmonary bypass (CPB) have led to the development of less invasive cardiac surgical techniques. These techniques are intended to decrease postoperative morbidity, reduce length of hospital stay, reduce costs, and hasten recovery of lifestyle (Table 144.1). Three major techniques have been proposed.

Minimally invasive direct coronary artery bypass (MIDCAB) differs from conventional CABG mainly in the type of surgical incision. Instead of a median sternotomy, access is obtained via a left or right thoracotomy, a parasternal incision, or a partial sternotomy. Although the proposed benefit of such an approach is the reduction in morbidity related to median sternotomy, this advantage has not been demonstrated. MIDCAB grafting is a challenging technique and should be performed only in selected patients with favorable coronary anatomy. Both bare-metal and drug-eluting stenting have been shown to be inferior to MIDCAB for proximal left anterior descending coronary artery lesions, owing to higher reintervention rates and similar results in mortality and morbidity.[4,10]

Off-pump coronary artery bypass (OPCAB) is performed on a beating heart without the benefit of CPB. The proposed advantage of this procedure is the reduction of morbidity related to hypothermia and CPB. The procedure is undertaken using partial to full heparinization. Extubation may be achieved earlier in these patients because

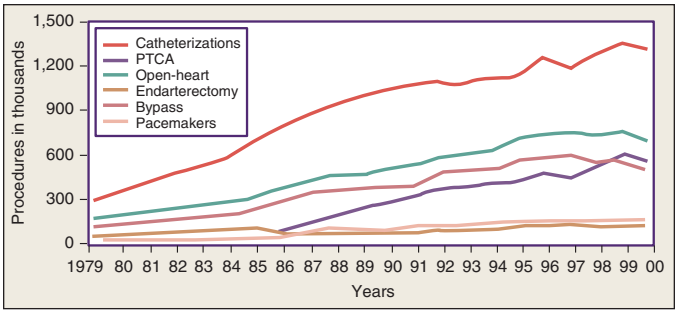

Fig. 144.1 Trends in cardiovascular operations and procedures in the United States, 1979–2000. *PTCA,* Percutaneous transluminal coronary angioplasty. (From American Heart Association. *Heart Disease and Stroke Statistics—2003 Update*. Dallas, TX: AHA; 2003.)

they do not require rewarming and are less coagulopathic. A subset of patients cannot tolerate the extent of retraction of the heart required for the surgery and need to be urgently placed on CPB. These patients may suffer ischemic myocardial injury and require support with inotropes or intraaortic balloon pumping (IABP) during the postoperative period.

A third method of minimally invasive cardiac surgery is the port access technique. This operation entails obtaining access for CPB with the use of endovascular catheters. It allows surgery to be performed using CPB via either a left or right thoracotomy. The technique is particularly useful for mitral valve replacement through a right thoracotomy and for redo CABG (avoiding the complications associated with repeat sternotomy). The port access technique has been shown to be safe and is associated with shorter lengths of stay, reduced transfusion requirements, fewer infections, decreased incidence of renal failure, and less atrial fibrillation (Afib) compared with conventional techniques.[11] Widespread adoption of this technique has been limited by the technical complexity of placing the required catheters, which requires both extra time and a specially trained, skilled operative team. As the techniques of minimally invasive cardiac surgery continue to evolve, the intensivist caring for cardiac surgical patients must continue to keep abreast of these new methods.

Organization of the Postoperative Cardiac Surgery Unit

Optimal results from cardiac surgery require a skilled, dedicated, and multidisciplinary ICU team. Patients undergoing cardiac surgery are usually admitted to the hospital on the day of surgery and arrive in the ICU directly from the operating room (OR). A typical patient is transferred to a step-down unit on the morning after surgery. This unit allows continued monitoring with telemetry for an additional 24–48 hours. Patients remaining in the ICU beyond 48 hours tend to become similar to a standard ICU population, as they develop secondary complications such as sepsis, pneumonia, and acute respiratory distress syndrome (ARDS).

Guidelines developed by the American Heart Association and the American College of Cardiology outline the requirements for cardiac surgical ICUs.[12–14] These include the development of protocol-driven care, a minimum number of cardiac surgical ICU beds that is half the number of surgeries performed per week, and one-to-one nursing care during the first night in the unit. The ICU coverage by a dedicated intensivist has been shown to improve outcomes in other types of major surgeries and should be recommended after cardiac surgery as well.[7]

Surgeon-Intensivist Relationship

Cardiac surgery involves a continuum of care from presentation to postdischarge management and rehabilitation. The intensive care specialist must be involved in this continuum, rather than functioning in isolation from surgeons, anesthetists, and cardiologists.

SEPARATION FROM CARDIOPULMONARY BYPASS AND THE END OF SURGERY

Successful management of a postoperative cardiac surgery patient begins by understanding what occurs in the OR because operative problems often persist after transfer to the ICU. An understanding of the

TABLE 144.1 Comparison of Minimally Invasive Cardiac Surgery Techniques

Technique	Incision Site	Cannulation Site	Advantages	Disadvantages
Conventional	Median sternotomy	Ascending aorta	Excellent exposure	Mediastinitis
CABG	Median sternotomy	Right atrium and Ascending aorta	Stable closure and extensive experience	Postoperative respiratory function limited by pain
MIDCAB	Left or paramedian or right thoracotomy or partial sternotomy	Ascending aorta and right atrium	Avoids median sternotomy	Limited exposure. May require multiple incisions
Port access	Right anterior thoracotomy, *or*	Ascending aorta via right paramedian port	Avoids median sternotomy Avoids atriotomy	Increased cost of equipment Contraindicated in patients with ascending aortic pathology
	Paramedian or left thoracotomy	Femoral vessels	Access to mitral valve Smaller skin incision	Limited operative exposure Significant learning curve.
OPCAB	Median sternotomy, *or* Right or left thoracotomy, Partial sternotomy	None	Avoids aortic manipulation Avoids atriotomy and CPB	Cost of equipment Learning curve Worse graft longevity

CABG, Coronary artery bypass grafting; *CPB,* cardiopulmonary bypass; *MIDCAB,* minimally invasive direct coronary artery bypass; *OPCAB,* off-pump coronary artery bypass.

Modified from Reves JG, Hill SE, Sum-Ping ST, et al. Perioperative management of the cardiac surgical patient. In Murray MJ, Coursin DB, Pearl RG, et al, eds. *Critical Care Medicine: Perioperative Management*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2002:356.

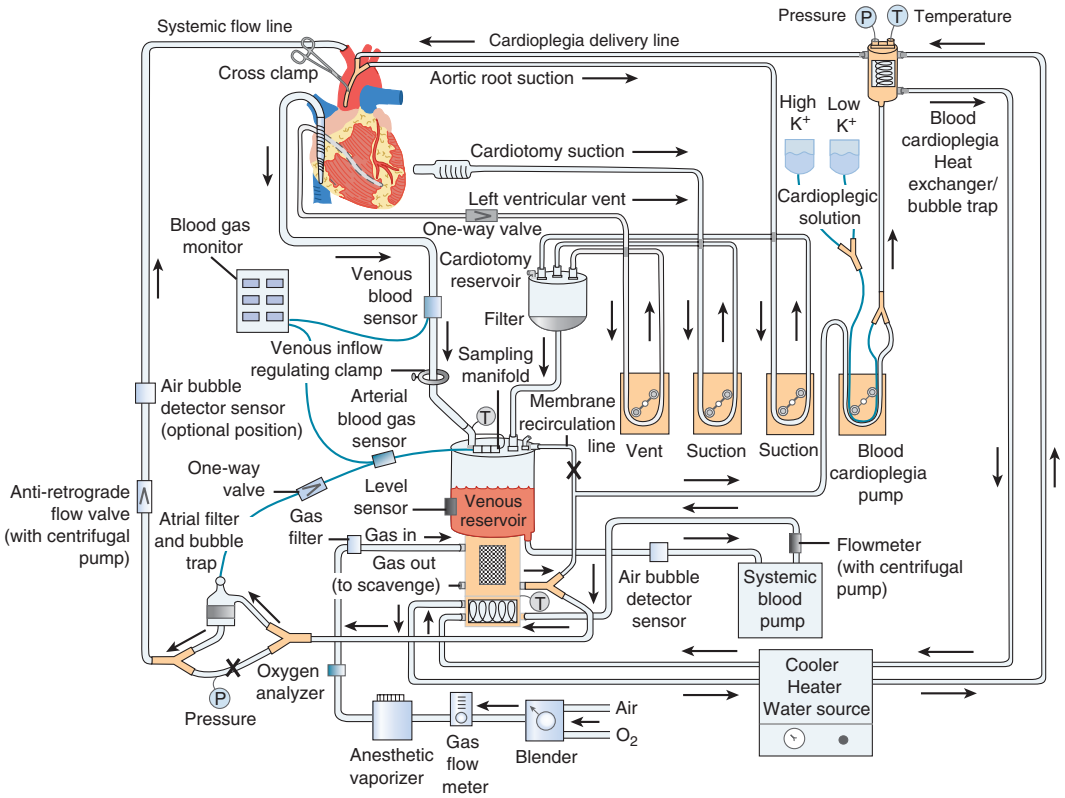

Fig. 144.2 Cardiopulmonary bypass circuit. (Adapted with permission from Gravlee GP, Davis RF, Kurusz M, et al, eds. *Cardiopulmonary Bypass: Principles and Practice*. 2nd ed. Baltimore, MD: Lippincott Williams & Wilkins; 2000:70.)

technical and pathophysiologic aspects of CPB may help an intensivist better manage the postoperative cardiac surgical patient.

Cardiopulmonary Bypass

The goal of CPB is to separate the heart and lungs from the systemic circulation so that the heart may be arrested while the surgical repair is performed. Blood is drained from the right side of the heart via a cannula in the right atrium or via the femoral vein advanced into the right atrium. The blood is collected in a reservoir and then pumped through an oxygenator that contains a membrane where the blood is oxygenated and carbon dioxide is removed (Fig. 144.2). A perfusionist controls both the fraction of inspired oxygen and the rate of oxygen flow through the circuit, thereby controlling the patient's arterial oxygen and carbon dioxide levels, respectively. The treated blood then passes through an air filter and is returned to the patient via an arterial cannula placed in either the ascending aorta or the femoral artery. The perfusionist controls the amount of systemic flow provided to the patient (i.e., CO). Mild to moderate systemic hypothermia (28°C–34°C) is used during bypass to minimize oxygen consumption by both the body and the brain. After adequate CPB is established, an aortic cross-clamp is applied to the ascending aorta, between the aortic cannula and the heart. The interval when the cross-clamp is applied is referred to as *ischemic* time, because no blood is circulated through the heart during this period. The heart is arrested by infusing a high-concentration potassium solution into the native coronary arteries (antegrade cardioplegia) via a cannula placed between the aortic cross-clamp and the heart. Cardioplegia may also be given "backward," through the venous system of the myocardium (retrograde cardioplegia) via a catheter placed in the coronary sinus. Potassium is used as the arresting agent because it stops the heart from beating and minimizes myocardial oxygen consumption.

Myocardial Protection

Several measures are taken to protect the heart during ischemic time, because irreversible myocardial damage may otherwise occur. Electromechanical arrest is the most important protective measure, because the beating action of the heart accounts for about 85% of the heart's total oxygen consumption. The heart is usually cooled to about 10°C with a cold cardioplegia solution (4°C) supplemented with topical ice slush. Additionally, the left ventricle is "vented" to prevent distention, which could lead to subendocardial ischemia. Finally, various additives are included in the cardioplegia solution to minimize myocardial edema, maintain normal intramyocardial pH, and provide substrates for anaerobic metabolism. The adequacy of intraoperative myocardial protection is critical for determining the subsequent course and final outcome for a patient.

Separation from Cardiopulmonary Bypass

Weaning from CPB is the process whereby cardiopulmonary function is transferred from the bypass system back to the patient's own heart and lungs. Successful separation from CPB requires that the metabolic, cardiac, and respiratory parameters are as close to normal as possible. Separation from CPB implies that the native circulation will be required to support the body's metabolic demands. The surgical team manipulates the heart rate and rhythm, preload, afterload, and myocardial contractility to achieve this goal.

In most cases, normal sinus rhythm is restored after discontinuation of cardioplegia and rewarming of the heart. Occasionally, discontinuation of

cardioplegia and rewarming lead to the onset of ventricular fibrillation; in such cases, electrical defibrillation is required. Other dysrhythmias commonly encountered are atrioventricular dissociation and Afib. An attempt should be made to convert these to sinus rhythm by pharmacologic means. Bradyarrhythmias are treated by pacing, using temporary epicardial wires placed by the surgeon after completion of the repair. A heart rate of 70–90 beats/min usually is optimal. Pharmacologic support of the circulation may be needed to provide appropriate afterload or systemic vascular resistance (SVR) during separation from CPB. Most patients are vasodilated to some extent, possibly as a result of a systemic inflammatory response to CPB or the effects of rewarming, or both. As a consequence, the infusion of a vasoconstrictor is often required. Care must be taken to strike a proper balance so that increased SVR maintains adequate arterial blood pressure without excessively increasing left ventricular afterload and compromising CO.

Most often, myocardial function is adequate, and the infusion of an inotrope is not necessary. However, inotropic support is often needed for patients with a poor preoperative ventricular function or inadequate myocardial protection or revascularization during CPB. The optimal inotrope in this situation is a matter of considerable debate, and data are lacking to support a strong recommendation for a specific agent. Epinephrine, norepinephrine, dopamine, dobutamine, amrinone, and milrinone have all been used successfully. Intraoperative monitoring using transesophageal echocardiography (TEE) is particularly useful for titration of inotropic therapy.

Once all preparations for separation from CPB have been made, the perfusionist begins to wean the patient from bypass. This is done by slowly decreasing the amount of blood drained from the right atrium while simultaneously reducing flow into the aorta. Once the patient is off CPB (i.e., no blood is being drained from the right atrium into the circuit), the perfusionist, at the direction of the anesthesiologist or surgeon, may continue to infuse through the aortic cannula. This maneuver allows optimization of ventricular filling or preload. However, care must be taken not to overdistend the heart; also, during this period, TEE is extremely useful.

Reversal of Anticoagulation

After weaning from CPB, protamine is given to neutralize any residual heparin. Dosing may be based on the patient's weight, the total amount of heparin given, or an assay of residual heparin activity. Institutional preference governs the technique employed, but all have been proven effective. Several adverse responses to protamine administration are possible, including histamine-induced systemic hypotension, immunoglobulin E–mediated allergic reactions, and complement-mediated catastrophic pulmonary hypertension. The clinical sequelae of cardiopulmonary bypass are summarized in Table 144.2.[15]

TABLE 144.2 Clinical Sequelae of Cardiopulmonary Bypass

Intraoperative Event	Sequelae	Postoperative Manifestation
Aortic cannulation and clamping	Atheroembolism Aortic dissection	Stroke Splanchnic embolization Organ ischemia
Right atrial cannulation	Atrial wall injury	Bleeding and arrhythmias
Femoral artery cannulation	Distal leg ischemia Vascular trauma Retrograde aortic perfusion	Muscle injury and necrosis Compartment syndrome Hematoma Need for vascular repair Lymphocele Retrograde embolism Cerebral hypoxemia Left ventricular distension
Femoral vein cannulation	Vascular trauma	Hematoma Deep venous thrombosis Lymphocele
Graft twisting	Mechanical obstruction to blood flow	Myocardial injury and dysfunction
High-dose heparin	Systemic anticoagulation	Coagulopathy Heparin-induced thrombocytopenia
Crystalloid priming of CPB circuit	Hemodilution	Volume overload Dilutional anemia Dilutional coagulopathy
Extracorporeal circulation	Complement activation Fibrinolysis Systemic inflammatory response Microvascular hypoperfusion Microemboli	Coagulopathy Vasoplegia, hypotension, inflammatory end-organ damage (e.g., lung injury) Impairment of renal and mesenteric blood flow Stroke (small vessel)
Cardioplegic arrest	Inadequate cardioprotection	Myocardial injury and dysfunction Heart failure Conduction disturbance Arrhythmias

TABLE 144.2 Clinical Sequelae of Cardiopulmonary Bypass—cont'd

Intraoperative Event	Sequelae	Postoperative Manifestation
Hypotension on CPB	Sympathetic hyperactivity Renin-angiotensin activation Cerebral and visceral hypoperfusion	Arrhythmias Blood pressure lability End-organ damage
Hypothermia	Splanchnic vasoconstriction Impairment of coagulation cascade Shivering Sympathetic hyperactivity	Mesenteric and renal ischemia Coagulopathy, hemorrhage Increased O_2 consumption, increased CO_2 production Arrhythmias Blood pressure lability
Hypothermic circulatory arrest	Cerebral ischemia Somatic and spinal ischemia	Stroke Encephalopathy Paralysis Kidney injury Mesenteric ischemia Myonecrosis
Reaction to protamine	Anaphylactoid generalized reaction Noncardiogenic pulmonary edema	Hypotension Bronchoconstriction Hyperinflation of the lungs Pulmonary hypertension
Coronary air embolism	Coronary ischemia	Myocardial injury and dysfunction

CPB, Cardiopulmonary bypass.
Modified from Stephens RS, Whitman GJ. Postoperative critical care of the adult cardiac surgical patient. Part I: Routine postoperative care. *Crit Care Med.* 2015;43(7):1477–1479.

Transport and Admission to the Intensive Care Unit

After chest closure, confirmation of hemodynamic stability, and adequate medical and surgical hemostasis, the patient is transferred to the ICU. Transport of a critically ill patient is a potentially dangerous process and requires extreme vigilance. Transport between the OR and the ICU should be done with the same degree of monitoring as would be available at either end. This usually includes continuous monitoring of arterial blood pressure, pulmonary artery pressure and/or central venous pressure (CVP), electrocardiogram (ECG), and pulse oximetry. The transport bed should be equipped with a full oxygen tank, a bag valve mask, intubation equipment, resuscitation drugs, and defibrillator. Care must be taken to ensure that infusions of vasoactive drugs are not interrupted.

On arrival in the ICU, the intensivist-led team assumes patient care. A detailed sign-out from the operative team ensures continuity of care. The sign-out should include a detailed history, including an assessment of preoperative cardiac functional status, a list of preoperative medications, and a detailed description of the surgery. Key facts are the type of repair performed, target vessels (if the patient has undergone CABG), duration of CPB and cross-clamping, difficulties encountered in separation from CPB, presence of abnormal bleeding, and postoperative assessment of cardiac function. All treatments administered in the OR should be detailed, in particular, fluids, blood products, and vasoactive drugs.

Structured Handover

Handover should be structured to minimize disruption and maximize communication. The priorities are to confirm surgical procedure and any complications, confirm integrity and position of the endotracheal tube, re-establish mechanical ventilation of both lungs, re-establish all patient monitoring, access details of premorbid conditions, confirm venous, arterial and central access, heart rhythm and presence and mode of any pacing devices. The handover should also include details of the chest drains, establishing a blood pressure target, document results of any intraoperative echocardiography regarding ventricular function, provide details of intraoperative transfusion of blood or factors together with the results of any benchtop or laboratory tests of hemostasis and getting an early 12-lead electrocardiograph to exclude or identify acute ischemia.

Once care has been handed over to the ICU team, a thorough examination of the patient should immediately follow. This examination should include verification of endotracheal tube placement, type and position of arterial or central venous lines, chest tube position and patency, and presence and location of any epicardial pacing wires.

MONITORING THE POSTOPERATIVE CARDIAC SURGERY PATIENT

Hemodynamic Monitoring

All patients admitted to the ICU after cardiac surgery will have their blood pressure continuously monitored using an intraarterial line, which is usually placed in either a radial or a femoral artery. Accuracy of the measurements depends on strict attention to calibration, leveling, and removal of air from the tubing. After CPB, femoral arterial pressure may more accurately reflect central aortic pressures,[16] but this problem is usually resolved by the time the patient arrives in the ICU. If the radial artery is cannulated, the hand should be examined for signs of ischemia.[17] Vascular complications of femoral arterial lines are extremely rare, but femoral catheters may be associated with an increased incidence of infection.[18]

Central venous access is required in all patients for drug administration and hemodynamic monitoring. In low-risk patients, a CVP catheter may be all that is needed, particularly if echocardiography is available as a backup. Pulmonary artery catheters have the advantage of allowing measurement of pulmonary artery occlusion pressure (PAOP), thermodilution, and CO, in addition to sampling of the mixed venous blood saturation (SvO_2). Use of the pulmonary artery catheter remains controversial. Improved outcome resulting from the

use of a pulmonary artery catheter for monitoring cardiac surgical patients has not been demonstrated.[19] Some studies showed an increased risk of death or adverse outcome when treatment was guided by the use of a pulmonary artery catheter.[20,21] However, many of these studies have been criticized on methodologic grounds, and the use of a catheter in cardiac surgery remains widespread.[22] Current guidelines recommend the use of a pulmonary artery catheter in high-risk patients undergoing surgery (severely decreased left ventricular [LV] function [ejection fraction <30%], right ventricular [RV] failure, pulmonary hypertension, severe renal insufficiency, or thoracic transplantation) in an appropriate practice setting.[23] Such a setting is the one in which the physician and nursing staff are familiar with the catheter and trained to properly interpret the information obtained. If echocardiography is readily available, it is possible to manage even high-risk patients using a CVP catheter.

Electrocardiography

On admission to the ICU, the patient is connected to a continuous ECG monitor, and a formal 12-lead ECG is obtained. The cardiogram is examined for rate, rhythm, QRS complex morphology, and signs of myocardial ischemia. For patients who are being paced postoperatively, the type of pacing and the degree of capture should be assessed.

Continuous ECG monitoring allows detection of arrhythmias. If an arrhythmia is detected, a 12-lead ECG should be obtained and serum electrolyte concentrations should be measured. Treatment of arrhythmias should be carried out using established protocols.[24] If a malignant arrhythmia occurs, myocardial ischemia should be considered as a possible precipitating cause.

Monitoring of trends in ST-segment elevation or depression allows early detection of postoperative myocardial ischemia. Although transient ST-segment changes are relatively common and of unclear significance, persistent changes should be investigated by obtaining a 12-lead ECG and measuring circulating levels of creatine kinase myocardial band (CK-MB), troponin-T, or troponin-I.[25,26] If ischemia is strongly suspected, echocardiography followed by coronary angiography should be considered. Findings from these studies may indicate the need for further coronary revascularization.

Chest Radiography

The postoperative chest radiograph should be systematically evaluated. Proper placement of the endotracheal tube and any central lines inserted should be confirmed. If a pulmonary artery catheter is placed, the location of its tip should be noted and adjusted as needed. The lung fields should be examined for the presence of pneumothorax (PTX) or consolidation. Additional air may be noted as subcutaneous emphysema or pneumopericardium, although these findings are of little clinical significance. Further examination of the lung fields commonly shows small areas of atelectasis and pleural effusion. The cardiac silhouette is often enlarged after surgery as a result of myocardial edema and accumulation of fluid in the open pericardial sac. Increasing size of the cardiac silhouette or pleural effusions on serial chest radiographs may be evidence of ongoing mediastinal bleeding. The admission radiograph detects abnormalities in up to 35% of patients, although few of these result in a change in therapy.[27]

Echocardiography in the Intensive Care Unit

Echocardiography is an excellent tool for evaluating chamber size and function and the adequacy of valve repair or replacement. Indications include postoperative assessment of LV function, assessment of unexplained sudden hemodynamic deterioration, evaluation to rule out pericardial tamponade, and workup of new cardiac ischemia. Limitations to transthoracic echocardiography include inadequate windows early after operation because of air and edema in the soft tissues and wound dressings.

TEE is increasingly being used as a tool to facilitate decision making in managing critically ill patients, including cardiac surgical patients. In the cardiac surgical ICU, this modality may have a particularly high yield when used to establish the cause of postoperative hypotension.[28] In one large series, a new diagnosis was established or an important pathology was excluded in 45% of TEE examinations performed in the ICU. Pericardial tamponade was diagnosed in 34 cases (11%) and excluded in 36 cases (12%). Other diagnoses included severe LV failure and the presence of large pleural effusions. The results of TEE had an impact on therapy in 220 cases (73%) by leading to a change of pharmacologic treatment and/or fluid administration, reoperation, or a decision that reoperation was unnecessary.[29]

However, the early postoperative period after cardiac surgery presents unique challenges to image optimization because of mechanical ventilation and surgical dressings and drains and to image interpretation because of diagnostic findings unusual in other clinical settings.

Pericardial hematoma can cause focal cardiac chamber compression; thus every cardiac chamber must be clearly visualized. Rarely, massive hemothorax can cause tamponade. Dynamic left ventricular outflow tract (LVOT) obstruction should be suspected in the patient with mitral valve repair, hypertrophic left ventricle, or aortic valve replacement for aortic stenosis who develops shock that fails to respond to catecholamines or intraaortic balloon counterpulsation.

Echocardiography in these patients demonstrates a high LVOT flow velocity and mitral regurgitation. RV dysfunction may occur in isolation because of inadequate intraoperative cardioplegia. Increased intrathoracic pressure may present with hemodynamic features similar to pericardial tamponade, but should be recognized from assessment of ventilation. On echocardiography there are features of acute cor pulmonale. Patient prosthesis mismatch results in a high transvalvular pressure gradient and difficultly weaning from mechanical ventilation. Other causes of prosthetic valve dysfunction (e.g., leaflet entrapment or paravalvular leak) warrant expert and TEE evaluation.

CLINICAL MANIFESTATIONS IN THE POSTBYPASS PERIOD

The Normal Course

Patients are typically admitted to the ICU intubated and ventilated. Sedation with a short-acting agent, typically propofol, is continued until the patient is ready for extubation.[30,31]

Hypothermia (<36°C) is used intraoperatively to preserve cardiac and neurologic function postoperatively. Unfortunately, hypothermia carries the risk of adverse effects, including increased SVR, increased risk of arrhythmias, shivering, and coagulopathy. Shivering is of particular concern, as it increases oxygen (O_2) consumption while also increasing carbon dioxide (CO_2) production, sometimes precipitating acidosis. Pethidine and dexmedetomidine have been shown to treat shivering.[32,33] The increase in SVR can mask hypovolemia and increase afterload, which increases myocardial demand. The dangerous combination of increased SVR and coagulopathy can also lead to mediastinal bleeding. Without active rewarming with forced air, hypothermia and its complications, particularly the prolongation of anesthetic time half-life, can also prolong intubation times. There is evidence that the risk of wound infection also increases with hypothermia as well, likely owing to the immunosuppressive effects of hypothermia. Therefore upon arrival to the ICU, steps should be taken to increase core body temperature to normal using forced air, as that has been shown to be

more effective at expeditiously increasing core body temperature than radiant heaters or warming blankets.

Once hemodynamic stability is ascertained and chest tube drainage is judged to be under control, the patient is allowed to awaken. There is no need for prolonged weaning from mechanical ventilation. A short trial of spontaneous ventilation is sufficient to determine whether respiration will be adequate without mechanical support. Chest tubes are commonly removed on the first postoperative day. The pulmonary artery catheter, if present, is discontinued, and the patient may be transferred to a step-down unit.

The current trend in cardiothoracic surgery is toward early extubation, variably described as extubation within 6 hours or up to 12 hours. Extubation criteria may differ among cardiothoracic groups, but, at a minimum, patients should be awake with stimulation and following commands, moving all extremities (i.e., without neuromuscular blockade), minimal chest tube drainage (<50 or 100 mL/hr), core temperature above 35.5°C, hemodynamically stable with a CO >2.2 L/min per meter squared, free of arrhythmias, with ventilator stability with respiratory rate between 12 and 30 breaths/min, and reassuring arterial blood gas (ABG) levels.

Fast-tracking of cardiac surgical patients refers to a comprehensive program designed to reduce both length of stay and hospital costs.[34,35] As a part of this program, multiple anesthetic techniques designed to allow earlier postoperative extubation have been proposed, studied, and shown to be safe. The key to proper use of this technique is patient selection. Patients who are at risk of prolonged intubation are those with increasing age, chronic obstructive pulmonary disease, tobacco use, chronic kidney disease, peripheral vascular disease, depressed LV fraction (ejection fraction <30%), myocardial infarction within the past 90 days, preoperative ventilation, prior cardiac surgery, or urgent or emergent surgery. Intraoperative risk factors also exist, such as deep hypothermic circulatory arrest, coagulopathy, and long pump runs (>4 hours). Postoperatively, mediastinal bleeding, hemodynamic instability, respiratory failure, and stroke are the major risk factors for prolonged intubation. It is estimated that about 5%–10% of patients are unable to be extubated early and remain intubated for 48 hours or longer.[36] The fast-track group has been shown to have shorter extubation times, shorter ICU or postanesthesia care unit stays, and a lower incidence of low CO syndrome.[31]

Low Cardiac Output Syndrome

Low CO is the most common problem encountered in the postoperative cardiac surgical patient. A hallmark of low CO is low blood pressure. However, a patient may have a low CO with tissue hypoperfusion and still maintain what appears to be an adequate blood pressure. In the postoperative state, the physician must continuously examine and monitor the patient for signs of hypoperfusion. Physical signs of inadequate tissue perfusion include altered mental status; cool, pale, or even cyanotic extremities; diaphoresis; and low urine output. Global measures of hypoperfusion include increased base deficit, elevated blood lactate concentration, and decreased SvO_2. Although the clinician must consider CO in terms of adequacy of perfusion, blood pressure per se is still important. Both the brain and kidneys depend on adequate blood pressure to maintain tissue perfusion. Additionally, coronary artery blood flow is dependent on the diastolic blood pressure.

When assessing a patient with hypotension or signs of hypoperfusion, it is useful to consider the problem in relation to the components of CO—namely, preload, contractility, afterload, and rate and rhythm.

Preload

Preload refers to the stretch of the left ventricle at the end of diastole and is determined by the extent of diastolic ventricular filling. Adequate filling is required to ensure ejection in the subsequent systole. The most common cause of inadequate preload in postoperative patients is hypovolemia. Intravascular volume status should be continually monitored by assessing changes over time with respect to physical examination, chest tube output, and filling pressures (CVP, PAOP, or pulmonary artery diastolic pressure). Because none of the clinically measured filling pressures correlates perfectly with actual ventricular preload (i.e., end-diastolic volume) and correlation is particularly poor when the heart is diseased, it is often useful to obtain a snapshot of ventricular filling using echocardiography. By this means, it is possible to assess the relationship between measured filling pressures and actual preload in a specific patient. Preoperative catheterization data may also be helpful for determining this relationship. Hypovolemia should be treated with fluid replacement. Crystalloids are generally used. Surprisingly, there is no generally accepted hemoglobin concentration or hematocrit that should be used as a trigger for ordering transfusion of packed red blood cells (PRBCs).[37]

Dynamic approaches to assessing preload, such as respiratory arterial pulse pressure variation (PPV) and stroke volume variation (SVV, based on pulse contour analysis), using an approximate threshold value of more than 11% to indicate a volume deficit, may be more accurate in predicting fluid responsiveness.[38] However, these techniques require controlled mechanical ventilation, the absence of spontaneous breathing, and normal cardiac rhythm; they are inaccurate in patients with open chests.[39] The use of lower tidal volumes (<8 mL/kg) may limit the accuracy of PPV and SVV.[40] Ultrasound measurement of inferior vena cava diameter does not appear to be useful after cardiac surgery.[41]

Fluids and Fluid Therapy

Despite generous intraoperative fluid administration, effective hypovolemia is common in the early postoperative period, especially as warming with associated vasodilatation occurs. Hence administration of intravenous fluid is common. However, no benefit for any specific resuscitation fluid has been established, and an excessively positive fluid balance may increase perioperative complications. More recently, use of small-volume resuscitation with hyperoncotic albumin, when compared with crystalloid fluid, has resulted in less positive fluid balance and provides several hemodynamic and potential ICU treatment advantages in post–cardiac surgery patients.[42] In some cases, low preload is not caused by absolute hypovolemia, but by relative or distributional hypovolemia. CPB and subsequent rewarming may lead to vasodilatation and subsequent hypotension. Intravascular volume expansion may be required to maintain perfusion. An acceptable alternative is administration of a low dose of vasopressor such as phenylephrine or norepinephrine to maintain an adequate perfusion pressure. Vasopressin in doses between 0.01 and 0.1 units/min has been demonstrated to be effective in this situation.[43,44] Vasodilatation is usually a transient problem that resolves during the first several hours after separation from CPB. Continued vasodilatation after this period should prompt a search for another cause, particularly infection.

Pump Failure

Either or both ventricles may fail postoperatively (Box 144.1). Decreased myocardial contractility may be caused by impaired preoperative function, inadequate revascularization at surgery, post-CPB reperfusion injury, or perioperative myocardial ischemia or myocardial infarction (MI). The incidence of infarction is approximately 5% in a large series.[45] Preoperative myocardial function and the adequacy of revascularization at surgery should be clear from the history. Determination of circulating levels of CK-MB or troponin postoperatively may provide evidence of perioperative ischemia or infarction.[25,26] Often, diminished contractility

BOX 144.1 Causes of Pump Failure After Cardiac Surgery

Ischemic-Mediated
- ST-elevated myocardial infarction
- LIMA spasm
- Failed/inadequate cardioplegic protection
- Graft twisting
- Graft air embolism
- Complications from myocardial infarction
  Ventricular septal rupture
  Free wall rupture
  Papillary muscle rupture and mitral regurgitation

Cardiomyopathy
- Acute myocarditis
- Takotsubo
- Hypertrophic/obstructive

Valvular
- Aortic stenosis
- Mitral regurgitation
- Left ventricular outflow tract obstruction
- Paravalvular leak

Endocrine
- Adrenal insufficiency
- Hypothyroid/myxedema

Right Ventricular Failure
- Myocardial dysfunction after cardiopulmonary bypass

LIMA, Left internal mammary artery.

after operation is caused by inadequate myocardial protection during surgery. Decreased myocardial contractility secondary to inadequate myocardial protection usually resolves within the first 24 hours postoperatively.

Persistent new myocardial dysfunction associated with ECG changes and echocardiographic evidence of new wall-motion abnormalities should raise suspicion that the problem is an occluded graft and MI. Measurements of CK-MB in serum are of limited usefulness because levels of this enzyme are commonly elevated after surgery as a result of manipulation of the heart and incision of the atria. If CK-MB levels are very high (>80 mg/dL), perioperative MI is likely.[46] Cardiac troponins are more specific for diagnosing perioperative infarction. A comparison of CK-MB, troponin-T, and troponin-I showed that a troponin-I level of greater than 5 μg/L was the most accurate indicator of MI.[47] Elevated serum concentrations of troponin-I are associated with a cardiac cause of death and major postoperative complications.[48] In addition, troponin-T concentrations measured after surgery are an independent predictor of in-hospital death after cardiac surgery.[26] If ischemia or MI is diagnosed, the patient may be taken urgently for angiography or re-exploration and revascularization.

Postoperative valvular insufficiency may occur not only in patients with preexisting valvular lesions but also as a result of injury during surgery. The mitral valve is most commonly affected. Ischemia of the papillary muscles because of inadequate myocardial protection or perioperative MI may lead to acute mitral regurgitation in the postoperative period. Diagnosis is often made by TEE in the OR, but inadequate CO and a new systolic murmur should prompt echocardiographic evaluation.

Myocardial Dysfunction After Cardiopulmonary Bypass

A temporary impairment in contractility is seen after CPB. There are multiple theories to explain this, but the concept of myocardial stunning seems to be the prevailing thought at this time. The inflammatory state induced during heart surgery may also play a role in this impairment in contractility seen after the myocardium is reperfused. This is a transient phenomenon and resolves within 24–48 hours. Management of these patients includes inotropic support and management of the volume overload that was related to the vasodilatation and capillary leak seen and addressed intraoperatively.

Right Ventricular Dysfunction

RV failure after cardiac surgery is reasonably common. Common etiologic factors include direct RV ischemia or infarction, poor myocardial protection, an anteriorly placed right ventricle, and preexisting pulmonary hypertension. Management of RV dysfunction is challenging, and management involves careful volume resuscitation, maintenance of RV perfusion pressure with vasoconstrictors, intraaortic balloon counterpulsation, and inotrope administration. RV afterload reduction is an integral part of this, and useful afterload-reducing agents include nitric oxide, prostaglandins, and sildenafil. Delayed sternal closure has an established role.

Postoperative diastolic dysfunction must also be taken into consideration. Impaired relaxation of the left ventricle is particularly common in the elderly and in patients with significant LV hypertrophy. Postischemic injury and myocardial stunning related to CPB may exacerbate the problem. These patients will require a higher left ventricular end-diastolic pressure (LVEDP) to maintain an adequate postoperative preload. Progressive impairment in diastolic function is a hallmark of aging, even in patients with apparently normal systolic function and without hypertrophy of the left ventricle. On a structural level, aging results in a decreased number of ventricular myocytes and an increase in the amount of connective tissue matrix. The result is a stiffer, less compliant ventricle. The degree of diastolic dysfunction in a given patient may be demonstrated through the use of various echocardiographic techniques. Patients with diastolic dysfunction may demonstrate increased sensitivity to changes in loading conditions, making them less able to tolerate rapid volume shifts. Nevertheless, their ventricle will be intensely dependent on preload to maintain filling. Positive lusitropic agents such as milrinone may be of benefit in the immediate postbypass period.[49]

Rate and Rhythm

CO is the product of heart rate and stroke volume. Many dysrhythmias may adversely affect CO. If the heart rate is too low, CO may be compromised. If the heart rate is too fast, ventricular diastolic filling may be impaired, thus decreasing CO. Rhythm disturbances are common after cardiac surgery and may be divided into bradyarrhythmias and tachyarrhythmias; these categories are further divided into atrial and ventricular arrhythmias.

Bradycardia may lead to ventricular distention, increasing wall tension and decreasing coronary perfusion pressure, factors that may promote the development of ischemia and heart failure. A heart rate of 80–90 appears to be optimal, allowing adequate filling and preventing overdistention but not causing rate-related ischemia. Bradycardia may be corrected by pacing. In general, epicardial pacing wires are left in place after chest closure and are attached to an external pacemaker in the immediate postoperative period. If the dysrhythmia is sinus bradycardia, atrial pacing is usually optimal. The second most common cause of bradyarrhythmia after cardiac surgery is atrioventricular dissociation. The combination of atrial and ventricular leads allows atrioventricular pacing for managing dissociation.

Synchronization of the atrioventricular interval between 0.1 and 0.225 seconds optimizes CO.[50]

Afib is the most common tachyarrhythmia. It occurs in 10%–35% of patients after cardiac surgery, usually on the second or third postoperative day. Postoperative Afib is associated with increased morbidity and mortality and with longer, more expensive hospital stays.[51] Independent predictors of postoperative Afib include advanced age, male sex, history of Afib, history of congestive heart failure (CHF), and pre-CPB heart rate greater than 100 beats/min.[52] Surgical practices such as pulmonary vein venting, bicaval venous cannulation, postoperative atrial pacing, and longer cross-clamp times also were identified as independent predictors of postoperative Afib. Patients who developed postoperative Afib had longer lengths of stay, both in the ICU and in the ward, compared with patients who did not develop the complication.

Although premature ventricular contractions are common, sustained ventricular arrhythmias are far less frequent. Severe ventricular arrhythmias occurring after cardiac surgery are related to ischemia, hypoxemia, hypovolemia, electrolyte abnormalities, effects of vasoactive drugs, or underlying preexisting cardiomyopathy.[53] In a series of 2100 cardiac operations, only 16 patients (0.8%) developed ventricular fibrillation or sustained ventricular tachycardia during an interval from 3 days to 3 weeks after surgery. Ten of these patients had undergone valve surgery.[54] Prognosis in these patients is dependent on the preoperative ventricular prognosis. In those with an LV ejection fraction of less than 40%, the mortality rate may be as high as 75%.[55] Hypomagnesaemia and hypokalemia are frequent in the early postoperative stage and are exacerbated by polyuria. It is generally considered that levels should be maintained in the high-normal range.

Clinical and laboratory assessment of perfusion is still the cornerstone of managing these patients. A physical examination demonstrating warm extremities with strong pulses and good urine output is reassuring for adequate perfusion but should be supplemented by objective data. Lactate is an extremely sensitive marker of impaired perfusion, and even minimally elevated levels can identify patients with occult hypoperfusion. Higher lactate levels (>3–4 mmol/L) and slow lactate clearance accurately predict major complications after cardiac surgery.[56]

Afterload

Ventricular afterload is the impedance to ventricular ejection during systole. Hypertension develops in as many as 60% of patients after surgery. Increased arterial blood pressure occurs even among patients without a preoperative history of hypertension. Predisposing factors include hypoxemia, hypercapnia, inadequate rewarming, pain, fluid overload, and increased sympathetic tone. Perioperative discontinuation of beta-adrenergic blockers also may contribute to the development of postoperative hypertension. Hypertension and increased afterload may lead to myocardial ischemia by augmenting ventricular stroke work. Additionally, hypertension may lead to bleeding from surgical sites, aortic dissection, and increased risk of stroke.

Tamponade

Tamponade refers to the hemodynamic consequences of a collection of blood or other fluid in the pericardial sac. In postsurgical patients, the presentation of tamponade may be subtle and differ significantly from classic descriptions. Equilibration of filling pressures typically is not seen. More commonly, patients present with isolated elevation of right atrial pressure caused by compression of the right atrium and superior vena cava. After cardiac surgery, as many as 66% of pericardial fluid collections are loculated posterior effusions.[57]

Bleeding from the atrial cannulation site is a common cause of tamponade. As the pressure on the right atrium increases, ventricular filling is impaired and CO decreases. The diagnosis of tamponade is made difficult by the high overall frequency of pericardial effusions after surgery. Echocardiographic studies have shown that moderate effusions are present in 30% of patients on the eighth postoperative day, with 2% of patients having large effusions.[58]

Diagnosing tamponade in the postoperative patient requires a high index of suspicion and prompt intervention. Any hemodynamic instability should be assessed for tamponade. Low CO, hypotension, and tachycardia accompanied by an elevation of the left, right, or both atrial pressures should lead to a prompt echocardiogram. Other signs that may be present include a widened mediastinum on chest radiography, dysrhythmias, and decreased ECG voltage. Because of the influence of positive-pressure ventilation, the classic sign of pulsus paradoxus may not be present.

If time permits, the diagnosis of tamponade may be confirmed with the use of echocardiography. Although effusions are common, signs of compression or collapse of either atrium or the right ventricle are diagnostic.[59–61] It is important to remember that the diagnosis may be made on clinical suspicion alone and that treatment should not be withheld to await confirmation. Once tamponade is diagnosed, volume transfusion may temporize the situation. Pericardiocentesis is not effective in this situation, and prompt re-exploration for hemostasis and evacuation of a clot is indicated.

Respiratory Complications

Patients undergoing cardiac surgery are at risk for multiple pulmonary complications. These include PTX and pleural effusion in the immediate postoperative period. After the first 24 hours, patients sometimes develop acute lung injury (ALI), ARDS, or pneumonia. Diaphragmatic dysfunction secondary to phrenic nerve injury may occur.

Residual PTX is often seen on the initial postoperative chest radiograph and is commonly on the left side as a result of opening the left parietal pleura during dissection of the left internal mammary artery (LIMA). The PTX usually resolves spontaneously as the chest tubes are placed on suction. Occasionally, a PTX is seen on the right side as a result of accidental incision of the right parietal pleura. Right PTX may progress to tension PTX and significant hemodynamic deterioration. This diagnosis should be considered in any unstable patient. Treatment consists of insertion of an additional chest tube.

Pleural effusion in the first 24 hours after cardiac surgery should raise the suspicion of hemothorax. Effusions should be watched carefully for expansion and correlated with other signs and symptoms of continued bleeding. Massive, expanding hemothorax is an indication for immediate re-exploration and hemostasis. Pleural effusion after the first 24 hours is generally a benign process. Most pleural effusions resolve spontaneously. Thoracocentesis should be performed only if the effusion occupies more than 50% of the lung field on radiography or if the patient has significant impairment of respiratory function.

Atelectasis, especially of the left lower lobe, remains an important problem in the management of cardiac surgery patients. There have been many improvements in surgical techniques, but entering the thoracic cavity and pleura irritation from chest tubes can be painful. Adequate analgesia and incentive spirometry are mainstays in the management in the first 24–48 hours. Volume overload can lead to hypoexpansion, especially in the lung bases. Earlier mobilization helps, but it also leads to increased blood flow in the bases, which may increase hypoxemia by shunting. Patients can develop fever, impaired gas exchange, and if not addressed, postoperative pneumonia in the areas of atelectasis. Treatment is best begun proactively. Correction of volume overload, pain management, early mobilization, incentive spirometry, and aggressive pulmonary toilet with noninvasive positive pressure may also be beneficial. Continuous positive airway pressure

and high-flow nasal oxygen are some of the modalities that may be used by respiratory therapy to help avoid reintubation.

Cardiac surgery is associated with surfactant dysfunction[62]; however, ALI and ARDS are rare (<0.5%) complications after cardiac surgery, CPB, and blood transfusion. The mortality rate associated with this complication ranges between 15% and 70%.[63] During the postoperative period, patients with ARDS were more likely to have had prior cardiac surgery or received more blood products and developed shock more frequently than patients without ARDS.[64] Transfusion-related lung injury (TRALI) is a common cause of morbidity or mortality related to the administration of blood products.[65] The current hypothesis is that there is a "two-hit phenomenon." The first insult is that the patient is in a heightened inflammatory state. This sensitizes the individual for the second "hit," which is the transfusion with blood products that further activates or enhances the proinflammatory state.[66] CPB provides the first hit with overall activation of the immune system. The intraoperative or postoperative need for transfusion is the second insult. Treatment of TRALI is supportive. The principles that apply to ALI are used in this disorder. Volume restriction and low tidal volume ventilation are mainstays of therapy.

Nosocomial pneumonia may complicate any ICU stay. Patients who require mechanical ventilation for longer than 48 hours are at particular risk. These pneumonias are usually caused by aspiration of oral or gastric secretions into the lungs. The incidence of nosocomial pneumonia may be reduced by diligent mouth care to prevent pooling of secretions and elevation of the head of the bed to greater than 30 degrees. Nosocomial pneumonia carries a mortality rate of 24%–50% and warrants appropriate broad-spectrum antimicrobial therapy.[67] Early broad-spectrum antibiotics (based on the cardiac ICU–specific antibiogram) should be initiated and then deescalated once the results of quantitative cultures are available.

Diaphragmatic dysfunction is usually caused by a cold-induced injury of the phrenic nerve as a result of the application of ice slush to the heart as part of the cardioplegia regimen. This complication occurs in up to 2% of patients undergoing cardiac surgery with topical hypothermia.[68,69] While the patient is being ventilated with positive pressure, this injury will not be apparent. If preoperative pulmonary function was normal, unilateral diaphragmatic paralysis usually is well tolerated. Pulmonary function may be severely compromised if pulmonary problems were present preoperatively or if bilateral diaphragmatic injury occurs.[70] Such patients are at an increased risk of developing nosocomial pneumonia, failing to wean from the ventilator, and succumbing to death. Bedside ultrasound has been used as a diagnostic tool for both unilateral and bilateral dysfunction and can also be used to monitor recovery of the paralyzed diaphragm. Diaphragmatic dysfunction usually resolves spontaneously within 3–4 months.

The risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) is increased in individuals with immobility, delayed recovery, or CHF. The risk may be accentuated in this group by prior history of DVT/PE, recent MI, obesity, hyperlipidemia, and heparin-induced thrombocytopenia (HIT). Given the high risk of DVT in patients undergoing cardiac surgery, the actual incidence of PE is low, and fatal PE is negligible. Even though these rates are lower than other major surgical specialties, this should not be an argument against DVT prophylaxis. Strong consideration should be given to prophylaxis in the first 48 hours postoperatively. Sequential decompression devices have been used in patients who remain intubated in the ICU, but are not recommended as routine primary prophylaxis after cardiac surgery. There has been no evidence that prophylactic dosing of anticoagulants leads to increased bleeding in routine postoperative cardiac surgical patients if initiated after 48 hours.

Continued Bleeding

Continued bleeding is a common problem and requires immediate and aggressive management before the onset of further complications. The reasons for continued bleeding are often multifactorial and include inadequate surgical hemostasis, platelet dysfunction, coagulopathy, and inadequate heparin reversal. Often these factors occur in combination, and patients undergoing valve replacement are at an increased risk.[71]

Multiple clotting abnormalities are possible, most of which result either directly or indirectly from the use of CPB.[72] The tubing, blood reservoir, and oxygenator membrane are all foreign surfaces that may activate the clotting cascade. Because the pump must be primed with either normal saline or lactated Ringer's solution, the priming process leads to substantial dilution of all blood components, including red blood cells, platelets, and clotting factors. After CPB, the platelet count is decreased and the remaining platelets are functionally deranged.[73,74] There is sequestration of platelets in the liver, spleen, and CPB circuit itself. Systemic fibrinolysis caused by activation of this system by the CPB circuit occurs.

Inadequate reversal of heparin should be diagnosed at the bedside by the activated coagulation test (ACT) or by measuring the activated partial thromboplastin time (APTT). Because the half-life of heparin is longer than that of protamine, heparin-induced anticoagulation may rebound in the immediate postoperative period. The treatment is administration of additional protamine.

Currently the most accurate and effective measure of bleeding is obtained using a thromboelastogram (TEG). The drawback of even the rapid TEG is that the results take some time. However, it remains the most specific test to identify coagulopathies so that they can be identified and treated in a more targeted manner.[75] In the absence of a TEG, complete blood cell count, calcium levels, full metabolic panel (to evaluate uremia and hepatic function), prothrombin time, international normalized ratio, and fibrinogen levels can all be useful in identifying sources of bleeding requiring correction.

Renal Dysfunction

Mild renal dysfunction is a common postoperative event (7%),[76] with approximately 1% of patients diagnosed with acute renal failure (ARF) requiring renal replacement therapy. These patients have increased morbidity and mortality with prolonged ICU length of stay as much as fivefold.[76]

A multicenter study of 2222 patients undergoing CABG identified five independent preoperative predictors of renal dysfunction: age 70–79 years or 80–95 years, CHF, previous myocardial revascularization, type 1 diabetes mellitus (DM) or preoperative serum glucose levels exceeding 300 mg/dL, and preoperative serum creatinine levels of 1.4–2.0 mg/dL. Independent perioperative factors that exacerbated risk were CPB lasting 3 hours or longer and various measures of ventricular dysfunction.[76]

Renal dysfunction tends to follow one of the three main patterns.[77] *Abbreviated ARF* (creatinine peaks on postoperative day 4) is a transient event, most probably related to intraoperative renal ischemia. *Overt ARF* (creatinine peaks at a higher level than abbreviated ARF and then decreases over weeks) occurs when the duration of the predisposing insult, usually low CO, is longer. *Protracted ARF* (frequently irreversible renal failure) occurs when a second insult, commonly sepsis or hypotension, is superimposed on the resolving renal function.

Neurologic Complications

Neurologic sequelae of CPB range from subtle neurocognitive deficits (appearing in up to 80% of patients) to stroke. To estimate the relative risks of neurologic sequelae associated with various clinical factors, a logistic regression model was applied to prospectively collected data

from 273 patients enrolled at 24 American medical centers.[78] Adverse cerebral outcomes occurred in 16% of patients and were almost equally divided between type I (8.4%; 5 cerebral deaths, 16 nonfatal strokes, and 2 new transient ischemic attacks) and type II outcomes (7.3%; 17 new cases of intellectual deterioration persisting at hospital discharge and 3 cases of newly diagnosed seizure disorder). Resource use for these patients was significantly increased: median ICU stay was prolonged from 3 days to 6–8 days, and total duration of hospitalization was increased by 50% (type II outcomes) to 100% (type I outcomes). After discharge from the acute care setting, specialized care was required for 69% of the patients with adverse neurologic sequelae. Risk factors for type I outcomes related primarily to embolic phenomena include proximal aortic atherosclerosis, intracardiac thrombus, and intermittent clamping of the aorta during surgery. Risk factors for type II outcomes included, in addition to these factors, a preoperative history of endocarditis, alcohol abuse, perioperative dysrhythmia, poorly controlled hypertension, and low CO after CPB.

Injury to the brachial plexus during cardiac surgery is not infrequent but is underdiagnosed and underreported because it is often transient.[79] The mechanisms proposed for this injury are multiple. Hyperabduction of the arms, traction, and compression during sternal retraction and direct trauma owing to insertion of internal jugular lines have been postulated as possible mechanisms of injury. Harvesting of the internal mammary artery with asymmetric sternal retraction has been reported to have a higher rate of plexopathy.

Postoperative delirium is a prevalent issue across all ICUs.[80] Multiple factors contribute to this disorder. The aging population, disruption of sleep patterns, central nervous system (CNS) active medications, and loss of visual cues in unfamiliar surroundings are a few considerations that should be taken into account. Frequent reorientation, allowing for a more normal sleep-wake environment, and engaging familiar people or family may be useful nonpharmacologic maneuvers. Patients may need sedation if they are a threat to themselves or others, but these agents should be avoided because they may be of transient benefit in the short term and worsen or prolonged the delirium. The hyperadrenergic state that accompanies this delirium may be detrimental in the postoperative patient and should be treated with beta-blockers and other antihypertensives. Short-acting agents are preferred because as the delirium lifts, the adrenergic activation may resolve with resultant hypotension. Drug and alcohol withdrawal are important considerations and a frequently missed diagnosis in the ICU population with delirium. Finally, seizures are rare in the immediate postoperative period.[81] Seizures in the postoperative population either herald an underlying, unrecognized neurologic defect or are related to drug withdrawal (therapeutic drugs, illicit drugs, or alcohol). On rare occasions, a global tonic-clonic seizure may develop in patients who are hypoglycemic or hypoperfused. After seizures are controlled, a computed tomography (CT) scan of the brain should be performed to rule out CNS pathology. The next step would be an electroencephalogram, as some anticonvulsants may be proconvulsants at elevated levels. Some cardiac medications, like lidocaine at toxic levels, may lower the seizure threshold. This can be seen in individuals with renal failure at normal dosing of lidocaine. Tranexamic acid has proconvulsant activity.[82] This antifibrinolytic agent should be avoided in any individuals with a seizure disorder or in those who have exhibited seizures in the perioperative or postoperative period.

Gastrointestinal Complications

Acute abdominal complications are relatively rare after cardiac surgery. If they do occur, they are associated with extremely high rates of morbidity and mortality. One prospective study of 1116 patients undergoing CPB found that abdominal complications occurred in 23 (2.1%). Ten of these patients underwent subsequent abdominal surgery, and 20 died. Early complications occurred on postoperative days 6 and 7 and consisted of bowel ischemia or hepatic failure. These complications are probably related to perioperative hypotension and low CO.[83] Late complications consisted of pseudomembranous colitis, cholecystitis, pancreatitis, and rupture of a septic spleen.[84]

Mild transient increases in circulating levels of hepatocellular enzymes are common after surgery. These changes are generally of no consequence; however, increased serum transaminase levels, if sustained or very high (e.g., serum alanine aminotransferase concentration >500 IU/L), may represent evidence of severe ischemic injury of the liver and carry a high risk of mortality. This complication is strongly associated with low CO and increased filling pressures, suggesting that liver ischemia is induced by a combination of decreased perfusion and venous congestion.[85]

Infections

Sternal wound infections can be a late complication after surgery associated with significant morbidity. The risk factors associated with these infections are obesity, DM or perioperative hyperglycemia, mobilization of bilateral internal mammary artery for grafting, prolonged duration of surgery (>5 hours), staple use for skin closure, obstructive airway disease, prior cardiac surgery, blood transfusion, and end-stage renal failure on dialysis.

MANAGEMENT OF COMMON POSTOPERATIVE PROBLEMS

Optimization of Cardiac Output

Treatment of hypotension and low CO must be tailored to the cause (Box 144.2). Again, it is useful to consider treatment in terms of

BOX 144.2 Causes of Postoperative Hypotension

Hypovolemia
- Hemorrhage
- Vasodilation
  - Rewarming
  - Drugs: milrinone
  - Sepsis
- Vasoplegia secondary to circulatory bypass

Low cardiac output
- Preload
  - Hypovolemia, including hemorrhage
  - Tamponade, pericardial constriction
  - Left ventricular diastolic dysfunction
  - Right ventricular failure
- Afterload
  - Excessive vasoconstriction
  - Aortic stenosis
  - Functional left ventricular outlet obstruction
- Myocardial function
  - Mechanical (ventricular septal defect, valve pathology)
  - Diastolic dysfunction
  - Cardiomyopathy
  - Ischemia, postischemic stunning, LIMA spasm
  - Graft air embolism
- Metabolic, electrolyte abnormalities, pharmacologic depression

LIMA, Left internal mammary artery.

TABLE 144.3 Comparison of Relative Activity of Available Vasoactive Agents

Agent	α_1	β_1	β_2	Phosphodiesterase Inhibition	Dose (mcg/kg/min)
Epinephrine	++	+++	+	−	0.01–0.15
Norepinephrine	++++	+++	+	−	0.01–3
Dopamine	++	++	+	−	2–20
Dobutamine	+	+++	+	−	2–20
Phenylephrine	+++	−	−	−	0.4–9.1
Milrinone	−	−	−	+++	0.375–0.75

−, no activity; +, mild activity; ++, moderate activity; +++, strong activity.

preload, contractility, afterload, and rate and rhythm. Inadequate filling pressures are treated with volume infusion. The intravascular volume expander may be a crystalloid solution, a colloid solution, or packed red blood cells if hematocrit is low or there is evidence of ongoing bleeding. It is important to remember that inotropic therapy is ineffective and possibly detrimental if adequate blood volume is not restored.

If CO or blood pressure remains low despite intravascular volume resuscitation, then it is necessary to institute an inotropic or vasopressor support. No single agent is optimal in all cases. Rather, selection of the agent should be based on the suspected cause of low CO or hypotension and knowledge of pharmacologic effects of the various inotropic and vasopressor drugs that are available (Table 144.3). If the primary cause of hypotension appears to be vasodilatation, administration of a vasoconstrictor (e.g., phenylephrine, norepinephrine, or vasopressin) is indicated. If hypotension is related to inadequate ventricular ejection, then inotropic therapy (e.g., epinephrine, norepinephrine, dopamine, or dobutamine) with a beta-adrenergic agent should be instituted. In patients with chronic systolic dysfunction, response to these agents may be impaired. Chronically elevated levels of circulating catecholamines deplete myocardial norepinephrine stores and down-regulate the expression of myocardial beta-adrenergic receptors. In these patients, tachyphylaxis to beta-adrenergic agonists may develop rapidly. Adding a phosphodiesterase inhibitor (e.g., amrinone or milrinone) is often effective in these patients.[86,87] In all cases, agents should be titrated to achieve adequate end-organ perfusion.

Three recent large randomized controlled trials (RCTs)[88–90] did not demonstrate any benefit of perioperative levosimendan, and a meta-analysis of five low-risk-of-bias trials including 1910 patients showed no association between levosimendan use and mortality, acute kidney injury (AKI), need for renal replacement therapy, MI, or ventricular arrhythmias, but did show an association with a higher incidence of supraventricular arrhythmias.[91]

Mechanical Support of the Circulation

Failure to respond to appropriate vasopressor or inotropic therapy may necessitate mechanical support of the circulation. IABP is the most commonly used method. The balloon is positioned in the aorta just distal to the take-off of the left common carotid artery. Inflation of the balloon during diastole increases the diastolic pressure above the balloon, thereby increasing the coronary perfusion pressure. Conversely, deflation during systole decreases the LV afterload. This combination of hemodynamic effects ameliorates myocardial ischemia and improves CO. The common reasons for intraaortic balloon counterpulsation use in cardiac surgery are left main disease >70%, LV ejection fraction <0.4, unstable angina, reoperation, and failure to wean from CPB.

Ventricular assist devices (VADs) are more effective than IABP for maintaining CO. Either the left ventricle or the right ventricle or both may be supported with VADs. Currently, VADs may be used either as a bridge to transplantation or as a bridge to recovery. Either situation assumes that the VAD is a time-limited intervention. There are some data to support the view that resting the heart through the use of a VAD may allow some recovery of acutely injured myocytes, permitting eventual withdrawal of mechanical support. If the heart is chronically diseased, there is little hope of recovery, and the VAD serves to support the patient until transplantation becomes possible.[92–94]

Ongoing clinical trials are investigating the use of VADs as definitive therapy rather than as a bridge to transplantation. Implantation of these devices may increase the long-term survival of patients with end-stage heart failure.[95]

Emergency Reoperation

Emergency re-sternotomy is indicated as part of resuscitation when hemodynamic stability cannot be rapidly re-established with conventional means. Advantages compared with closed-chest resuscitation include establishment of the cause of instability, correction of the cause (e.g., tamponade, kinked graft), more effective cardiac massage, and direct establishment of atrial and ventricular pacing. Re-sternotomy also enables the re-establishment of CPB and regrafting or correction of mechanical abnormalities as required. Infectious complications of emergency re-sternotomy are probably increased, but the incidence is not prohibitive.

Cardiac arrest can occur as progression from refractory postoperative shock or as an unheralded event. Resuscitation protocols should be immediately initiated; however, the applicability of advanced cardiac life support protocols is limited in postoperative cardiac patients. Specific guidelines for the ICU resuscitation of postoperative cardiac arrest, known as *cardiac advanced life support,* have been published.[96] These include up to three immediate attempts at defibrillation of either ventricular fibrillation or ventricular tachycardia. Timely defibrillation is critical. Similarly, epicardial pacing can be attempted for asystole or severe bradycardia if epicardial leads are in place. Attempts at defibrillation or pacing should take precedence over chest compressions.

Management and Correction of Arrhythmias

Afib is the most commonly encountered arrhythmia after cardiac surgery. Prophylactic use of beta-adrenergic blockers reduces the incidence of postoperative Afib, and they should be administered after cardiac surgery to all patients unless specific contraindications are present.[97] Prophylactic treatment with amiodarone and atrial overdrive pacing should be considered for patients who are at high risk for postoperative Afib (e.g., those with a history of previous Afib or mitral valve surgery).[98]

If Afib develops after cardiac surgery, the intensivist needs to determine whether the primary strategy should be to control the ventricular rate or to restore normal sinus rhythm. If Afib is associated with hemodynamic instability or anticoagulation is contraindicated, rhythm management using electrical cardioversion or amiodarone is preferred.[99,100] Overdrive pacing using atrial pacing wires also may be effective. The appropriate strategy for most stable patients may be control of ventricular rate, because most will spontaneously revert to sinus rhythm within 8 weeks after discharge.[101,102] Appropriate agents to achieve ventricular rate control include intravenous or oral beta-adrenergic blockers or calcium channel blockers. All patients with Afib

persisting for longer than 24–48 hours should be anticoagulated unless there is a specific contraindication. Long-term outcomes are similar regardless of whether the rate-control strategy or the rhythm-control strategy is selected.[103,104]

Postoperative ventricular arrhythmias should be treated immediately according to the current advanced cardiac life support protocols.[24] Any postoperative ventricular arrhythmia should prompt a search for an underlying cause. Importantly, ischemia should be ruled out. Patients with sustained ventricular arrhythmias should undergo electrophysiologic testing before long-term antiarrhythmic therapy is instituted. The implantable cardioverter-defibrillator device has been shown to be superior to drug therapy for patients with hemodynamically significant arrhythmias.[105]

Hypertension in the Postoperative Period

Hypertension leading to an increase in ventricular afterload is a common cause of decreased CO. Hypertension may be controlled by an intravenous infusion of sodium nitroprusside, nitroglycerin, beta-adrenergic antagonists, or calcium channel blockers. These agents should augment CO by reducing blood pressure and afterload in the hypertensive patient. Frequently, acute hypertension resolves within 24–48 hours postoperatively. If hypertension persists beyond this initial period of recovery, intravenous agents should be weaned and oral therapy initiated. Both beta-adrenergic blockers and angiotensin-converting enzyme inhibitors have been shown to confer a long-term mortality benefit and should be started. If hypertension was not a problem preoperatively, prolonged antihypertensive therapy postoperatively usually will not be necessary.

Correction of Coagulopathy

Postoperative coagulopathy may promote bleeding and accumulation of blood in the chest or pericardial cavity. Aggressive measures must be used to correct the coagulopathy. A systemic approach to the evaluation and treatment of continued bleeding is needed; one such approach is outlined in Table 144.4. Hypothermia may contribute to coagulopathy. Therefore profoundly hypothermic ICU patients must be actively rewarmed with the use of transcutaneous warming. Laboratory evaluation of suspected coagulopathy should include measurements of platelet count, prothrombin time (PT), APTT, ACT, and bleeding time. The use of TEG may be useful to guide component transfusion requirements.

TABLE 144.4 Evaluation and Treatment of Postoperative Coagulopathy

Coagulation Test	Normal Range	Suggested Treatment
Body temperature	–	If less than 35.5°C, the patient should be actively rewarmed.
PT	11–13.3 seconds	Consider fresh frozen plasma or cryoprecipitate or prothrombin complex concentrate.
PTT	21–32 seconds	Consider additional protamine.*
Platelets	140,000–440,000/μL	If <100,000, transfuse platelets.
Fibrinogen	150–360 mg/dL	If <100, transfuse cryoprecipitate.
Bleeding time	2.5–9.5 min	If prolonged and platelet count is normal, consider platelet dysfunction and treat with DDAVP and/or cryoprecipitate.
ACT	90–120 seconds	Consider additional protamine.*

ACT, Activated coagulation test; *DDAVP,* desmopressin acetate; *PT,* prothrombin time; *PTT,* partial thromboplastin time.
*Excessive protamine may itself cause bleeding.[106]

Two RCTs have examined transfusion goals after cardiac surgery. In the Transfusion Requirements After Cardiac Surgery trial,[107] 502 patients were randomized to either a restrictive (maintain hematocrit ≥24%) or liberal (hematocrit ≥30%) transfusion strategy. There was no difference in mortality or major morbidity, and PRBC use was decreased by 60% by the restrictive strategy. The second trial is the Transfusion Indication Threshold Reduction trial, which randomized 2003 elective cardiac surgical patients to a restrictive (maintain hemoglobin ≥7.5 g/dL) or liberal (hemoglobin ≥9 g/dL) transfusion strategy.[108] In this study, blood use was significantly decreased by nearly 40% in the restrictive group (53% of patients received a transfusion vs. 92% in the liberal group), and there was no difference between the groups in the study's primary composite outcome of serious infection (sepsis or wound infection) or an ischemic event (permanent stroke [confirmation on brain imaging and deficit in motor, sensory, or coordination functions], MI, infarction of the gut, or AKI) within 3 months after randomization.

Management of Postoperative Bleeding

Bleeding that continues after correcting coagulopathy needs to be treated aggressively. Venous bleeding in the chest may be partially controlled by applying positive end-expiratory pressure (PEEP).[109,110]

Continuing mediastinal hemorrhage, or the suspicion of cardiac tamponade, is an indication for immediate re-exploration. Exsanguinating hemorrhage or impending arrest from tamponade may require that re-exploration be carried out at the bedside in an ICU. Bleeding that is unresponsive to medical therapy and requires re-exploration is usually associated with a surgical source. Accepted guidelines for reoperation include bleeding rates of 400 mL/hr for 1 hour, 300 mL/hr for 2 hours, or 200 mL/hr for 3 hours. A sudden decrease or total cessation of drainage from mediastinal tubes may be equally ominous. Cessation of drainage from a mediastinal or chest tube may be caused by clotted blood occluding the tube. If bleeding persists but drainage ceases, the result may be tamponade.

Re-exploration is associated with increased morbidity and mortality. However, this increased mortality and morbidity may be partially explained by delays in the decision to re-explore that lead to avoidable open-chest resuscitations in the ICU.[111,112]

Management of Postoperative Renal Failure

The cornerstone of prevention and treatment of renal failure in the cardiac surgical patient is the maintenance of adequate renal perfusion. This goal is best achieved by optimizing circulating blood volume and CO. Multiple pharmacologic regimens for renal protection have been described. Dopamine at low "renal" doses (1–3 μg/kg per minute) has been used. The rationale for this strategy is that dopamine activates type 1 dopaminergic (DA1) receptors, leading to renal artery dilation, natriuresis, and diuresis. However, numerous human studies have failed to show that low-dose dopamine prevents renal failure or improves survival.[113] Even low doses of dopamine increase CO, and this may be the basis for any increase in urine output observed.[114] Fenoldopam[115] and dopexamine[116] are DA1 receptor antagonists that have also been proposed as renal protective agents and used with mixed success.[117]

Loop diuretics such as furosemide have been proposed as renal protective agents, not only because of their ability to produce diuresis and natriuresis but also because these drugs may reduce medullary tubular oxygen consumption. Mannitol, an osmotic diuretic, has been

used to prevent the development of ARF. Neither mannitol nor furosemide has been shown to improve outcomes in patients with ARF.[76] Indeed, these drugs may be deleterious because of their ability to promote diuresis and thus exacerbate hypovolemia and inadequate renal perfusion.

The failure of pharmacologic means of preventing and treating renal failure has led to interest in other methods. Early and intensive use of continuous venovenous hemofiltration achieved a better-than-predicted outcome in patients with severe ARF who underwent cardiac operations.[118]

Glucose Control

Studies have shown that tight control of blood glucose level in the ICU is associated with an increase in morbidity and mortality. Hyperglycemia and insulin resistance are common in critically ill patients, even those who have not previously had DM. Results of a prospective randomized controlled study[119] in which 6104 critically ill adult patients were randomly assigned to receive either intensive insulin therapy (maintaining blood glucose concentration between 80 and 108 mg/dL) or conventional treatment (infusing insulin to keep blood glucose level 180 mg/dL or less) showed that, at 3 months, the intensive insulin therapy group had an increase in hypoglycemic episodes and ICU mortality.

OUTCOMES OF CARDIAC SURGERY

Increasingly, healthcare is being driven by outcome data. Cardiac surgery has been one of the leading specialties in this field. It is difficult to assess results from crude mortality data, because these do not take into account case complexity and differing preoperative risks among patients. Crude comparisons of death rates may be misleading and may encourage surgeons to practice risk-averse behavior. Death rates should be stratified by risk. It is, however, possible to make some generalizations. Among low-risk patients undergoing CABG, mortality rates lower than 2% are achievable.[120] Higher mortality rates are to be expected in selected subgroups of patients with major preoperative risk factors (e.g., poor ventricular function, advanced age, and comorbid conditions) or major operative risk factors (e.g., reoperative surgery and complex operations). Euro SCORE II is the predominant preoperative cardiac surgical risk score, but this performs less well as an ICU score. The majority of ICU scoring systems are also not designed with cardiac surgery patients in mind.

A prospective cohort of 27,239 consecutive patients undergoing isolated CABG was examined to determine the risk factors for hospital mortality. After adjustment for patient and disease characteristics, the following comorbid conditions were found to be related to postoperative mortality: DM, vascular disease, chronic obstructive pulmonary disease, peptic ulcer disease, and dialysis-dependent renal failure.[121]

Cardiac surgery is being performed more frequently in patients aged 80 years and older. In one study, the 30-day mortality rate for patients aged 65–75 years was 3.4% and for those older than 80 years was 13.5%. Older patients had longer ICU and postoperative lengths of stay. Although emergency operations and complex procedures carry high risks for octogenarians and increasing costs for society, most of these patients may be offered operation with short-term morbidity, mortality, and resource use that only modestly exceed those of younger patients.[122] Once discharged from the hospital, older patients report a high quality of life.[123]

Overall, fewer than 10% of cardiac surgical patients spend more than 48 hours in the ICU. Most survive and eventually report improved functional status and a reasonable quality of life.[124,125]

SPECIFIC PROCEDURES AND CONSIDERATIONS[126]

Coronary Artery Bypass Graft

Long-term graft patency has been dramatically improved by the use of arterial conduits; the LIMA is the conduit of choice for bypassing the left anterior descending coronary artery. Saphenous venous grafts are commonly used to bypass other vessels. Aspirin, at recommended doses of 100–325 mg daily, increases long-term graft patency and reduces mortality, MI, stroke, bowel infarction, and renal failure after CABG. Beta-blockers reduce the risk of postoperative Afib and may also reduce myocardial ischemia and mortality. It is reasonable to start with a low dose (e.g., metoprolol 12.5–25 mg twice daily) and increase as tolerated by heart rate and hemodynamics.

Off-Pump CABG

Compared with conventional CABG, off-pump CABG (OP-CABG) patients are less coagulopathic, have less bleeding, and require fewer transfusions; some studies have reported fewer immediate postoperative respiratory and renal complications than after on-pump CABG.[127] The rate of immediate perioperative strokes appears to be reduced, and OP-CABG may have a particular niche when aortic atherosclerosis precludes cross-clamping. However, there appears to be no difference between OP-CABG and conventional CABG in terms of risk of renal injury requiring dialysis, risk of stroke, or neurocognitive. dysfunction.

Endocarditis Vascular Surgery

These patients may have acute or subacute presentation. They should be managed by a multidisciplinary endocarditis team, including cardiac surgeons, cardiologists, and microbiologists. Early organism identification can aid antibiotic selection and duration. Prior undiagnosed end-organ damage may present postoperatively, and a high index of suspicion is required. If expedited surgery occurs, there may be a massive inflammatory response with bleeding and hypotension. If it persists, a secondary source of infection must be sought through clinical and radiologic examination.

Mitral and Tricuspid Valve Surgery

In the developed world, surgery for mitral incompetence is more common, whereas mitral stenosis predominates in nations with undeveloped economies. Pulmonary hypertension, RV pressure overload and impairment, and tricuspid valve regurgitation may develop with long-standing disease. These conditions significantly increase the risk of cardiac surgery; therefore expert management is demanded. Tricuspid valve repair with a de Vega suture or an annuloplasty ring is increasingly performed at the same time as left-sided surgery. The treatment of pulmonary hypertension with pulmonary vasodilators may be needed in addition to inotropic support of the right ventricle and appropriate ventilator settings. Monitoring with a pulmonary artery catheter and phosphodiesterase inhibitors have a role here, but dose titration to avoid refractory hypotension is important.

Long-standing mitral disease can cause pulmonary hypertension and RV compromise; the stress of surgery and CPB can incite acute postoperative RV failure. Inhaled pulmonary vasodilators may be useful if RV failure develops. A unique feature of mitral valve repair is the development of dynamic LVOT obstruction caused by systolic anterior motion (SAM) of the anterior leaflet of the mitral valve, which is typically the result of a mismatch between leaflet tissue and mitral annular size and occurs in approximately 5% of patients after mitral repair.[128,129] SAM occurs when the anterior leaflet or chordae of the mitral valve paradoxically moves toward the interventricular septum during systole, causing dynamic LVOT obstruction, reduced CO, and

potential hemodynamic collapse. SAM is exacerbated by an underfilled, hyperdynamic left ventricle; thus management consists of adequate volume resuscitation, avoidance of inotropes, minimizing tachycardia, and early beta-blockade.

Aortic Valve Surgery

Appropriate fluid management is essential, especially when surgery is performed for aortic stenosis (AS), as the hypertrophied left ventricle is exquisitely sensitive to preload. Blood pressure control after aortotomy is important to limit stress on the aortic suture line. Any sudden increase in bleeding should raise concern regarding the integrity of the aortotomy closure. The postoperative ECG must be evaluated for conduction disturbances and ischemia, as injury to the conduction system occurs not infrequently, often from placement of sutures through conduction tissue. Conduction disturbances typically manifest within the first 3 postoperative days.[130] Malpositioned aortic valve prostheses can occlude either coronary ostia; the right is particularly at risk. Finally, manipulation of the aorta is a risk factor for cerebral embolism, and a postoperative neurologic examination should be performed once feasible.

Surgery for Hypertrophy Obstructive Cardiomyopathy

Patients with symptomatic hypertrophic obstructive cardiomyopathy suffer from exertion dyspnea and fatigue. A dynamic outflow obstruction in the LVOT is often the underlying lesion. Surgery involves septal myectomy, which alleviates this obstruction and coexisting mitral regurgitation. Diastolic dysfunction is common in these patients, and they do not tolerate Atrial fibrillation (A-fib). In addition, inotropes should be avoided. There is an increased risk of heart block, and these patients may need permanent pacemakers.

Transcutaneous Aortic Valve Insertion

Transcutaneous aortic valve insertion (TAVI) allows treatment of AS in patients felt not to be medically fit for open surgery. This is often the result of advanced age, LV dysfunction, and multiple comorbidities. Compared with medical therapy for those patients unable to have open surgery, TAVI reduces mortality. However, there is an increase in stroke and vascular complications.[131] On the ICU, these patients have a high risk of delirium. Because of their premorbid state, the risks of other organ failure is raised, and they may benefit from prolonged postoperative monitoring.

Ascending Aorta and Aortic Arch Surgery

Ascending aortic procedures include aneurysm repair with interposition tube grafts, aortic root replacements, aortic arch replacements, and emergent repair of dissections.

Aortic surgery involves a period of deep hypothermic circulatory arrest, which can be up to 30 minutes at 18°C. These patients should be carefully rewarmed in theater, and the avoidance of pyrexia is a key postoperative precaution. Active cooling may be considered. High arterial pressures are avoided to minimize the risk of extending arterial intimal dissection; however, the maintenance of cerebral circulation must be considered. There is a high vascular complication rate in these patients, with a mortality rate of 8%–15% and stroke rates of 7%–11%.[132] Subtle long-term cognitive dysfunction is common.[133]

In aortic root replacement procedures (e.g., valve-sparing root replacement or replacement of the aortic root, valve, and ascending aorta with a composite prosthetic valve and graft [the Bentall procedure]), the coronary arteries are reimplanted into the graft, and coronary occlusion or kinking with resultant myocardial ischemia is possible. This typically involves the right coronary artery, and new RV failure should raise concern for right coronary artery occlusion.[134]

CONCLUSIONS

Most cardiac surgical patients may be discharged from the ICU to a step-down unit within 24–48 hours after operation, but an increasing number cannot. Patients who require longer and more intensive services in the ICU are typically older and sicker preoperatively. Adherence to best practices in the ICU optimizes the opportunity for even these high-risk patients to survive their operation and achieve a good quality of life after hospitalization.

The ongoing development of less invasive techniques in cardiology and cardiac surgery will paradoxically bring about a further increase in the complexity of cases treated in the cardiac surgical ICU, as patients who are less sick are treated elsewhere. This trend will lead to increasing challenges for intensivists working in these units and allow them to continue to be at the forefront of critical care medicine.

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KEY POINTS

- Developments in interventional cardiology have led to older and medically complex populations being referred for cardiac surgery.
- Much of the care of cardiac surgical patients should be protocol driven and conducted in specialized units.
- Most patients undergoing cardiac surgery require only a shorter ICU stay.
- Patients may be extubated once hemodynamic stability is achieved and mediastinal bleeding is deemed to be under control.
- Low CO after surgery should be treated based on the components of the CO: rate, rhythm, preload, afterload, and contractility.
- Afib continues to be a cause of significant morbidity.

References for this chapter can be found at expertconsult.com.

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Intensive Care Unit Management of Lung Transplant Patients

Satish Chandrashekaran, Amir M. Emtiazjoo, and Juan C. Salgado

OVERVIEW OF LUNG TRANSPLANT

Lung transplantation offers hope for improved survival and quality of life for selected patients with end-stage lung disease. The availability of suitable donor organs and preservation injury remain the initial limiting factors to successful transplantation. Novel techniques aiming to extend the donor pool have resulted in the ability to offer transplantations to more patients, both by allowing for better evaluation of questionable organs and by allowing potential treatment and repair of injured organs.[1,2] Like other solid organ transplants, rejection and infection, in addition to organ system dysfunction associated with the perioperative course, remain challenges.[3] However, over 40 years of experience have led to substantial improvements in early outcome. This experience has been reflected in changes in various aspects in the field, including a different allocation system wherein priority is given based on medical urgency and expected outcome,[4] donor and recipient assessments, innovative surgical techniques, better understanding of early complications, and the development of newer immunosuppressive medications.

Diagnoses for which adults undergo lung transplantation include chronic obstructive lung disease (COPD) from emphysema (32%); interstitial lung disease (24%); cystic fibrosis (16%); alpha-1 antitrypsin deficiency (5%); and other conditions, including sarcoidosis, congenital heart disease, and connective tissue disease complicated by advanced lung disease.[3] Over the past 2 decades, the number of single-lung transplant (SLT) procedures has remained stable, and the number of bilateral lung transplant (BLT) procedures has seen a steady increase. In recent years, most recipients who had the most common indications for lung transplantation underwent bilateral procedures, with COPD, either from emphysema or alpha-1 antitrypsin deficiency, being the most frequent diagnosis prompting transplantation. This has been the setting in which the trend toward bilateral transplantation has been more noticeable.[3]

Donor selection, procurement, and lung preservation protocols tend to be individualized on an institutional basis. The limited availability of donor lungs, however, has increased the scrutiny with which organs are judged in order to avoid rejecting them inappropriately. Significant lung contusion, smoking-related lung damage, pneumonia, pulmonary edema, and significant aspiration are prime concerns in evaluating the suitability of donor organs. Although already described as an independent association for primary graft dysfunction (PGD),[5] donor's older age is being challenged at some centers as a risk factor for worsened outcomes. More transplants are being performed when the donor does not meet overly stringent criteria.[6] Procurement and lung preservation protocols often include administration of antiinflammatory agents, pulmonary vasodilators, and antioxidants.

The surgical technique involves thoracotomy for SLT or transverse thoracosternotomy (clamshell incision) for BLT transplants. Minimally invasive techniques are being developed in some centers as well. The surgical procedure includes anastomoses of the pulmonary artery, atrium, and bronchus. Cardiopulmonary bypass (CPB) is avoided in the case of SLT and BLT, unless preexisting pulmonary hypertension precludes cross-clamping of the pulmonary artery or cardiorespiratory stability cannot otherwise be maintained. On completion of the operation, a double endotracheal tube (EBT) is exchanged for a standard endotracheal tube (ETT), unless allograft function appears tenuous or there is evidence of air trapping. Heart-lung transplants are performed using either a clamshell incision or sternotomy. CPB is obviously a requirement in these patients. The vascular anastomoses include the aorta and a cuff of the right atrium including both vena cavae. Bibronchial airway anastomoses, which are associated with less dehiscence than a single tracheal anastomosis, are performed.

MANAGEMENT OF CRITICALLY ILL LUNG TRANSPLANT CANDIDATES: BRIDGE TO LUNG TRANSPLANT

In recent years, the proportion of candidates requiring support beyond noninvasive measures, including mechanical ventilation and extracorporeal life support (ECLS), has increased, resulting in a larger proportion of patients requiring intensive care management and support before transplantation.[7]

The field has learned that, in large-volume centers,[8] outcomes are unaffected and that the technology around ECLS has evolved to become simpler.[9–12] Technologic advances include heparin-coated circuits, development of polymethylpentene oxygenator membranes, introduction of centrifugal pumps, dual-lumen cannulas, and miniaturized systems. Although these have translated into an increased interest toward the earlier implementation of ECLS, its use has been described as a risk factor for airway dehiscence, stroke, infection, and thromboembolic complications after transplantation.[11] Efforts toward ECLS without mechanical ventilator support—"awake ECLS"—aim to offset the risks of prolonged sedation and subsequent postoperative deconditioning.[13] Awake ECLS has resulted in improved early outcomes.[13]

Intraoperative Issues

The type of surgical incision (clamshell incision vs. anterolateral thoracotomies vs. median sternotomy) for lung transplantation depends on several factors, including single or bilateral lung transplantation, CPB use, history of prior thoracic surgery in the recipient, and surgeon's preference. Bilateral anterior thoracotomy (sternal sparing) performed for BLT has a lower rate of sternal infections and healing complications than the clamshell incision.[14] During surgery, three

anastomoses are made on each side. They include the bronchus, pulmonary artery, and cuff of the pulmonary veins to the left atrium from posterior to anterior. Bronchial artery anastomosis is usually not made. In addition, lymphatic and nerve-ending anastomoses are not made. About 30%–40% of patients require CPB support intraoperatively for hemodynamic instability, hypoxemia, and right ventricular failure after clamping the first or second pulmonary artery. CPB is also commonly needed in recipients with pulmonary hypertension or in situations where independent lung ventilation is impossible.[15] The tubing, cannulas, membrane oxygenators, and pumps used in the CPB machine often trigger a systemic inflammatory response, and patients tend to be hypotensive from the resulting vasoplegia. Intraoperative extracorporeal membrane oxygenator (ECMO) machines have several advantages over CPB. They decrease the length of the circuit, thus decreasing the blood–air interface. There are fewer blood products that are transfused and a lower incidence of PGD.[16] After the surgery, the double-lumen ETT used for independent lung ventilation is exchanged for a single-lumen ETT. The patient is transferred to the intensive care unit (ICU) after chest closure. The patient is then weaned off the ventilator and from EMCO in the ICU.

Lung transplant recipients who have pulmonary hypertension require special attention. During surgery, every effort is made to prevent a sudden rise in pulmonary pressure that may cause right ventricular failure. Intraoperative transesophageal echocardiography (TEE) helps monitor the right ventricular function very closely. Inhaled nitric oxide (iNO), inhaled prostacyclin, and intravenous milrinone are used to support right ventricular function intraoperatively and during the immediate postoperative period.[17]

Immediate Postoperative Intensive Care Unit Management

Weaning the patient off the mechanical ventilator and ECMO is performed by the ICU physician who collaborates with the thoracic surgeon.[18] Stabilization of respiratory function and ventilator weaning are the initial goals when the patient arrives in the ICU from the operating room. Either pressure- or volume-targeted ventilation is used. The goal is to keep the airway pressures low to avoid barotrauma and gas leakage through the fresh bronchial anastomoses, prevent atelectasis, and at the same time avoid volutrauma to the newly implanted grafts. Lung-protective ventilation strategy with tidal volumes (V_T) around 6 mL/kg of predicted body weight and low to moderate positive end-expiratory pressure (PEEP) should be used.[19] High PEEP should be avoided. In patients who undergo SLT, it might be challenging to ventilate the graft, as the compliance of the native lung will be different. Care should be taken to avoid overinflation of the native emphysematous lung, as this might lead to hemodynamic compromise from auto-PEEP (intrinsic PEEP). Patients typically present with hypoxemia, hypercapnia, and hemodynamic instability.

Decreasing the respiratory rate, increasing the expiratory time, and decreasing the PEEP can help. If these measures do not help, brief disconnection from the ventilator circuit should be considered. If the situation continues, double-lumen tube placement and independent lung ventilation should be considered.[20] Likewise, the compliance of the native fibrotic lung will be worse when compared with the new graft. This might risk the overinflation of the newly transplanted allograft. Mild pulmonary edema is a common finding in transplanted lungs because of the absence of lymphatic drainage. This usually clears up in the first few days. If end-organ perfusion is adequate, as indicated by adequate urine output and downtrending lactate, an increase in fluids to boost preload is avoided.[19,21] iNO is frequently used in patients with pulmonary hypertension and right ventricular failure in the operating room. However, the intraoperative use of iNO does not seem to decrease the incidence of PGD.[22,23] The patient is rapidly weaned from iNO in the ICU. As soon as clinical stability is achieved, weaning from the mechanical ventilator is started. The oxygen fraction is steadily decreased if tolerated.[19] The majority of the patients can be weaned and extubated within the first 24 hours.[20,23] Early extubation minimizes the chance of pulmonary infections and lowers stress on the bronchial anastomoses. Patients can be extubated to noninvasive positive-pressure ventilation (NIPPV). This helps in the unloading of the respiratory muscles, decreasing respiratory rate and dyspnea and improving ventilation/perfusion mismatch. NIPPV can also be used in recipients who demonstrate phrenic nerve dysfunction.[24] Patients requiring prolonged mechanical ventilation should be considered for early tracheostomy.[24] In these patients, early tracheostomy would minimize sedation and help with physical therapy while providing easier access for secretion clearance.[15] Patients who require reintubation can also be considered for tracheostomy. If patients cannot be extubated, the decision to perform a tracheostomy should be made by the end of the first week.[25] Although lung transplant recipients who end up with a tracheostomy tend to be sicker, have a longer ICU stay, and require prolonged ventilation, there is no difference in their short- and long-term survival rates compared with recipients who do not have a tracheostomy. Tracheostomy in this population is an important option that enables weaning from the mechanical ventilator and is associated with better patient tolerance.[26] Chest tube removal depends on the 24-hour drainage from each tube. Apical chest tubes are removed first, followed by the basilar tubes, provided their drainage is less than 150 mL/24-hour period.[15] Vigorous airway clearance techniques to mobilize secretions are an essential component of the recovery process after extubation. The cough reflex is blunted in these patients because of denervated lungs and splinting of the chest because of the pain resulting from the incision and the presence of chest tubes. Airway clearance techniques include bronchodilators, incentive spirometry, the flutter valve, chest physiotherapy, and nebulized hypertonic saline.

Pain control is an essential component of postoperative ICU care. Adequate analgesia is critical to prevent splinting of the chest that would cause atelectasis. Fentanyl infusion and patient-controlled analgesia pumps are used once patients are more awake in the immediate postoperative period. Morphine is avoided, as the creatinine clearance tends to fluctuate with the initiation of calcineurin inhibitors, and there is a risk of accumulating toxic metabolites of morphine. During surgery, patients undergo stretching of thoracic joints, ribs, vertebrae, and muscles; manipulation of pleura and lungs; and chest tube placement. All of these cause considerable pain upon waking from anesthesia. Inadequate pain control prevents patients from coughing and expanding the graft, thus increasing pulmonary complications. Moreover, the transplanted lungs are denervated and lack cough reflex. Patients tend to splint from pain, and as a result, diaphragmatic excursions are decreased, causing retention of mucus that leads to atelectasis. Thoracic epidural analgesia is used for unilateral or bilateral thoracotomy. Epidural analgesia also reduces opiate requirements, thus decreasing sedation from opiates and enabling patients to participate more in mobilization and physical therapy.[27] Oxycodone is started once patients are extubated and able to tolerate oral medications. Nonsteroidal antiinflammatory drugs are avoided for analgesia, as they tend to worsen renal function, especially in patients who are on tacrolimus or cyclosporine. More recently, thoracic paravertebral catheter and intercostal cryoanalgesia have been used for postoperative pain control from the clamshell incision and pain emanating from the chest tubes. In thoracic paravertebral catheter analgesia, four paravertebral catheters are placed, two at the T4 level for controlling pain from the clamshell incision and two at the T8 level for pain emanating from chest

tubes. Intercostal cryoanalgesia is performed intraoperatively on intercostal nerves 3–9 bilaterally. Both modalities decrease the amount of opiate required in the postoperative period and aid with pulmonary rehabilitation.[28,29]

Immunosuppression

Immunosuppression is initiated in the operating room. The first dose of an induction agent, basiliximab, is administered on the day of surgery, just before the graft's first perfusion. The second dose is repeated on the fourth postoperative day. The first dose of Solu-Medrol (methylprednisolone) (10 mg/kg) is also administered before the first graft's perfusion. This is followed by 1 g of intravenous mycophenolate mofetil. Tacrolimus is initiated after the arrival of the patient in the ICU. This practice might vary slightly from one center to another.

After transplantation, the main immunosuppressive drugs include a combination of calcineurin inhibitors (tacrolimus or cyclosporine), antimetabolites (mycophenolate mofetil or azathioprine), and steroids. Calcineurin inhibitors are the cornerstone of the regimen. We default all patients to tacrolimus, mycophenolate mofetil, and prednisone. The dose of tacrolimus is gradually titrated to a tacrolimus trough level of 10–14 ng/mL by the end of the first postoperative week while closely monitoring serum creatinine levels. Mycophenolate mofetil is administered at a dose of 1 g twice daily while cautiously monitoring for cytopenias.

Antimicrobials

Broad-spectrum antibiotics that would cover gram-positive and gram-negative organisms are initiated before making skin incisions on the recipient. Typical antibiotics include a combination of vancomycin and cefepime—donor bronchus culture and prior cultures from recipient sputum guide the types and duration of the antibiotics. Trimethoprim-sulfamethoxazole, prophylaxis against *Pneumocystis jiroveci,* is started and given three times a week. Antifungal prophylaxis depends on pretransplant risk factors for *Aspergillus*. Recipients with cystic fibrosis and cavitary disease are thought to have a high risk and are prophylaxed with oral voriconazole or posaconazole or isavuconazole and inhaled amphotericin. Patients who are at low risk for aspergillosis are prophylaxed with itraconazole. The oral prophylaxis is continued for 6 months. Cytomegalovirus (CMV) prophylaxis depends on the CMV serologic status (IgG) of the donor and recipient before the transplantation. If the donor is positive and the recipient is negative (D+/R−, CMV mismatch), the recipient is prophylaxed with daily valganciclovir for a year or longer. If the donor is CMV negative and the recipient is CMV positive (D−/R+) or if the donor and recipient are CMV positive (D+/R+) (intermediate-risk group), the recipient is prophylaxed with Valcyte for 9–12 months. If the donor and recipient are CMV negative (D−/R−, low-risk group), the recipient is prophylaxed with acyclovir, which is effective against all herpesviruses other than CMV.

General Measures

Patients tend to get constipated from immobilization and opiate analgesics used in the immediate postoperative period. This is prevented by instituting scheduled laxatives. Constipation and ileus also interfere with the absorption of immunosuppressive medications. Hence, great care is taken to avoid constipation and the slowing of gut motility. This is especially true in patients with cystic fibrosis who might require more aggressive measures that include osmotic laxatives in addition to stimulant laxatives.[18] On a similar note, electrolyte imbalance could make constipation and ileus worse. Magnesium, calcium, potassium, and creatinine levels need to be monitored closely. Hypomagnesemia results from tacrolimus, proton pump inhibitors, and diuretics in the initial postoperative period. Intracellular levels of magnesium might be lower despite normal serum levels. This should be aggressively corrected to minimize neurotoxicity and cardiac dysrhythmias. Magnesium is a vital cofactor in muscle function and gastrointestinal motility.[18] The incidence of venous thromboembolism in lung transplant recipients is much higher than in other populations. It is thought to be between 8% and 29%. As a result, deep vein thrombosis prophylaxis is enforced as soon as possible with low-molecular-weight heparin.[30]

Lung transplant recipients have a high risk of gastroesophageal reflux from underlying esophageal dysmotility and recent thoracic surgery. Measures to control acid reflux and aspiration include keeping the head of the bed elevated at a 30-degree angle or more and using a proton pump inhibitor. Early and aggressive physical therapy is crucial in the success of lung transplantation to avoid critical care illness neuromyopathy. Once patients are extubated, they are mobilized to sit in a chair twice a day. If patients can achieve adequate analgesia, walking with assistance is encouraged.

POSTOPERATIVE COMPLICATIONS

Infectious Complications

Infectious complications are higher in lung transplant recipients compared with other solid organ transplantations. This most likely relates to the fact that the allograft is exposed to the environment. Moreover, immunosuppression in lung transplantation recipients is much higher than other solid organ transplantations.[31] Bacterial infections of the lower respiratory tract are the most common infectious complications. The risk factors for these include immunosuppressed status, mechanical ventilation, and blunted cough because of pain.

Bleeding Issues

Increased bleeding is frequently seen in recipients who have had previous pleurodesis and use of intraoperative or preoperative extracorporeal circulation (ECMO/CPB). Coagulopathy should be rapidly corrected with the transfusion of blood products. If there is increased bloody chest tube drainage of more than 200 mL/30 min, exploratory surgery should be considered. Even if the source of bleeding is not identified, the evacuation of blood products from the pleural space prevents collapse of the graft and development of compartment syndrome.[19]

Acute Renal Failure

Acute renal failure is a common complication from calcineurin inhibitors. It results from intense afferent arteriole vasoconstriction caused by tacrolimus or cyclosporine, resulting in decreased renal blood flow and glomerular filtration rate. Hypotension or systemic hypertension further worsens renal function. Hypertension should be well controlled, preferably with calcium channel blocking agents.[15,31] Nonsteroidals should be avoided for analgesia. Diuretics should be used sparingly.

Atrial Tachyarrhythmias (Atrial Fibrillation, Atrial Flutter, and Supraventricular Tachycardia)

Atrial tachyarrhythmia is common in this population, occurring in 34%–47% of patients.[15] The incidence is higher in double-lung transplants than in SLTs and tends to appear 3–7 days after surgery. The incidence is also high in older patients, patients who had been on CPB, and patients who had atrial manipulations. Electrolyte imbalance, sympathetic stimulation from pain, and anxiety precipitate atrial fibrillation. Rate control with beta-blockers is preferred. Antiarrhythmic drugs are used if patients fail to respond to initial treatment. Different centers have used amiodarone, sotalol, and propafenone.[32–34]

Phrenic Nerve Injury and Diaphragmatic Paralysis

Phrenic nerve injury and diaphragmatic paralysis are underdiagnosed complications, with an incidence of around 1%–3%. Difficulty weaning from the ventilator or thoracoabdominal asynchrony during spontaneous breathing trials, the disproportionate elevation of one hemidiaphragm on postoperative chest x-rays, or postoperative hypercapnia otherwise unexplained should raise suspicion for this complication. The diagnosis can be confirmed on a chest ultrasound or fluoroscopy when the recipient is breathing spontaneously. Decreased, absent, or paradoxical movement of the hemidiaphragm further confirms the diagnosis. Diaphragmatic weakness causes prolonged mechanical ventilation and increased length of hospital stay.[19]

Gastroparesis and Gastroesophageal Reflux

Vagal nerve injury during surgery might result in gastroparesis and gastroesophageal reflux. Patients might experience delayed gastric emptying, early satiety, epigastric fullness, nausea, vomiting, and worsening acid reflux. Acid reflux increases the risk of microaspiration and injury to the new graft and can cause acute rejection. Hence, during the immediate postoperative recovery in the ICU, it is essential to remain vigilant for complications. The head end of the bed has to be kept elevated to prevent aspiration. Likewise, prokinetics like azithromycin and metoclopramide are administered for gastroparesis until there is spontaneous recovery.[19]

Thrombotic Microangiopathy

Microangiopathic hemolytic anemia (MAHA) refers to nonimmune intravascular red blood cell fragmentation that produces schistocytes in peripheral blood smear. Direct Coombs test is negative, lactate dehydrogenase and indirect bilirubin increase, and haptoglobin remains low or undetectable. Thrombotic microangiopathy (TMA) refers to MAHA with thrombocytopenia. TMA is a life-threatening complication caused by small-vessel microthrombi. It results from endothelial injury, microcirculatory thrombosis, fibrin deposition, and platelet consumption. MAHA, renal failure, and thrombocytopenia are present in TMA, whereas neurologic abnormalities are rare. TMA post–lung transplant could be drug-induced or complement-mediated.

Drug-induced TMA after lung transplantation results from dose-dependent nonimmune-mediated effects from drugs like tacrolimus, cyclosporine, and mammalian target of rapamycin (mTOR) inhibitors. The incidence of TMA from calcineurin inhibitors is thought to be between 3% and 4.5%.[35] It is more common in the first 3 months after transplantation.[15] Once drug-induced TMA is identified, the offending drug should be stopped. The majority of the care is supportive. Once the condition improves, another calcineurin inhibitor can be attempted under close monitoring.

Complement-mediated TMA is sudden in onset, preceded in some cases by a diarrheal illness. It is associated with general malaise and poor appetite, hypertension, and acute renal failure. The role of complement testing (C3, C4, CH50) is unclear. Decreased levels of complement might suggest complement-mediated TMA. However, normal levels do not exclude the possibility. The complement levels might take days to weeks to result. In complement-mediated TMA, eculizumab should be started as soon as possible, even while the results of complement levels are pending. As there is an increased risk of meningococcal infection, a meningococcal vaccine is required. In addition, empiric antibiotics should be considered for 2 or more weeks.

Hyperammonemia

Hyperammonemia after lung transplantation is a rare but often fatal complication. It manifests as an elevation of serum ammonia level that leads to encephalopathy, cerebral edema, seizures, coma, cerebral herniation, and death. Incidence of hyperammonemia ranges from 1% to 4%, with fatality rates exceeding 75%. The exact etiology is unclear, but it is thought to result from a deficiency in hepatic glutamine synthetase, a urea cycle enzyme that plays an essential role in processing nitrogenous waste.[31] More recently, infection with urea-splitting microorganisms has been reported.[36] Once hyperammonemia is recognized (serum ammonia levels >60 μmol/L), management includes discontinuing all protein intake for the first 24–48 hours, including tube feeds. After this pause, the protein intake is resumed at 0.25 g/kg and gradually increased to the goal. Antibiotics to cover *Mycoplasma* and *Ureaplasma* like azithromycin or levofloxacin or doxycycline are started. Nitrogen scavengers like sodium phenylbutyrate, sodium benzoate, arginine, and levocarnitine are initiated. In cases where the ammonia levels go above 250 μmol/L, intermittent hemodialysis and continuous renal replacement therapy in hemodynamically unstable patients should be initiated. Bowel decontamination with lactulose, metronidazole, and rifaximin should be performed.[37]

Bronchial Necrosis and Dehiscence

Bronchial circulation is not established during transplantation. Perfusion to airways and parenchyma depends solely on the pulmonary arterial circulation. Pulmonary artery blood supply may be insufficient during the perioperative period, especially when vasopressors are used for hypotension. This perfusion inadequacy might result in ischemic injury to the anastomosis or postanastomotic bronchus.[38] Relative ischemia, exacerbated by intraoperative or postoperative hypotension and hemodynamic fluctuations, makes anastomoses susceptible to necrosis, dehiscence, and infection. The severity of necrosis varies from commonly encountered mild focal necrotic sloughing to extensive necrosis, perforation, and bronchial dehiscence.[38] This usually occurs 1–5 weeks postoperatively with an incidence of 1%–10%.[39] Hence, anastomosis should be examined carefully during every bronchoscopy. Clinical features include dyspnea, pneumomediastinum, subcutaneous emphysema, pneumothorax, lung collapse, and persistent air leaks in the early posttransplant period.[40] Because chest x-rays are unreliable if bronchial dehiscence is suspected, computed tomography (CT) of the chest should be considered, as it will very clearly delineate the bronchial defects and extraluminal air around the anastomosis.[38] Placement of self-expanding metallic stents that promote granulation can be used to aid healing.[38,39]

Pulmonary Artery Stenosis

Patients with pulmonary artery stenosis present with hypotension and severe right heart failure. This condition, which mimics pulmonary embolism, can be treated with surgical correction or stent placement.

Pulmonary Vein Stenosis/Pulmonary Venous Obstruction

Pulmonary venous obstruction after lung transplantation is a very rare complication. It is associated with high morbidity and mortality unless recognized very early in the postoperative period. Patients present with progressive hypoxemia and infiltrate in the grafted lung on chest x-ray, mimicking acute pulmonary edema. Respiratory secretions in the endotracheal tube could be frothy pink or hemorrhagic. The pulmonary capillary wedge pressure may be high. This condition is diagnosed with TEE. The severity of the hypoxemia depends on the number of lungs transplanted, whether pulmonary venous obstruction is unilateral or bilateral, and whether the recipient had prior pulmonary hypertension. In patients who have undergone SLT and have prior pulmonary hypertension, pulmonary venous stenosis in the graft will cause severe hypoxemia and graft failure very early on. Bedside TEE is a beneficial tool to detect this condition. CT angiography is another option. Once diagnosed, patients need to be taken back to the operating room for the reconstruction of the venous anastomoses.[41]

Thoracic Compartment Syndrome

Thoracic compartment syndrome is seen in the immediate postoperative period, either immediately after chest closure or several hours later. Patients present with hemodynamic instability. This complication occurs most commonly in BLT, especially if there is a prolonged intraoperative course and transfusion of multiple blood products and/or use of CPB. Clinical features include high ventilator airway pressures, refractory hypotension, and progressive acidosis. Worsening lactic acidosis, tissue perfusion, renal function, and urine output are also noted. Immediate thoracotomy and delayed closure are recommended.[42]

PRIMARY GRAFT DYSFUNCTION AFTER LUNG TRANSPLANTATION

PGD is a form of acute lung injury that occurs within the first 72 hours after lung transplantation and is triggered by ischemia-reperfusion injury. PGD manifests as progressive hypoxemia and the presence of radiographic pulmonary infiltrates without other identifiable causes such as cardiogenic pulmonary edema, pneumonia, hyperacute rejection, or pulmonary venous anastomotic obstruction. It affects almost one-third of lung transplant recipients and is the major cause of early morbidity and mortality after lung transplantation.[43] In addition, PGD has been associated with an increased risk of chronic lung allograft dysfunction (CLAD), which is the major cause of late mortality after lung transplantation.[44]

In 2005 the International Society of Heart and Lung Transplantation (ISHLT) Working Group on PGD proposed a standardized definition and grading system based a ratio of PaO_2:FiO_2 (P:F or arterial oxygen partial pressure/fraction of inspired oxygen) and the radiographic presence of infiltrates in the transplanted lung(s) assessed within the 6 hours after lung transplantation (T0) and at 24 hours (T24), 48 hours (T48), and 72 hours (T72) posttransplantation (Table 145.1).[45,46] The definition was updated in 2017 to classify patients receiving posttransplant ECMO because of hypoxemia as severe PGD (PGD grade 3) and those on ECMO for reasons other than hypoxemia (i.e., cardiac support) as ungradable PGD. Furthermore, unlike in the 2005 definition, the 2017 definition recommended that the use of inhaled pulmonary vasodilator agents such as iNO and aerosolized epoprostenol that may improve oxygenation not be considered when grading severity of PGD. Additionally, the new update provided an alternative grading schema using a ratio of oxygen saturation/fraction of inspired oxygen SaO_2/FiO_2 in cases where a PaO_2 measurement was unobtainable with adjusted cutoffs of 235 and 315 (see Table 145.1).[46]

Subsequent validation studies using the standardized definition of PGD demonstrated better discrimination of grade 3 PGD to predict early mortality. Specifically, grade 3 PGD beyond 48 hours after transplantation demonstrated the most robust associations with early and overall mortality after lung transplantation compared with the other grades of PGD.[47–50]

Prior studies have proposed several risk factors for the development of PGD based on the donor, recipient, and surgical variables. Risk factors such as donor smoking, donor alcohol use, undersized donor:recipient lung matching based on the predicted total lung capacity (pTLC), recipient diagnosis of sarcoidosis, recipient elevated mean pulmonary artery pressure, and high fraction of inspired oxygen at allograft reperfusion are likely to be associated with development of PGD (Table 145.2). Some of these risk factors are potentially modifiable (e.g., avoiding undersized donor:recipient lung matching, FiO_2 at reperfusion, obesity) and thus may suggest preventive strategies.[47,51]

The pathogenesis of PGD is an area of intense investigation. The underlying etiology is thought to be the airway epithelial and vascular endothelial cell damage caused by the ischemia-reperfusion injury (IRI) after lung transplantation. This results in release of damage-associated molecular patterns (DAMPs) that are recognized by pattern recognition receptors (PRRs), which stimulate inflammatory cytokine gene expression, and ultimately leads to activation of the innate immune system, including the complement cascade, alveolar macrophages, and an influx of neutrophils into the lungs. This inflammatory cascade will cause alterations in the integrity of the endothelial barrier and alveolar epithelial capacity to resorb fluid, leading to development of PGD.[55–57]

During the past decade, several strategies targeting putative pathways in PGD have been studied, such as the use of iNO, modulation of the complement cascade, instillation of surfactant, and prevention of neutrophil extracellular trap (NETs) formation using an antiplatelet agent or intraalveolar disruption of NETs using DNase I.[58–60]

TABLE 145.1 2005 ISHLT Primary Graft Dysfunction Taxonomy

Grade	Pulmonary Edema on Chest x-ray	PaO_2:FiO_2	Specific Exceptions
0	−	Any	
1	+	>300	
2	+	200–300	
3	+	<200	Any patients on ECLS for hypoxia and pulmonary edema

If PaO_2 is not available for calculation of a arterial oxygen partial pressure/fraction of inspired oxygen (*PaO_2:FiO_2*) ratio, then oxygen saturation/fraction of inspired oxygen (SaO_2/FiO_2) ratio should be calculated and the 200 and 300 PGD grading cutoffs should be adjusted to 235 and 315. Use of nitric oxide, aerosolized epoprostenol, or other pharmacologic agents that may improve oxygenation should not change grading methods. Use of extracorporeal lung support (*ECLS*) with bilateral pulmonary edema on chest x-ray image should be graded as grade 3, and ECLS use should be explicitly recorded. The use of ECLS for nonhypoxic indications without pulmonary edema on chest x-ray imaging should be considered ungradable and explicitly recorded separately. Time window notes: PGD is graded at 4 time points: every 24 hours and over the first 72 hours after transplantation (T0, T24, T48, and T72 hours). Time starts at reperfusion of the second lung. T0, T24, T48, and T72 have time windows ±6 hours. If multiple blood gas values are available, the worst PaO_2/FiO_2 ratio on a given calendar day should be used. Adapted from Snell GI, Yusen RD, Weill D, et al. Report of the ISHLT Working Group on Primary Lung Graft Dysfunction, part I: Definition and grading—A 2016 Consensus Group statement of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant*. 2017;36:1097–1103.

TABLE 145.2 Risk Factors for Development of Primary Graft Dysfunction Based on Donor, Recipient, and Surgical Variables

Donor	Recipient	Operative
Smoking	Sarcoidosis	Undersized donor:recipient lung matching
Alcohol use	Pulmonary hypertension	High fraction of inspired oxygen at allograft reperfusion
Specific genetic factors	Elevated mean pulmonary artery pressure	Transfusions >1:2 FFP:PRBC transfusion
	Diastolic dysfunction	
	Abdominal subcutaneous adipose tissue (overweight/obese) phenotype	
	Specific biomarkers	
	Specific genetic factors	

FFP, Fresh frozen plasma; *PRBC,* packed red blood cell.
Adapted from references[47,] and [52–54]

Currently, the therapy for PGD remains generally supportive and draws from therapies applied in patients with acute respiratory distress syndrome (ARDS), including lung-protective ventilation strategies. Additionally, pressure-controlled ventilation modes may be used to minimize barotrauma and airway anastomosis complications. Diuresis should be initiated, with blood pressure support, if needed, and excess fluid administration should be avoided.[61] Despite the encouraging results with iNO administration to prevent and treat severe PGD suggested by several animal studies and case series,[62–65] randomized controlled studies did not support efficacy for iNO use in the clinical setting.[22,66] However, despite the lack of an established role for iNO in prevention or treatment of PGD, its use may be justified as salvage therapy in selected cases for improving oxygenation, reducing mean pulmonary arterial pressure, and increasing mean systemic arterial pressure early after transplant.[67]

Institution of ECMO in patients with severe PGD has gained in popularity, with better outcomes reported in cases of early ECMO initiation, preferably within the first 24 hours after transplantation.[68–71] In cases with refractory respiratory failure, retransplantation has been performed. However, predicted survival is poor, and this practice is generally not recommended.[58,72]

Acute Rejection after Lung Transplantation

Acute rejection after lung transplantation is common and continues to affect approximately 40% of lung transplantation recipients in the first year posttransplantation.[73] The clinical manifestations are variable, nonspecific, and potentially confounded by coexisting diseases and processes. The presentations range from being asymptomatic with no radiographic changes, detected via routine posttransplantation surveillance biopsies, to a clinical picture resembling ARDS.[74] Acute rejection after lung transplantation encompasses acute cellular rejection (ACR) and antibody-mediated rejection (AMR).

Acute Cellular Rejection

ACR is the result of an immune reaction against donor antigens that are expressed on the surface of donor cells and recognized by recipient lymphocytes. Recipient lymphocytes can react to various donor antigens, such as blood group antigens and human leukocyte antigens (HLAs). HLAs are polymorphic cell-surface molecules and can lead to a robust immune response when mismatched between donor organ and recipient. The lung is a rich lymphoid organ and possesses all immune cell lines necessary for initiation and maintenance of an immune reaction. Shortly after transplantation, the donor HLA proteins are presented to recipient T cells by the donor's own antigen-presenting cells (APCs) ("direct pathway") or later by migrated recipient APCs to the transplanted lung ("indirect pathway"). APC stimulation induces naive T cells to become memory T cells capable of direct and rapid recognition of alloantigens and subsequent injury.[75,76]

ACR is defined as the presence of lung perivascular and/or peribronchiolar lymphocytes in the absence of infectious etiologies. To date, bronchoscopic transbronchial biopsy remains the gold standard for diagnosis of ACR.[77,78] However, multiple studies have been conducted in assessing less invasive tests such as bronchoscopy-guided airway brushings,[79] bronchoalveolar lavage (BAL),[80–82] or serum biomarkers for diagnosis of ACR.[83] Similarly, spirometry testing has utility but is not diagnostic.[84] Thus after several decades of attempts to find a less invasive, more precise surrogate marker of ACR in lung transplantation, bronchoscopic tissue analysis remains the most reliable diagnostic modality.

Acute rejection can be seen as early as a week after lung transplantation. Although ACR is more often present as a nonspecific decline in spirometry with no significant radiographic changes, it can manifest as a fatal hypoxic respiratory failure with diffuse pulmonary infiltrates in its severe form. This can make the diagnosis and treatment of other ICU complications difficult. ACR presentation can mimic symptoms of pneumonia, and sometimes ACR can be triggered by earlier pneumonia. Therefore development of new infiltrates after lung transplantation requires diagnostic evaluation using bronchoscopy with BAL and transbronchial biopsy. Importantly, ACR is directly responsible for only a small proportion of deaths in lung transplantation recipients. In fact, less than 4% of deaths are attributable to ACR in the first posttransplant month, and, at later time points, this incidence decreases to less than 2%.[73] Nevertheless, much attention has been paid to the early diagnosis and treatment of ACR, as it remains the most significant risk factor for the development of CLAD, which is the ultimate cause of mortality from lung transplantation.[85,86]

The most commonly administered first-line therapy for ACR is high-dose steroids with intravenous methylprednisolone; doses range from 10 to 15 mg/kg daily for 3 days, followed by a prednisone taper.[87–89] The therapeutic plans for persistent or recurrent acute rejection that warrants further augmentation of immunosuppression are variable among centers. This scaling up can be achieved by a repeat course of pulse steroids, optimization of maintenance immunosuppression,[87–91] anti–T-cell agents such as polyclonal antithymocyte globulins (ATGs), or an anti-CD52 monoclonal antibody (alemtuzumab) in the treatment of severe and refractory ACR.[89,92]

Antibody-Mediated Rejection

AMR is a widely accepted cause of graft dysfunction after lung transplantation.[89,93,94] It is mediated by donor-specific antibodies (DSAs), produced by B cells or plasma cells, and upon binding to their cognate antigen in the transplanted lung, they cause a deleterious effect via complement-dependent[95] and complement-independent pathways.[95,96] DSA may be present at the time of transplantation (sensitized recipient) or develop de novo after transplantation.[97]

The presence of DSA before transplantation can lead to hyperacute rejection, which is the most severe form of AMR and occurs within minutes to hours after lung transplantation. Clinical manifestations include the rapid development of diffuse pulmonary infiltrates and hypoxia followed by systemic inflammatory response syndrome, including coagulopathy, thrombocytopenia, oliguria, and hemodynamic instability.[94,98–100] Although hyperacute rejection is generally considered to be a fatal complication after lung transplantation, there are a few case reports of survival after enforcing aggressive immunotherapy strategies.[101–103] A therapeutic approach to hyperacute rejection includes various combinations of high-dose steroids, plasmapheresis, cyclophosphamide, high-dose intravenous immunoglobulin (IVIg), ATG, and rituximab, an anti-CD20 monoclonal antibody.[94,98–103]

Aside from the risk for development of hyperacute rejection, the presence of DSA before lung transplantation has been associated with ACR, AMR, and CLAD.[104–107] Therefore prevention through the avoidance of the donor with known DSA HLA targets has been common, but doing so can significantly limit access to a transplant in the sensitized recipients.[108–110] Alternatively, pretransplantation desensitization using a combination of plasmapheresis, ATG, IVIg, and mycophenolate has been reported with equivalent posttransplantation outcomes to unsensitized patients.[104,111–113] Overall, hyperacute rejection has become rare since the implementation of more sensitive methodologies for screening recipient HLA antibodies before transplantation.

Pretransplant DSA, in addition to the de novo development of DSA after lung transplantation, can be asymptomatic (silent) or result in clinical manifestations of antibody-mediated rejection.[104–106,112] The clinical presentations of ACR and AMR are indistinguishable.

Additionally, ACR and AMR can manifest together, or one can trigger the other form of rejection.[114,115] Unfortunately, AMR in lung transplantation has remained a diagnostic challenge.[97,116] The lung transplant recipient presenting with an otherwise unexplained drop in lung function, anti-HLA DSA, a neutrophilic capillaritis, and positive C4d staining on transbronchial biopsy is highly likely to have AMR as the cause for graft dysfunction. In such cases, a diagnosis of "definite AMR" is suggested.[97,99,116] However, this scenario is uncommon, and the more common clinical presentation is of a patient with an unexplained deterioration of pulmonary function and a new or increasing titer DSA. In these cases, lung biopsy does not suggest an alternative diagnosis or demonstrate confirmatory features of AMR. Therefore the absence of confirmatory histology should not automatically rule out the diagnosis of AMR.[99,116]

Because of the variability in diagnosis of AMR across transplant centers, a working group was created in 2016 by the ISHLT with the aim of determining criteria for pulmonary AMR and establishing a definition. Pulmonary AMR was defined as clinical when there is allograft dysfunction, as evaluated by pulmonary function test (which can be asymptomatic otherwise), or subclinical when there is normal allograft function. Both clinical and subclinical AMR were further subcategorized into three mutually exclusive possibilities (definite, probable, and possible). These categories were based on the degree of certainty related to the presence or absence of a number of pathologic, serologic, clinical, and immunologic criteria (Table 145.3).[117]

In general, there is no consensus agreement about the choice of agent or duration of therapy for AMR. Therapeutic options have been extrapolated from renal transplant and other areas of medicine without clinical trials. Treatment has generally consisted of multiple sequential interventions. It is very common to initiate therapy with pulse steroids (methylprednisolone 0.5–1 g daily for 3–5 days),[118] followed by plasmapheresis, high-dose IVIg, and B-cell depletion therapy with rituximab.[119–123] In recent years, a plasma cell-targeted therapy using proteasome inhibitors such as bortezomib and carfilzomib has been used in the management of AMR.[124,125]

Chronic Lung Allograft Dysfunction

CLAD is characterized by substantial and persistent decline in and loss of pulmonary function (≥20% measured FEV_1 value), which cannot be explained by other potentially reversible complications such as acute rejection, infection, or bronchial stenosis.[125] It affects up to 50% of lung transplant recipients after 5 years and is the major cause of overall morbidity and mortality after lung transplantation.[7,126,127] CLAD can present either as a predominantly obstructive ventilatory pattern, a restrictive pattern, or a mixed obstructive and restrictive pattern.[125,127,128] Obstructive CLAD includes bronchiolitis obliterans syndrome (BOS), which is caused by recurrent inflammation, destruction, and eventual fibrosis of small airways, forming obliterative bronchiolitis (OB) lesions in the lung allograft. It presents as a persistent, nonreversible obstructive ventilatory decline in spirometric measures of lung function with an essentially clear chest radiograph. High-resolution CT imaging of the chest often demonstrates air trapping, tree-in-bud opacities, or bronchiectasis. Because of the patchy distribution of OB lesions in the lungs, transbronchial biopsy is insufficiently sensitive to achieve diagnosis. Therefore the diagnosis of BOS is made by at least a 20% decline in FEV_1 from the best postoperative baseline, assessed by two measurements with a minimum interval of 3 weeks.[127,129,130] BOS is often irreversible; however, recently it became clear that 30%–40% of patients with a diagnosis of BOS may respond to treatment with azithromycin. A placebo-controlled trial in patients with BOS confirmed that azithromycin was superior to placebo for improvement in FEV_1 in established BOS.[131,132] Most patients who responded to azithromycin had elevated BAL neutrophilia during diagnosis. This observation led to a further subclassification of obstructive CLAD to BOS and a new phenotype known as *neutrophilic-reversible allograft dysfunction* or *azithromycin-responsive allograft dysfunction*.[127,129,130]

Approximately 70% of CLAD is attributable to obstructive CLAD and 30% to the restrictive phenotype of CLAD, also known as *restrictive allograft syndrome* (RAS).[128] RAS is characterized by a restrictive pulmonary function decline and persistent parenchymal infiltrates on chest radiography. CT of the chest can demonstrate subpleural thickening and nonspecific interstitial changes. Additionally, organizing pneumonia, pleuroparenchymal fibroelastosis, and OB may be seen in the histopathology.[133] Unfortunately, the median survival after development of RAS is limited to 6–18 months, as opposed to 3–5 years in BOS.[128]

In general, the diagnosis of CLAD is made after carefully ruling out other causes of declining lung function, which are not related to intrinsic graft dysfunction, as outlined in Box 145.1.[125] The medical management of CLAD centers around stabilizing rather than restoring graft

TABLE 145.3 Definition and Diagnostic Certainty of Clinical Pulmonary Antibody-Mediated Rejection

	Allograft Dysfunction	Other Causes Excluded	Lung Histology	Lung Biopsy C4d	DSAs
Definite	+	+	+	+	+
Probable	+	+	+	−	+
Probable	+	+	+	+	−
Probable	+	+	−	+	+
Probable	+	−	+	+	+
Possible	+	+	+	−	−
Possible	+	+	−	−	+
Possible	+	+	−	+	−
Possible	+	−	+	+	−
Possible	+	−	+	−	+
Possible	+	−	−	+	+

DSAs, Donor-specific antibodies; +, item present; −, item absent or missing.

Data from Verleden GM, Glanville AR, Lease ED, et al. Chronic lung allograft dysfunction: Definition, diagnostic criteria, and approaches to treatment—a consensus report from the Pulmonary Council of the ISHLT. *J Heart Lung Transplant.* 2019;38(5):493–503.

BOX 145.1 Processes and Diseases That May Lead to Chronic Loss of Allograft Function and Are Not Included in the Current Definition of CLAD

A. Factors where recalculation/resetting of the FEV_1 reference value may be valid (if FEV_1 remains stable for at least 6 months):
   1. Decreasing lung function because of the normal aging process
   2. Surgical factors
      - Transplant lung resection, chest-wall surgery, phrenic nerve damage
   3. Mechanical factors
      - Persistent pleural effusion
      - Persistent lung edema because of significant kidney/heart/liver failure
      - Airway stenosis
      - Myopathy, neuropathy, and Parkinson disease
      - Weight gain
      - Native lung hyperinflation after single-lung transplant
   4. Localized infection with chronic scarring
      - Abscess/empyema/mycetoma

B. Factors that cannot be differentiated easily from CLAD and do not ever allow recalculation/resetting of the FEV_1 reference value:
   1. Any from (A) above where there is not a period of at least 6 months of stability
   2. Infiltration with tumor
   3. Infiltration of the allograft with proven disease recurrence from the underlying transplant indication (e.g., LAM, sarcoidosis)
   4. Drug or other induced pulmonary toxicity (e.g., sirolimus, methotrexate, amiodarone, radiotherapy)
   5. Pulmonary arterial strictures or emboli
   6. Acute/subacute generalized infection
   7. Acute/subacute cellular or antibody-mediated rejection
   8. Acute/subacute effects of aspiration

C. Failing to reach normal predicted lung function (i.e., low FEV_1 reference value such that FEV_1 is ≤80% of the recipient predicted value). This situation may include an age difference between donor and recipient, where older donor lungs are implanted, or when an intraoperative allograft reduction surgery/lobectomy is performed.

CLAD, Chronic lung allograft dysfunction; *FEV_1,* forced expiratory volume in 1 second; *LAM,* lymphangioleiomyomatosis.
Data from Verleden GM, Lievens Y, Dupont LJ, et al. Efficacy of total lymphoid irradiation in azithromycin nonresponsive chronic allograft rejection after lung transplantation *Transplant Proc.* 2009;41:1816–1820.

function. Effective medical treatment for CLAD is an unmet need, and retransplantation remains the only effective therapeutic option for advanced CLAD.[125] For management of BOS, current guidelines recommend transitioning from cyclosporine to tacrolimus, antireflux surgery (e.g., Nissen fundoplication or Toupet fundoplication) in cases of documented gastroesophageal reflux, and a trial of azithromycin for more than 8 weeks.[125,129,130] Additionally, total lymphoid irradiation (TLI) or extracorporeal photopheresis (ECP) may reduce the rate of decline in certain patients with obstructive CLAD.[125,134,135] Currently there are no formal guidelines for management of patients with restrictive CLAD. Some beneficial effects have been reported using pirfenidone and alemtuzumab in RAS.[129] Although in selected cases clinicians may consider retransplantation for end-stage BOS, emerging data discourage this in RAS.[129,130,136] For the majority of patients with end-stage CLAD, palliation becomes the priority. Symptom control in advanced disease remains challenging. Noninvasive ventilation for hypercapnia is generally ineffective, and ventilatory support and subsequent weaning are usually unsuccessful.[134,137,138]

KEY POINTS

- Lung transplantation continues to offer hope for many advanced lung disease processes. Much has been learned about the natural history of these otherwise terminal lung diseases, which has influenced significant changes in the overall practice of lung transplantation, including the lung allocation system and the donor selection criteria.
- Primary graft failure (dysfunction) is a severe form of ischemia-reperfusion injury and carries enormous morbidity and mortality.
- Lung transplant recipients with postoperative respiratory compromise should be maintained "on the dry side."
- Growing evidence suggests that suboptimal early immunosuppression, in addition to recurrent aspiration from reflux disease, are the two most modifiable risk factors associated with chronic rejection. Patient selection, consideration of antireflux surgery before transplantation or early after, and appropriate immunosuppression schedules should be implemented in protocols at every center.
- Hyperammonemia continues to be a rare but feared complication after lung transplantation, given that its mechanism has yet to be understood. Aggressive management options, including gut decontamination, high levels of dialysis, and pharmacologic treatments targeted at urea-cycle enzyme deficiencies, are the only available tools but have yet to show promise in changing outcome.

References for this chapter can be found at expertconsult.com.

ANNOTATED REFERENCES

Christie JD, Edwards LB, Aurora P, et al. The Registry of the International Society for Heart and Lung Transplantation: Twenty-sixth official adult lung and heart-lung transplantation report—2009. *J Heart Lung Transplant.* 2009;28:1031–1049.

This yearly document published by the International Society for Heart and Lung Transplantation summarizes and explicitly describes the statistical trends of lung and heart-lung transplantation. This registry allows the reader to put in perspective the indications for transplantation; the donor characteristics; their impact on transplantation outcomes, including rejection, complications, and survival; and the centers offering transplantation and their influence on these outcomes in terms of the case load they are challenged with. It allows an organized chronologic understanding of lung and heart-lung transplantation outcomes.

Christie JD, Sager JS, Kimmel SE, et al. Impact of primary graft failure on outcomes following lung transplantation. *Chest.* 2005;127:161–165.

This single-center retrospective study conducted by field experts looked into the overall incidence of grade III primary graft failure in 255 consecutive procedures done in a period of over 10 years. It demonstrated an incidence of 11.3% of PGD, an increased mortality, worsened hospital length of stay, and increased duration of mechanical ventilation. A reported 73.3% of patients who received the diagnosis of primary graft failure died during their hospitalization versus 14.2% of those who did not. A 1-year follow-up also demonstrated significantly affected physical function in those who had experienced primary graft failure.

Hachem RR, Trulock EP. The new lung allocation system and its impact on waitlist characteristics and post-transplant outcomes. *Semin Thorac Cardiovasc Surg.* 2008;20:139–142.

This review clearly explains the current lung allocation process, which basically is geared toward making organs available to those who need them more urgently because of their underlying disease process and its expected outcome. A thorough comparison of the prior allocation process to the current one in terms of waiting time, waiting mortality, and more importantly, the steady proportional increase of idiopathic pulmonary fibrosis as the underlying cause of transplantation is made. This increase is explained by the comparable uncertainty of the disease's natural history and the high mortality of its exacerbations.

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Perioperative Management of the Liver Transplant Patient

Caleb Fisher and Stephen Warrillow

INTRODUCTION

The introduction of liver transplantation over 50 years ago has revolutionized outcomes for patients with both acute and chronic liver failure. Since experimental beginnings, liver transplantation has grown worldwide, with the number of transplants per year ranging from approximately 400 in Australia to over 1000 in the UK and over 8000 in the United States.[1–3] Concurrently, survival from transplantation continues to improve, with 5-year survival reported between 75% and 85%, depending on reporting jurisdiction.[1–3] This has been largely the result of improvements in surgical technique, anesthetic management, and postoperative critical care.

DONOR SELECTION

Liver transplantation is a treatment option for patients with both acute and chronic liver failure. Common causes include chronic liver disease as a result of alcohol use disorder; viral hepatitis; metabolic conditions such as Wilson disease and alpha-1-antitrypsin deficiency; and autoimmune conditions such as autoimmune hepatitis, primary sclerosing cholangitis, and primary biliary cirrhosis.[4–6] Selection for liver transplantation in chronic liver disease is largely based on disease severity and the likelihood of death on the transplant waiting list. The Model for End-Stage Liver Disease (MELD) score is the most commonly used criteria for transplantation listing, with the cutoff of 15 used as a trigger for commencement of the transplant assessment process in many jurisdictions.[6–8] A separate cohort are patients with hepatomas, who are listed on the basis of malignant disease burden.[9,10] Eligibility for transplantation has changed such that even critically ill patients are now often listed. These patients often exhibit acute-on-chronic liver failure (AoCLF) and require high-level critical care support for preoperative optimization followed by a frequently slow postoperative recovery.[11–14] In contrast, patients with acute liver failure (ALF) are almost always managed in the intensive care unit (ICU) at the time of transplant listing. Various predictive criteria have been developed to determine the likelihood of survival without liver transplantation in ALF, although their utility is increasingly questioned as improvements in both understanding of the pathophysiology of ALF and improved critical care management have led to improved outcomes.[15–17] Regardless of the indication for transplant, an essential requirement for effective care is a systematic and coordinated approach to management (Table 146.1 and Fig. 146.1).

A SYSTEMS-BASED APPROACH TO MANAGEMENT OF THE POST–LIVER TRANSPLANT PATIENT

Cardiovascular

Patients with end-stage liver disease (ESLD) have a characteristic cardiovascular profile. The classic pattern is a hyperdynamic circulation with low systemic vascular resistance and an increased cardiac output. The mean arterial pressure (MAP) tends to remain low/normal despite these changes.[18–21] Furthermore, ESLD patients have an abnormal distribution of total body blood volume because of complex alterations in the splanchnic, renal, and systemic circulations.[20,21] This involves the redistribution of blood into the splanchnic circulation secondary to the overproduction of nitric oxide (NO) and other proinflammatory mediators. The overproduction of inflammatory mediators is believed to be compounded by gut bacterial translocation in the setting of raised portal pressures.[22,23]

The postoperative hemodynamic course of these patients is influenced considerably by persistence of these preoperative hemodynamic disturbances. The hemodynamic changes of cirrhosis can take days to weeks to fully resolve after transplantation.[18,24] Because of the marked hemodynamic instability that can occur during the peritransplant period, invasive monitoring in the ICU is necessary to guide therapy and optimize graft function.[25] Traditionally, the pulmonary artery catheter has been the gold standard for intraoperative and postoperative monitoring; however, its utility has been questioned on the basis of its invasiveness, inability to predict fluid responsiveness, and lack of evidence for improving patient outcomes.[26,27] Less invasive techniques such as pulse contour analysis have gained popularity in other critical care populations, but their utility in the complex hemodynamic changes occurring during liver transplantation has recently been questioned.[27,28]

Hypotension is the most common hemodynamic abnormality encountered postoperatively. Causes include postoperative bleeding, persistence of the preexisting vasodilated state, postreperfusion vasoplegia, the effects of narcotics and sedatives, and fluid shifts causing hypovolemia.[20] Refractory vasoplegia postreperfusion can continue into the postoperative period; however, its incidence and impact upon outcomes are not known.[29] Common to other vasoplegic syndromes, hypotension that is refractory to standard vasoconstrictors may be amenable to treatment with methylene blue.[30,31]

Initial treatment aims to restore normovolemia by judicious use of fluid resuscitation. There is no consensus on the preferred fluid in this setting. Experience derived from the care of other critically ill patients suggests that balanced crystalloids may be preferred, as they avoid inducing hyperchloremia.[32,33] Albumin-containing solutions are an attractive alternative in patients who are hypoalbuminemic and offer potentially protective effects to the endothelial glycocalyx with improved postoperative outcomes.[34–36]

The optimal target for arterial blood pressure has not been established; however, a MAP of 65 mm Hg seems appropriate in these patients to ensure adequate end-organ perfusion, especially for the engrafted liver. A higher MAP may be required in the presence of poor hepatic arterial flow because of high resistive indices. A central venous pressure of 8–12 mm Hg appears to be safe; however, further resuscitation and increases in volume state may have deleterious effects on

TABLE 146.1 Management Challenges in Patients Undergoing Liver Transplantation

Body System	Management Challenge
Cardiovascular	Vasodilatation, hypotension, cirrhotic cardiomyopathy, redistributed blood volume
Respiratory	Fluid overload, hydrothorax, atelectasis, hepatopulmonary syndrome, portopulmonary hypertension
Renal	Acute kidney injury, end-stage kidney disease, hepatorenal syndrome
Gastrointestinal	Ascites, spontaneous bacterial peritonitis, bacterial translocation, ileus, poor nutrition, hypoalbuminemia
Neurologic	Encephalopathy, delirium, potential increased sensitivity to neuroleptic agents
Coagulation	Rebalanced hemostasis, thrombocytopenia, hypofibrinogenemia, potential hyperfibrinolysis

hepatic outflow, leading to graft congestion and poor function.[20,37] In the presence of hypotension not related to bleeding or resolving with judicious fluid resuscitation, the application of vasoconstrictor agents is required. There is little evidence on which to prefer one agent over another, although norepinephrine is often used. Terlipressin is commonly used in the preoperative setting for decompensated liver failure, and in the postoperative setting some evidence exists suggesting use may decrease ascitic drain output and the incidence of acute kidney injury; however, its routine use is not recommended.[38]

Although cardiac performance is generally preserved in patients undergoing liver transplantation, there are occasional instances where this may not hold true. Cirrhotic cardiomyopathy occurs to some extent in up to half of cirrhotic patients.[39,40] In contrast to traditional cardiomyopathies, patients with cirrhotic cardiomyopathy have normal cardiac function in terms of both output and contractility, but have evidence of blunted systolic contractile response to stressors and the presence of diastolic dysfunction at rest.[39] As liver transplantation is a major physiologic stressor, overt cardiac dysfunction may only become apparent during the perioperative period. The major implications for management in the postoperative period are to ensure normovolemia and prevent significant fluid shifts.[41] Additionally, prevention of electrolyte abnormalities and avoidance of other factors that may further depress cardiac function (e.g., hypothermia, severe acidosis) is required.[41] In the presence of an established low cardiac output state with a corresponding decrease in end-organ perfusion, the use of inotropic agents such as milrinone or dobutamine may be necessary.

As patients waitlisted for liver transplant are increasingly older and more comorbid, underlying cardiovascular disease has become more common.[42,43] Larger numbers of patients with nonalcoholic steatohepatitis cirrhosis and metabolic syndrome also make this scenario more common.[43,44] It is recognized that patients with established coronary artery disease undergoing liver transplant have poorer outcomes posttransplantation.[45,46] Correspondingly, an appropriate risk assessment and consideration for revascularization is required for those being evaluated for transplantation.[46] Recent studies have shown a higher rate of arrhythmic complications but a low rate of ischemic events.[47,48] The timing of recommencing antiplatelet agents is challenging and requires multidisciplinary review to ensure the maximal protection of existing stents is balanced against the risk of bleeding.

Patients undergoing transplantation for ALF often have additional cardiovascular challenges, with vasoplegic shock similar to that seen in severe sepsis being typical, especially for hyperacute presentations.[49] Massive hepatic necrosis releases inflammatory mediators, which persist in the circulation because of a lack of hepatic clearance.[16] This pattern may take days to resolve after successful liver transplant.

Respiratory

Respiratory complications are common after liver transplantation, with a reported incidence of over 50% depending on the definition and method of assessment.[50,51] The optimal timing of extubation remains unclear.[52–54] In the majority of liver transplants, prolonged mechanical

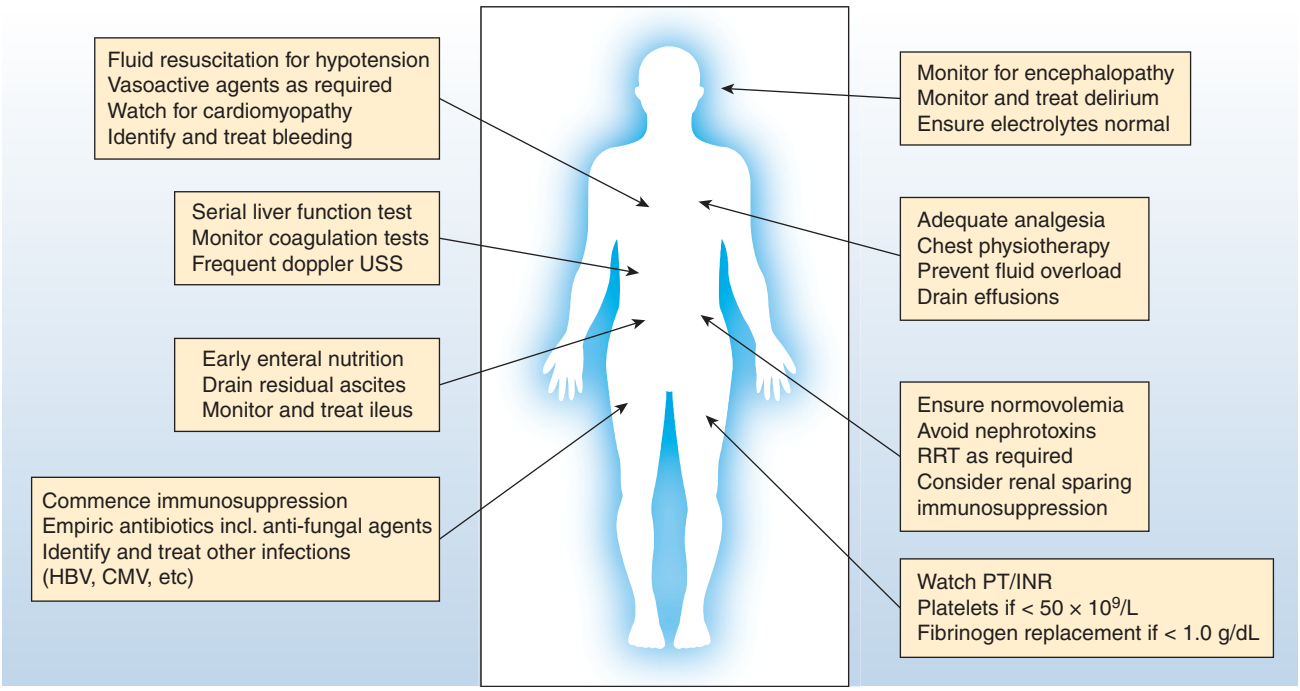

Fig. 146.1 Systematic approach to critical care after liver transplant. *CMV,* Cytomegalovirus; *HBV,* hepatitis B virus; *INR,* international normalized ratio; *PT,* prothrombin time; *RRT,* renal replacement therapy; *USS,* ultrasound.

ventilation is not required, and with the use of short-acting sedative and narcotic agents, immediate extubation in the operating room or postanesthetic recovery unit can sometimes occur. An early extubation approach is supported by evidence from the cardiac and thoracic surgical literature, suggesting no increased risk of complications and possible decreased ICU length of stay.[55] Conversely, the benefit of delayed extubation allows for ongoing hemodynamic stabilization, correction of hemostasis, assessment of early graft function, and optimization of analgesia before liberation from ventilation. Overall, the majority of liver transplant recipients can be extubated shortly after admission to the ICU.

In common with other major abdominal surgeries, the provision of appropriate analgesia, preemptive physiotherapy, and early mobilization may reduce the risk of pulmonary atelectasis and hospital-acquired pneumonia, thereby reducing ICU length of stay.[56] Common respiratory problems include preexisting cirrhotic complications such as pleural effusions/hydrothoraces and pulmonary edema/fluid overload caused by large volumes of intraoperative fluid administration. Hypoalbuminemia can exacerbate all the previously mentioned respiratory complications. Careful postoperative critical care management involves the achievement of gentle negative fluid balance, provision of noninvasive ventilation as required, and the consideration of the placement of intercostal catheters to drain symptomatic effusions.[57,58]

Overt postoperative respiratory failure, as defined as the requirement for reintubation or the need for mechanical ventilation for longer than 48 hours posttransplant, is associated with significant morbidity and mortality.[59] Risk factors include older age, elevated MELD score, operative bleeding, acute kidney injury, and preexisting respiratory compromise.[59] Acute lung injury/acute respiratory distress syndrome (ALI/ARDS) has a reported incidence of between 4% and 16% in posttransplantation and has been associated with increased morbidity and mortality.[60–62] Posttransplant ALI/ARDS is a multifactorial process occurring as a consequence of blood product administration, large-volume fluid shifts, hepatic ischemic/reperfusion injury, and preexisting hypoalbuminemia. The management of ALI/ARDS remains largely supportive, with a low tidal volume and open-lung–based ventilation strategy being the mainstays of therapy. The prevention of a positive fluid balance and treatment of any potential infective or mechanical contributions can also be beneficial. The optimal positive end-expiratory pressure (PEEP) in this setting is not known, as it is necessary to balance the need for adequate oxygenation for the new liver graft and the risk of higher levels of PEEP impeding hepatic outflow and compromising graft function. It is currently believed that hepatic venous outflow is not impaired by PEEP of up to 10 cm H_2O.[63]

Two unique cardiorespiratory complications of liver disease require special mention: hepatopulmonary syndrome (HPS) and portopulmonary hypertension (POPH).

HPS is diagnosed by the triad of hypoxemia, intrapulmonary vascular shunts as documented by echocardiography or lung contrast scans, and the presence of cirrhosis and/or portal hypertension.[64] The incidence has been reported to range between 4% and 47%, but may be affected by the choice of diagnostic technique and the high frequency of asymptomatic patients.[64] The disorder is believed to be related to intrapulmonary vasodilation and aberrant pulmonary angiogenesis secondary to increased NO production, resulting in arteriovenous shunting and systemic hypoxemia.[64] Liver transplant is the only definitive treatment for HPS. Postoperative management includes the avoidance of fluid overload in addition to usual postoperative pulmonary care.[57] Despite such measures posttransplant, some HPS patients may develop profound hypoxia. Management of patients in this setting revolves around strategies to address intrapulmonary shunting, such as the provision of 100% oxygen, or inhaled pulmonary vasodilators, such as epoprostenol or NO.[64] Intravenous methylene blue has been used successfully in a number of case reports.[65] In cases of refractory HPS, embolization of target pulmonary vessels can be considered along with venovenous extracorporeal membrane oxygenation support. However, given that it may take months for HPS to reverse, careful consideration with regard to duration of therapy is required. Even though many grafts tolerate moderate levels of hypoxia, there is the risk that in marginal or extended criteria grafts, refractory hypoxia may impair graft function, with refractory hypoxia in posttransplant HPS having a reported of mortality up to 50%.[66]

POPH is the presence of pulmonary hypertension in the setting of cirrhosis/portal hypertension and the absence of another contributing cause.[64] POPH is a rare condition with a reported incidence of less than 5% of all cirrhotic patients being worked up for transplantation.[67] The pathophysiology is believed to be pulmonary arterial vasoconstriction and endothelial proliferation caused by increased circulation of vasoactive mediators.[67] It is best diagnosed by echocardiography and confirmed with dedicated right heart catheter studies, with severity based on the mean pulmonary artery pressures (MPAPs).[67] Initial management of POPH involves confirming the diagnosis and excluding other causes of increased pulmonary pressures. Important exclusions include fluid overload and the presence of a hyperdynamic circulation, as they both increase the pulmonary vascular resistance in the absence of structural change. Subsequent management is based on reversing the structural changes that similarly occur with other forms pulmonary hypertension, with the use of endothelial antagonists, inhaled prostacyclin, and inhibitors of phosphodiesterase type 5.[64] The appropriateness of liver transplantation for patients with POPH is unclear, with previous studies suggesting near-universal mortality while undergoing liver transplant.[64] However, further understanding and treatment of POPH have demonstrated that select patients who are pulmonary vasodilator therapy responsive have acceptable outcomes provided MPAP remains lower than 45–50 mm Hg.[68] In patients undergoing liver transplant, pulmonary pressures should be monitored with a pulmonary artery catheter, and pulmonary hypertension therapy should be continued throughout the transplant period. Standard measures at optimizing the pulmonary vascular pressures and right heart function, such as maintaining optimal oxygen and carbon dioxide levels, and selective use of vasoactive agents such as noradrenaline, milrinone, and dobutamine should be applied.[69] It is less clear whether POPH resolves with successful liver transplant, with the results of a small series showing variable improvement in pulmonary hemodynamics and ability to be weaned off long-term POPH therapy.[70]

Renal System

Renal dysfunction is common throughout the perioperative period for liver transplant recipients. Acute kidney injury (AKI) occurs in up to 50% of patients before transplantation and is strongly associated with portal hypertension–mediated splanchnic vasodilation.[71] Management of AKI leading into transplantation predominately consists of treating underlying sepsis;, volume expansion with fluids such as concentrated albumin, a balanced crystalloid, or blood in the event of upper gastrointestinal bleeding; relief of large-volume ascites (with supplementation of concentrated albumin); and withdrawal of nephrotoxic agents such as furosemide and spironolactone. The early initiation of vasoconstrictor therapy—terlipressin or noradrenaline—has been shown to improve outcomes.[72] To date, there have been no randomized studies looking at the early (pretransplantation) initiation of renal replacement therapy (RRT) in liver transplant patients. Early initiation may be considered in those patients awaiting urgent transplant in order to allow early optimization of hyponatremia and prevention of further organ dysfunction secondary to fluid overload.

Renal dysfunction post–liver transplant has a reported incidence of 8%–64%[73,74] and is associated with increased graft failure, infectious complications, longer ICU length of stay, greater hospital costs, and higher mortality.[75,76] Posttransplant AKI is usually multifactorial, influenced by preoperative, intraoperative, and postoperative factors. Preoperative factors include prior renal function; severity of underlying liver disease; the presence of hepatorenal syndrome; and other medical risk factors such hypertension, diabetes, and hypercholesterolemia.[74] Intraoperative factors include duration of caval occlusion, postreperfusion syndrome, and blood loss.[74] Postoperatively, early allograft dysfunction, hypovolemia, sepsis, and direct toxic effects of calcineurin inhibitors (CNIs) are common factors.[74] Management of patients with AKI or at risk of posttransplant AKI consists of optimization of fluid balance with a preference for albumin solution, maintenance of organ perfusion, and avoidance of nephrotoxic agents, in particular CNIs.[77]

There is currently limited evidence to guide timing of initiating RRT in this population; however, it is likely that earlier institution will improve graft function and patient outcomes, particularly in the setting of cumulative positive fluid balance.[78] Given that renal impairment tends to improve as hepatic function is established in the early posttransplant period, the need for RRT is often brief.

Renal dysfunction in ALF is different than in those with chronic liver disease. Renal failure in ALF has an incidence of up to 70% and is almost never the result of hepatorenal syndrome.[79] Risk factors for AKI in ALF include paracetamol toxicity (direct toxic effect), older age, severity of multiorgan failure, and concurrent sepsis.[79] Management principles are similar to those applicable to AKI in the setting of severe septic shock. The role of RRT in ALF is evolving, with accumulating evidence for possible neuroprotective effects through the improved control of hyperammonemia from early initiation of continuous RRT (CRRT).[80,81] Most patients who undergo transplantation for ALF will continue to require CRRT in the immediate postoperative period, with the majority experiencing complete renal recovery in the long term.[79,82] For the small number who have delayed renal recovery, a transition to intermittent hemodialysis may be considered as they progress through the recovery phase of their illness.

Gastrointestinal System

A number of gastrointestinal issues affect management of the post–liver transplant patient. Despite improvements in surgical technique, surgical complications occasionally occur after liver transplantation. The most commonly encountered complications involve the biliary system, namely strictures, obstructions, and leaks; fluid collections such as bilomas or seromas; and bleeding or hematoma formation.[83,84] These complications are best detected by maintaining a high risk of suspicion in the setting of ongoing vasopressor requirement, anemia, new organ dysfunction (especially AKI), unexplained early allograft dysfunction, or new fever and sepsis. Imaging plays a key role in the diagnosis of these complications, and options include ultrasound, computed tomography, dedicated T-tube cholangiograms, or magnetic resonance cholangiopancreatography.[84,85] Management options need to be made in conjunction with the local expertise of the transplant surgical teams, with options including surgical revision, stenting, re-exploration, or radiologic drainage. Common to other forms of major abdominal surgery, ileus occurs frequently post–liver transplantation, with the identification and treatment of precipitating factors, provision of adequate analgesia, balanced fluid and electrolyte management, bowel rest, and decompression being the mainstay of management.[86] Prolonged ileus may necessitate changing to intravenous forms of CNIs or mycophenolate to achieve adequate immunosuppression. Early consultation with the transplant hepatologist and pharmacists is essential to guide management under such circumstances.

It is crucial that patients undergoing liver transplantation have an adequate nutritional assessment. Malnutrition and sarcopenia are frequent complications of cirrhosis, and adequate nutritional support is required to optimize recovery and prevent complications after transplantation.[87,88] Evidence from the wider critical care and surgical literature suggests that early enteral nutrition has significant benefits in preventing infective complications, postoperative ileus, and subsequently allowing optimal early graft function.[89] Recent consensus opinion suggests that the provision of energy of up 30–35 cal/kg/day, with protein 1.2–1.5 g/kg/day, is required.[90] Currently, there is no evidence to suggest that routine supplementation of enteral nutrition with parental nutrition confers additional benefit.[91] For patients who are unable to tolerate enteral nutrition because of prolonged ileus or surgical complications, it is appropriate to consider early parental nutrition; however, this decision needs to be balanced by the possible increase risk of infectious, cholestatic, and metabolic complications.[90] In the setting of ALF, ammonia levels should be monitored during commencement of enteral feeding to ensure that there is no associated rebound of ammonia to dangerously high levels.[90]

Coagulation System

Recent studies demonstrate that patients with both acute and chronic liver failure have evidence of rebalanced hemostasis.[92] In the postoperative period, careful monitoring of hemostatic parameters is required. Bleeding is a major complication, occurring in up to 20% of patients, and is associated with poor outcomes.[93] Risk factors for bleeding include severity of underlying liver disease, surgical technique, and AKI.[94] Hemostatic resuscitation of the bleeding liver transplant patient should be managed according to major guidelines and may be guided by point-of-care viscoelastic testing.[95] In the absence of major surgical bleeding, a restrictive transfusion approach may be beneficial, as the administration of blood products is associated with decreased graft and patient survival, with associated immune dysfunction a likely key factor.[95] The prothrombin time (PT)/international normalized ratio (INR) is a well-established parameter for assessing liver function, and serial monitoring can identify early graft dysfunction.[96] However, it has limited ability to accurately predict spontaneous bleeding risk, and in the absence of active hemorrhage, an abnormal INR should not usually be treated with coagulation factors.

Other aspects of the coagulation system can affect postoperative care. Multifactorial thrombocytopenia is common, and the transfusion of platelets may be required if there is evidence of ongoing blood loss or concerns regarding the safe removal of intravascular devices; a target aim of 30–50 $\times$ 10^9/L appears safe in this setting.[95,97] Hypofibrinogenemia can occur, particularly in the setting of early graft dysfunction, and replacement with cryoprecipitate or fibrinogen concentrate should occur and evidence of hyperfibrinolysis sought.[95,97] The decision on timing of commencement of venous thromboprophylaxis can be difficult, as many posttransplant patients may be hypercoagulable despite disordered hemostatic parameters.[98] The use of mechanical thromboprophylaxis is recommended until the patient is able to adequately mobilize. The ideal timing of pharmacologic thromboprophylaxis is unclear, and individualized decision making, depending on graft function and other organ failure, is required.[98]

Neurologic System

The incidence of neurologic complications after liver transplantation is up to 47%, with delirium, new-onset seizures, strokes, drug toxicity (in particular, CNI therapy), and prolonged hepatic encephalopathy all reported.[99] Consistent with other critically ill populations, delirium is

the most common neurologic complication and is associated with increased ICU length of stay and mortality.[100]

Management of delirium involves treating any precipitating factors such as sepsis, unnecessary medications, electrolyte disturbance, or organ dysfunction (in particular, renal, cardiac, or pulmonary). Nonpharmacologic methods such as reorientation, establishment of day-night cycles, early mobilization, and involvement of family members can be beneficial in select cases. However, in most cases pharmacologic therapy is required to ensure patient and staff safety—recent trials have shown that atypical antipsychotics may reduce the duration of delirium and should be first-line agents.[101] The centrally acting alpha-2 agonist dexmedetomidine decreases time to extubation but may be harmful in the setting of hemodynamic instability and prolonged use.[102]

Aside from delirium, liver transplant recipients have a much higher rate of neurologic complications than other solid organ transplants.[103] The reason may relate to overt or subtle neurotoxicity from chronic hyperammonemia.[103] Further research in this area is required. In ALF, cerebral edema and associated neurologic injury may occur during or after otherwise successful liver transplantation; therefore the provision of CRRT and other neuroprotective measures for a short period posttransplantation may be wise.

Immune System

The liver is a unique immunologic organ, playing key roles in immune surveillance and in the innate and adaptive immune responses.[104] In patients with ALF and ESLD, the loss of hepatic function results in the development of an immunocompromised state. Factors contributing to this include impaired immune surveillance caused by injury of the reticuloendothelial system, reduced activation and phagocytic ability of the innate immune system, and generalized systemic inflammation.[104] This combination of preexisting immune dysfunction coupled with the strong immune suppression required in the early posttransplant period places patients at high risk of infective complications. Most major centers use prophylactic broad-spectrum antibiotics and antifungal agents in this period, although the recommended duration is unclear.[105,106] Antimicrobial selection should be based on local resistance patterns and expert advice.

The provision of immunosuppression is crucial in the early transplant period; local regimens vary but commonly involve high-dose steroid therapy and CNI therapy (Table 146.2).[107] More recently, there is an increase in use of individualized regimens, including selective agents tailored to an individual patient's particular risk profile.[108] These regimens aim to minimize the risk of immunosuppression-related complications. Monitoring levels of immunosuppressive medications requires daily blood levels and close consultation with transplant hepatologists to ensure appropriate dose adjustment to avoid CNI toxicity in the early posttransplant period.

ASSESSMENT OF GRAFT FUNCTION

Monitoring and assessment of graft function are of fundamental importance in the early posttransplant period and are commonly undertaken through clinical assessment, measurement of biochemical and coagulation parameters, and results of imaging (Table 146.3). As the new graft is reperfused and begins to resume function, the patient's hemodynamics state usually stabilizes and postperfusion acidosis resolves. A persistent or increasing vasopressor requirement or worsening metabolic acidosis may be a sign of early graft dysfunction. Biochemical and coagulation values provide an excellent guide to early graft function. Hepatic transaminases (alanine transaminase [ALT] and aspartate transaminase [AST]) frequently rise early as the graft is reperfused and then trend downward over the following 24- to 48-hour period. A slowing of the transaminase downward trend or a sustained rise suggests new graft injury. Restoration of liver function leads to a reduction in the PT/INR as new coagulation factors are synthesized, and failure of this to occur warrants investigation. The use of Doppler ultrasound to assess hepatic vasculature can identify early complications in the hepatic artery and hepatic and portal veins and assist in the detection of bleeding complications and is now considered standard of care.[109,110] Hepatic artery thrombosis (HAT) is the most feared early vascular complication of liver transplantation and occurs in between 2% and 9% of patients.[111] Although many risk factors for HAT have been reported, both surgical and nonsurgical, the exact pathologic mechanism often remains unclear.[111,112] Treatment options include percutaneous thrombolysis, surgical re-exploration, and relisting for transplantation. Prophylactic aspirin therapy has been postulated to decrease the risk of HAT, but convincing evidence is lacking.[113]

The increased prevalence in the use of marginal or extended criteria grafts and patients with significant frailty has amplified the importance of vigilance for identifying poor graft function. *Early allograft dysfunction (EAD)* is a term used to describe an early poorly functioning graft; however, there is currently no consensus definition of

TABLE 146.2 List of Commonly Used Immunosuppressive Agents After Liver Transplantation

Class	Agents	Use	Common Side Effects
Corticosteroids	Methylprednisolone, prednisolone	Induction of immune suppression Acute rejection management	Short term: delirium, hyperglycemia Long term: metabolic syndrome, obesity, osteoporosis
Calcineurin inhibitors	Tacrolimus, cyclosporin	Maintenance of immunosuppression	Renal dysfunction, hypertension, neurotoxicity
Antiproliferative	Mycophenolate mofetil, azathioprine	Maintenance of immunosuppression, Acute rejection management	Nausea, vomiting, diarrhea, bone marrow suppression
mTORi	Sirolimus, everolimus	Maintenance of immunosuppression, Acute rejection management	Hyperlipidemia, oral ulcers, delayed surgical wound healing, early use associated with HAT
Interleukin-2 monoclonal antibody	Basiliximab	Induction of immunosuppression, Use in renal-sparing regimens	Infective complications
T-cell–depleting antibody (monoclonal, polyclonal)	Alemtuzumab, ATG	Induction of immunosuppression, Steroid-resistant rejection	Leucopenia, transfusion reactions, increased infective risk, especially HCV recurrence and CMV reactivation

ATG, Antithymocyte globulin; *CMV,* cytomegalovirus; *HAT,* hepatic artery thrombosis; *HCV,* hepatitis C virus; *mTORi,* mammalian target of rapamycin inhibitors.

TABLE 146.3 Common Postoperative Investigations and Significance

Investigation	Significance
Liver function tests	Declining transaminase indicates good graft health, delayed cholestatic pattern can be benign or sign of graft rejection
Coagulation studies	Normalization of PT/INR strong indicator of underlying graft function
Arterial blood gas	Declining lactate and resolution of acidosis indicate good early graft function
Doppler ultrasound	Assess patency of hepatic vessels, in particular hepatic artery; can also assess resistance across graft, suggesting poor graft function

INR, International normalized ratio; *PT,* prothrombin time.

BOX 146.1 Risk Factors for Ischemic Reperfusion Injury

Donor and recipient age
Illness severity at time of transplantation
Donor warm ischemic time
Donor cold ischemic time
Donor hepatic steatosis >30%
Altered coagulation profile

EAD.[114] Graft dysfunction may be identified by increasing transaminase levels, serum bilirubin concentration, PT/INR, and ammonia levels.[114] EAD may be viewed as an extreme endpoint of ischemic reperfusion injury (IRI), as many of the risk factors for EAD are influenced by the degree of IRI.[115] IRI occurs after successful implantation, when the liver graft is exposed to oxygenated blood, and results in free radical production, endothelial cell damage, and graft dysfunction. Currently, management of established EAD/IRI is largely supportive, with the identification of potential contributing factors such as concomitant sepsis, organ failure—in particular renal, and maintenance of electrolyte and fluid balance (Box 146.1). Recent research has explored the potential to decrease the risk of IRI and EAD by the use of liver perfusion devices to decrease the impact of risk factors.[116] Evidence thus far has demonstrated lower peak transaminase rises, decreased biliary complications, and lower incidences of EAD and primary nonfunction; however, these trials are small in number, and we await the outcomes in larger, more diverse populations.[116] Although widely used, there is no evidence that the use of prostacyclin or such agents improves patient or graft outcome.[117]

CONCLUSIONS

Liver transplantation has progressed over recent years with significant improvements in all aspects of care. Along with this progress, long-term survival has also continued to improve. However, patients undergoing transplantation continue to have multiorgan dysfunction both before and after liver transplantation. ICUs play a key role in the provision of life-sustaining therapies preoperatively—in particular the management of those with ALF. Postoperatively, critical care continues to provide specialized high-quality, multiorgan support that is required for optimal outcomes in this complex surgical population.

KEY POINTS

- Post–liver transplant outcomes continue to improve with high-quality ICU care.
- Nonhepatic organ failures influence postoperative outcomes, most commonly cardiac, respiratory, and renal issues.
- A systematic approach is required for optimizing care.
- Multimodal assessment of graft function is crucial to early detection of complications.
- Multidisciplinary decision making is essential throughout the period around transplantation.

References for this chapter can be found at expertconsult.com.

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Intestinal and Multivisceral Transplantation: The Ultimate Treatment for Intestinal Failure

Arpit Amin, Vikram K. Raghu, George V. Mazariegos, and Geoffrey J. Bond

INTRODUCTION

Intestinal and multivisceral transplantation remains a dynamic process, moved forward by advances in the multidisciplinary care of intestinal failure, surgical techniques, innovative immunosuppressive strategies, and an improved understanding of intestinal transplantation immunology. More recently, great strides have been made in the medical and surgical management of patients with intestinal failure, which has resulted in a decrease in the number of patients added to the intestinal transplant waiting list and subsequently undergoing intestinal transplantation (Figs. 147.1 and 147.2).[1,2] Multidisciplinary dedicated intestinal rehabilitation and transplantation units have become established at high-volume centers, where patients are managed with an available armamentarium of medical therapy, intestinal rehabilitation surgeries, and intestinal transplantation. The goal of these multidisciplinary dedicated intestinal rehabilitation and transplantation units is that patients likely to require transplantation will be listed, followed, and transplanted at the optimum time after weighing the risks and benefits and complications of each of these modalities (medical therapy, intestinal rehabilitation surgery, intestinal transplantation).

In the United States alone, 1204 patients were alive with a functioning intestinal allograft as of June 2018.[1] Immunosuppression for intestinal and multivisceral transplantation commonly involves some form of perioperative (antibody) induction protocol, although many centers now tailor induction and maintenance protocols to individualize strategies based on each patient's situation, often by employing immunologic testing (crossmatching and donor-specific antibody testing) to help determine optimum strategies.

The future of intestinal transplantation depends on the prevention and treatment of chronic rejection, which disproportionately affects isolated intestinal allografts. Chronic rejection continues to be a fundamental barrier to achieving successful long-term outcomes and is the ongoing subject of rigorous investigation. Long-term data on nutritional outcomes and transplantation morbidity help further determine the optimal timing and role of intestinal and multivisceral transplantation in patients with intestinal failure.

DEFINITION AND MANAGEMENT OF INTESTINAL FAILURE

As per the most recently updated guidelines published by the European Society of Clinical Nutrition and Metabolism (ESPEN) in 2018, intestinal failure is defined as "the reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that intravenous supplementation is required to maintain health and/or growth."[3,4] Patients with intestinal failure are initially managed by administration of parenteral nutrition (PN) through central venous access.

The duration of intestinal failure is variable and, in certain patients, unpredictable, from shortterm to lifelong, and depends largely on the adaptation capacity of the remaining viable intestine, which is dependent on variable factors such as patient age and underlying diagnosis. As such, intestinal failure can be functionally classified based on ESPEN guidelines published in 2015 into three categories:

1. Type 1—acute intestinal failure, short-term, self-limiting
2. Type 2—prolonged acute intestinal failure requiring PN over periods of weeks to months
3. Type 3—chronic intestinal failure requiring PN over months to years

Furthermore, 2015 ESPEN guidelines further help conceptualize intestinal failure by classifying it into five major pathophysiologic classifications: (1) short bowel syndrome (reduced absorptive mucosal surface), (2) intestinal fistula (bypass of large areas of absorptive mucosal surface), (3) intestinal dysmotility (intolerance to oral/enteral nutrition because of nonmechanical intestinal obstruction), (4) mechanical obstruction, and (5) extensive small bowel mucosal disease (inefficient absorptive and/or nutrient-losing mucosal surface).

Optimal management of patients with intestinal failure is achieved after a detailed multidisciplinary evaluation. Obtaining a comprehensive history is critical and must include birth details (such as prematurity) and disease history; complicating comorbid medical history; past surgical procedures; infections; number and location of previous central venous lines; presence of central venous thrombosis; a detailed nutrition history, including duration of PN, details of PN prescriptions, and maximal enteral feeding tolerance and its trajectory (still advancing or static); medication history; and frequency/volume of stools. A careful history and physical examination performed by the intestinal rehabilitation team is critical to the process of achieving a complete pretransplant work-up. Further investigations include blood tests, upper gastrointestinal (GI) contrast study with small bowel follow-through; contrast enema if indicated; abdominal sonogram to assess for hepatosplenomegaly; and an examination of central venous anatomy either by ultrasound, computed tomography (CT) or magnetic resonance (MR) venography, or traditional venography. Occasionally, endoscopy with small intestinal aspiration for quantitative microbial culture and mucosal biopsy is recommended. In equivocal cases, liver biopsy is recommended if there is evidence of liver dysfunction or portal hypertension to determine if concomitant liver-containing transplantation is required.

Management of patients with intestinal failure focuses on optimization of gut adaptation and recovery of intestinal function to achieve enteral autonomy. With improved management of PN and minimization of complications, longer durations of PN can be achieved to allow for gut adaptation.[5] Clinical trials have shown favorable outcomes with the use of the glucagon-like peptide analogue (GLP-2) teduglutide in increasing intestinal adaptation and increasing the likelihood

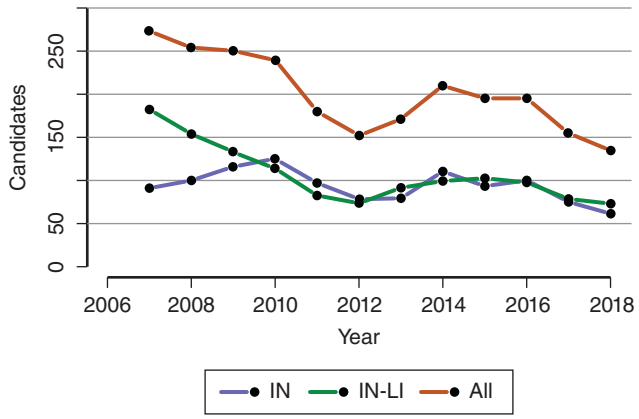

Fig. 147.1 New candidates added to the intestine transplant waiting list (2007-2018). *IN,* Intestine without liver; *IN-LI,* intestine with liver. (Adapted from Smith JM, Weaver T, Skeans MA, et al. OPTN/SRTR 2018 Annual Data Report: Intestine. *Am J Transplant.* 2020;20[Suppl s1]: 300–339.)

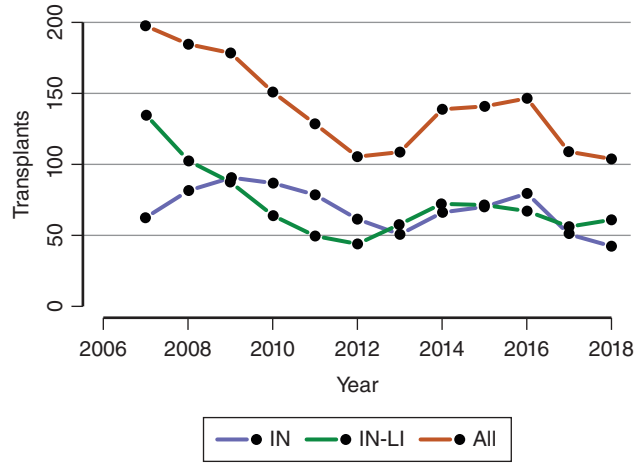

Fig. 147.2 Number of intestinal transplants performed per year (2007–2018), including adult and pediatric, retransplant, and multiorgan recipients. *IN,* Intestine without liver; *IN-LI,* intestine with liver. (Adapted from Smith JM, Weaver T, Skeans MA, et al. OPTN/SRTR 2018 Annual Data Report: Intestine. *Am J Transplant.* 2020;20[Suppl s1]:300–339.)

of weaning off PN in short bowel syndrome patients. As a result, the Food and Drug Administration (FDA) has approved the use of teduglutide for the management of patients with short bowel syndrome over the last decade.[6,7] A small portion of patients have shown excellent response with the ability to greatly reduce or even completely eliminate parenteral support. However, the high cost of the medication, estimated at >$400,000 per year per patient, limits its general use, especially without guidance on which patients will achieve enteral autonomy with therapy.

Simultaneously, progress has been made in intestinal rehabilitative surgical therapies, including autologous reconstructive surgeries (repairing enterocutaneous fistulae, restoring enteral continuity with primary reconstruction or use of alimentary conduits) and bowel-lengthening procedures such as the longitudinal lengthening procedure described by Bianchi and the serial transverse enteroplasty (STEP).[8–10] A recent study focusing on outcomes of the full spectrum of intestinal rehabilitative surgeries and bowel-lengthening procedures on 500 consecutive patients with intestinal failure has shown remarkable results, with restored nutritional autonomy in 82% of patients with a 5-year survival of 70%.[11]

Alternatively, if gut dysfunction is considered irreversible, management of these patients concentrates on maintaining optimal growth in children and nutritional repletion in adults to prepare them for likely intestinal transplantation. Recently, there has been a shift in timing of intestinal transplantation, focused more on the individualized risks and complications of PN versus intestinal transplantation. In other words, if patients, especially children where there still may be hope for further adaptation, are stable on PN with no significant complications, then deferring transplant is quite reasonable.

Small bowel bacterial overgrowth (SBBO) is a common clinical problem in patients with intestinal failure and is treated with a variety of antibiotic regimens. To date, no comparative studies are available to enable an evidence-based approach to treat SBBO. The use of metronidazole for anaerobic overgrowth, combined with trimethoprim and sulfamethoxazole or an oral aminoglycoside for gram-negative organisms, is a common theme. Metronidazole monotherapy is used if the dominant symptoms suggest predominantly anaerobic overgrowth (such as bloating, increasing diarrhea, and D-lactic acidemia). The extreme sensitivity of anaerobes to oxygen makes the use of small bowel aspirate cultures relatively unreliable as a means of microbial surveillance or indication to treat SBBO. Probiotics such as *Lactobacillus* and *Saccharomyces* have been used in an attempt to limit SBBO. Given the absence of randomized evidence to support the efficacy of probiotics, coupled with reasonable concerns about impurities and possible contamination with other bacteria (e.g., *Leuconostoc*), the use of probiotics is controversial and mostly discouraged in patients with central venous catheter access and intestinal failure and especially after transplantation because of increased immune suppression.

Parenteral nutrition–associated liver disease (PNALD), also referred to as *intestinal failure–associated liver disease* (IFALD), remains a critical problem in this patient population, affecting infants disproportionately. The 1-year mortality of patients with PNALD exceeds 20% in the absence of PN weaning or transplantation.[12] Although not always feasible, the best strategy to prevent and treat PNALD involves a commitment to the advancement of enteral nutrition. Despite a conscientious approach to PN therapy, many children and adults still develop cholestasis relatively early in their clinical course. Prevention and timely treatment of infection, minimizing SBBO, preventing overfeeding with dextrose, providing adequate amino acids, cycling PN, or providing PN-free days when possible are probably important measures to slow the progression of PNALD.[13] Stasis of bile in the nonstimulated biliary system and gallbladder can lead to sludge buildup and cholelithiasis. In the authors' experience, cholecystectomy may be beneficial to minimize the risks of developing biliary obstructive episodes and pancreatitis and should be considered early in any operative course as part of a combined procedure. Cholecystectomy on its own is rarely done, as it seldom improves liver function and is not indicated for PNALD alone. Bowel reconnection, even in patients with very short guts, may relieve some of the high pressure in the upper GI tract and issues of reflux cholangitis, which may allow for long-term improvements in liver function.

Rates of PNALD have significantly decreased with novel methods to reduce phytosterol exposure from parenteral lipid emulsions through lipid minimization protocols with the reduction of traditional soybased lipid solutions and even their eventual removal by substituting with Omegaven (a fish oil–based, intravenous [IV] lipid solution rich in omega-3 fatty acids). Omegaven has recently been FDA approved (as of July 2018) for use in neonatal and pediatric patients suffering from PNALD.[14] Another option in patients with PNALD is the use of a mixed oil lipid-based emulsion such as SMOF (soybean oil, medium-chain triglycerides, olive oil, fish oil) lipid, which is currently approved for use in adults in the United States with an ongoing pediatric trial. SMOF lipid may offer another alternative in pediatric patients with PNALD

who demonstrate poor weight gain or develop essential fatty acid deficiencies while on fish oil–based emulsions.[14,15] Although biochemical improvement in liver disease has been shown with these alternative lipid formulations, it is unclear whether they actually alter histologic progression of liver disease.

In addition to PNALD, patients on long-term PN are at risk of developing metabolic bone disease (MBD). Associated with an insidious onset of bone pain that can become quite severe, patients with MBD will present with normal serum calcium, phosphorus, vitamin D, and parathyroid hormone, but with hypercalciuria. Nontraumatic spinal and rib fractures have been reported in these patients. To optimize bone maintenance in patients on PN, it is important to include calcium in parenteral formulations, prevent metabolic acidosis, and minimize aluminum contamination. Symptoms of MBD tend to resolve only after stopping PN.

Many intestinal transplant recipients will require intensive care unit (ICU) management during the pretransplant period, although the number of patients being transplanted from home (outside of a hospital setting) has increased with improved medical management and resulted in improved outcomes in this subset of patients. Sepsis and GI hemorrhage are common reasons for ICU admission in patients with intestinal failure. Blood products, though necessary in the resuscitation of GI hemorrhage, should be used judiciously in the absence of acute bleeding. Pretransplant exposure to blood products, particularly platelets, can predispose intestinal transplant recipients to developing antibodies and can place them at a higher risk of developing antibody-mediated rejection after transplantation. Leukoreduced blood products may be preferable in patients awaiting transplant.

Central line–associated bloodstream infections (CLABSIs) unfortunately are common in PN-dependent patients. All attempts should be made to avoid this event, with fastidious central line care at the core of the matter. Centers have employed central line care bundles to aid in sterile central line care at home. Lock therapy has played an important role in further reducing the incidence of CLABSI with ethanol, taurolidine, and sodium EDTA locks all showing various degrees of effectiveness.[16] One of the determining factors to move forward with transplantation is loss of venous access. Hence, although infection (especially fungal and life-threatening gram-negative infections) may necessitate removal of a tunneled central venous catheter, all attempts at salvaging the line, or at least the venous site, should be considered. Smaller pediatric patients and patients with a history of thrombosis may have limited venous access, necessitating preservation and treatment through an infected line. Percutaneous lines should be placed with caution in these patients, as great vessels may no longer be patent, and the trauma to the remaining vessels may have serious consequences. Many surgeons, anesthesiologists, and intensivists now place central lines under ultrasound guidance, although the more difficult and chronic-issue lines are best served in interventional radiology, with their vast cadre of specialized techniques. Ultrasound evaluation of deep veins to assess for patency is notoriously variable and often unreliable, and in difficult or concerning cases venography remains the gold standard. Many centers now use cross-sectional imaging through MR or CT venography in place of traditional fluoroscopic venography. Mapping should be considered before excessive loss of venous access occurs.

Nutritionally deplete patients are relatively immune suppressed and prone to severe community-acquired infections. Pediatric patients with intestinal failure and IFALD are at increased risk of respiratory failure even with common viral infections. Because children have a compliant chest wall, increased abdominal girth creates a mechanical disadvantage even during normal tidal volume breathing. In the setting of pulmonary infection, volume overload, or decreased cardiac output, the work of breathing can lead to fatigue.

Neurodevelopmental outcomes of children with intestinal failure have been understudied. Conflicting evidence exists regarding neurodevelopmental outcomes, with some reports of gross motor and cognitive deficits identified within the first few years of life.[17]

INDICATIONS FOR TRANSPLANT

The goals of the transplant team are to determine whether the patient may benefit from transplantation, assess alternatives to transplant, evaluate any contraindications to transplantation, and provide education to the patient and caregivers about the complex process of undergoing transplantation. After evaluation by the multidisciplinary team and open and frank discussion among all the team members, the usual result is one of three choices: (1) the patient may be followed closely as an intestinal care patient and listing status deferred depending on progress; (2) the patient may be listed as a status 2 recipient to accrue time on the list while awaiting possible medical improvement or bowel adaptation but realizing that transplantation is still quite likely; or (3) the patient may be listed as a status 1 intestinal recipient if the patient has met criteria for complications of irreversible intestinal failure, or as a liver intestine recipient if the patient is deemed to have irreversible intestinal failure and associated irreversible significant liver dysfunction for immediate consideration where criteria make transplantation inevitable.

In October 2000, the Centers for Medicare and Medicaid Services approved intestinal, combined liver-intestine, and multivisceral transplantation as a standard of care for patients with irreversible intestinal failure who could no longer be maintained with PN. As experience with intestinal rehabilitation and transplantation has increased over the last two decades, there has been debate about updating the original guidelines published in 2001 about indications of intestinal transplants. As a result, a working group of worldwide experts on intestinal failure and transplantation was assembled at the XIV International Small Bowel Transplant Symposium in 2015. Based on this deliberation, a recent consensus statement about updated indications of intestinal transplantation was published in 2019.[18] Most notably, extreme short bowel and transplantation for quality of life are absent from the revised indications, largely because of the advances in intestinal rehabilitation and resultant improvements in quality of life on PN. Based on these updated 2019 guidelines, indications for intestinal transplantation in the current era can be summarized as follows:

1. Evidence of advanced or progressive IFALD defined as either (a) hyperbilirubinemia >4.5 mg/dL that persists for more than 2 months despite IV lipid modification strategies or (b) any combination of elevated serum bilirubin, reduced synthetic function (low albumin or elevated international normalized ratio [INR]), and laboratory indications of portal hypertension and hypersplenism (especially low platelets) persisting for more than 1 month in the absence of a confounding infectious event(s).
2. Progressive loss of central venous access, typically defined by loss of at least two upper body central venous sites (left subclavian, left internal jugular, right subclavian, or right internal jugular) or occlusion of a brachiocephalic vein in children. In adults, this criterion should be evaluated on a case-by-case basis.
3. Life-threatening morbidity in the setting of indefinite PN dependence of either anatomic or functional etiology, as suggested by (a) in children, two admissions to the ICU (after initial recovery from the event resulting in intestinal failure) because of cardiorespiratory failure (mechanical ventilation or inotrope support) resulting from sepsis or other complications related to intestinal failure and (b) in adults, on a case-by-case basis.
4. Invasive intraabdominal desmoids in adolescents and adults.

TABLE 147.1 Indications for Intestinal and Multivisceral Transplantation

Pediatric Patients	Adult Patients
Volvulus	Superior mesenteric artery thrombosis
Gastroschisis	Crohn disease/irritable bowel disease (IBD)
Necrotizing enterocolitis	Desmoid tumor
Pseudo-obstruction	Volvulus
Intestinal atresia	Trauma
Microvillous inclusion disease	Familial polyposis
Hirschsprung disease	Budd-Chiari disease
Trauma	Intestinal adhesions
	Pseudo-obstruction
	Radiation enteritis

5. Acute diffuse intestinal infarction with hepatic failure.
6. Failure of first intestinal transplant.

Owing to the particularly high morbidity and mortality of children with IFALD, increasing efforts have been made by the pediatric medical community to optimize timing of referral of these patients to specialized intestine failure rehabilitation centers and transplant centers to improve overall outcomes. In addition to the earlier criteria for intestinal transplantation, a recent expert consensus panel recommended the following patients be evaluated for intestinal transplant: (1) children with massive small bowel resection, (2) continuing prognostic or diagnostic uncertainty, (3) microvillous inclusion disease or intestinal epithelial dysplasia, and (4) the request of the patient or family.[19] This initiative, to a large extent, has been relatively successful in breaking down previously held prejudices and allowed for prompt and, at times, very early evaluation. This in turn has allowed for more coordinated expert multidisciplinary management of these patients. With fewer patients now heading into liver failure with improved preservation of the liver, it gives the medical and surgical teams more time to let the native bowel adapt, so that more patients, even after 5 or more years of PN therapy, are eventually able to wean off of PN who previously would never have been given this chance.

The initial underlying pathophysiologic disorders leading to intestinal failure and subsequently intestinal transplantation in children and adults are summarized in Table 147.1. Based on data from the Intestine Transplant Registry published in 2015, short gut syndrome is the most common pathophysiologic mechanism responsible for intestinal failure requiring intestinal transplantation in children and adults.[2] The relative distribution of various pathophysiologic indications leading to intestinal failure and subsequently to intestinal transplantation in children and adults is summarized in Fig. 147.3.

Transplantation is unlike any other surgical procedure in that it is rarely an isolated event, unlike general surgical procedures, and has significant short- and long-term medical and surgical issues that need to be considered. Nowadays, as the overall management of PN improves, the indication and timing of transplantation become a balancing act, trying to weigh the risks and complications of PN versus the potential short- and long-term risks of intestinal transplant.

EVALUATION FOR TRANSPLANT

For both children and adults, the evaluation of intestinal and multivisceral candidates usually begins as an inpatient process because of the complexity of the case and the need for many different services to see the patients and investigations that may be required. Most intestinal failure units use multidisciplinary teams that assess patients during evaluations. This comprises the GI team, other medical teams as indicated (cardiac, renal, genetic, immunology, pulmonology, etc.); general surgery (especially pediatric surgery); transplantation; and many allied services including psychology, social work, pharmacy, and others as indicated in each case. Transplant teaching is a vital component, as is determining fiscal ability and supportive structures for potential recipients. Each team provides recommendations, and, in particular, the GI team may make recommendations with the PN and IV fluids and medications that may be quite beneficial to the patient and the referring team. At times, especially in a multidisciplinary center with both good pediatric surgical and transplant skills, these patients may undergo surgical exploration and attempts at reconstruction and/or bowel-lengthening procedures before transplantation. These are done with an attempt to either avoid transplantation, or at least minimize the need for PN and concomitant liver disease and delay the need for transplantation, or to make the conditions at transplant better (i.e., obtain colonic growth and health in previously disconnected patients or resecting enteric fistulae/intraabdominal abscesses that may be contributing to sepsis). Having a surgeon well versed in medical management strategies, able to operate as a general surgeon to try to help restore enteral

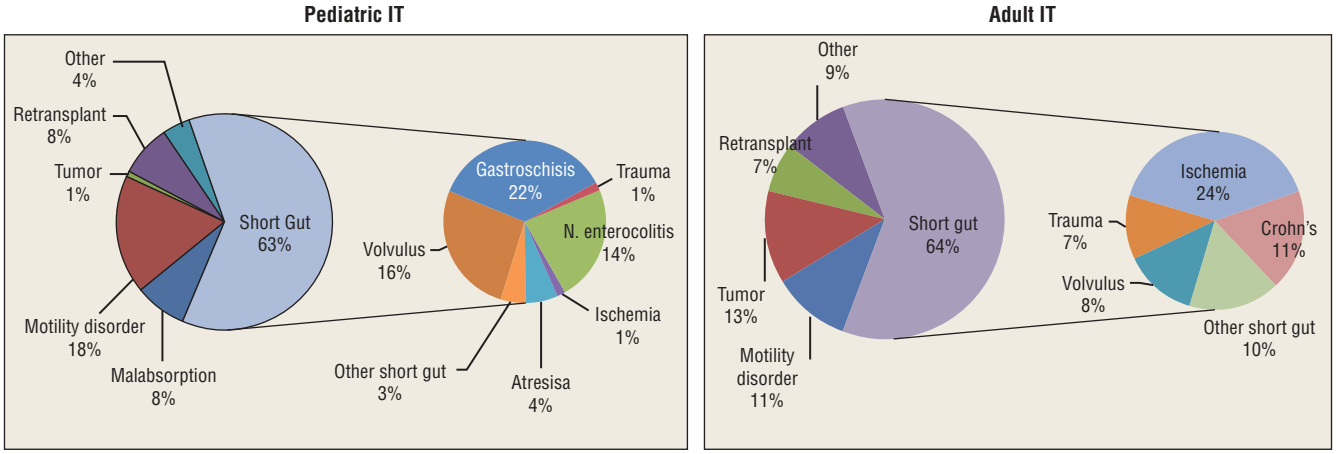

Fig. 147.3 Indications of intestinal transplantation in children and adults. (Adapted from Grant D, Abu-Elmagd K, Mazariegos G, et al. Intestinal Transplant Registry report: Global activity and trends. *Am J Transplant.* 2015;15[1]:210–219. doi: 10.1111/ajt.12979. Epub 2014 Dec 1.)

autonomy by surgical means, and be able to set the patient up for transplant is advantageous for both the patient and intestinal failure unit, allowing for more aggressive surgical interventions to try to avoid or delay transplantation.

Determining which type of allograft to use in patients with intestinal failure involves a comprehensive evaluation of the function and anatomy of the remaining bowel along with other abdominal organs. Intestinal failure patients are considered candidates for isolated intestinal transplant (with or without colon), combined liver and intestine transplant, multivisceral transplant (including liver, stomach, duodenum, pancreas, and small bowel with or without colon), or modified multivisceral transplant that excludes the liver. There has been ongoing debate in the transplant community regarding the previously mentioned nomenclature; however, from a practical and immunologic point of view, the major differentiation is the inclusion of the allograft liver as part of the transplant bloc. Whether to perform simultaneous hepatic replacement remains a challenging decision even to experienced transplant surgeons, particularly for patients with borderline liver dysfunction and a biopsy that shows fibrosis (Ishak level 3–4 and above) and some degree of synthetic dysfunction suggestive of portal hypertension. Nevertheless, it must be realized that the classic symptoms and signs of impending liver failure may not be the same in patients with limited or no intestine, and the use of Omegaven or SMOF may normalize the bilirubin but not affect fibrosis. This also affects the Model of End-Stage Liver Disease (MELD) and Pediatric End-Stage Liver Disease (PELD) score in these potential recipients; hence the essential need for "supplemental" points to be added to their total when the intestine is added to the United Network for Organ Sharing (UNOS) liver transplant listing. This has been allowed in the pediatric population for some time now but remains a vexed issue in the adult population.

The key factors in determining whether to perform liver transplant in patients with intestinal failure are the extent of portal hypertension and the severity of parenchymal liver disease. In general, patients with mild portal hypertension should be cautiously considered for isolated intestinal transplant. Under these circumstances, it is mostly recommended that venous outflow from the intestinal allograft bypass the portal circulation and be drained to the recipient systemic circulation through the inferior vena cava. This is especially relevant as there has been no documented proof that portal drainage is more beneficial or that relative portal and mesenteric hypertension may have deleterious effects on intestinal allograft function. The other predicament is the patient with marginal intestinal length who may, under ideal circumstances and more time, be able to adapt and come off of PN but the liver has undergone such considerable damage that it needs to be replaced. In this circumstance, liver transplantation alone in the face of short gut syndrome can and has been done but is fraught with potential dramatic consequences and the potential need for liver and intestine retransplantation if it is not successful.

TRANSPLANTATION PROCEDURES

Brief descriptions of recipient operations are provided here. The multivisceral donor procurement operation has previously been well described.[20] It is important to note that to a large extent, the future course after transplant is significantly determined by the quality of the donor and success of the donor recovery and back-table preparation. The intestine is perhaps the most sensitive donor organ and prone to ischemic events either by nature of the cause of death or because of pharmacologic agents (vasopressors) that are used to support the donor leading up to and after neurologic determination of death. It is thought that damage to the bowel sets up an inflammatory cascade that in turn makes the organ more immunogenic, or at least more susceptible to a rejection episode once it is reperfused in the recipient. Hence, the recipient surgeon is extremely judicious in the selection of a suitable donor and the number of acceptable donors is restricted. Other factors that play into this decision include blood group (generally identical), size-matching issues because of restricted abdominal domain (reduced grafts have been shown to have short- and long-term issues), and some potential crossmatch issues (especially in retransplant patients). Because of stringent donor selection criteria, the intestinal allograft is one of the more infrequently recovered allografts from available donor pool.[21]

Isolated Intestinal Transplant

For isolated intestinal transplants (Fig. 147.4), the donor intestinal graft (jejunum and ileum) is procured along with donor vascular conduits, including an artery (iliac and/or carotid) and a vein (iliac, occasionally jugular). The donor superior mesenteric vessels are occasionally anastomosed directly to the recipient superior mesenteric artery and vein if adequate length is achieved. More commonly, interposition vascular conduits are anastomosed to the recipient infrarenal aorta and recipient superior mesenteric vein (portal drainage) or inferior vena cava (systemic drainage) to provide sufficient length and proper orientation for the allograft.

The intestinal reconstruction involves a proximal duodenojejunostomy or jejunojejunostomy, depending on individual recipient considerations of remnant bowel viability and anatomy. The distal end of the intestinal allograft may be used as a permanent end ileostomy if the recipient has no remaining viable colon or may be anastomosed to the remnant colon, leaving a short portion of allograft distal to the enterocolic anastomosis to bring out as a temporary end ileostomy (Bishop-Koop ileostomy) that allows access to the bowel for endoscopic surveillance and mucosal biopsies.

Colonic transplantation with the small bowel has been used more frequently, especially in situations where the native colon is very short or nonfunctional (such as Hirschsprung disease or pseudo-obstruction). In this case, a loop ileostomy is formed so that the small bowel can be biopsied and the colon normally brought out as an end colostomy, or if anastomosed to the remaining colon, a loop allograft colostomy may be

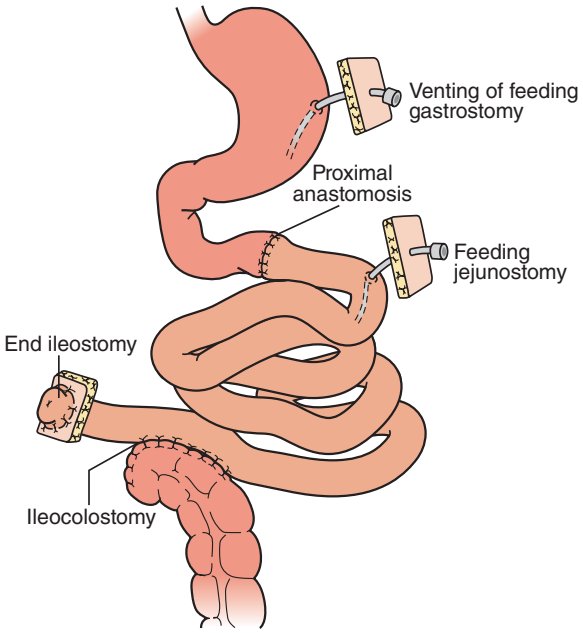

Fig. 147.4 Isolated intestinal transplant.

formed as well. Inclusion of colonic graft with small bowel graft has been shown in a recent study to provide improved postoperative renal protection along with increasing rate of interval ileostomy reversal in intestinal transplant recipients.[22]

In patients with gastric dysmotility, although a stomach-inclusive allograft may be ideal, because of donor availability (size and/or anatomic vascular aberrations), it may not be recoverable; hence a gastrojejunostomy may also need to be performed as an alternative to drain the stomach. Single or multiple feeding tubes (gastrostomy tube, jejunostomy tube, and combined gastrojejunostomy tube) may be placed based on multiple considerations, including recipient pretransplant oral intake capacity and dysmotility issues.

Combined Small Bowel and Liver Transplant

For combined small bowel and liver transplants (Fig. 147.5), the recipient hepatectomy is routinely performed with preservation of the native retrohepatic inferior vena cava. The recipient foregut, including stomach, native pancreas, and proximal duodenum, is also preserved and its venous outflow maintained with a permanent end-to-side portocaval shunt. The composite donor allograft includes the primary organs (liver and small bowel) and the donor duodenum and pancreas, allowing for maintenance of donor hepatobiliary continuity. Arterial inflow to the composite donor allograft is achieved using an arterial interposition conduit from the recipient infrarenal aorta to the reconstructed donor aorta placed onto the Carrel patch of donor celiac artery and superior mesenteric artery. Allograft venous outflow via the suprahepatic inferior vena cava commonly involves the well-described "piggyback" technique, anastomosing the donor suprahepatic inferior vena cava/hepatic veins cuff to the confluence of the recipient hepatic veins and cava. Occasionally, a "standard" bicaval anastomosis is performed. Intestinal reconstruction is performed in a similar fashion to an isolated intestinal transplant, mostly with the upper anastomosis being a jejunojejunostomy. Feeding tubes are placed as indicated.

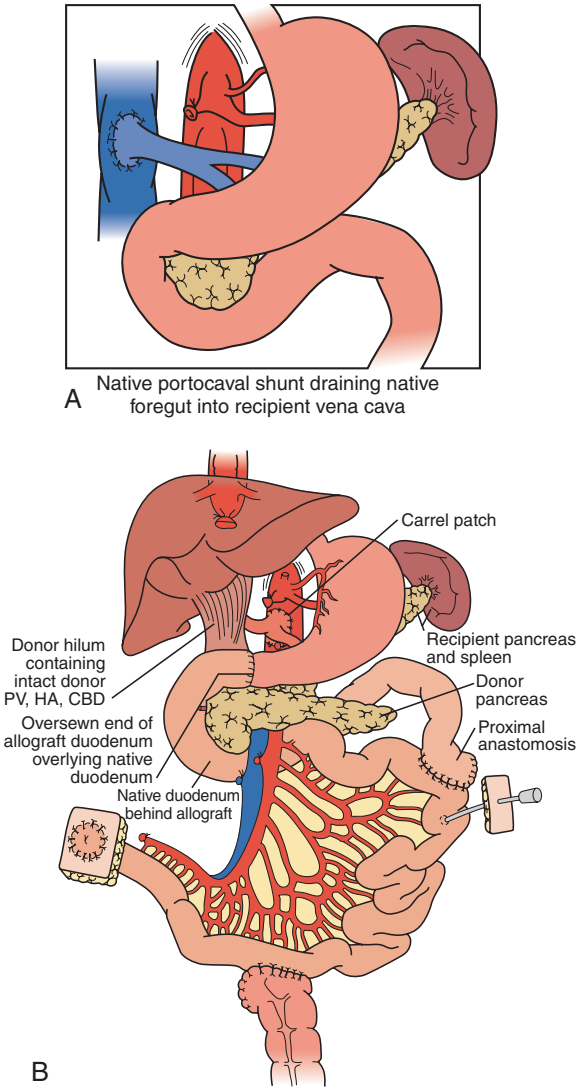

Fig. 147.5 Combined liver and intestinal transplant. **A,** Portocaval shunt draining native foregut. **B,** Combined liver and intestinal transplant with feeding jejunostomy. *CBD,* Common bile duct; *HA,* hepatic artery; *PV,* portal vein.

Full Multivisceral Transplant

In the majority of cases of full multivisceral transplant procedures (Fig. 147.6), before implantation, the recipient distal stomach, duodenum, pancreas, liver, and remaining small bowel are resected. The recipient inferior vena cava is routinely meticulously preserved. The absence of remaining foregut or midgut precludes the need for a portocaval shunt. Vascular inflow is similar to composite liver-bowel transplant but now includes celiac inflow to the stomach as well. Vascular outflow is identical to composite liver-bowel transplant. The donor spleen is removed from the composite allograft on the back table before reperfusion. Intestinal reconstruction is performed proximally with a gastrogastrostomy anastomosis, and the distal anastomosis is similar to previously described intestinal transplants. To avoid gastric outlet obstruction resulting from vagal denervation, a Heineke-Mikulicz pyloroplasty is routinely performed after reperfusion. Feeding tubes are placed as indicated.

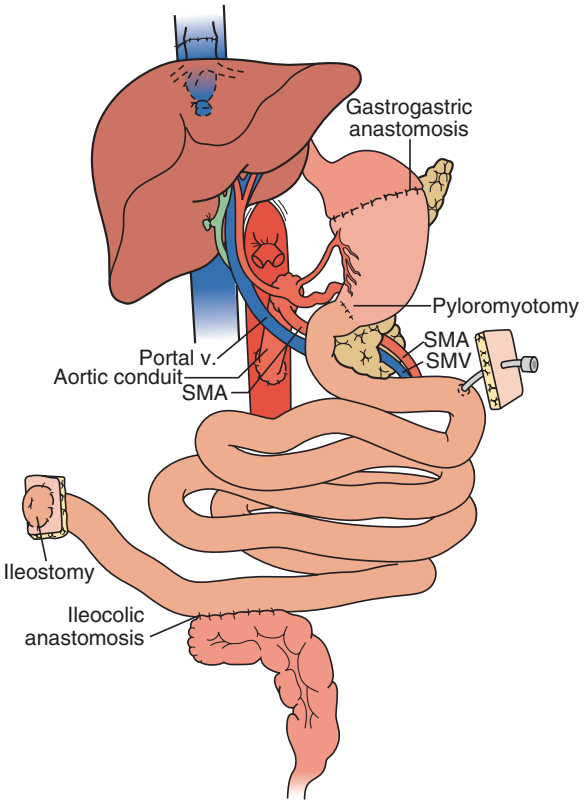

Fig. 147.6 Full multivisceral transplant. *SMA,* Superior mesenteric artery; *SMV,* superior mesenteric vein.

Modified Multivisceral Transplant

A "modified" multivisceral transplant (Fig. 147. 7) involves transplantation of a full composite allograft without a liver. The recipient liver is preserved along with its vasculature and the extrahepatic biliary system with duodenum, pancreas, and spleen. Vascular conduits are used routinely (Fig. 147.8). If the native enterohepatic biliary system is intact, the native duodenum or jejunum is drained into the allograft duodenum or jejunum. If, however, the procedure involves disruption of hepatobiliary continuity, the native bile duct can be drained via Roux-en-Y hepaticojejunostomy constructed from donor intestinal allograft (often the case in children where the donor bile duct is very small), or in adults and older children via a choledochoduodenostomy (duct-to-duct) anastomosis.

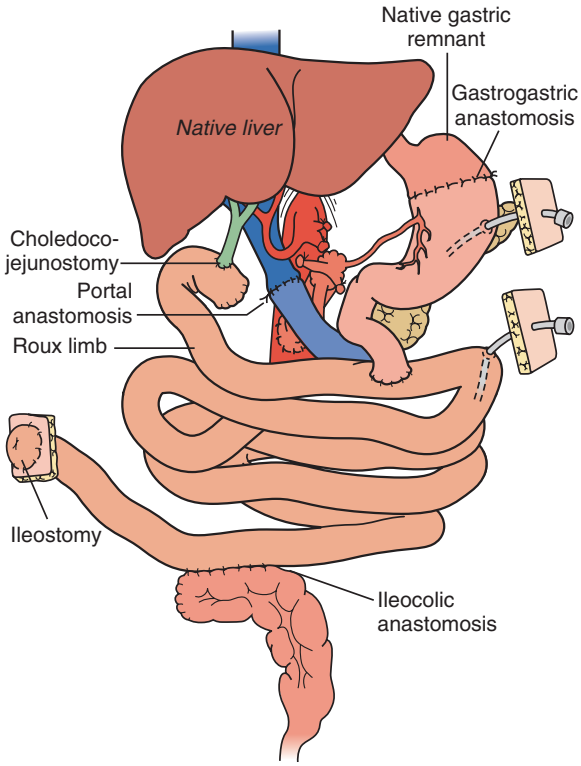

Fig. 147.7 Modified multivisceral transplant.

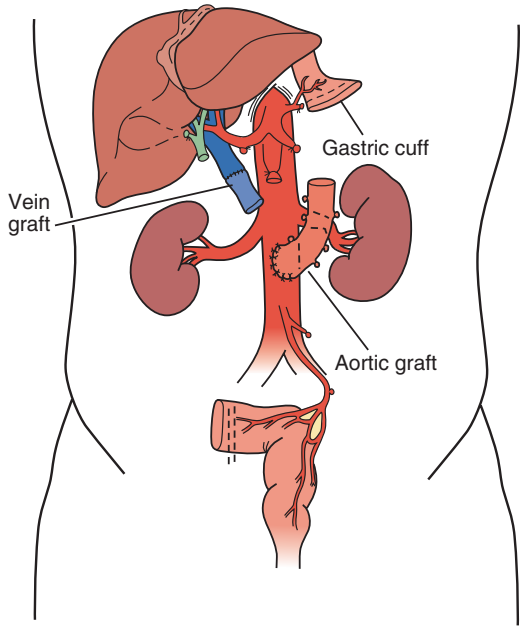

Fig. 147.8 Vascular conduit extensions for modified multivisceral transplant.

Abdominal Wall Closure After Intestinal Transplantation

Fascial closure after intestinal transplant can be difficult because of reduced abdominal domain, loss of fascial compliance from prior laparotomies, and possible concern for abdominal compartment syndrome. Previous studies have shown that abdominal fascia cannot be closed in about one-third of intestinal transplant cases. Low donor to recipient weight ratio (<0.8) has been shown to be an important predictive factor for allowing fascial closure after intestinal transplant.[23,24] A recent study identified high-risk recipient factors (preexisting enterocutaneous fistulas, male sex, and age over 4 years) contributing to an inability to achieve sustained abdominal wall closure after intestinal transplant.[25] Currently available options for abdominal closure in these cases include skin-only closure, advanced reconstructive surgical options including use of biologic mesh and delayed skin grafting, and consideration of abdominal wall transplant at the time of intestinal transplant.[25]

POSTOPERATIVE MANAGEMENT

Advances in the technical aspects of intestinal and multivisceral transplantation have occurred in parallel with improvements in intraoperative monitoring and postoperative critical care management of these challenging patients.

Ventilatory Management

Extubation is commonly achieved within 48 hours of the transplant operation in adult patients. Mitigating factors that might delay extubation include graft malfunction, delayed abdominal wall closure, volume overload, sepsis, organ failure, and surgical complications such as bleeding. In children, delayed abdominal wall closure is commonly necessary because of allograft size constraints and swelling postreperfusion and requires continued neuromuscular blockade and mechanical ventilation while diuresis is performed. Given that recipients tend to be nutritionally compromised preoperatively and that intestinal and multivisceral transplant operations are relatively long in duration (8–18 hours), a careful assessment of weaning parameters before extubation is essential. Changes in intraabdominal pressure and abdominal girth may adversely affect respiratory mechanics, leading to rapid, shallow breathing. These problems are most common in children, in small adults who receive large allografts, and in patients whose course is complicated by large-volume ascites. Pleural effusions are common because of nutritional depletion with hypoalbuminemia and intraoperative manipulation of the diaphragm. Although attempts to overcome them by diuretics may be attempted, thoracentesis and placement of pleural tubes often are necessary.

Renal Function

It is common for intestinal transplant recipients to demonstrate some degree of renal dysfunction pretransplant, owing to multiple episodes of sepsis with hypotension, the side effects of antibiotics, chronic dehydration, and hepatic dysfunction. Although patients receive significant volumes of fluid during the long course of the transplant operation, intravascular volume depletion can be a problem in the immediate posttransplant period. Significant fluid volume may accumulate in the intestinal allograft secondary to preservation injury (peaking at 48–72 hours), and large-volume ascites or chylous ascites

production because of mesenteric lymphatic leakage may occur. Either of these processes can lead to profound and sometimes underappreciated intravascular volume depletion and can worsen the nephrotoxicity of immunosuppressive agents and antibiotics.

Maintenance of ideal volume status is challenging in these patients, and interventions should be directed at optimizing cardiac output and organ perfusion. Extravascular volume overload is common and should be interpreted with caution, particularly in the immediate posttransplant period. In patients with impaired renal function or high tacrolimus drug levels, urine output may not be an accurate indicator of perfusion. Skin perfusion, mixed venous oxygen concentration, and serum lactate are useful surrogates. Because intestinal transplant recipients are commonly nutritionally deplete, use of 5% albumin as a volume expander may be preferable to larger volumes of crystalloid solution. In patients with large-volume stoma output or ascites drainage, standing orders for fluid replacement may be necessary. Balancing adequate volume resuscitation with the avoidance of volume overload in the setting of baseline renal dysfunction can be a significant challenge that requires considerable clinical experience and meticulous attention to detail.

Infection

Recipients of intestinal or multivisceral transplants will routinely receive prophylactic broad-spectrum antibiotics intratransplant and posttransplant. Any history of nosocomial infections before transplant should be addressed with administration of the appropriate specific antibiotics. Colonizing organisms growing from enterocutaneous fistula tracts should also be covered appropriately. Selective bowel decontamination with nonabsorbable oral antibiotics is performed routinely in the donor and in some intestinal transplant recipients.

Translocation of bacteria or bacterial toxins from the intestine into the bloodstream can cause sepsis or systemic inflammatory response syndrome (SIRS). In a recent study evaluating the incidence of bacterial bloodstream infections within 6 months after intestinal transplant, about 50% of intestinal transplant recipients developed bloodstream infection, typically within 3 months of intestinal transplant.[26] The most common sources of bacterial bloodstream infections were gut translocation concurrent with rejection episode (35%), central line infection (20%), and intraabdominal abscesses (14%).[26]

A history of repeated exposure to broad-spectrum antibiotics leads to colonization with multiple resistant organisms in many intestinal transplant recipients. In a recent study analyzing intraabdominal infections after intestinal and multivisceral transplant, about 43% of recipients developed intraabdominal infections within 2 years posttransplant, with the most common isolates being enterococci, *Escherichia coli,* and *Klebsiella* species. The majority of the enterococci infections (63%) were vancomycin-resistant enterococci, and about 22% of gram-negative infections were noted to be resistant to extended-spectrum penicillins.[27]

Some centers also perform surveillance stool cultures on a regular basis posttransplant. In the absence of positive blood cultures to direct antibiotic therapy, organisms growing from quantitative stool cultures in significant numbers ($>10^8$ colony-forming units [CFU]/mL) in patients with sepsis or acute cellular rejection may be considered potential causes of bacteremia and may be treated with IV antibiotics. The high incidence of renal dysfunction in intestinal transplant recipients should prompt use of nonnephrotoxic antibiotics when possible and careful monitoring of antibiotic levels when necessary.

One of the major complications posttransplantation requiring frequent readmissions is enteritis of the intestinal graft (viral or bacterial). In a recent study, the incidence of viral enteritis in intestinal transplant recipients was noted to be 43.9% within the first year posttransplant, and pediatric intestinal transplant recipients had a higher incidence of viral enteritis compared with adult intestinal transplant recipients. Viral enteritis episodes usually resolved within 1 week after supportive treatment with IV hydration and gradual reintroduction of enteral feedings once diarrhea resolves.[28] Similarly, there is a higher incidence (40%) of *Clostridium difficile* enteritis in intestinal transplant recipients within the first year posttransplant.[29] Standard antibiotic therapy with vancomycin or metronidazole therapy usually is enough to treat *C. difficile* enteritis.[29]

In addition, fungal infections must always be considered in recipients with persistent fevers and negative cultures, and often appropriate antifungal treatment is commenced empirically pending extended culture results and imaging studies.

Antiviral Prophylaxis

Opportunistic viral infections play a significant factor in postoperative complications. Antiviral prophylactic strategies have evolved with intestinal transplantation. Viral infections can cause significant morbidity, especially in pediatric recipients in the early postoperative period. Common pathogens include cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes simplex virus (HSV), adenovirus, and influenza viruses. Many pediatric recipients have no prior protective exposure to these viruses, so primary infection occurs in these patients while they are highly immunosuppressed. Recent advances in prophylaxis and preemptive therapy have significantly decreased early morbidity associated with EBV, CMV, and HSV, lowering the incidence of clinically significant infections to less than 5%.

Lack of definitive treatment for infections with respiratory viruses such as influenza and adenovirus in the early postoperative period can be catastrophic because of clinical sequelae, including disseminated viremia, necrotizing pneumonitis, and bacterial superinfection. At UPMC Children's Hospital of Pittsburgh, the current protocol for anti-CMV prophylaxis includes a 2-week course of IV ganciclovir (IV dose 5 mg/kg twice daily), except in the case of donor CMV negative to recipient CMV donor negative. CMV infection most commonly presents as intestinal graft enteritis. CMV graft enteritis and/or viremia posttransplant is frequently treated with a reduction in immunosuppression dosing, IV ganciclovir, and concomitant administration of cytomegalovirus-specific hyperimmune globulin (Cytogam). EBV infection can lead to posttransplant lymphoproliferative disorder (PTLD), and its management is further elaborated under the PTLD section later in this chapter. Close monitoring of CMV and EBV polymerase chain reaction (PCR) is performed frequently posttransplant and spaced out, moving away from the time of transplant and as indicated.

Nutritional Support

Immediate posttransplant nutritional support is administered using standard PN, which is tapered gradually as enteral feeding is advanced. Tube feedings with isotonic formula are started based on clinical determination of intestinal allograft function. In the authors' experience, most intestinal transplant patients, especially children, do not voluntarily ingest adequate amounts of nutrition in the early postoperative period. To achieve maximal nutritional repletion, tube feeding is usually required once the intestinal tract becomes functional. Resistance to oral feedings is a clinical challenge in younger pediatric recipients, many of whom demonstrate oral aversion. A recent study examining factors that affect eating behaviors in pediatric intestinal transplant recipients found that learning to eat at the recommended age along with positive pretransplant eating experiences in pediatric intestinal failure patients was associated with significantly less oral food aversion behavior postintestinal transplant.[30] Hence, oral aversion must be recognized pretransplant and efforts made to gradually encourage oral feedings pretransplant by the clinical teams.

Immunosuppression

Although a variety of combinations of immunosuppressive drugs have been used in intestinal transplant recipients, most patients are maintained on tacrolimus (Prograf [Astellas, Tokyo, Japan]) therapy along with other adjunctive medications. Organ Procurement and Transplantation Network (OPTN) data show that 99% of intestinal transplant recipients receive tacrolimus as part of their maintenance immunosuppression at the time of posttransplant discharge. Moreover, during the first posttransplant year, only a select number of patients are taken off of tacrolimus (mostly for complications perceived to be related to tacrolimus), with nearly 97% remaining on tacrolimus-based therapy. Recent international Intestinal Transplant Registry data suggest that rapamycin may have some improved outcomes and could be used as an alternative or in combination with tacrolimus. However, further research is needed to validate these data.[2] Currently, the most common regimen at 1-year posttransplant is tacrolimus in combination with steroids, with tacrolimus monotherapy being the second most common.[1] In some patients who have had significant rejection, a third agent may be employed in addition to tacrolimus and steroids, like mycophenolate mofetil (MMF) or azathioprine (Imuran).

Two classes of immunomodulatory drugs have been used for intestinal transplantation and have been associated with improvements in 1-year patient and graft survival. Depleting antilymphocyte antibody therapies include rabbit antithymocyte globulin (rATG, Thymoglobulin [Genzyme Corp., Cambridge, MA]), and rarely now, alemtuzumab (Campath-1H [Genzyme Corp.]). The individual use of these agents by high-volume single centers has demonstrated improved short-term survival and decreased rejection rates and severity of rejection, especially during the early posttransplant period.[31–34] Associated with similar improvements in survival and decreased incidence of acute rejection and severity, induction with the nondepleting interleukin (IL)-2 receptor antagonists daclizumab (Zenapax) and basiliximab (Simulect) has also gained increasing acceptance by many intestinal transplant programs. In select cases of suspected antibody-mediated rejection (class II donor-specific antibodies [DSA] and evidence of histologic injury), other agents such as rituximab or bortezomib may also be used (often in addition to pheresis and intravenous immunoglobulin [IVIg]). Immunosuppression for intestinal and multivisceral transplantation now involves perioperative antibody induction protocols in over 60% of cases.[1]

Immunologic Monitoring

The gold standard for monitoring and diagnosing rejection in intestinal and multivisceral transplant recipients to date remains routine ileoscopy and proximal enteroscopy with histopathologic examination of multiple random mucosal biopsies. Significant investigation is under way into the development of tools to guide and monitor the immunologic state of intestinal transplant recipients. Ideally, noninvasive markers such as serologic, proteomic, or genomic markers may identify those patients who are at increased risk of rejection and, conversely, those who might benefit from decreased levels of immunosuppression.[35,36] A recently developed Pleximmune test may be helpful, in conjunction with other studies, to determine both those who seem to be at risk for or are currently undergoing rejection and warrant augmented levels of immunosuppression or, conversely, maintain or lower immunosuppression in those who appear to be at lower risk of rejection.[37] Further validation in a larger cohort of patients is needed. Preformed antibody and de novo anti-DSA measurements may be of assistance in determining the risk of rejection.[38,39] When technically feasible, the presence of circulating donor cells in the recipient peripheral blood should be serially evaluated after transplantation by either flow cytometry or PCR. The presence of DSAs, especially class II, in intestinal transplant recipients may prompt aggressive therapy with augmentation of immunosuppression and addition of other agents and, in some circumstances, serial plasmapheresis and IVIg until clearance of antibodies has been confirmed. The use of fecal calprotectin or serum citrulline as noninvasive biochemical markers of allograft rejection has certain restrictions in timing of the test and sensitivity issues, especially in the initial posttransplant phase, and does not appear to be warranted based on currently available data.[40,41]

As mentioned, to date the gold standard for detection of rejection after intestinal transplant is histologic evaluation. At the majority of intestinal transplant programs, surveillance endoscopy and biopsy (esophagogastroduodenoscopy [EGD], ileoscopy, colonoscopy) are performed biweekly for the first 4–6 weeks posttransplant and then weekly for an additional 4–6 weeks to monitor for rejection. After the first 3 months posttransplant, the frequency of surveillance endoscopies performed in recipients is based on individual clinical assessments. More frequent endoscopes and biopsies are performed where clinically or histologically indicated. More recently, there have been a few reports in the literature suggesting that endoscopic surveillance and biopsy of intestinal grafts be performed "only for cause" (i.e., only in intestinal transplant recipients exhibiting signs and symptoms of rejection) as compared with routine protocol-driven surveillance endoscopy and biopsy.[42] However, additional studies on this topic are required to resolve this controversy about performing routine protocol-driven surveillance endoscopy versus "only for cause" endoscopy surveillance in intestinal transplant recipients.

Assessment of Intestinal Allograft

The process of examining the anatomic and functional integrity of the intestinal allograft begins in the operating room. The normal intestinal allograft after reperfusion appears pink and nonedematous, with occasional contractions. Altered appearance can be observed in the operating room, especially in the mucosa when the bowel is opened for the anastomosis, and in the proximal jejunal and distal ileal segments using endoscopy postoperatively.

Surveillance for intestinal allograft rejection in the early postoperative period focuses on clinical evaluation and gross morphologic examination of the stoma and distal ileum. Frequent routine endoscopic surveillance is the most reliable method for achieving an early diagnosis of intestinal rejection (Fig. 147.9). Endoscopic evaluations are performed initially twice a week through the allograft ileostomy. Upper endoscopy is reserved for occasions where clinical changes are not well explained by distal allograft evaluation and biopsy. Common physical changes to the normal appearance of an intestinal allograft include edema, cyanosis, congestion, and increased stomal output. These changes should prompt an immediate work-up, with a differential diagnosis that includes preservation injury (Fig. 147.10), sepsis, rejection, enteritis, and vascular compromise (such as thrombosis).

The allograft stomal output is assessed for volume and consistency. Normal stomal output during the early postoperative period is characteristically clear and thin. During the first week posttransplant, normal stomal output is 1–2 L/day and 40–60 mL/kg/day for adult and pediatric recipients, respectively. If these stomal volumes are exceeded in the absence of significant pathology, agents to control volume of output can be started, including loperamide, diphenoxylate-atropine, paregoric (tincture of opium), pectin, rarely somatostatin, or oral antibiotics. The presence of blood in the stomal output is an ominous sign and a concern for acute rejection, until proven otherwise. Other causes, however, include anastomotic bleeds in the early posttransplant period, perianastomotic ulcers in the later period, or postbiopsy bleeding, which is often seen initially or 5–7 days after the biopsy.

Intestinal allograft absorption of nutrients and medications develops gradually and commonly requires several weeks posttransplant to

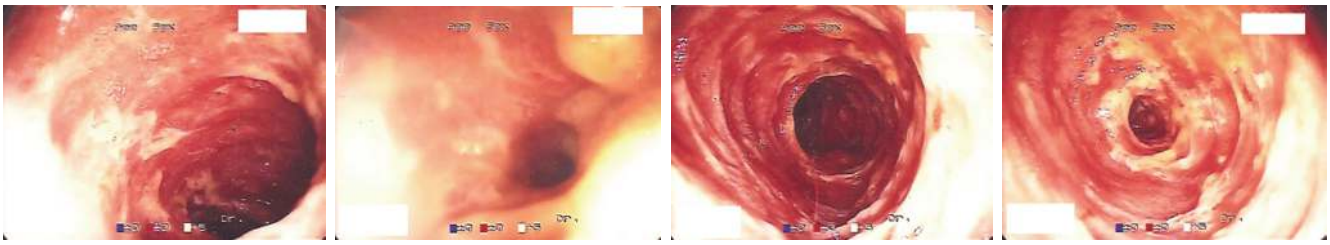

Fig. 147.9 Enteroscopic findings consistent with acute cellular rejection of intestinal allograft. (Courtesy Kareem Abu-Elmagd, MD.)

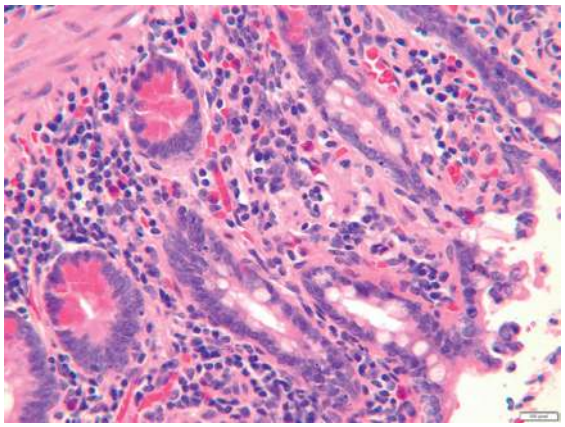

Fig. 147.10 Ischemia-reperfusion injury. Reperfusion injury is characterized by extensive loss of villi, followed by pronounced regenerative changes of crypt epithelium with conspicuous mitosis, capillary congestion, shortening of villi, and variable degrees of neutrophil-rich inflammatory infiltration.

improve. Abnormal absorption/stomal output after approximately 1 month should prompt an aggressive search for underlying pathology, especially rejection. The ability to maintain whole-blood tacrolimus trough levels above 15 ng/mL on oral therapy alone is a good indicator of adequate absorption. In the authors' experience, intestinal transplant recipients demonstrate evidence of sufficient absorptive function at a mean of 28 days after transplantation.

MANAGEMENT OF ALLOGRAFT REJECTION

Allograft rejection (Fig. 147.11) is strongly associated with graft loss and mortality and remains a significant obstacle to achieving successful long-term outcomes for intestinal and multivisceral transplant recipients. Historically, acute cellular rejection was reported in 70%–90% of intestinal allografts within 90 days posttransplant. In contrast, rejection rates of 30%–40% are currently reported by large centers because of advances in allograft histopathologic surveillance, immunosuppression, and immunologic monitoring. There does appear to be disparity between some centers where reported rejection rates may be

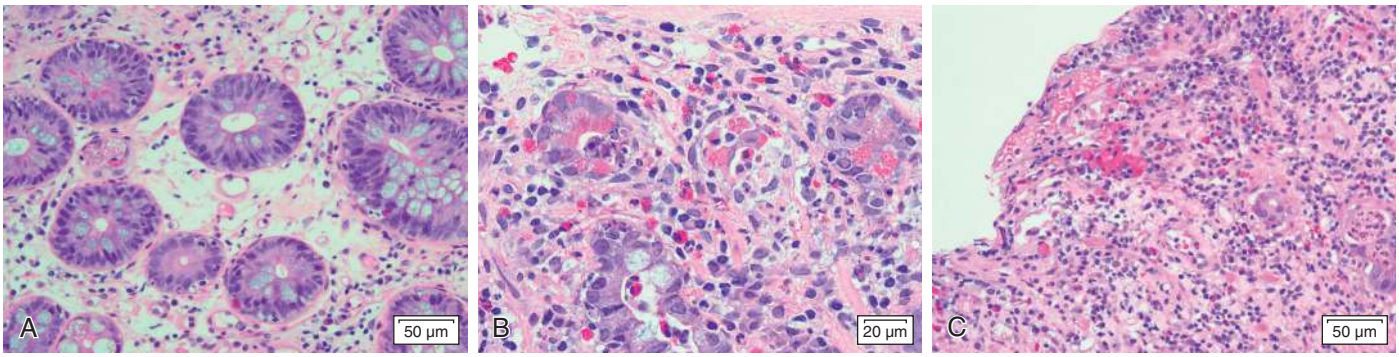

Fig. 147.11 Acute cellular rejection of intestinal allograft: mild (A), moderate (B), and severe (C). **A,** Mild acute rejection is characterized by a generally mild and localized inflammatory infiltrate, which tends to be concentrated around small venules in the lamina propria. Mucosa is intact, but crypt epithelium displays evidence of injury: mucin depletion, cytoplasmic basophilia, decreased cell height, nuclear enlargement with hyperchromasia, and inflammatory infiltration. Crypt epithelial apoptosis is increased, usually with more than six apoptotic bodies/10 crypts. If sampled by biopsy specimen, preexisting lymphoid aggregates (Peyer patches) demonstrate an intense accumulation of activated lymphocytes. Villi are variably shortened, and architecture may be slightly distorted owing to expansion of lamina propria by inflammatory infiltration. **B,** In moderate acute rejection, inflammatory infiltrate is widely dispersed within the lamina propria. Crypt injury and cryptitis are distributed more diffusely than in mild acute rejection, and villi tend to have a greater degree of flattening. Number of apoptotic bodies is greater than in mild acute rejection, usually with focal "confluent apoptosis." Mild to moderate intimal arteritis may be seen. Mucosa remains intact without ulceration, although focal superficial erosions can be present. **C,** Severe acute rejection is distinguished by a marked degree of crypt damage and mucosal ulceration, with lymphocytic infiltration extending deep into allograft wall and involving nerves and ganglia. As a consequence of mucosal destruction, luminal contents gain access to submucosa, prompting a neutrophil-rich infiltrate and an overlying fibropurulent (pseudomembranous) exudate with widespread mucosal sloughing as the final result. Adjacent viable epithelium usually shows rejection-associated changes such as crypt epithelial damage and abundant apoptosis. Severe intimal arteritis or transmural arteritis may be seen.

very low (less than 10%), whereas others still have higher rates (greater than 50%), possibly because of differing induction therapies or monitoring and reporting trends. Unlike liver allograft rejections, the natural history of rejection of intestinal allografts is unforgiving, making early diagnosis and treatment critical for successful reversal of the rejection process.

Until proven otherwise by culture and allograft biopsy, each episode of allograft dysfunction should prompt an expeditious evaluation for acute rejection. No reliable laboratory tests are currently available to warn of allograft dysfunction or rejection for intestinal transplantation, although preliminarily the Pleximmune assay has shown good sensitivity and specificity when used in certain criteria. Clinical features of intestinal allograft rejection include nonspecific signs and symptoms such as diarrhea (increased stomal output), nausea/vomiting, fever, and abdominal pain. Infectious enteritis and medication-related loose bowel movements are common etiologies of allograft dysfunction that present with a clinical picture similar to allograft rejection. The stoma may become edematous, erythematous, and friable. Endoscopy may demonstrate normal mucosa despite mild to moderate grades of ongoing acute cellular rejection. Moderate to severe rejection of the intestinal allograft usually leads to mucosal inflammation beginning with erythema and friability, progressing to mucosal slough and exudates overlying ulcers, with eventual loss of the mucosal layer. Histologically, there is variable presence of edema in the lamina propria and villous blunting. However, mononuclear cell infiltrates and intestinal crypt apoptosis with eventual crypt loss are the hallmark signs of intestinal allograft rejection that establish the diagnosis.

Treatment of intestinal acute cellular rejection initially involves steroids. At UPMC Children's Hospital of Pittsburgh, methylprednisolone is usually given, either by three boluses of 10 mg/kg/day over 3 days or, more routinely, by a single 10 mg/kg bolus and subsequent cycle of tapering doses over a more extended duration. Antilymphocyte antibodies for steroid-resistant rejection include antithymocyte globulin (rATG, Thymoglobulin) and, rarely nowadays, alemtuzumab (Campath-1H [Genzyme Corp.]). Unfortunately, the discontinuation of muromonab-CD3 (OKT3, a murine monoclonal anti-CD3 antibody) has been detrimental to the field. Adverse immune-mediated drug reactions to immunomodulatory antibodies can be life threatening. These agents are usually administered to patients with cardiopulmonary monitoring after premedication with steroids, antipyretics, and histamine blockers. In many cases, it is appropriate to initiate therapy in an ICU setting. During and after the treatment of acute rejection, tacrolimus whole-blood levels are maintained around 15–20 ng/mL in intestinal and multivisceral allograft recipients. Maintenance steroid therapy usually consists of 1–2 mg/kg/day of IV methylprednisolone converted to oral prednisone, tapered over several weeks to months based on individual clinical assessments. Addition of a third agent such as MMF (CellCept [Roche]) or sirolimus (Rapamune) or azathioprine (Imuran) may be indicated if rejection is refractory or recurrent.

A fundamental principle that guides treatment of allograft rejection is the preservation of as much intestinal function as possible. Each episode of rejection likely shortens the longevity of intestinal graft function, so the diagnosis of steroid-resistant rejection in intestinal allografts must be made in a timely fashion than in a more tolerant and recoverable organ such as the liver. Sequential biopsies separated by reasonable time intervals allow for objective confirmation of steroid treatment failure. Once confirmed, antilymphocyte therapy will rapidly reduce the overall number of immunocompetent cells and is usually a highly effective treatment. In those cases of intestine recipients with preexisting immune debilitation or a predisposition to a life-threatening illness such as PTLD, allograft enterectomy may be safer than escalation of immune suppression, and this can potentially be lifesaving.

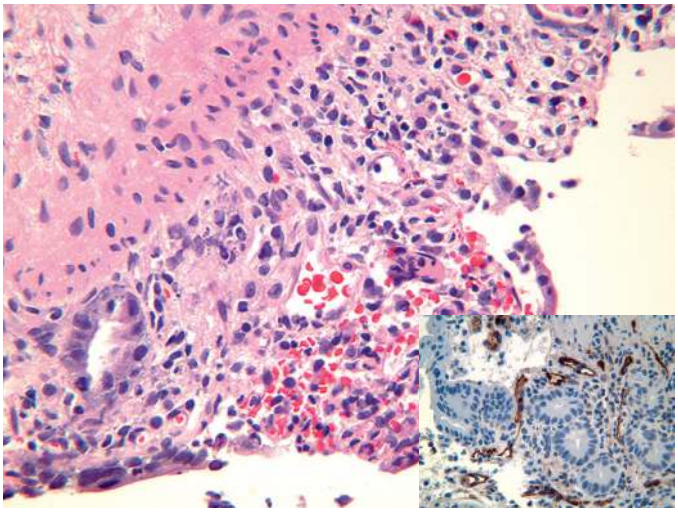

Fig. 147.12 Antibody-mediated rejection of intestinal allograft. Humoral rejection is characterized by a grossly cyanotic small-intestine allograft. Histologic findings include severe congestion, neutrophilic margination, and fibrin-platelet thrombi within the lamina propria microvasculature, along with focal hemorrhage. Immunohistochemical staining to C4d confirms the diagnosis of antibody-mediated rejection with heavy and diffuse staining of the lamina propria capillaries.

Antibody-mediated rejection (AMR) of the intestinal allograft (Fig. 147.12) is characterized by intestinal dysfunction, diffuse C4d staining on allograft biopsy, and usually identification of DSAs. Recent studies in the literature focusing on the concept of DSAs and graft rejection have shown that preformed DSA before transplant, persistence of DSAs posttransplant, and development of de novo DSAs posttransplant are factors associated with increased risk of rejection and graft loss.[43,44] In addition, these studies have shown that liver inclusive intestine allografts demonstrated greater clearance of DSAs posttransplant and had lower rate of de novo DSA formation post-transplant leading to better graft survival compared with intestine-only allografts.[43,44] Treatment of AMR remains challenging. A combination of IVIg, rituximab, plasmapheresis, and/or bortezomib needs to be considered in addition to standard treatment with steroids and/or thymoglobulin in these cases.

Chronic rejection remains the most significant complication affecting long-term graft survival. Chronic rejection (Fig. 147.13) is observed in 10%–15% of pediatric and adult intestinal allografts, but occurs more commonly in isolated intestinal allografts. In adult recipients at the University of Pittsburgh, multivisceral transplants including a liver allograft demonstrated a significantly better chronic rejection–free survival compared with the liver-free intestinal and modified multivisceral transplant recipients.[43] Risk factors for chronic rejection include type of allograft and loss of previous intestinal allograft. The clinical presentation of chronic rejection may include weight loss, chronic diarrhea, intermittent fevers, recurrent subacute bowel obstruction and distal intestinal allograft obstruction, or GI bleeding. Histologically, chronic rejection is characterized by villous blunting, focal ulcerations, epithelial metaplasia, and scant cellular infiltrates on endoscopic mucosal biopsies but can be difficult to diagnose based on just a mucosal biopsy, as larger vessels need to be ascertained. Full-thickness biopsies of intestinal allografts with chronic rejection demonstrate the classical obliterative arteriopathy with thickening of not only intestinal arterioles but also even bigger vessels.

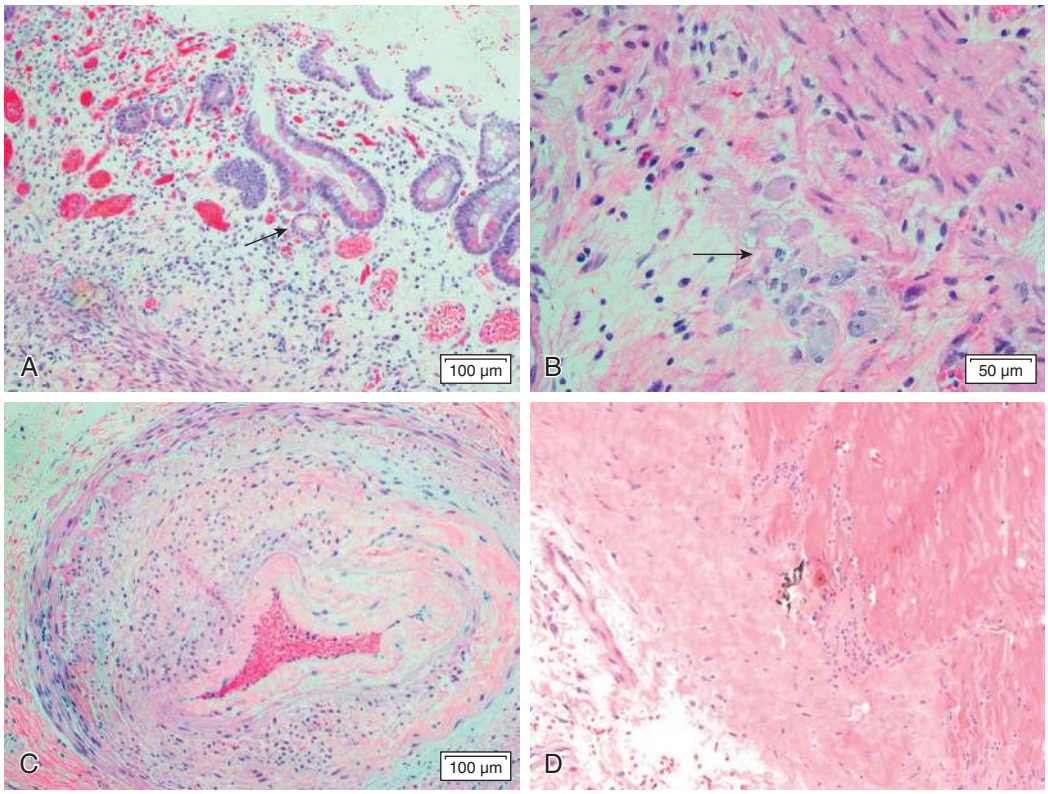

Fig. 147.13 Chronic rejection of intestinal allograft. Mucosa shows loss of villous architecture, chronic ulcers with exudate and granulation tissue, widespread loss of the crypts of Lieberkühn, crypts of Lieberkühn with pyloric gland metaplasia (**A,** *arrow*), neuronal hyperplasia (**B,** *arrow*) and mucosal fibrosis. Histologic findings in resection specimens are obliterative arteriopathy **(C)**, lymphoid deletion, and mesenteric sclerosis **(D)**.

MANAGEMENT OF COMPLICATIONS

Postoperative Hemorrhage

Recipients of intestinal and multivisceral transplants will commonly demonstrate varying degrees of liver dysfunction, qualitative and quantitative platelet abnormalities, and fibrinolysis that can lead to profound intraoperative coagulopathy. Induction intraoperatively with thymoglobulin may also lead to hematologic and clotting diathesis and warrant cessation or delay of the infusion. Intraoperative bleeding can also develop from lysis of vascularized adhesions resulting from previous surgeries and portal hypertension. Transient graft reperfusion coagulopathy mediated by plasminogen activators from the graft may also occur. Every effort is made to address these factors in the operating room, and usually whatever coagulopathy persists postoperatively is mild. Postoperative hemorrhage is most often a technical problem arising from vascular anastomoses or extensive raw peritoneal surfaces. Even mild coagulopathy should be completely corrected if bleeding is suspected in the posttransplant recipients, although caution must be taken to avoid issues with hypercoagulation and thrombosis of the allograft. Any bleeding that causes hemodynamic alteration should be managed by early prompt surgical exploration.

Vascular Complications

Superior mesenteric artery thrombosis is a catastrophic complication that leads to rapid and massive necrosis of the intestinal allograft. Elevation of hepatic enzymes (with liver allografts) and pallor of the intestinal stoma are accompanied by clinical deterioration, usually fulminant sepsis, and hepatic coma (with liver allografts). Isolated small bowel allografts can be explanted with a reasonable expectation of patient survival, but in patients with composite allografts, removal for arterial thrombosis leads to almost certain death in the absence of an immediate retransplant. Clinical suspicion of arterial thrombosis in the immediate postoperative period should be definitively evaluated in the operating room and not delayed by performance of Doppler ultrasound examination. In cases of delayed presentation, arteriography in interventional radiology can often be useful diagnostically and therapeutically.

Acute venous thrombosis also leads to loss of the intestinal allograft without timely surgical intervention. Clinical signs of venous thrombosis include acute massive ascites and stomal congestion. Mesenteric infarction is the ultimate outcome of unresolved venous thrombosis, necessitating explant of the intestinal allograft.

Incomplete obstruction of major inflow or outflow vessels may be suspected based on allograft biopsies or on clinical and laboratory signs of graft dysfunction. Contrast vascular radiographic studies are confirmatory, and the correction is either surgical or endovascular, based on individual assessments and available clinical expertise.

In a recent study focusing on thrombotic vascular complications after pediatric intestinal transplants, 15% of intestine transplant recipients developed arterial or venous thrombosis, with graft loss and patient death occurring in 60% of these patients. The findings of this study highlights that although vascular complications are rare after intestinal transplant, they are associated with high morbidity and mortality.[45]

Gastrointestinal Complications

GI bleeding after intestinal transplantation is an ominous sign that requires timely evaluation. Except for early postoperative bleeding, acute rejection and infectious enteritis are the most likely etiologies

and should be diagnosed or excluded based on endoscopic biopsy results. Arterioenteric fistulae must also be considered, as this can be catastrophic. The diagnosis of rejection relies primarily on histologic evidence but also on the endoscopic appearance of the mucosa. Bleeding from ulcerated EBV- or CMV-induced lesions may be differentiated by gross endoscopic examination, but confirmatory stains and serum PCR testing often help validate the diagnosis. Empiric therapy for rejection of intestinal allografts is rarely indicated except when suspicion on clinical and/or endoscopic evaluation is high, infectious parameters have been low, and obtaining pathologic confirmation is delayed.

Anastomotic leaks may occur in all intestinal transplant recipients, but are more common in pediatric patients. Clinical presentation commonly involves florid sepsis, drainage via abdominal drain, or wound drainage and infection. Confirmation is achieved with oral contrast imaging, although diagnostic laparotomy may be indicated in the setting of sepsis with equivocal imaging studies. Owing to immunosuppression, bowel leaks often do not improve with medical management alone. Almost all bowel leaks require surgical revision, including evacuation of any peritoneal contamination. Resolution is often confirmed via repeat laparotomy.

The propagation of motility patterns in the denervated intestinal allograft is still not fully understood. High allograft stomal output occurs early after transplant, and in the absence of infection or rejection, it can be regulated with agents such as loperamide, diphenoxylate-atropine, paregoric, or pectin. Conversely, poor upper motility often may exist between the native and allograft bowel, and promotility agents may be required.

At the majority of intestinal transplant centers, an ileostomy is created at the time of the initial transplant to allow for frequent endoscopic surveillance of intestinal grafts. In a recent study focused on outcomes related to ileostomy formation and takedown after intestinal transplant, major complications after ileostomy formation occurred in 23% of recipients. The most common complications included prolapse (6%), ischemia (4%), and parastomal hernia (4%).[46] Once the patient's intestinal graft function has been noted to be stable postoperatively for greater than 90 days, an assessment for ileostomy takedown is performed, usually with endoscopy and contrast enema studies to exclude any obstructive or pseudo-obstructive process in the distal bowel. Major complications after ileostomy takedown after intestinal transplant were reported in 28% of patients, with the most common complications being small bowel obstruction (8%), intraabdominal abscess (5%), and wound infection (3%).[46]

Renal Complications

Deterioration of renal function in intestinal transplant recipients remains a significant clinical challenge. Pretransplant renal dysfunction is exacerbated by overall higher target levels of immunosuppression in intestinal transplant recipients compared with other types of transplants, repeated exposure to nephrotoxic antibiotics, and episodes of dehydration with intestinal allograft dysfunction. The incidence of chronic renal failure for intestinal transplant recipients at 5 years posttransplant was noted to be 21.3%, which is significantly higher when compared with other nonrenal transplant recipients.[47] Overall, a review of the Scientific Registry of Transplant Recipients (SRTR) data shows that patients without severe pretransplant renal dysfunction who do not receive a kidney as part of the composite allograft will generally demonstrate a 50% increase in serum creatinine at their 5-year follow-up. In a recent study analyzing 288 adult intestinal transplant recipients, 13% required long-term renal replacement therapy and 6% required renal transplant after intestinal transplant. Three-year survival of intestinal transplant recipients requiring renal replacement therapy was noted to be 20% in this study, highlighting the major mortality risk associated with the development of renal failure in intestine transplant recipients.[48] In intestinal transplant recipients exhibiting signs of renal dysfunction, consideration must be given to decreasing the dose of calcineurin-based immunosuppression by adding rapamycin or other agents to the immunosuppression regimen.

Posttransplant Lymphoproliferative Disorder

The development of PTLD is almost always associated with EBV infection. Posttransplant infection with EBV results in a spectrum of diseases, from mononucleosis syndromes and plasma cell hyperplasia to neoplastic PTLD (Fig. 147.14). In a series of 500 intestinal and multivisceral transplants at the University of Pittsburgh, all but 2 of 57 recipients with PTLD developed the disorder as a consequence of confirmed EBV infection.[11] Early studies found that primary tacrolimus use in pediatric patients was associated with a 15% long-term risk of PTLD, with almost 80% of these cases occurring within the first 2 years after transplant. Achieving an optimal immunosuppression steady state and avoiding excessive therapy intervals appears to be key to minimizing EBV/PTLD complications. Cumulative PTLD-free survival for intestinal transplant recipients undergoing induction immunosuppression has improved to nearly 90%, possibly attributable to a lower incidence of acute rejection (and thus decreased need for escalation of immunosuppression) in addition to improved EBV viral load monitoring.

Patients presenting with PTLD complain of sporadic fever, lethargy, and malaise (and masses or lymphadenopathy). Weight loss, diarrhea, and GI complaints are common, as are signs of graft dysfunction. Standard laboratory evaluation may demonstrate neutropenia, atypical lymphocytosis, anemia, and thrombocytopenia. Further evaluation of PTLD is guided by findings on contrast-enhanced CT scanning of the head, neck, chest, abdomen, and pelvis, with or without endoscopy,

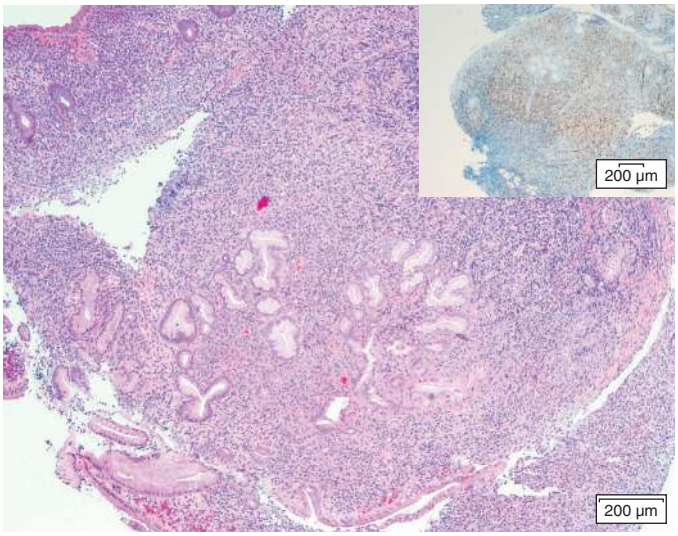

Fig. 147.14 Epstein-Barr virus posttransplant lymphoproliferative disorder (EBV/PTLD). At the early phase of EBV infection, tissue is expanded by scattered EBV encapsulated RNA (EBER)–positive lymphocytes. With disease progression, the number of positive cells increases, lymphocytes become activated and transformed, and ultimately, tissue architecture is effaced by a malignant lymphoproliferative process that replaces the duodenal mucosa seen in this example. The EBER in situ probe is shown in the *inset*.

based on results of noninvasive imaging. Histologic examination of the tissue is optimal, and specimens should be promptly submitted for fresh staining with the EBER-1 probe by experienced pathologists. An evaluation for CD20 staining should also be performed.

Ideally, the treatment of PTLD involves stopping immunosuppression completely, as can be done in most other types of allografts, but with the intestine, this may not be possible. The goal, however, is to lower the level of immunosuppression as much as possible (holding steroids and third agents and lowering the primary agent) and follow very closely with repeat scopes and biopsies looking for signs of imminent or active rejection. PTLD that is unresponsive to lowering/discontinuation of immunosuppression should be treated with monoclonal antibody, usually rituximab, if shown to be CD20 positive by biopsy. Complete remission rates of 60%–70% have been reported in children. The antibody therapy is relatively well tolerated, and for the 20% of patients who have recurrence, retreatment with rituximab can be curative. For PTLD refractory to monoclonal antibody, low-dose cytotoxic chemotherapy and steroids have been used effectively (Gross protocol).

Graft-Versus-Host Disease

Acute graft-versus-host disease (GVHD) results from immunocompetent donor T cells causing damage to recipient tissues after transplantation. The incidence of GVHD (Fig. 147.15) after intestinal transplantation ranges between 5% and 10% and usually occurs within the first 6 months posttransplant.[49] The use of multivisceral and modified multivisceral grafts is associated with a higher incidence of GVHD in intestinal transplant recipients, possibly related to removal of more native lymphatics, followed by replacement with a greater amount of donor lymphatic tissues when compared with intestine transplant recipients or liver/intestine transplant recipients.[50] The major targets of GVHD in intestinal transplant recipients are epithelial cells of skin, bone marrow, the native GI tract, and the native liver. Cardiac muscle involvement is not common but has been described. A recipient with GVHD commonly presents with fever and a maculopapular rash on the upper torso, neck, or palms of hands and feet, which may coalesce to form blisters or more diffuse erythema. Other clinical signs and symptoms include oral lesions, diarrhea, intestinal mucosal ulceration, native liver dysfunction, lymphadenopathy, and bone marrow suppression with pancytopenia. The variability of GVHD focality and severity leads to a wide spectrum of disease, from mild GVHD presenting with fevers and self-limiting rash to more severe forms leading to end-organ damage.

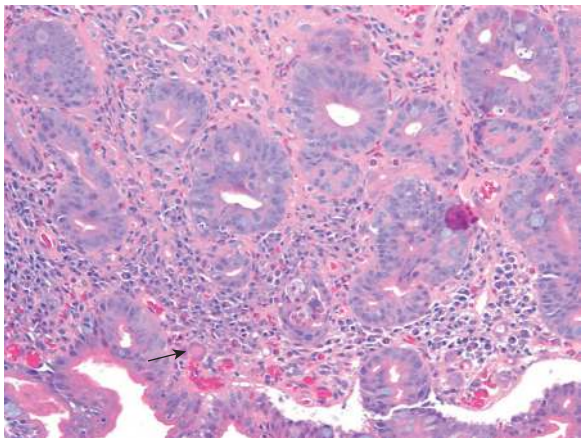

Fig. 147.15 Intestinal allograft graft-versus-host disease (GVHD). Mucosal biopsy of native small intestine showing crypt epithelial apoptosis and lamina propria inflammation. An incidental cytomegalovirus (CMV) inclusion is also noted in this biopsy *(arrow)*.

The diagnosis of GVHD is based on clinical presentation and confirmed histologically when possible. Corticosteroids are the first-line therapy to control epithelial damage caused by GVHD and are effective in around 50% of the cases overall. If unresponsive to steroids, GVHD can usually be controlled by reduction of calcineurin-based immunosuppression, although in some cases the level of immunosuppression needs to be augmented. Other forms of refractory GVHD have been treated successfully using antilymphocytic therapy (e.g., Thymoglobulin) and anti-IL therapy (e.g., Zenapax and Simulect) and anti–tumor necrosis factor (TNF) antibody therapy (e.g., Remicade).

OUTCOMES

Patient and Graft Survival

Outcome data after intestine transplant are available via analysis of two large registries:

1. Intestinal Transplant Registry, which captures worldwide intestine transplant activity
2. SRTR, which captures North American intestine transplant activity

From January 1985 to January 2015, according to the latest update of the Intestinal Transplant Registry, 3067 intestinal transplants have been performed in 84 centers around the world, with 30 centers still currently active.[2] Small bowel transplants alone account for 45% of the total, liver/intestine 31%, and multivisceral/modified multivisceral the remainder.[2] Approximately 48% of grafts overall contained a liver since 2001, which continues to decrease over time. Currently there are 1631 survivors.[2] The leading cause of recipient death is sepsis (65%), followed by graft failure including rejection (10%); lymphoma (5%); technical issues (4%); and then cardiovascular, renal, and liver failure.[2] The retransplantation rate is approximately 10%, with most being retransplanted with a liver included.[2] Intestinal Transplant Registry analysis has shown that intestinal graft and patient survival have improved over the last couple of decades when compared with the era before 2000. Since 2000, overall 1-year graft survival was 71%, overall 5-year graft survival was 50%, and overall 10-year graft survival was 41% and overall 1-year patient survival was 77%, overall 5-year patient survival was 58%, and overall 10-year patient survival was 47%.[2] A more recent analysis of the Intestinal Transplant Registry from 1985 to 2017 with a focus on outcomes of pediatric intestinal transplantation has shown that overall 1-year pediatric intestinal graft survival was 66% and overall 5-year pediatric intestinal graft survival was 48% and overall 1-year pediatric patient survival was 72% and overall 5-year pediatric patient survival was 48%.[51] Liver-inclusive grafts and first-time intestinal transplant was associated with better pediatric graft survival, whereas elective status (presentation from home) at transplant compared with hospitalized status was associated with better pediatric patient survival.[51] Rejection was the most common cause of long-term pediatric intestinal graft loss, and sepsis was the most common cause of patient death.[51] Other important relevant trends observed from the Intestinal Transplant Registry include (1) proportional increase in use of intestine-only grafts over liver-inclusive intestine grafts (Fig. 147.16) and (2) shift towards inclusion of colon graft with intestine grafts (because of perceived posttransplant renal protection with improved fluid absorption and decreased fluid loss associated with colon inclusion with intestine graft).

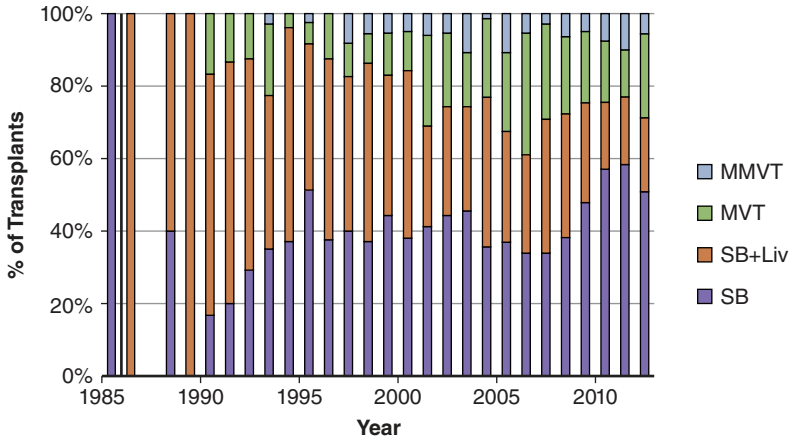

Fig. 147.16 The proportion of small bowel–only grafts (*SB*) has increased over time, whereas the proportion of liver-inclusive small bowel grafts (*SB+Liv*) has decreased over time. (Adapted from Grant D, Abu-Elmagd K, Mazariegos G, et al. Intestinal Transplant Registry report: Global activity and trends. *Am J Transplant.* 2015;15[1]:210–219. doi: 10.1111/ajt.12979. Epub 2014 Dec 1.)

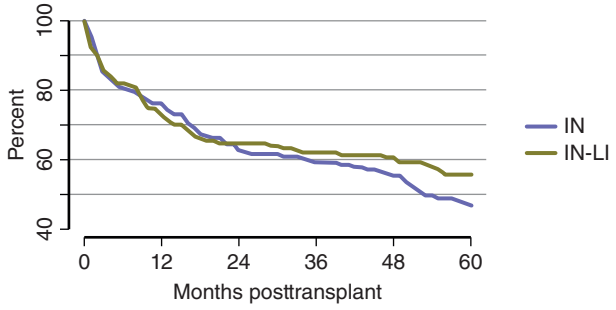

Fig. 147.17 One-year and 5-year graft survival of intestine-only grafts (*IN*) versus liver-intestine grafts (*IN-LI*) (2011–2013). (Adapted from Smith JM, Weaver T, Skeans MA, et al. OPTN/SRTR 2018 Annual Data Report: Intestine. *Am J Transplant.* 2020;20[Suppl s1]:300–339.)

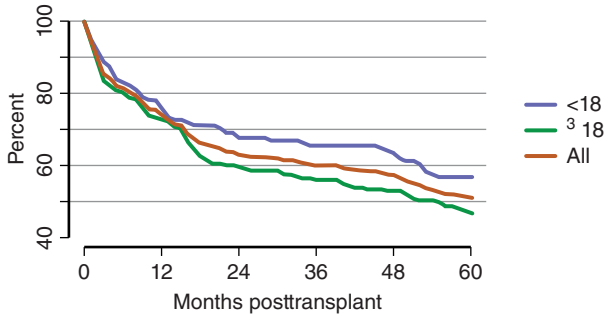

Fig. 147.18 Graft survival of all intestine grafts stratified by age. (Adapted from Smith JM, Weaver T, Skeans MA, et al. OPTN/SRTR 2018 Annual Data Report: Intestine. *Am J Transplant.* 2020;20[Suppl s1]:300–339.)

According to the latest update of the SRTR published in 2018, overall 1-year and 5-year graft survival for all intestinal transplants performed between 2011 and 2013 was 74% and 51%, respectively. Stratified by graft type (for all transplants performed between 2011 and 2013), 1-year and 5-year graft survival were 76% and 47%, respectively, for intestine-only recipients, and 1-year graft and 5-year graft survival was 73% and 56%, respectively, for intestine-liver recipients (Fig. 147.17).[1] Stratified by age group (for all transplants performed between 2011 and 2013), 1-year and 5-year graft survival were 76% and 57% for pediatric recipients versus 74% and 51% for adult recipients (Fig. 147.18).

Based on these large intestinal transplant registries, it can be concluded that short-term outcomes after intestinal transplantation have improved and are now comparable to and possibly better than outcomes after pancreas and lung transplantation. Contributing factors to this marked improvement in outcomes after intestinal transplantation include increased experience among intestinal transplant teams, improvements in anesthesia and critical care, advances in immunosuppression, and advances in the detection and treatment of rejection and opportunistic infection. In contrast to recent achievements in short-term outcomes, long-term survival after isolated intestinal transplantation has not significantly improved. Ten-year patient and graft survival remain 46% and 29%, respectively, for isolated intestinal transplantation and 42% and 39%, respectively, for intestine-with-liver grafts. These results are similar to those reported for lung and combined heart-lung transplantation but compare unfavorably to kidney, liver, and heart transplantations, where 10-year patient and graft survival exceeds 50%.

Long-Term Rehabilitation and Quality of Life

There are only a few reports pertaining to long-term outcomes, especially related to quality of life. This is partly as the field is still relatively new and only a few centers have significant numbers to make a useful assessment. Intestinal transplant recipients have been shown to have improved quality of life (improved overall general health, enteral autonomy, and ability to travel) when compared with patients with intestinal failure awaiting intestinal transplant.[52] A small preliminary study in pediatric recipients with functioning intestinal allografts more than 1-year posttransplant found that quality of life was perceived by recipients to be comparable to that of their peers, whereas parental proxy assessments compared less favorably in terms of physical functioning, general health, and family activities.[53] Younger recipients (5–10 years of age) demonstrated significantly worse outcomes than older recipients (11–18 years of age) in terms of global health assessments, general health perception, and family activities.[54] There have been reports demonstrating significant improvement in certain aspects of psychiatric health after transition from PN to posttransplant PN independence.[54] In these reports, long-term physical and psychiatric rehabilitation was achieved in over 80% of intestinal transplant recipients who survived beyond the sixth postoperative month.[53,54]

The most robust recent paper details 227 adult and pediatric recipients who survived beyond the 5-year milestone.[55] Conditional survival was 75% at 10 years and 61% at 15 years. Nutritional autonomy was achieved in 90% of the survivors. Morbidities with impact on global health included dysmotility (59%), hypertension (37%), osteoporosis (22%), and diabetes (11%) and were observed more in the adult population.[55] Survivors in general were reintegrated into society with self-sustained socioeconomic states. It is also vital to note that nonfunctional social support was one of the most significant survival risk factors. This evidence ties back to the original evaluation process and the importance of teaching and critically assessing adequacy of social support. No matter how good the medical, surgical, and transplant management may be, for continued long-term success, adequate and appropriate social resources are essential. The intestinal and multivisceral transplant process is demanding and forever ongoing for the recipient, the family, and the healthcare professional team. Hence, picking the appropriate recipient for transplantation is vital and, conversely, one of the reasons why all efforts are made to rehabilitate patients without transplantation, if possible, given these long-term concerns.

CONCLUSION

The field of intestinal failure has undergone ebbs and flows, based on medical, surgical, and transplantation advances and outcomes. Intestinal and multivisceral transplantation remains the ultimate therapy, but with improved medical and surgical management, the timing and utility of transplantation have shifted.

Significant improvements in outcomes from intestinal and multivisceral transplantation have been achieved through advances in the multidisciplinary care of intestinal failure, surgical techniques, innovative immunosuppressive strategies, and an improved understanding of intestinal transplantation immunology. These accomplishments, however, remain overshadowed by the remaining fundamental challenge of preventing or minimizing chronic allograft rejection that affects long-term survival. The relatively high waiting list mortality, particularly for infants and adults with concomitant liver failure, requires an ongoing reexamination of national guidelines for multivisceral procurement to maximize the usage of acceptable donor allografts. The limited long-term data on nutritional outcomes and transplantation morbidity indicate good allograft survival and quality of life for those who get through the early period: however, not without some significant morbidity. The limited progress in chronic graft loss, especially in the isolated intestine recipient, hampers wider acceptance of intestinal transplantation. More so, the recent dramatic improvements in the provision of exemplary care in the multidisciplinary intestinal care clinics have significantly altered the need, timing, and type of intestinal allograft needed. Still, until successful tissue engineering or an alternative treatment modality surfaces, intestinal transplant remains the ultimate and definitive form of intestinal failure salvage.

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KEY POINTS

- Intestinal rehabilitation programs have advanced the care of patients with intestinal failure, decreasing the need for intestinal transplantation.
- Early referral to an intestinal transplant center allows for a coordinated approach to determining the optimal timing of transplantation.
- Indications for intestinal transplantation have evolved, with many more patients requiring transplant for limitations in central venous access.
- Intestinal transplantation may be performed in isolation or combined with a liver, pancreas, stomach, and/or colon depending on the indication.
- Antibody-based induction immunosuppressive regimens have grown in popularity, but tacrolimus continues to predominate for maintenance.
- In the current era, 1-year and 5-year graft survival are 74% and 51%, respectively, and patient survival approaches 50% at 10 years.
- Long-term survivors of intestinal transplant have a 90% rate of achieving enteral autonomy and have excellent rehabilitative and developmental outcomes.

References for this chapter can be found at expertconsult.com.

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Kaufmann S, Avitzur Y, Beat S, et al. New insights into indications for intestinal transplantation—Consensus in the year 2019. *Transplantation.* 2019;104:937–946. doi:10.1097/TP.0000000000003065.
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Aortic Dissection

Akiko Tanaka and Anthony L. Estrera

INTRODUCTION

Aortic dissection, first described in the 18th century,[1] continues to be one of the most lethal cardiovascular emergencies in the current era despite the evolution in diagnostic modalities, medical management, and surgical techniques and technologies. Herein, we discuss the current practice for diagnosing and managing aortic dissections for optimal outcomes.

PATHOPHYSIOLOGY AND DEFINITION

The aortic wall consists of three layers, the intima, media, and adventitia, in order from the blood flow surface outward. Aortic dissection occurs when the intima is injured. Blood then flows into the media and splits the layer apart, forming a double-barreled aorta (Fig. 148.1). The site of disrupted intima is called as the *entry tear* or the *intimal tear.* The original blood channel is the true lumen, and the newly formed channel is the false lumen. The dissecting plane is most often observed in the outer one-third of the media, where the vasa vasorum runs. The reason the dissection plane develops at this site is unknown. Histologic changes that occur in the aortic media are cystic medial necrosis, elastin fragmentation, fibrosis, and medionecrosis. All of these changes may be seen in the normal aorta and progress with age.[2] Cystic medial necrosis occurs most frequently in the middle part of the media. Elastin fragmentation of the media, either by a congenital disturbance or secondary to smooth muscle cell necrosis, and fibrosis are both observed in the luminal and middle medial layers. Lastly, medionecrosis is most prominent in the luminal media. Thus the medial split may be occurring where the pathologic changes end. Some investigators believe that arteriosclerotic changes of the vasa vasorum lead to its spontaneous rupture[3] and ultimately develops into aortic dissection, thus occurring along the vasa vasorum.

In general, the true lumen is located in the lesser curvature of the aortic arch and then stays in the anteromedial portion of the aorta. Thus the celiac, mesenteric, and right renal artery branches arise from the true lumen, and in many cases, the left renal artery branch arises from the false lumen.[4] Aortic dissection propagates with high pressure, especially when a change in pressure over a change in time (dp/dt) exceeds a certain threshold.[5] The blood in the false lumen may travel back to the true lumen and create a re-entry tear, or it may penetrate out the adventitia and ultimately cause aortic rupture. If the blood oozes into the pericardial space, cardiac tamponade develops.

Ischemia associated with aortic dissection is referred to as *malperfusion*. When end-organ ischemia is not corrected in a timely manner, it can progress to end-organ malfunction with infarction, which is known as *malperfusion syndrome*.[6] Approximately 30%–40% of aortic dissection presents with malperfusion.[6–11] Several mechanisms cause it. An expanded false lumen compresses the true lumen and leads to *dynamic* ischemia (ischemia during systole). The first-order aortic branches pulled out from the true lumen may result in *static* ischemia. Aortic dissection directly extending into the branch itself can cause either *dynamic* or *static* (when the thrombus is formed in the false lumen) ischemia (Fig. 148.2). Lastly, the rare cause of ischemia is intimal intussusception,[12] in which the intima is circumferentially detached and leads to true lumen obstruction.

There is a unique form of aortic dissection known as *intramural hematoma* (IMH), originally reported as an aortic dissection *without* an intimal tear.[13] Historically, bleeding from a ruptured vasa vasorum was speculated to be the cause of IMH.[14] However, a recent report suggests that IMH is a subset of acute aortic dissections,[15] with a small intimal tear and resultant restricted flow in the false lumen leading to thrombosis. IMHs are known to be associated with older age and are less frequent compared with the classical dissection.[16,17] The guidelines of western countries published in the early 2010s recommend treating acute IMHs as classical aortic dissections.[18]

CLASSIFICATION

Time After Onset

The definitions used for the acuity of the disease vary depending on the report and guidelines. Acute, subacute, and chronic are commonly used. The classification by time is vital in treating aortic dissections, as survival after aortic dissection can be stratified by period. American guidelines defined acute as occurring within 2 weeks of onset, subacute between 2 and 6 weeks, and chronic more than 6 weeks.[19] European guidelines defined the subacute phase differently, 14–90 days,[18] which reasonably reflects the period that most commonly requires endovascular interventions.[20] One of the largest multicenter, multicountry registries in the world, the International Registry of Acute Aortic Dissections (IRAD), proposed the use of hyperacute (onset to 24 hours), acute (2–7 days), subacute (8–30 days), and chronic (>30 days) based on their experience.[21] The bottom line is that aortic dissections should be considered acute and unstable up to 14 days from onset.

Extent of Aortic Dissection: DeBakey Classification, Stanford Classification, and New Reporting Standards

There are two commonly used classification systems to describe the extension of aortic dissections. One is the DeBakey classification,[22] which comprises type I, II, and III. Type I depicts the dissections involving the ascending aorta that extend beyond the transverse aortic arch. Type II is aortic dissection confined to the ascending aorta. Type III is aortic dissection without the involvement of the ascending aorta and is further subclassified into IIIa and IIIb: type IIIa localizes the lesion above the diaphragm; type IIIb has dissection extended below the diaphragm. The other system is the Stanford classification,[23] which has two types: A and B. Stanford type A is a combination of DeBakey

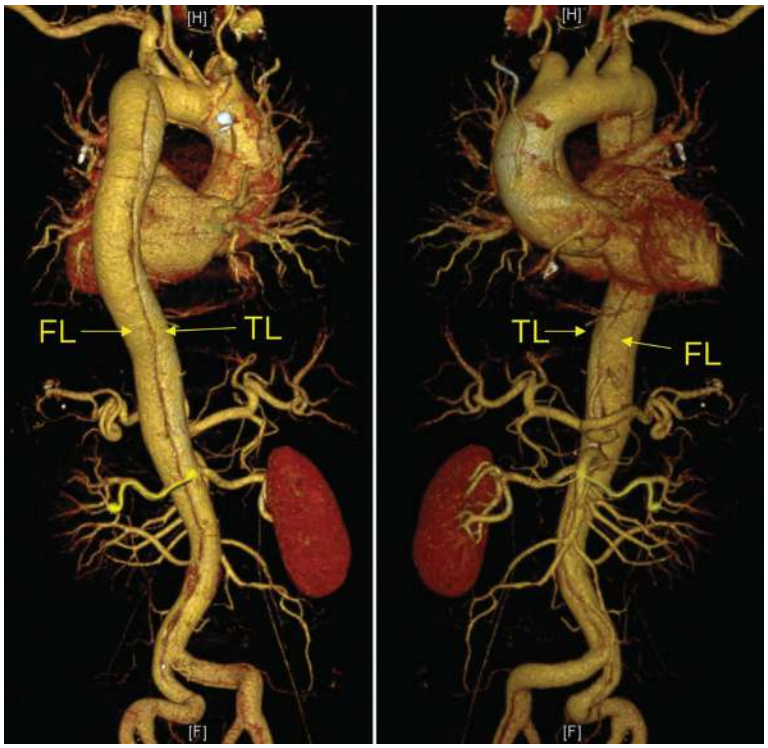

Fig. 148.1 Three-dimensional computed tomographic angiogram of type A aortic dissection. **(A)** anteroposterior view; **(B)**, posteroanterior view. *FL,* False lumen; *TL,* true lumen.

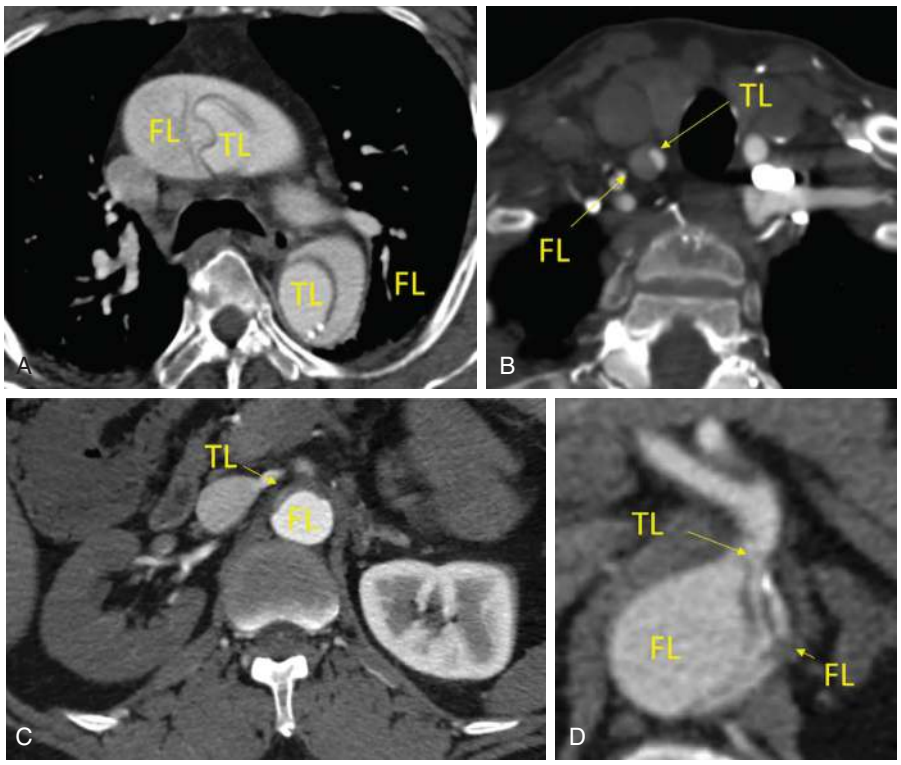

Fig. 148.2 Computed tomography in a patient with malperfusion syndrome (axial view). **(A)** Axial image of a type A aortic dissection at the level just below the tracheal bifurcation. **(B)** The right common carotid artery is dissected and the true lumen is compressed by the false lumen. This patient presented with altered mental status. **(C)** The right renal artery branches off from the compressed true lumen with resultant malperfusion (no enhancement with the contrast). **(D)** The celiac artery branches off from the narrowed true lumen. However, the patient did not present with malperfusion syndrome (normal liver functions, no abdominal pain). *FL,* False lumen; *TL,* true lumen

type I and II; type B is equivalent to type III. However, both classifications left the unclassified, so-called "non-A-non-B aortic dissections" (i.e., dissection extends from the ascending aorta to the aortic arch and from the aortic arch to the descending thoracic aorta).[24] In 2019 the Society of Thoracic Surgeons and Society for Vascular Surgery launched reporting standards, including these ambiguous types,[25] which are expected to be more frequently used in the future.

Clinical Presentation: Complicated vs. Uncomplicated

Clinical classifications with the terms "complicated" and "uncomplicated" are commonly used. These are also important for optimal treatment planning. Complicated aortic dissection includes rupture (impending rupture), intractable pain, uncontrolled hypertension, malperfusion syndrome (malperfusion with end-organ dysfunction), rapid expansion of the aorta, cardiac tamponade, and severe aortic insufficiency. Malperfusion syndrome may present as strokelike symptoms for cerebral ischemia; paraplegia/paraparesis for spinal ischemia; numbness, weakness, or pain for limb ischemia; and abdominal pain or lactic acidosis for visceral ischemia.

EPIDEMIOLOGY AND PROGNOSIS

Aortic dissection is a life-threatening condition, with a reported incidence of 3–6 per 100,000/year.[26] Male-to-female ratio is 2:1.[27] Two-thirds of patients have dissection involving the ascending aorta and present with a mean age of 61 years, whereas the remaining one-third with a disease-free ascending aorta present with a mean age of 64 years.[27] Aortic dissection is reported to correlate with circadian rhythm, activities, and season. It usually occurs during the daytime, with a peak from 8 to 10 A.M.,[28,29] and with winter being the most common season,[30] peaking in January.[31]

When the dissection involves the ascending aorta, deaths before arrival to the hospital may be seen in 21%–35%,[26,32] and mortality in the first 12 hours may reach 50% if untreated. Postmortem imaging studies demonstrated that 8% of out-of-hospital arrests were caused by acute type A aortic dissection.[33] The leading causes of early deaths are tamponade and aortic rupture,[1] followed by visceral ischemia.[34] The mortality rate after surgical repair of Stanford type A aortic dissection is 17%–18%,[27,35] which is superior to that of medical management, reported around 55% in the modern era. In contrast, the mortality rate for Stanford type B aortic dissection after surgical repair exceeds that of medical management (20%–30% after surgical repair vs. 7%–12% with medical management).[27] Early mortality in acute type B dissection is dictated by the presence of complications. In essence, uncomplicated type B aortic dissection has a mortality rate of less than 10% (2% in our experience[36]), whereas that of complicated type B is as high as 50%[37] (19% with medical management in our experience[36]).

It is also vital to treat aortic dissection as a lifelong disease. Continuous expansion of the affected aorta may require subsequent interventions to prevent it from rupture. Even after the open surgical or endovascular treatment for aortic dissection, the dissected aorta often remains in the distal or the proximal lesion. Thus periodical surveillance is crucial in this patient population. Modern literature reports that a need for distal reoperation is seen in 10% of the patients who had repairs for Stanford type A aortic dissection.[10,38–41] Known risks of aneurysmal formation are the size of the descending aorta (especially >40 mm) at the time of presentation of acute aortic dissection and younger age.[42,43] Also, many of these patients present to the emergency department with chest pain or back pain after the repair. It is important to evaluate that this is not the sign of progression of the disease.

RISK FACTORS

Predisposing factors are listed in Box 148.1.[27,44] Hypertension is the most common factor and is seen in 50%–86% of aortic dissections. Obstructive sleep apnea has been proven to be a significant cause of cardiovascular disease, found in 13% of cases.[45] Genetic/congenital factors have also been reported,[46] with Marfan syndrome having the highest prevalence, around 5%.[32,47] Bicuspid aortic valve is present in 2%. Other hereditary diseases may also be underreported, as many do not have physical characteristics, such as with Marfan syndrome. Physical activity such as weightlifting can temporarily cause the blood pressure to shoot over 300 mm Hg and trigger the event.[48] Straining is also a known trigger, as reported in the case of King George II in the 18th century.[1]

CLINICAL PRESENTATION

History taking and physical examination provide vital information for the timely diagnosis of aortic dissection. Patients with acute aortic dissection usually present with a sudden onset of severe pain. The pain is often described as a tearing, worst-ever pain. Shortness of breath is also commonly seen. Other presentations include syncope, abdominal pain, hemiplegia, paraplegia, weakness, and leg pain.[27] The use of drugs, especially cocaine, should be checked.[49] It is essential to ask for family history with not only the aortic disease but also sudden unexplained death, as aortic death may have been the undiagnosed aortic event.[50] History of intracranial aneurysm should also be questioned.[51]

BOX 148.1 Predisposing Factors for Aortic Dissection

Hereditary/Congenital Conditions
Marfan syndrome (FBN1)
Bicuspid aortic valve
Familial thoracic aortic aneurysm and dissections
Turner syndrome
Ehlers-Danlos syndrome (COL3A1)
Loeys-Dietz syndrome (TGFB2/TGFBR1/TGFBR2/SMAD3)
Shprintzen-Goldberg syndrome (FBN1)
Kommerell diverticulum
Aortic coarctation
Polycystic kidney disease (autosomal dominant)
Other gene mutations (ACTA2, MYH11, MYLK, SMAD4, PRKG1, LOX)

Inflammatory/Autoimmune Conditions
Takayasu arteritis
Giant cell arteritis
Syphilitic aortitis

Acquired Conditions
Hypertension
Obstructive sleep apnea
Smoking
Cocaine
Pregnancy
Trauma
Weight lifting
Iatrogenic
- Catheterization
- Cardiac surgery

Clinical findings commonly seen are hypertension, unless tamponade has developed or ruptured. Heart rate and respiratory rate are usually increased. A physical examination may show diminished or absent pulses in the affected limb. Patients with type A dissection may have cardiac murmurs associated with aortic regurgitation or have distant cardiac sound caused by tamponade. Hypoxemia is frequently seen, which is triggered by the systemic inflammatory reaction associated with aortic dissection.[52] Young patients with heritable aortic diseases may not have characteristic features, such as Marfan syndrome (tall stature, long arm span, deformed chest wall, lens dislocation, etc.). Current guidelines recommend immediate consultation to the surgical team in patients at high risk for acute aortic dissection before further imaging or laboratory testing.[19] High-risk patients are people who present with chest, back, or abdominal pain; syncope; or malperfusion symptoms with two or more high-risk features, such as having or suspected heritable aortic disease,[46] abrupt pain in onset, ripping/tearing/sharp/stabbing, physical examination consistent with malperfusion syndromes, murmur of aortic insufficiency, or hypotension/shock.

DIAGNOSIS

Fig. 148.3 depicts a diagnostic and treatment algorithm for aortic dissection. Because of the acutely ill presentation with pain, a blood test with cardiac enzymes and troponins, an electrocardiogram, and a chest x-ray are often performed. There is no single laboratory test that can confirm the diagnosis of aortic dissection alone. Tests should be used as a screening to prepare for possible intervention.[19] Leukocytosis is commonly seen, and anemia and thrombocytopenia are dependent on the progression of the disease.[1] Lactic acidosis may suggest the presence of cardiac tamponade or visceral and/or limb malperfusion. Elevated cardiac enzymes, positive troponins, and ST-T changes in the electrocardiogram are much more frequently seen in native coronary disease. However, they may reflect coronary malperfusion associated with aortic dissection. Chest pain with features at high risk for aortic dissection warrants computed tomography (CT) before proceeding to thrombolysis. A similar scenario can be seen with pulmonary embolism (PE), as patients with both PE and aortic dissection often present with chest pain and shortness of breath. D-dimer is generally elevated in both conditions. A negative D-dimer and a low clinical score for aortic dissection (i.e., patients without the hereditary aortic disease, pain without abrupt onset or not intense, normal physical examination) are helpful to rule out the disease.[53] A CT-PE protocol may provide the diagnosis of aortic dissection, but the phase of contrast and the caudal extent are not optimal and may require another scan or imaging modality, such as echocardiogram. The reported incidence of aortic dissection in patients who had the CT-PE protocol for markedly elevated D-dimer and clinically suspected PE was 2.4%.[54]

Widened mediastinum on a chest x-ray may be seen in 50% of patients. Thus a chest x-ray can be used as a screening test to rule out other causes of the symptoms but may not lead to the diagnosis.

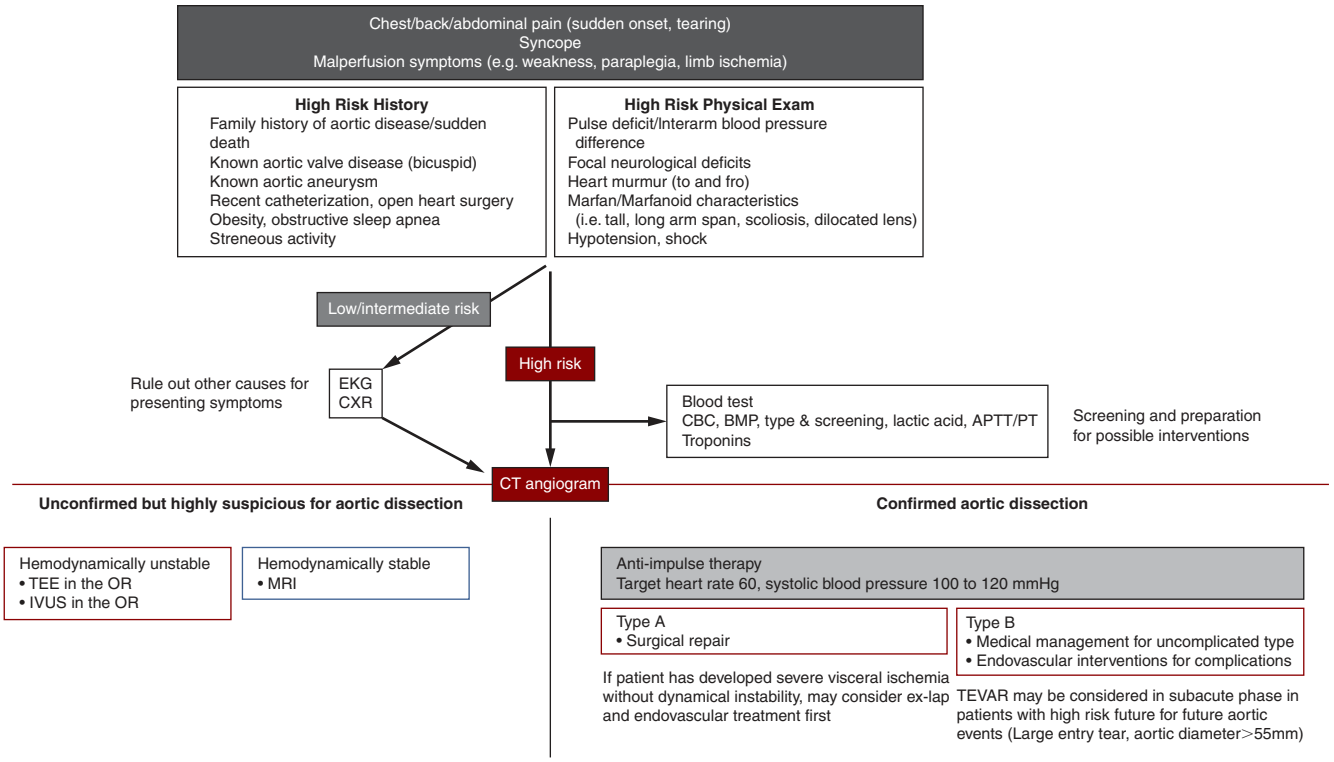

Fig. 148.3 Diagnostic and treatment algorithms of aortic dissection. *APTT/PT,* Activated partial thromboplastin time/prothrombin time; *CBC,* complete blood count; *CT,* computed tomography; *CXR,* chest x-ray; *EKG,* electrocardiogram; *IVUS,* intravascular ultrasound; *MRI,* magnetic resonance imaging; *OR,* operating room; *TEE,* transesophageal echocardiogram; *TEVAR,* thoracic endovascular aortic repair. (Modified from Hiratzka LF, Bakris GL, Beckman JA. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. *J Am Coll Cardiol.* 2010;55[14]:e27–e129.)

Historically, angiogram and transesophageal echocardiogram (TEE) were standard examinations. They have been replaced by CT angiogram, which is now used in 73% of cases as initial imaging modality. (TEE is now only used in 23%.) However, TEE still has a crucial role when the diagnosis is not confirmed with CT, such as in patients with borderline renal function who cannot have contrast injected, those with body habitus resulting in poor-quality CT, or to rule out localized flap in the ascending aorta and aortic root. As TEE requires at least moderate sedation, the patient may be brought to the operating suite and performed under general anesthesia with preparation to open surgery. Electrocardiogram-gated CT is useful with stable patients when obtaining more precise information, such as detecting entry tear. Intravascular ultrasound (IVUS) provides real-time imaging of the aorta, branch vessels, and flap. It can be used for the diagnosis of malperfusion[55] and intraoperative assistance during endovascular procedures by identifying the true and false lumen.[56] Magnetic resonance imaging (MRI) is accurate in the diagnosis of aortic disease with equivalent—or even superior—sensitivities and specificities to those of CT. However, in the acute setting, the long image acquisition and lack of availability prevent it from being the first choice. After making the diagnosis of aortic dissection, surgical consultation should be obtained regardless of the type.

MEDICAL MANAGEMENT FOR ACUTE AORTIC DISSECTION

Regardless of the extent of dissection, it is crucial to initiate anti-impulse therapy without delay. As discussed earlier, dp/dt is the single critical factor that propagates the disease. Thus not only the blood pressure but also the heart rate needs to be controlled, with a target of 100–120 mm Hg in systolic blood pressure and a heart rate of 60 beats per minute or less.[19] Pain control and monitoring are also essential.[19] High dp/dt can progress the dissection and cause pain, and vice versa (pain can result in high dp/dt). Patients should be admitted to the intensive care unit for monitoring. For better control of hemodynamics, intravenous (IV) administration of the drug is recommended. Central venous line and arterial line placement may be encouraged for strict management. Before the placement of an arterial line, peripheral pulses and blood pressures in all the limbs must be examined to ensure that the appropriate site is selected for monitoring, as branch dissection or true lumen compression can result in reduced blood flow to the affected limb and thus blood pressure measurements would be falsely dropped. The first-line agent is IV beta-blockers.[19] Antihypertensive agents are summarized in Table 148.1.[57] In case of a cocaine-induced condition, selective beta-blockers, such as metoprolol and esmolol, should be avoided but mixed alpha-/beta-blockers, such as labetalol, can be given.[58] When a beta-blocker is contraindicated, nondihydropyridine calcium channel blockers are the second choice to control heart rate. If systolic blood pressures remain above 120 mm Hg after adequate heart rate control, angiotensin-converting enzyme inhibitors and/or other vasodilators, such as a dihydropyridine calcium channel blocker or nitroprusside, should be used. It is important not to use the vasodilators before heart rate control, as these agents may cause reflex tachycardia, which will increase dp/dt. Caution is needed when using beta blockade in patients with severe aortic regurgitation because these drugs can cause compensatory tachycardia or worsen heart failure symptoms.

TABLE 148.1 Antihypertensive Therapy

Antihypertensive Agents	Dosing
First-Line Agents	
Esmolol (β1 antagonist)	IV infusion: bolus of 500 μg/kg over 1 min, followed by 50 μg/kg/min, titration up to 300 μg/kg/min
Labetalol (combined α1/β1/β2 antagonist)	IV: bolus of 20 mg over 2 min, repeated incremental dose of 20–80 mg q10min IV infusion: loading dose of 20 mg followed by 1–2 mg/min infusion
Metoprolol	IV: bolus of 5 mg over 2 min, repeat dose q5min up to 3 doses
Second-Line Agents	
Diltiazem (nondihydropyridine calcium channel blocker)	IV infusion: bolus of 0.25 mg/kg over 2 min followed by 5–10 mg/hr infusion, titration up to 15 mg/hr IV infusion: 5 mg/hr, titration by 2.5 mg/hr min up to 15 mg/hr
Additional Vasodilators (After Heart Rate Control)	
Nicardipine (dihydropyridine calcium channel blocker)	IV infusion: 0.3 μg/kg/min, titration q2min with maximum dose of 10 μg/kg/min; hypotensive effect can be unpredictable, may cause cyanide toxicity
Sodium nitroprusside	IV infusion: 5 μg/min, titration by 5 μg/min q5min with maximum dose of 200 μg/kg/min; unsuitable for prolonged use
Nitroglycerin	

INTERVENTIONS FOR ACUTE AORTIC DISSECTION

Two key purposes of aortic intervention are (1) entry tear resection to prevent aortic rupture and (2) redirect blood flow into the true lumen to correct malperfusion. In addition, type A aortic dissection often requires repair of aortic valve insufficiency. Chronic aortic dissections generally follow the surgical/interventional indications for true aneurysms and will not be discussed in this chapter.

Treatment Strategy for Acute Type A Aortic Dissection

Open Surgical Repair vs. Endovascular Repair vs. Medical Management

Open surgical repair remains a mainstay in acute type A aortic dissection, and patients should urgently be taken to the operating suite. As discussed earlier, medical management carries a higher mortality rate compared with surgical repair. Thoracic endovascular aortic repair (TEVAR) for type A aortic dissection has not been established because of challenges in the landing zone, such as close proximity to the coronary arteries and large landing zone diameter, and the presence of aortic regurgitation that warrants surgical repair.[59] Hybrid repair, open surgical repair for ascending and aortic arch, and concomitant distal stent grafting (frozen elephant trunk) have gained influence, with expectations for resolving downstream malperfusion and positive aortic remodeling,[9,60,61] but have not yet become a standard treatment because of additional surgical risks, including cerebral and spinal complications. Both off-the-shelf ascending stent graft and hybrid frozen elephant trunk prostheses (a stent graft integrated to a Dacron graft) are not readily available in the United States and are currently being tested in clinical trials.

Cerebral Protection During Acute Type A Aortic Dissection Repair

Acute type A aortic repair involves the aortic arch and necessitates temporary arrest of cerebral circulation.[62] Thus several cerebral protection strategies are developed to avoid ischemic insults to the brain. Commonly used cerebral protection strategies include simple profound deep hypothermic (below 14°C) circulatory arrest and moderate (20°C–28°C) to deep (14°C–20°C) hypothermic circulatory arrest with cerebral perfusion. There are two methods for cerebral perfusion: retrograde cerebral perfusion via the superior vena cava and antegrade cerebral perfusion with direct cannulation using balloon-tipped catheters or axillary cannulation. Simple deep hypothermic circulatory arrest and retrograde perfusion provide better visualization of the operative field and do not require exposure or manipulation of arch vessels or axillary artery. Thus most surgeons prefer either of these two methods during hemi arch repair, resecting and replacing the ascending aorta and the proximal aortic arch. However, in patients undergoing total arch repair, prolonged circulatory arrest and arch vessel reconstructions are inevitable. Thus some surgeons prefer antegrade cerebral perfusion to further minimize the ischemic injury during total arch replacement.[63]

Extent of Distal Repair in Acute Type A Aortic Dissection

In most of the cases, aortic dissection extends beyond the transverse aortic arch, and complete resection of all the affected lesions is not possible. It is now well known that eliminating the intimal tear is crucial in preventing the imminent rupture and subsequent distal reintervention.[64] Thus the tear-oriented approach that determines the extent of repair as much as needed for the complete resection of the tear[65] has been widely accepted to minimize surgical risks. About 30%–50% of the entry tear is located in the ascending aorta, 25%–30% in the transverse arch,[8,10,66] and 10% in the distal arch or unknown origin in patients presenting with acute type A aortic dissection.[10,67] When the tear is located in the ascending aorta, the proximal arch, or the lesser curvature of the transverse arch, hemiarch replacement is performed. The arch vessels are preserved by beveling the distal anastomosis and extending the posterior suture line beyond the entry tear in this procedure. When the tear is present in the greater curvature of the transverse arch or extending to the arch vessels, total arch replacement is chosen. Other circumstances that warrant total arch replacement are excessive enlargement and rupture of the false channel in the arch[64] and aortic dissection associated with a large aortic arch aneurysm.

Aortic Root Repair During Acute Type A Aortic Dissection

The proximal extension of aortic dissection and associated aortic valve regurgitation is not uncommon to acute type A aortic dissection. Aortic root replacement and valve replacement are often not necessary—aortic reconstruction using circumferential pledgeted sutures and/or surgical glue to approximate the layers is usually sufficient to repair the lesion. However, if the aortic root is dilated over 55 mm or there is a tear in the root itself, aortic root replacement is reasonably considered. In such cases, valve-sparing aortic root replacement to preserve the native aortic valve and reimplanting the valve in the Dacron graft is used, or the entire root is replaced with a valved conduit. In general, bioprosthetic valves do not require anticoagulation but have shorter durability, which is recommended in older patients (above 60–65 years of age) and patients contraindicated for anticoagulation therapy. On the contrary, mechanical valves require permanent anticoagulation but have lifelong durability, which is recommended in younger patients. The valve-sparing technique is technically demanding and not suitable for damaged or degenerative valves. The choice of valve, bioprosthetic vs. mechanical, or valve-sparing should be comprehensively judged based on the patient's age, concomitant comorbidities, condition of the valve (torn, degenerated), experience of the surgeon, and patient's will.

Cardiac Tamponade

The efficacy of preoperative pericardiocentesis in patients with tamponade in the emergency department has been reported.[68] It should only be indicated in patients who do not respond to aggressive IV resuscitation, and routine performance is never recommended. Intermittent, limited drainage of 30–40 mL is usually sufficient enough to maintain systolic pressure around 90 mm Hg. After transferring the patient with cardiac tamponade to the operating suite, care must be taken at the time of anesthetic induction, as the patient is at risk for further decompensation. It is also important for surgeons to communicate with the anesthesiologists that aggressive volume resuscitation is vital, but administration of pressor agents, especially by bolus, should be avoided. Blood pressure will dramatically recover once the tamponade is released, and the bolused agents will abruptly circulate in the body, which will overshoot the pressure and completely rupture the aorta. When opening the pericardial sac, it should be performed in a controlled fashion with a finger applied to the opening. The speed of drainage is adjusted according to the arterial pressure.

Malperfusion in Type A Aortic Dissection

More than 80% of limb malperfusion spontaneously resolved after central aortic repair,[69] and extraanatomic bypass or endovascular intervention is considered if limb ischemia persists after the repair. Similarly, stroke symptoms associated with cerebral perfusion may resolve symptoms in 80% after the aortic repair.[70] Surprisingly, nearly 80% of patients who present with a coma recover.[70] However, hospital mortality in this subset reaches 60%. It is reported that when a central repair was performed within 5 hours of the onset of coma, mortality was 14% and full recovery of consciousness was observed in 86%, whereas those who presented beyond the 5-hour window were 67% and 17%, respectively.[71] Thus it is reasonable to wait for the comatose patient to regain neurologic function if the time from the onset has passed 5 hours. Lastly, in case of mesenteric malperfusion, because of the high mortality rate—reported as high as 89%[7,10,27,38,39]—a staged approach with fenestration or stenting to restore the blood flow to the viscera may be considered in hemodynamically stable patients before the central repair, in particular, when a patient presents with severe tenderness and/or peritonitic signs.

Postoperative Care for Acute Type A Aortic Dissection

The postoperative team bundle report in the intensive care unit should include the extent of aortic dissection, extent of repair, circulatory arrest time, cardiopulmonary bypass time, and transfusion amount—in addition to the patient's baseline demographics. It is also important to notify the care team about concerns, such as malperfusion syndrome present on admission, as even intraoperative findings may suggest a resolution. Visceral malperfusion on arrival warrants serial abdominal examination, and limb malperfusion needs attention for the development of compartment syndrome. Peripheral pulses in all four extremities should be checked, as they will help for early detections of malperfusion in other organs. For example, patients with diminished upper extremity pulses may have cerebral malperfusion, or patients with lower extremity pulses may have visceral ischemia. Serial neurologic assessment is essential, as the surgical repair can

result in cerebral insults from aortic arch manipulation. When there is a known carotid artery dissection with preoperative stroke symptoms, carotid duplex may be indicated to evaluate the need for subsequent intervention if neurologic symptoms persist. Many of the patients with aortic dissection have underlying long-standing hypertension. Thus systolic blood pressure less than 120 mm Hg may be ideal to prevent propagation of the remaining dissection and prevent suture-line bleeding, but in reality, 140 mm Hg may be needed to sustain renal function. Patients should be warmed when the body temperature is below 36°C. During warming, vasodilation is expected, and appropriate fluid resuscitation and adjustment of antihypertensive drips are needed. In addition to routine blood testing, coagulation tests should be checked. The use of hypothermia during aortic repair and consumption of coagulants in the false lumen may cause postoperative coagulopathy. Thromboelastography is also helpful for the diagnosis. Lactic acidosis at the time of arrival to the unit is often seen because of preoperative malperfusion syndrome and intraoperative circulatory arrest. However, persistent lactic acidosis of more than 2–3 hours should trigger further investigations to rule out visceral/limb malperfusion and low cardiac output. After confirming that no further interventions are planned (i.e., re-exploration for bleeding, stenting, fasciotomies) and the patient is hemodynamically stabilize, the patient can be extubated. Postoperative hypoxemia in patients with aortic dissection is not uncommon because of the inflammatory process from the disease and hypothermic circulatory arrest. Urine output should be monitored for volume and color. If oliguria is seen, renal duplex should be obtained to evaluate the blood flow. Wine-colored urine suggests hemolysis that can be associated with paravalvular leakage and a kinked graft. If a mechanical prosthesis has been used to replace the aortic valve, anticoagulation can generally be held for 48 hours postoperatively. Aspirin is given when branches were reconstructed. Guidelines recommend contrast-enhanced CT scan is obtained before discharge to assess the repair and extent of any residual dissection.[19]

Treatment Strategy for Acute Type B Aortic Dissection

Open Surgical Repair vs. Endovascular Repair vs. Medical Management

Unlike type A aortic dissection, medical management is the gold-standard treatment for acute type B aortic dissection, unless symptomatic or complicated. American guidelines recommend TEVAR as the first option to treat acute type B dissection with complications,[19] whereas open repair is reserved for patients who are anatomically unfit for endovascular repair. Approximately one-third of acute type B aortic dissections present as—or progress to—complicated type.[7–11,72]

Favorable long-term outcomes after TEVAR for uncomplicated acute type B aortic dissections during the subacute phase were reported in a randomized controlled study (Investigation of Stent Grafts in Patients with Type B Aortic Dissection, INSTEAD-XL trial) after 2 years of follow-up.[73] Considering the outcomes of INSTEAD-XL and the literature reporting positive remodeling after TEVAR in uncomplicated type B aortic dissection,[74] European guidelines recommended considering TEVAR for the subset. Thus uncomplicated type B dissection patients with high-risk features with late aortic interventions may reasonably receive TEVAR in the subacute phase. There are two other ongoing trials[74] to further prove the safety and durability of TEVAR for uncomplicated type B aortic dissections. In the near future, more aggressive indications of TEVAR in uncomplicated acute type B aortic dissections may be justified. Although IMHs are treated as classical aortic dissections in acute type A, acute type B IMHs should be treated differently from the classical type B. Acute type B IMHs are known to regress in 32% and resolve in 60%,[75] and there is no evidence to treat uncomplicated type B IMHs.

TEVAR for Acute Type B Aortic Dissection

The primary goals of TEVAR are to seal the entry tear and to re-expand the true lumen. The secondary goal is to stabilize the dissected aorta to induce positive remodeling and prevent future complications. The technology has improved over the decade, and low-profile delivery systems (16–26 French) are available. Thus most of the procedures are performed percutaneously. An iliac conduit (a Dacron graft to the iliac artery anastomosed in an end-to-side fashion) may be required in small or diseased iliac/femoral arteries. Four companies supply eight different covered stent grafts to the U.S. market, with anatomic requirements and instructions for use varying based on device: landing zone diameter of 16–45 mm, and most of the devices require at least 20 mm (one with 15 mm) landing zone length. Covered stents are used to close the entry tear, but the distal extension beyond T8 carries higher risks for postoperative spinal cord ischemia. When true lumen compression is seen in the thoracoabdominal aorta, the extension with uncovered stents may be used.

Endovascular Fenestration for Aortic Dissection Complicated with Malperfusion Syndrome

Fenestration of the dissection flap with endovascular intervention can also be used for true lumen expansion. Catheter-based fenestration is performed with either IVUS or fluoroscopic guidance. In general, a dissection septum is punctured with a needle-based re-entry catheter or a catheter with a super-stiff wire to create a hole in the septum.[76,77] Then, a guidewire is passed through the re-entry catheter and across the membrane, and the hole is dilated with balloons large enough to increase the flow in the true lumen. The other technique, named the "cheese-wire" maneuver, snares the guidewire crossing the septum from the contralateral transfemoral access to slice through the membrane.[78] When a static malperfusion is present in the visceral branches, stenting of the branches is performed with a transfemoral, transaxillary, or transbrachial approach.

Descending Thoracic and Thoracoabdominal Aortic Replacement

Open replacement of the descending thoracic and thoracoabdominal aorta is performed via a left posterolateral thoracotomy or thoracoabdominal incision under single-lung ventilation. Partial left heart bypass with pulmonary vein drainage and femoral artery return or full cardiopulmonary with femoral vein drainage (or pulmonary artery drainage) and femoral artery return are used for support. The goal of the operation is to eliminate the entry tear as in type A aortic dissection. During distal aortic repair, the spinal cord, viscera, and kidney are at risk for ischemic insults. Hypothermia, cerebrospinal fluid drainage, and distal aortic perfusion are essential adjuncts to protect the spinal cord. Selective visceral and renal perfusions are applied when these are involved in the repaired segment. The aorta is replaced with a Dacron graft, and intercostal arteries in T8–T12—the levels of a major spinal cord feeder (artery of Adamkiewicz)—are recommended to reattach to the graft to prevent both immediate and delayed spinal cord injury.[19] When complete resection of the dissection is not performed, the distal anastomosis is performed to occlude the false lumen to reconstruct the aorta. If the false lumen has vital branches coming off, the dissection septum in the remaining distal segment is cut to allow the blood to flow as a double-barrel.

Open Aortic Fenestration

This procedure is now rarely performed since the advent of endovascular techniques. A report from the Mayo Clinic in 2002 showed they required the technique in only 1.6% (14/857) of the aortic dissection patients.[4] It is usually reserved for patients requiring expeditious relief of multiorgan ischemia (i.e., a combination of visceral, renal, and limb malperfusion) without degenerative or aneurysmal changes in the affected aorta. It is effective in more than 90% of the cases presenting with end-organ ischemia.[4] The technique does not necessitate single-lung ventilation, and the short clamp time minimizes ischemic insults to organs. The goal of open aortic fenestration is to create a large enough re-entry to allow flow in the true lumen in the thoracoabdominal aorta where the vital branches take off. The supraceliac aorta and infrarenal aorta are clamped, and the longitudinal aortotomy is made in the thoracoabdominal aorta to visualize the branches in case of branch thrombectomies. The dissection septum is excised up to the level of the celiac trunk and below the renal arteries. The aortotomy is then closed with a running suture.

Postoperative Management After Interventions for Acute Type B Aortic Repair

Postoperative management is performed in a similar way to acute type A aortic dissection repair. Strict blood pressure should be performed, in particular, in patients who had open aortic fenestration because of the long suture line in a thin and fragile aorta. In addition, monitoring for spinal cord injury is required. The care team should be informed of the level the aorta was treated, as risks of spinal cord injury are much higher with more extensive repair, and T8–T12 is involved in the treated lesion. When a cerebrospinal fluid drain is placed in the operating suite, it should be drained at the maximum rate of 15 mL/hour to maintain the cerebrospinal pressure below 10 mm Hg. Once the presence of spinal cord ischemia is suspected, the cerebrospinal fluid should be drained without a limit to target the pressure below 5 mm Hg. Systolic blood pressure is raised above 140 mm Hg, blood is transfused to maintain hemoglobin level above 10 mg/dL, and cardiac index is targeted above 2.5 L/min/m^2.

LONG-TERM MANAGEMENT OF AORTIC DISSECTION

Aortic disease is a lifelong, progressive illness. Patient education on compliance with antihypertensive medications and imaging surveillance is imperative (Fig. 148.4). Compliance with beta-blocker use and blood pressure control is warranted to avoid future aortic events.[79] A recent study from Sweden[80] showed that long-term survival after type A aortic dissection repair had similar survival, up to 7 years, when compared with that of age- and sex-matched controls. However, mortality in patients with type A aortic dissection repair acutely rose after 8 years, with a 10-year mortality of 130% compared with the control. The increased mortality is most likely from the progression of the disease. Again, the importance of lifelong surveillance cannot be overemphasized.

CONCLUSIONS

Recognition of patients with high-risk features for acute aortic dissections is essential for timely diagnosis. Chest/abdomen/pelvis CT angiogram is the gold-standard imaging modality to evaluate the aorta and for classifying type A and type B aortic dissections. Strict control of heart rate and blood pressure is initiated without delay, regardless of type. Patients should further be assessed for complications, such as malperfusion syndrome. Acute type A dissection warrants urgent surgical repair, whereas acute type B dissection should be medically treated, unless complications are present or develop. Uncomplicated type B aortic dissection may be indicated for TEVAR to induce positive aortic remodeling and prevent future aortic events. However, before extending this indication, further data acquisition is warranted for feasibility and durability. Imaging surveillance is crucial to screen for aortic dilation during follow-up.

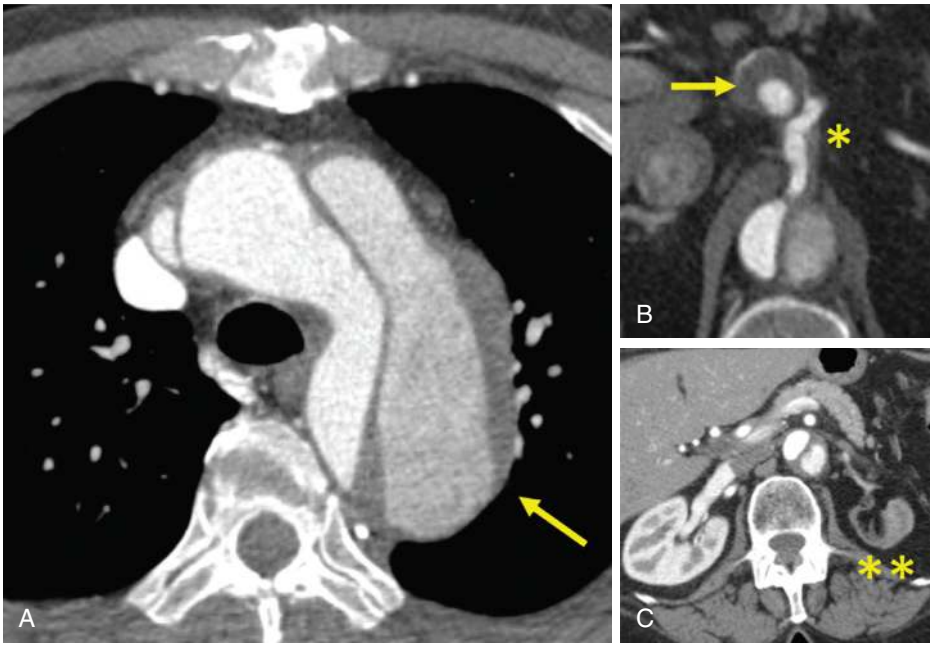

Fig. 148.4 Chronic residual type A aortic dissection (axial view). A proximal descending aortic aneurysm has developed **(A)**, along with a celiac artery aneurysm **(B)**. The left renal artery branches off from the false lumen, and a resultant atrophic left kidney is seen **(C)**. *Arrow,* aneurysmal change; *, dissected celiac artery; **, atrophic left kidney.

KEY POINTS

- Patients highly suspicious for acute aortic dissection should undergo urgent CT angiogram along with surgical consultation.
- After diagnosis is obtained for aortic dissection, anti-impulse therapy with beta-blockers as first-line agents should be initiated without delay. Vasodilators should not be given before heart rate control.
- Open surgical repair remains the mainstay for acute type A aortic dissection.
- Complicated acute type B aortic dissection should undergo endovascular treatment when anatomically applicable.
- Uncomplicated acute type B aortic dissection may benefit from endovascular treatment in the subacute phase.
- Postoperative care of both type A and type B aortic dissection consists of blood pressure management, addressing coagulopathies, and monitoring for malperfusion complications.
- Lifelong imaging surveillance and blood pressure control are warranted in patients with any type of aortic dissection.

References for this chapter can be found at expertconsult.com.

ANNOTATED REFERENCES

Charlton-Ouw KM, Sandhu HK, Leake SS, et al. Need for limb revascularization in patients with acute aortic dissection is associated with mesenteric ischemia. *Ann Vasc Surg.* 2016;36:112–120.

This is an important paper that shows limb malperfusion in acute type A aortic dissection spontaenously resolves in 80% after central repair.

Hiratzka LF, Bakris GL, Beckman JA, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. *J Am Coll Cardiol.* 2010;55(14):e27–e129.

These are the guidelines established by the American societies in 2010, which continue to be the gold standard for diagnosisng and treating thoracic aortic disease.

Lombardi JV, Hughes GC, Appoo JJ, et al. Society for Vascular Surgery (SVS) and Society of Thoracic Surgeons (STS) reporting standards for type B aortic dissections. *J Vasc Surg.* 2020;71(3):723–747.

This is the new reporting system developed by the Society of Thoracic Surgeons and Society for Vascular Surgery for acute aortic dissection to better accomodate the modern era with endovascular aortic repair options. This system classifies aortic dissections into type A, type B, and type I, depending on the entry tear site and not the extension of the dissection.

Yang B, Patel HJ, Williams DM, et al. Management of type A dissection with malperfusion. *Ann Cardiothorac Surg.* 2016;5(4): 265–274.

This is a well-summarized paper containing many diagrams on how to manage patients with malperfusion in acute type A aortic dissection.

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Mesenteric Ischemia

Dean J. Arnaoutakis and Thomas S. Huber

INTRODUCTION

Mesenteric ischemia is a generic term that implies inadequate blood flow to the intestines. It is relevant from a clinical standpoint as two separate disease processes: acute mesenteric ischemia (AMI) and chronic mesenteric ischemia (CMI). Although the underlying process is similar (i.e., inadequate intestinal blood flow) between the two conditions, the clinical presentation, diagnostic concerns, and treatment algorithms are different. CMI is usually related to mesenteric artery atherosclerotic occlusive disease and is relevant to intensive care physicians primarily because of the multiple organ dysfunction syndrome (MODS) that occurs after revascularization. AMI can arise from a variety of underlying conditions, including arterial emboli, in situ thrombosis in the setting of mesenteric arterial occlusive disease, mesenteric venous thrombosis, nonocclusive mesenteric ischemia (NOMI), and acute aortic dissections. AMI is relevant to intensivists because it often develops in critically ill patients (e.g., post–coronary artery bypass, acute pancreatitis), and revascularization can lead to a profound inflammatory response. A thorough understanding of both clinical entities is essential for all intensive care physicians. The underlying pathophysiology and treatment of CMI will be discussed first to provide a foundation for addressing AMI. Although not traditionally considered AMI, isolated colon ischemia will also be discussed for completeness.

CHRONIC MESENTERIC ISCHEMIA

Pathophysiology

The underlying pathophysiology of CMI is the inability to achieve postprandial hyperemic intestinal blood flow. Intestinal blood flow in the normal fasting state is fairly modest, but may increase up to 35% after eating, with the magnitude contingent upon the size and composition of the meal.[1,2] The majority of the hyperemic changes occur in the pancreas and small bowel with a peak within 30–60 minutes after eating.[3,4] In patients with significant mesenteric arterial occlusive disease, this postprandial hyperemia is not possible, and patients develop ischemic pain similar to angina pectoris, appropriately termed *mesenteric angina.*

The normal mesenteric circulation is fairly redundant and has a rich collateral network (Fig. 149.1). The celiac axis (CA) communicates with the superior mesenteric artery (SMA) through the superior and inferior pancreaticoduodenal arteries. The SMA communicates with the inferior mesenteric artery (IMA) via the meandering mesenteric artery that travels within the proximal mesentery. This collateral has multiple eponyms, but should be differentiated from the less significant collateral, the marginal artery of Drummond, that is located in the distal mesentery. Lastly, the IMA communicates with the internal iliac artery via the superior and middle hemorrhoidal arteries. The symptoms of mesenteric ischemia usually do not occur unless two of the three mesenteric vessels (i.e., CA, SMA, and IMA) are significantly diseased because of this rich collateral network. However, symptoms may occur with isolated SMA disease in the absence of adequate collaterals.[5–7]

The overwhelming majority of mesenteric artery stenoses are the result of atherosclerosis. A variety of other etiologies have been reported, including neurofibromatosis, fibromuscular disease, rheumatoid disorders, aortic dissection, isolated mesenteric artery dissection, radiation, Buerger disease, and certain drugs, although these are collectively less common. Clinically symptomatic mesenteric artery occlusive disease (i.e., CMI) is relatively rare despite the prevalence of asymptomatic mesenteric artery stenoses. Indeed, a hemodynamically significant mesenteric artery stenosis (>50% diameter reduction) has been reported in up to 27% of patients with peripheral arterial occlusive disease undergoing a catheter-based arteriography[8] and in up to 5%–10% of unselected patients at autopsy.[9] The atherosclerotic process usually involves just the origin of the mesenteric vessels. Patients with occlusive disease in the CA and SMA often have renal artery stenoses, along with disease in the cerebral and lower extremity arteries—these risk factors for atherosclerosis are similar for all vascular beds.

Clinical Presentation and Diagnosis

The appearance and presentation of patients with CMI is fairly characteristic. The typical patients are cachectic, elderly women with a history of extensive tobacco use. Indeed, CMI is one of the few cardiovascular problems more prevalent in women than in men. A recent meta-analysis of almost 19,000 patients undergoing revascularization for CMI (both open and endovascular) reported that the mean age was 68.7 years: 77.8% were women, the majority were smokers, hypertensive, and had evidence of peripheral arterial disease.[10]

Abdominal pain is usually the presenting symptom. It initially occurs postprandially, although it may progress to a persistent nature in the latter stages of the disease process. Unfortunately, the pain has no specific characteristics. As a result of the pain, patients develop a fear of food and avoid eating. The net result is a predictable weight loss with a mean of 20–30 lbs. in several recent clinical series.[11–13] Notably, Mansukhani and colleagues[14] reported that 35% of the patients undergoing mesenteric revascularization for CMI in their series had a body mass index (BMI) >25, and they attributed this to the epidemic of obesity in our country. It should be noted that the etiology of weight loss is presumably from poor nutrition rather than an abnormality in intestinal absorption, although the exact impact of chronic malperfusion on the gut microbiome and enterocyte function has yet to be elucidated. In addition to postprandial abdominal pain, patients may develop nausea, emesis, constipation, and/or diarrhea. Patients with CMI frequently have evidence of diffuse peripheral vascular disease, although there are no characteristic physical examination findings.

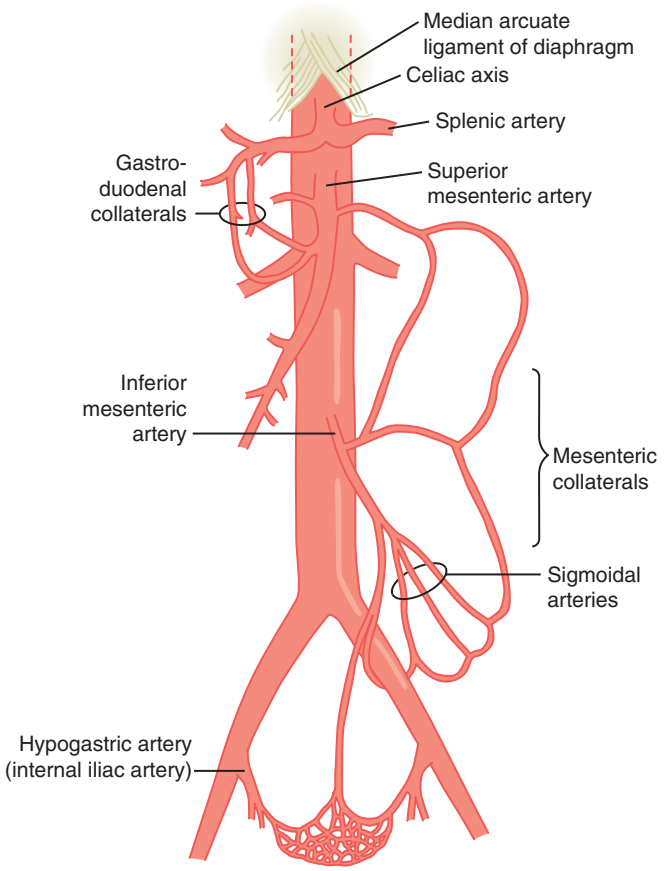

Fig. 149.1 Diagram of the collateral pathways for the mesenteric. The celiac axis and superior mesenteric arteries communicate through the superior and inferior pancreaticoduodenal arteries, respectively. The superior and inferior mesenteric arteries communicate through the meandering artery and the marginal artery of Drummond, with the meandering artery serving as the dominant collateral. The inferior mesenteric artery communicates with the internal iliac artery through the hemorrhoidal vessels. (Modified from Hanson KJ. Mesenteric ischemia syndromes. In Dean RH, Yao JST, Brewster DC, eds. *Current Diagnosis and Treatment in Vascular Surgery.* Englewood Cliffs, NJ: Appleton & Lange/Prentice Hall; 1995:264.)

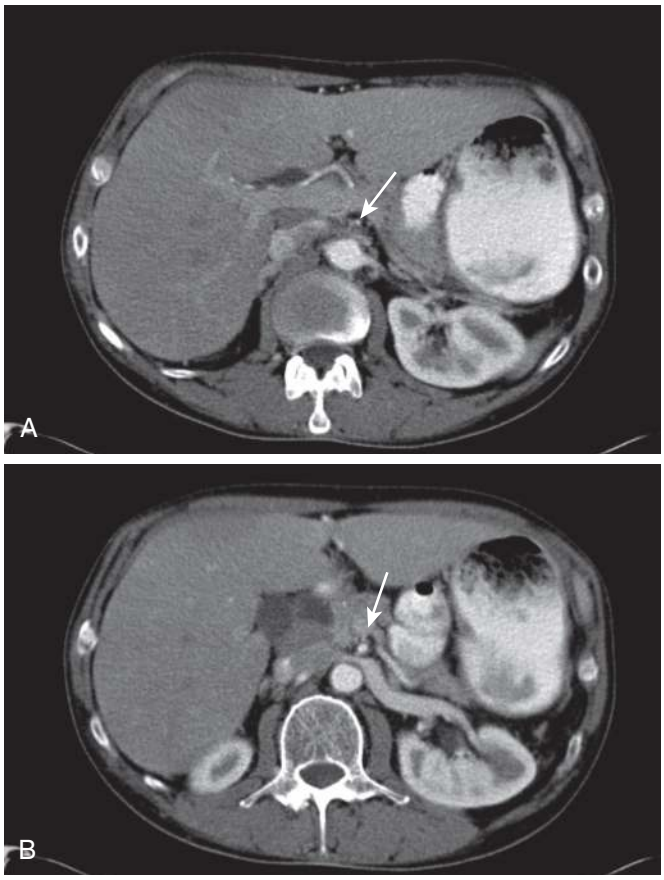

Fig. 149.2 CT arteriograms in a patient with an occluded celiac axis and superior mesenteric artery (SMA). **A.** The origin of the SMA is shown with the arrow. There is no contrast within the lumen of the vessel at this cross section. **B,** The SMA is shown with the *arrow* in this cross section that is 10 mm caudal to the first image. The artery is patent at this level, as reflected by the contrast within the lumen.

The diagnosis of CMI requires the appropriate clinical history and the presence of significant mesenteric artery occlusive disease. The diagnostic approach is a stepwise one with consideration of the more common problems first. Although the appearance and clinical presentation of patients with CMI is fairly characteristic, the differential diagnosis of patients with abdominal pain and weight loss is extensive and includes gastrointestinal malignancy first and foremost. Indeed, CMI is usually not even considered by most primary care providers, and this is reflected by the fact that the mean duration from presentation to diagnosis oftentimes exceeds a calendar year and 2.8 diagnostic tests.[15] The initial diagnostic work-up for patients with abdominal pain and weight loss should include esophagogastroduodenoscopy, colonoscopy, abdominal ultrasound, and an abdominal/pelvic computed tomography (CT) scan.[16,17] Notably, gastric ulcers are relatively common in patients with CMI and likely result from ischemia.[18,19] A surprising number of patients are subjected to cholecystectomy as part of their work-up before the definitive diagnosis of CMI is made.

Mesenteric duplex is an excellent *screening* tool for mesenteric artery stenosis, with reported sensitivity and specificity rates of approximately 80%.[20,21] However, it is technically challenging, operator dependent, and not available in all centers. A variety of criteria have been proposed to grade the severity of stenoses based upon the systolic/diastolic velocities or frequency shifts, with a peak systolic velocity of >275 cm/s and 200 cm/s being reliable predictors of a >70% stenosis in the SMA and CA, respectively.[21,22] A variety of provocative tests have been proposed to unmask clinically significant mesenteric artery stenoses, although their utility is unclear and they have not achieved widespread use.[23,24]

Multidetector helical CT arteriography with 1-mm collimation and three-dimensional reconstructions has largely replaced catheter-based contrast arteriography as the *diagnostic* study of choice for patients with CMI (Fig. 149.2) and is usually sufficient to plan surgical revascularization.[16,17,25–28] CT arteriography is safe, noninvasive, readily available, and accurately identifies occlusive disease in the SMA and CA. Furthermore, it is useful for visualizing large, meandering collateral vessels between the mesenteric vessels that suggest hemodynamically significant stenoses. Additionally, CT is now the first-line diagnostic modality for many other intraabdominal processes.

Catheter-based contrast arteriography is useful for evaluating the mesenteric circulation and has traditionally been used as the definitive *diagnostic* test for CMI (Fig. 149.3A). The major advantage of catheter-based arteriography over CT arteriography is that therapeutic interventions can be performed at the time of the diagnostic procedure. Furthermore, intraarterial pressure measurements can be obtained across a stenosis to determine their hemodynamic significance. However, it is an

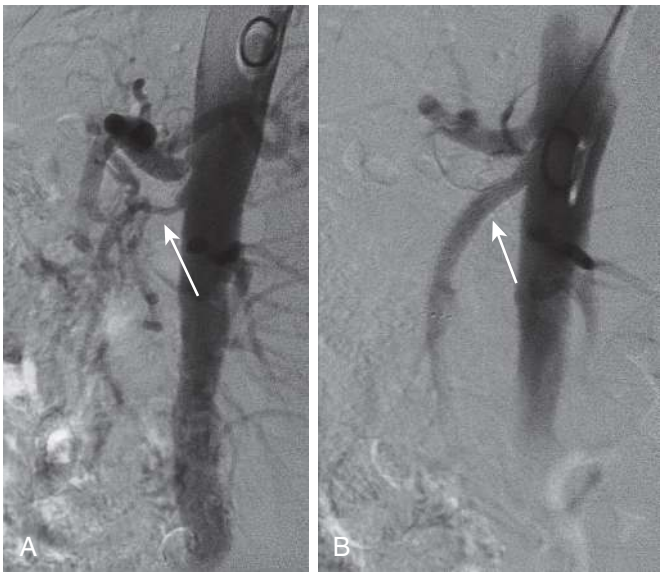

Fig. 149.3 Lateral catheter-based aortogram of a patient with chronic mesenteric ischemia. **A**, There is a moderate stenosis in the proximal superior mesenteric artery (SMA), as shown with the *arrow*. **B,** No residual stenosis is seen in the superior mesenteric artery (SMA) after placement of a covered intraluminal stent.

invasive procedure with a small, yet finite complication rate. A lateral arteriogram is mandatory as part of the examination to accurately assess the origins of the CA and SMA because of their location on the anterior aspect of the aorta. The significant findings on arteriogram include the presence of ostial stenoses of the CA and SMA, large mesenteric collaterals, and central aortic atherosclerosis. A small percentage of patients with CMI may have mesenteric artery aneurysms, presumably from increased flow through the collateral vessels.

Magnetic resonance (MR) arteriography has been used as a diagnostic study for patients with CMI and offers many of the advantages of CT arteriography.[29–31] However, it is not as universally available as CT arteriography. Furthermore, it is not practical and may be contraindicated for many patients, including those in the intensive care unit. Lastly, MR arteriography tends to overestimate the degree of stenosis in the mesenteric vessels.

Treatment Strategies

All patients with CMI require revascularization unless they are so debilitated that intervention is not indicated or they have opted for palliative care.[16,17] The natural history of the untreated CMI is death either from inanition or bowel infarction. The theoretical treatment options include medical management with total parenteral nutrition or revascularization by either endovascular or open surgical techniques. The role of long-term parenteral nutrition is very limited given its complexity, expense, and complications, particularly those associated with the infusion catheters. As such, revascularization via endovascular or open surgery is the mainstay of treatment. Endovascular treatment (i.e., angioplasty with intraluminal stent) has been adopted by most centers as the initial revascularization option given its minimally invasive approach. Open surgical revascularization has been reserved for patients that are not amenable to endovascular treatment, endovascular failures, and a select group of younger, healthier patients. Several meta-analyses comparing open and endovascular revascularization for CMI have reported that the endovascular approach is associated with a lower periprocedure complication rate and a higher longer-term recurrence rate, but no significant difference in perioperative or longer-term mortality.[10,32–35] Notably, the development of recurrent stenoses and the need for remediation have not been associated with a decrease in survival and has not necessarily resulted in the development of AMI. The recent development of lower-profile (i.e., smaller-diameter) angioplasty balloon/stent systems has further extended the applications of the endovascular approach, and reasonable, short-term results have been reported for patients with occluded mesenteric vessels (vs. stenotic) and other complex lesions that have traditionally precluded endovascular intervention.[36,37]

Endovascular Revascularization

The preoperative evaluation before endovascular treatment is essentially the same for all catheter-based contrast arteriography. Patients with a contrast allergy should be treated with an appropriate steroid preparation, and patients with elevated serum creatinine levels (serum creatinine 1.5–2.0 mg/dL) should receive gentle periprocedural hydration.

Percutaneous arterial access can be obtained through either the femoral, brachial, or radial approach. The upper extremity approach is usually favored for therapeutic procedures given the downward orientation of mesenteric vessels off the anterior aspect of the aorta and the vector forces associated with the catheters/sheaths. A flush aortogram is performed in both the anteroposterior and lateral projections. Because most lesions in the SMA and CA are orificial and located in the proximal 2 cm, selective catheterization is not usually necessary unless a distal lesion is suspected or the extent of the lesion cannot be determined. A >50% diameter reduction of the SMA is usually considered clinically significant regardless of whether or not the CA is involved. However, the diagnosis of CMI should be questioned in the presence of an isolated CA stenosis. Symptomatic stenoses can be treated at the time of the diagnostic catheter-based arteriogram (see Fig. 149.3B). The orificial stenoses in the mesenteric vessels are usually refractory to angioplasty alone, and primary stenting with a covered stent is recommended.[16,17] Balloon angioplasty with selective stenting is reserved for midsegment lesions. Balloon-expandable stents (vs. self-expanding stents) are preferred for the orificial stenoses because of their superior radial forces and controlled deployment mechanism. The benefit of covered stents in this location may be related to the physical barrier of the fabric that inhibits the intimal hyperplastic ingrowth.[38–40]

The postoperative care after mesenteric angioplasty/stenting is comparable to that for other peripheral endovascular procedures. Patients are typically observed in the hospital overnight and started on dual antiplatelet therapy. The optimal antiplatelet regimen and duration remains unresolved, but most providers favor 1–6 months of dual antiplatelet therapy.[41,42] Patients should likely be maintained (or started) on a cholesterol-lowering agent (i.e., statin), and there may be a role for rivaroxaban, although the utility of this in the setting of CMI remains poorly defined.[41,43] Most patients notice a marked improvement of their postprandial symptoms shortly after the procedure. A fasting mesenteric duplex ultrasound scan can be obtained on the morning after the procedure to serve as a baseline. Elevated velocities are occasionally noted in the duplex scan despite a technically satisfactory arteriographic result and complete resolution of the preoperative symptoms.[44–46] The explanation for these abnormal duplex findings is unclear, and thus the decision to reintervene is based on the presence of recurrent symptoms and/or a significant progression in the abnormal duplex findings. A repeat duplex examination is performed at 1 month and then every 6–12 months thereafter.[17] Aspirin (81 mg/day) is continued indefinitely after the dual antiplatelet regimen is completed.

Open Surgical Revascularization

The preoperative work-up for patients undergoing open mesenteric revascularization is comparable to that for other major vascular surgical procedures and includes optimization of all organ systems. Multiple

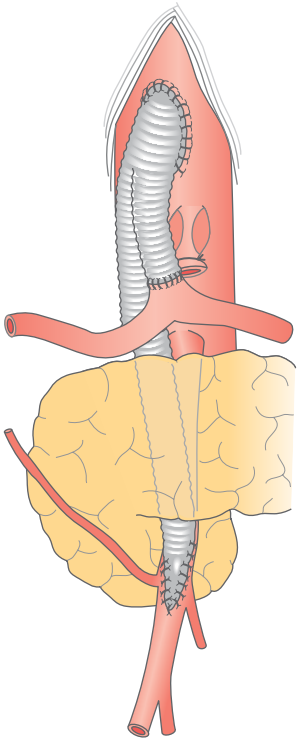

Fig. 149.4 Completed antegrade bypass from the supraceliac aorta to both the celiac axis and the superior mesenteric artery. (From Huber TS, Lee WA. Mesenteric vascular disease: Chronic ischemia. In Cronenwett JL, Johnston W, eds. *Rutherford's Vascular Surgery,* 7th ed. Philadelphia, PA: Elsevier; 2010: Fig. 148.6.)

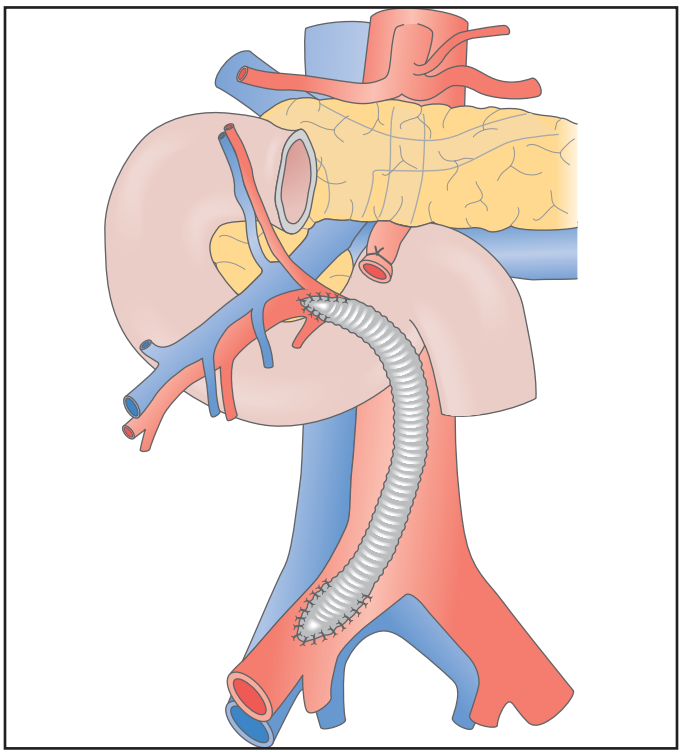

Fig. 149.5 Completed retrograde bypass from the terminal aorta/proximal right common iliac artery to the superior mesenteric artery bypass. (From Huber TS, Lee WA. Mesenteric vascular disease: Chronic ischemia. In Cronenwett JL, Johnston W, eds. *Rutherford's Vascular Surgery,* 7th ed. Philadelphia, PA: Elsevier; 2010: Fig. 148.7.)

algorithms have been developed to reduce the cardiac risk for vascular surgical patients undergoing noncardiac procedures, including those from the American Heart Association and the American College of Cardiology.[47] Importantly, the preoperative work-up should be expedited given the severity of the underlying condition and the potential to progress to AMI. All patients should likely be on an antiplatelet agent and a cholesterol-lowering agent, preferably a statin.[48] A CT or catheter-based contrast arteriogram is mandatory to both confirm the diagnosis and plan the operative procedure.[17] There is no clear role for extended preoperative parenteral alimentation to replete the nutritional stores and, indeed, it may be detrimental.

A variety of open surgical procedures have been reported, although the antegrade aortoceliac/SMA bypass (Fig. 149.4) and the retrograde aorto/iliac-celiac/SMA bypass (Fig. 149.5) are the most common.[11,49] Unfortunately, a randomized controlled trial comparing these two approaches has not been performed because of the relative infrequency of the underlying problem. The advantages of the antegrade aorto-CA/SMA bypass are that both mesenteric vessels are revascularized and the supraceliac aorta (the origin of the bypass) is usually free of atherosclerotic occlusive disease. The major disadvantage is the complexity of the procedure related to aortic exposure and clamping along with tunneling of the bypass graft. In contrast, retrograde aorto/iliac-CA/SMA bypass entails a more straightforward exposure and avoids the need for an aortic cross-clamp, provided that the graft comes off of the iliac artery. However, there is a theoretical concern that the graft is prone to kinking given its obligatory retrograde course that traverses both caudal to cephalad and posterior to anterior. The optimal choice for a specific patient is dictated by their anatomy (i.e., distribution of their occlusive disease), comorbidities, and provider expertise. Notably, neither configuration has been shown to be superior in terms of longer-term patency.[11,17,49]

The immediate postoperative care for patients undergoing revascularization for CMI is frequently complicated by the development of MODS and is distinctly different from that associated with most other abdominal vascular surgical procedures such as aortobifemoral bypass for aortoiliac occlusive disease.[11,50] This propensity to develop MODS likely accounts for the prolonged intensive care and total hospital length of stay and is one of the leading causes of death in the postoperative period. The responsible mechanism for this MODS is likely related to a mesenteric ischemia-reperfusion injury inherent to the revascularization. This process has been shown to induce a severe inflammatory response mediated by cytokines, interleukins, and other inflammatory mediators that can cause both local and distant organ injury.[51] In a detailed study, Harward and colleagues[50] characterized the individual organ system dysfunction after revascularization for both AMI and CMI. They reported that the serum hepatic transaminases (i.e., serum glutamic-oxaloacetic transaminase [SGOT] and serum glutamic-pyruvic transaminase [SGPT]) increased 90- to 100-fold immediately postoperatively and did not normalize for 7–10 days, the platelet counts fell below 40,000 units within 12–24 hours and remained abnormal for the first 3–6 days, and the prothrombin time (PT) and partial thromboplastin time (PTT) became elevated and stayed elevated also for 3–6 days. Perhaps most notably, they reported that the overwhelming majority of patients developed a significant pulmonary injury characterized by an elevated mean shunt fraction and a radiographic picture of the acute respiratory distress syndrome that manifested between 1 and 3 days and persisted for 5–8 days. Jimenez and colleagues[11] documented a 64% incidence of MODS and a 53% incidence of prolonged mechanical ventilation after antegrade revascularization for CMI and further corroborated the findings by Harward and colleagues[50]

The optimal management strategy for patients in the early postoperative period after open mesenteric revascularization is to support the individual organ systems until the dysfunction resolves. Admittedly, not all patients develop organ dysfunction, but the incidence is moderately high and somewhat unpredictable. The optimal ventilator management remains unresolved. Patients are typically extubated in the early postoperative period when they satisfy the various weaning criteria and clinicians have been reluctant to maintain them on mechanical ventilation in anticipation that they may develop a lung injury. However, it is relatively common that they need to be reintubated and started back on mechanical ventilation. The thrombocytopenia and coagulopathy are usually managed expectantly, with platelet and/or plasma transfusions reserved for severely depressed platelet counts and/or any clinical evidence of bleeding. Notably, the report by Harward and colleagues[50] suggested that the inherent coagulopathy after mesenteric revascularization was not responsive to vitamin K. Patients should be started and maintained on total parenteral nutrition throughout the postoperative period until their bowel function returns. This is particularly important given the fact that the majority of patients are severely compromised from a nutritional standpoint. Unfortunately, patients may have a prolonged ileus after revascularization, and total parenteral nutrition may be required until bowel function returns. The bypass should be interrogated with a mesenteric duplex or axial imaging before discharge to confirm the technical adequacy of the reconstruction. Patients with acute changes in their clinical status should also undergo mesenteric imaging to confirm that their bypass is patent. It can be difficult to differentiate between MODS that is a sequelae of the ischemia-reperfusion injury and AMI secondary to bypass graft thrombosis. Serum lactate levels may be helpful in this setting.

All patients who undergo revascularization for CMI require long-term follow-up. Patients are seen frequently in the early postoperative period until all their active issues resolve and then every 6 months thereafter with a mesenteric duplex to confirm graft patency and to identify any graft- or anastomotic-related problems. The proposed surveillance protocol with serial imaging outlined after endovascular revascularization is appropriate after open revascularization.[17] Objective assessment of graft patency is critical and significantly better than the return of symptoms that has been used as a surrogate marker.[52] Recurrent symptoms of CMI should be managed similar to the index presentation in terms of diagnosis and treatment.[17]

Diarrhea is a common complaint after revascularization for CMI and can persist for several months. It is more common in patients with perioperative diarrhea and can be so severe that it necessitates total parenteral nutrition. Notably, Jimenez and colleagues[11] reported that 33% of the patients in their series experienced significant postoperative diarrhea, with 24% experiencing symptoms beyond 6 months. Furthermore, Kihara and colleagues[53] reported that patients had almost 2 stools/day (1.9 ± 0.4) after revascularization for CMI. The etiology of the diarrhea is unclear but may be related to intestinal atrophy, derangements in the gut microbiome, or disruption of the mesenteric neuroplexus.

Outcome

The outcome after mesenteric revascularization for CMI is quite good.[10,32–35] The perioperative mortality rate after open surgical revascularization is <5% in high-volume centers and <15% in series reporting the nationwide experience.[11,12,49,52–57] The mortality rate after endovascular treatment is consistently <5%.[13,58–63] The corresponding complication rates are approximately 30%–50% and 15% for the open and endovascular treatments, respectively. The initial technical success rate for the endovascular treatment is approximately 90%. The objectively documented 5-year patency rates after open revascularization are approximately 75%; patency rates after endovascular treatment are not as well described, but likely fall short of those reported for the open treatment. The 5-year survival after either treatment is approximately 75%, and most patients return to their presymptom weight.

ACUTE MESENTERIC ISCHEMIA

AMI is the endpoint for several distinct disease processes. Mesenteric emboli and in situ thrombosis are the most common etiologies, accounting for approximately 50% and 25% of AMI cases, respectively.[64,65] NOMI (20%), mesenteric venous thrombosis (5%), and aortic dissections account for the remaining cases. The underlying pathophysiology of AMI is that the impaired intestinal perfusion leads to mucosal compromise. This results in the release of the intracellular contents, increased cellular permeability, and influx of substances (including bacteria and lipotoxins) from the lumen of the bowel into the circulation. This can lead to the massive activation of the systemic inflammatory response, resulting in both local and distant organ dysfunction (e.g., lung injury). If the impaired perfusion persists, bowel infarction with perforation and peritonitis ensues. The immediate clinical concerns for patients with AMI are to reverse the underlying clinical condition and prevent bowel infarction. The clinical presentation, diagnostic approach, and treatment for the various causes of AMI are similar, but there are distinct differences that mandate individual consideration. AMI from an embolus will be discussed in depth given the fact that it is the most common etiology, and the respective differences will be highlighted for the other causes. Fortunately, the underlying etiology can usually be determined from the history and clinical setting. Not surprisingly, the morbidity and mortality associated with AMI are significant.[16] The optimal therapy requires prompt diagnosis and definitive treatment, although this is often difficult given the susceptible patient population and common clinical scenarios. Indeed, AMI may be either the cause or the effect of the patient's critical illness.

Embolus

Pathophysiology

The emboli responsible for AMI usually originate from the heart and lodge in the SMA. The intracardiac thrombus is related to atrial fibrillation, an acute myocardial infarction, or a ventricular aneurysm. Patients frequently have prior embolic events from the same source, although they are not necessarily limited to the superior mesenteric artery (e.g., common femoral artery bifurcation presenting with acute lower extremity ischemia), and it is common to have synchronous emboli (e.g., splenic artery). Notably, the material that comprises these macroemboli is quite large in contradistinction to the micron-sized atheroemboli that commonly cause "blue toes" after invasive arteriographic procedures (i.e., artery-to-artery emboli). These macroemboli tend to lodge at areas of narrowing in the arterial circulation, typically branch points (e.g., common femoral bifurcation, popliteal artery bifurcation). The extent of bowel ischemia and/or infarction after an embolus to the SMA is contingent upon the extent of the collateral circulation, the pattern of the arterial occlusion, and the duration of the ischemia. In this setting, the bowel progresses from ischemia to infarction in a time-dependent fashion, although it may remain viable for 6–12 hours. Acute embolic occlusion of the SMA usually results in ischemia/infarction from the midjejunum to the transverse colon because the embolic material frequently lodges at the distal SMA just beyond the origin of the middle colic artery. The duodenum and descending colon are usually spared because they are supplied by branches of the CA and IMA, respectively.

Clinical Presentation and Diagnosis

The diagnosis of AMI from an embolus (or other causes of AMI) may be difficult. The differential list of diagnoses includes all the more common causes of acute abdominal pain. The diagnosis is confounded by the fact that patients are often critically ill, and thus their history/physical examination may not be reliable. Diagnosis requires a high index of suspicion and an aggressive approach because delays adversely affect outcome. This requires an appreciation of the types of patients and clinical scenarios in which AMI occurs, including patients with end-stage renal disease[66] and those sustaining a myocardial infarction or undergoing coronary artery bypass grafting.[67,68]

Patients with AMI from an embolus usually present with diffuse abdominal pain. The classic description of the pain secondary to AMI is "pain out of proportion" to the physical examination findings, although this scenario is not always present. Unfortunately, the pain is neither specific nor localized to a particular abdominal quadrant. Peritoneal signs can be present, but they usually occur late in the process and suggest bowel perforation. Patients often experience nausea, vomiting, and/or diarrhea, but again these are fairly nonspecific. Notably, AMI is a potent cathartic. Similar to the physical examination, the routine chemistry and hematologic laboratory studies are usually nonspecific and insensitive. Patients frequently have mild abnormalities of their laboratory values, including an elevated white blood count, a decreased platelet count, an elevated hematocrit, and a mildly elevated amylase level. The serum lactate level can be elevated, although the associated sensitivity and specificity in this setting are such that they are not recommended in the recent European guidelines.[16] The hemodynamic status of the patients at the time of presentation ranges from normovolemia to profound hypovolemic shock with acidosis and is contingent upon the status of the bowel and the duration of symptoms.

A variety of studies are available to help confirm the diagnosis of AMI secondary to an embolus. Plain abdominal radiographs have been used traditionally for patients with acute abdominal pain and can be helpful to demonstrate "free air" from a perforated viscus. However, patients with AMI frequently have either normal plain radiographs or demonstrate nonspecific findings (e.g., ileus). CT arteriography with 1- to 2-mm cuts has emerged as the diagnostic study of choice for patients with AMI secondary to an embolus.[16,20,69–71] The study is performed using only intravenous contrast because both oral and rectal contrast potentially interfere with the arteriogram itself. Furthermore, the CT arteriogram is likely justified in this setting in patients with compromised renal function, despite the contrast load, given the severity of the underlying AMI. Both stenoses and occlusions in the mesenteric vessels are well demonstrated on CT arteriography. In patients with AMI secondary to an embolus, a "meniscus sign" can often be seen in the mid/distal SMA. The images obtained using the CT arteriogram protocol are also excellent for the nonvascular structures. The significant nonvascular findings of AMI include bowel wall thickening, pneumatosis, bowel/solid organ infarction, and portal venous gas. Notably, Paran and colleagues[71] reported that the majority of patients with portal venous gas had mesenteric ischemia and that the associated mortality rate was 86%. Mesenteric duplex, although an excellent *screening* test for CMI, is not usually helpful in the majority of patients with AMI because abdominal distention/gas precludes the accurate interrogation of the mesenteric vessels.

Standard catheter-based contrast arteriography can be used as an alternative to CT arteriography, and, indeed, has been the traditional imaging study for the mesenteric vessels in the setting of AMI from an embolus or in situ thrombosis. Similar to patients with CMI, it can potentially serve as both a diagnostic test and therapeutic modality because an intervention can be performed at the same time. The major disadvantages are the obligatory time required to obtain the procedure and the small, but finite, complications associated with the contrast agent and arterial access. Given the availability of hybrid operating rooms, diagnostic catheter-based contrast arteriogram could be performed in an operating room with a fixed imaging unit followed by a definitive operative procedure in the same setting/location should the arteriogram confirm the diagnosis.

Laparoscopy offers an additional diagnostic modality for patients with AMI, as it can be used to assess bowel viability, thereby aiding the diagnosis and treatment plan.[72,73] Furthermore, it can be performed at the bedside in the intensive care unit with sedation at some institutions and therefore is feasible for unstable patients with a suspected intraabdominal process. However, laparoscopy likely has a limited role in the diagnosis of AMI but can be helpful if other diagnostic studies are inconclusive. Exploratory laparotomy remains the definitive diagnostic test for patients with AMI. However, the diagnostic studies outlined earlier are usually sufficient.

Treatment Strategies

Patients should be taken emergently to the operating room or imaging suite for definitive treatment once the diagnosis of AMI from an embolus is made. An extensive preprocedure evaluation is unnecessary and potentially harmful in light of the narrow window for salvaging the bowel. There is essentially no role for medical management alone in this setting. Patients should be systemically anticoagulated with heparin to prevent further clot development and started on broad-spectrum antibiotics against enteric organisms. Importantly, patients with AMI are frequently hypovolemic and should be volume resuscitated before the induction of anesthesia. This can be performed fairly expeditiously and should not delay transfer to the operating room or imaging suite.

Both midline and transverse abdominal incisions provide adequate exposure to the mesenteric vessels, and the choice is contingent upon surgeon preference. The diagnosis of AMI from an embolus is usually confirmed by the distribution of the ischemic/infarcted bowel that extends from the mid jejunum to the transverse colon. However, the diagnosis should be further substantiated by interrogating the mesenteric vessels with continuous wave Doppler. The embolus may be extracted from the SMA using a Fogarty thromboembolectomy catheter. Although there are several approaches to the SMA, the easiest approach is to mobilize the duodenum by incising the ligament of Treitz. The SMA courses through the small bowel mesentery at this location and can usually be palpated immediately adjacent to the vein. The arteriotomy in the SMA may be performed either longitudinally or horizontally. Although a longitudinal arteriotomy needs to be closed with a vein patch to prevent narrowing its lumen, it is the preferred approach if the artery has some underlying atherosclerotic disease because it affords greater flexibility in case a bypass is required. Furthermore, the patch repair results in a patulous lumen and obviates any concerns about narrowing the vessel with the transverse arteriotomy.

The management of the bowel for patients with AMI merits further comment. All of the bowel that is obviously dead should be resected, and intestinal anastomoses should be avoided in favor of proximal and distal stomas or simply a stapled closure. This mandates a second procedure to restore bowel continuity, but it allows the bowel (i.e., mucosa of the stoma) to be examined at the bedside during the postoperative period. Furthermore, it avoids using ischemic or borderline ischemic tissues for the anastomosis. Bowel that is ischemic, though not frankly necrotic, should be revascularized and then re-examined before any final decision about resection. A conservative approach is justified in this setting because many of the borderline areas will remain viable after revascularization. Admittedly, the differentiation between viable

and nonviable bowel is difficult. A variety of complicated modalities have been described to help differentiate viable from nonviable bowel in this setting, although they have not been universally adopted. Simple adjuncts include visual inspection for peristalsis, use of continuous wave Doppler to detect arterial signals within the mesentery, and intravenous fluorescein in combination with a Wood's lamp. Notably, approximately 100–150 cm of small bowel is necessary for nutritional absorption.

A decision to perform a second-look operation to reassess the viability of the bowel should be made at the time of the initial procedure. This is routinely performed 24–48 hours after the first procedure, a time sufficient for the marginal bowel to declare itself. A retrospective review has questioned the role of the second-look operation and reported that survival was actually greater in those patients in which it was not performed.[74] Admittedly, there was a tremendous selection bias in this review, and the authors conceded that the experience of the surgeon is likely the key factor regarding the decision to perform a second look. A "damage control" operation may be justified in a small subset of unstable patients with AMI, as suggested by Freeman and Graham.[75] This includes emergent laparotomy, resection of obviously dead bowel, creation of proximal/distal stomas (or simply just stapling off the ends of the bowel), leaving the abdomen open with a negative-pressure vacuum-assisted dressing, and deferring the definitive vascular/gastrointestinal procedure until later.

Endovascular treatment with aspiration embolectomy and SMA thrombolysis (particularly in the setting of in situ thrombosis) have emerged as an alternative to open surgical thrombectomy for patients with AMI.[16,76–80] Notably, the endovascular approach has been recommended as the first-line therapy in the European guidelines for patients with AMI from in situ thrombosis.[16] However, the technical success rate for the endovascular thromboembolectomy and the requisite time for chemical lysis must be balanced against the acuity of the procedure and the potential to progress from ischemic bowel to infarcted bowel. Furthermore, a purely percutaneous approach (vs. a hybrid open and endovascular approach) does not allow direct assessment of the bowel, and the chemical lysis may cause intestinal bleeding from mucosal sloughing. It is conceivable that the endovascular approach may have a role for patients with a subacute presentation.

The postoperative course after embolectomy for AMI is similar to that after revascularization for CMI, although the incidence of postoperative complications and MODS is greater. As noted earlier, revascularization may cause an ischemia-reperfusion injury that affects both local and distant organ systems. Accordingly, patients are at risk for developing an abdominal compartment syndrome. Bladder pressures can be measured, and the abdomen closure can be dissembled if necessary. Patients should be continued on broad-spectrum antibiotics throughout the early postoperative period. Furthermore, they need to be anticoagulated long term because of the potential for recurrent emboli.

Outcome

The mortality rate for patients with AMI is approximately 70%, and this rate has changed very little over the past several decades.[65,81–83] Unfortunately, the majority of the case series tend to encompass all of the etiologies rather than a specific one (e.g., embolus). A systematic review by Schoots and colleagues[81] reported that the mortality rates of AMI from mesenteric venous thrombosis were better than those for arterial problems and that the mortality rates for mesenteric emboli were better than those for in situ thromboses. The aggregate mortality rates in their study by etiology are listed: mesenteric venous thrombosis, 32%; embolus, 54%; NOMI, 74%; in situ thrombosis, 77%. A variety of predictable factors have been associated with mortality in the various case series, including patient age, time to definitive surgery, shock, acidosis, leukocytosis, cardiac status, and coagulopathy.[82,84,85] The majority of deaths in a recent report were related to MODS.[57]

In Situ Thrombosis

Patients with mesenteric artery occlusive disease may also present with AMI secondary to in situ thrombosis. The presentation is superimposed upon the symptoms of CMI in more than 50% of the patients[86] and can usually be differentiated from the other causes of AMI by the history and clinical setting. However, it is important to emphasize that patients may present with AMI as the initial symptom of their mesenteric occlusive disease. The clinical presentation, diagnostic approach, and immediate postoperative care of patients with AMI secondary to in situ thrombosis is similar to that outlined earlier for emboli, although the operative approach is somewhat different.

Patients with AMI secondary to in situ thrombosis require a mesenteric revascularization, either open or endovascular. Although the choice of open revascularization options is somewhat equivocal in the setting of CMI (i.e., antegrade vs. retrograde bypass), retrograde bypass from the infrarenal aorta or common iliac artery is likely the optimal procedure for AMI given the urgency of revascularization (see Fig. 149.5). Interestingly, Scali and colleagues[87] compared the antegrade and retrograde bypass for AMI and reported no differences in perioperative outcome, although the antegrade bypass was associated with a lower reintervention rate long term. The objectives and treatment are somewhat different in the acute setting (i.e., AMI vs. CMI). The main objective is to restore blood flow to the ischemic vascular bed as safely and expeditiously as possible. This usually requires only bypass to the SMA. Patients with isolated CA stenosis rarely develop AMI because the collateral blood flow to the foregut is so good and the liver may be sustained on portal blood flow alone. Prosthetic conduits are relatively contraindicated in the setting of bowel infarction and/or perforation because of the potential for postoperative graft infection, but may be indicted in a "damage control" scenario. Autogenous conduits with either the saphenous or superficial femoral vein are suitable, although the latter may be more durable, but the time to harvest these conduits must be considered.

The role of endovascular treatment for patients with AMI secondary to in situ thrombosis is evolving. The concerns about the urgency of revascularization and the effectiveness of the endovascular procedure outlined previously are relevant, regardless of the etiology (i.e., embolus or in situ thrombosis). Retrograde open mesenteric stenting (ROMS) is a hybrid alternative (i.e., open and endovascular approach) that affords the advantages of both approaches.[88,89] Specifically, it allows assessment of the bowel and is potentially less morbid than the more traditional open revascularization.

Occasionally patients will undergo bowel resection for infarction by a nonvascular surgeon and the diagnosis of mesenteric ischemia will be missed, both preoperatively and intraoperatively. It is important to emphasize that infarction of the bowel is not a spontaneous event, but rather an end-stage complication of another disease process; it is imperative that the etiology of all bowel infarctions be established in an attempt to prevent recurrences. An appropriate imaging study (i.e., CT arteriogram, catheter-based contrast arteriogram) should be obtained in the early postoperative period and the necessary treatment implemented, including anticoagulation and revascularization, in a timely fashion.

Nonocclusive Mesenteric Ischemia

Pathophysiology

NOMI represents an abnormal or paradoxical mesenteric vasoconstriction characterized by the loss of autoregulation. Shock, or "circulatory stress," normally causes mesenteric vasoconstriction in an attempt

to maintain cerebral and/or cardiac perfusion. The mesenteric vasoconstriction ordinarily resolves when the underlying circulatory disorder is corrected; persistent vasoconstriction results in NOMI. There are multiple potential etiologies for NOMI, including cardiogenic shock, sepsis, burn injury, trauma, pancreatitis, digitals, vasopressors, and renal failure.[90–95] Indeed, almost any underlying condition that can precipitate shock or "circulatory stress" may precipitate NOMI.

Clinical Presentation and Diagnosis

Similar to the other causes of AMI, the diagnosis of NOMI requires a high index of suspicion and the proper clinical setting. Patients may develop abdominal pain, although the physical examination is frequently unreliable because of the other active medical issues and altered sensorium. Laboratory abnormalities are common, including acidosis, leukocytosis, elevated lactate levels, and hyperamylasemia, but these are all relatively nonspecific markers of the underlying shock state. Catheter-based contrast arteriography remains the diagnostic study of choice and is also potentially therapeutic.[16] The significant findings on the catheter-based arteriogram for patients with NOMI include segmental stenosis/narrowing of the SMA in a "string of beads" appearance. Furthermore, there is narrowing of the branches of the SMA at their origins, spasm of the mesenteric arcades, and impaired filling of the intramural branches. The catheter-based arteriogram can also be helpful to rule out the other potential causes of AMI. CT arteriography may have a role in the setting of NOMI[96–98]; however, it is somewhat limited by the inability to assess the flow dynamics through the mesenteric vessels. Similar to other settings, the CT arteriography may be helpful to exclude other intraabdominal concerns and other potential causes of AMI.

Treatment Strategies

The initial treatment of patients with NOMI is nonoperative and directed at correcting the underlying condition that precipitated the "circulatory stress." Specifically, patients should be resuscitated in an attempt to improve their cardiac output and systemic perfusion. All vasoactive drugs should be stopped (if possible), and patients should be started on broad-spectrum antibiotics directed against enteric organisms. Furthermore, patients should be systemically anticoagulated unless contraindicated. Despite these efforts, the characteristic mesenteric vasoconstriction may persist. Continuous intraarterial papaverine, administered through an infusion catheter placed into the SMA, may reverse the vasoconstriction.[99,100] A 45-mg test dose of papaverine (i.e., short-acting calcium channel blocker) should be given over 15 minutes and a continuous infusion of 30–60 mg/h should be started if no adverse reactions are encountered. Serial mesenteric arteriograms should be performed to monitor the response to papaverine, with the first performed 1 hour after initiating therapy. The intraarterial infusion may be continued up to 24 hours. It should be noted that the infusion will reverse the mesenteric vasoconstriction only if the underlying hemodynamic instability is corrected. Operative treatment of NOMI should be reserved only for the clinical scenario when bowel infarction is suspected.

Mesenteric Venous Thrombosis

Pathophysiology

Mesenteric venous thrombosis may also result in AMI and is considered in this section for completeness. However, the associated degree of bowel ischemia is usually less than with arterial occlusion from either an embolus or in situ thrombosis. The pathophysiology is similar to venous thrombosis in other vascular beds and may be explained in terms of the Virchow classic triad of stasis, intimal injury, and hypercoagulable states. Mesenteric venous thrombosis results in edema in the bowel wall and the mesentery with significant third-space fluid losses. This may result in bloody ascites and, indeed, a bloody tap at the time of paracentesis may be diagnostic. Progression to bowel infarction is contingent upon the magnitude of the thrombotic burden and its distribution. Clot localized to the portal or superior mesenteric vein does not usually lead to bowel infarction because of the collateral channels, whereas thrombus within the peripheral mesenteric veins is more likely to do so. The natural history of untreated mesenteric venous thrombosis is poor and almost universally progresses from bowel infarction to perforation and death.

Mesenteric venous thrombosis may result from abnormalities in any of the components of the Virchow triad (i.e., stasis, intimal injury, hypercoagulable state). Stasis may result from congestive heart failure or portal hypertension, whereas intimal injury may result from general anesthesia or any number of intraabdominal infectious processes. A hypercoagulable state is perhaps the strongest of the contributory factors and has been identified in up to 90% of patients with mesenteric venous thrombosis.[101–103] Notably, the mesenteric venous thrombosis can be the first presentation of the hypercoagulable condition.

Clinical Presentation and Diagnosis

Patients with mesenteric venous thrombosis usually present with vague, mild abdominal pain. The pain is usually insidious in onset and frequently present for some time before patients seek medical attention. Furthermore, the pain is not usually localized to any specific quadrant. Physical examination is notable only for mild, diffuse abdominal pain. Peritoneal signs suggest bowel infarction, but are only found later in the disease process. An abdominal CT scan is the diagnostic study of choice.[20,104,105] The significant findings include bowel edema and thrombus within the mesenteric veins with inflammation of the vessel wall (Fig. 149.6). Plain abdominal radiographs may suggest abdominal wall edema and are helpful to rule out other causes of the abdominal pain. Standard catheter-based contrast arteriography may be helpful, but is inferior to CT. The arteriographic findings that suggest mesenteric venous thrombosis include arterial spasm with a prolonged arterial phase, opacification of the bowel wall, extravasations of the contrast into the bowel lumen, and visualization of the venous thrombus.

Treatment Strategies

The primary treatment of patients with mesenteric venous thrombosis is anticoagulation to arrest the thrombotic process and potentially

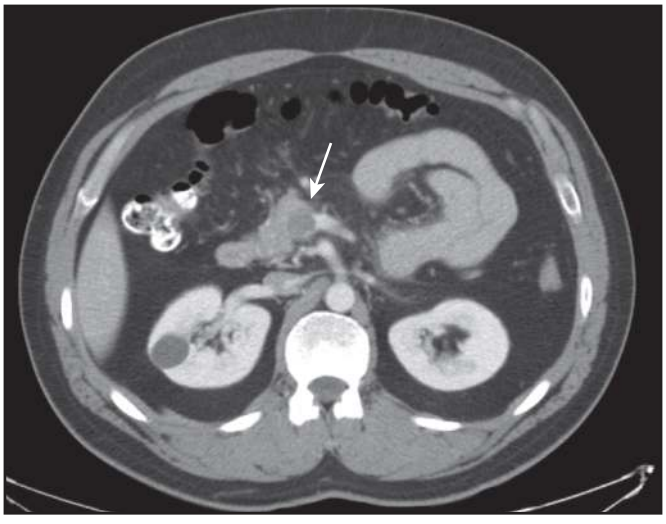

Fig. 149.6 CT scan of a patient with mesenteric venous thrombosis. Note the thrombus in the superior mesenteric vein at its confluence with the splenic vein, as shown with the *arrow*.

facilitate recanalization. Patients should be aggressively anticoagulated with heparin when the diagnosis is made and should be maintained on long-term oral anticoagulation. Similar to patients with massive iliofemoral deep venous thrombosis, it may be difficult to achieve effective anticoagulation initially using the standard dosing schedules for heparin (i.e., 80–100 units/kg bolus, 18 units/kg/h drip), presumably secondary to the clot burden. Larger doses of heparin may be required, and the adequacy of heparinization (e.g., partial thromboplastin time) may need to be monitored more frequently. Although the required dosage of heparin may be unsettling, the potential clot propagation and its associated complications likely exceed any increased risk from bleeding. A hypercoagulable work-up for the standard hematologic abnormalities should ideally be performed before initiation of anticoagulation; however, this laboratory work-up should not delay treatment. Long-term anticoagulation should be continued even in the absence of an identifiable hypercoagulable state because it is likely that many of these patients have some type of hypercoagulable disorder even though it may not be characterized on initial screening. Additionally, patients frequently require fluid resuscitation at the time of diagnosis because of the significant third-space losses from the bowel edema. Nasogastric decompression, broad-spectrum prophylactic antibiotics, and repletion of electrolytes are all useful adjuncts.

Exploratory laparotomy should be reserved for cases in which bowel infarction is suspected. The intraoperative findings include edematous/rubbery bowel, bloody ascites, and thrombus within the mesentery. A wide resection of the bowel should be performed in the presence of infarction. Primary enteric anastomosis is probably safe if the margins of resection are free of thrombus within the mesentery. Proximal and distal stomas (or temporary stapled closures) are advisable if the viability of the bowel at the margins of resection is questionable or if the bowel wall is edematous. Patients are at risk for additional or ongoing thrombosis, with the most common site being the margins of the resection and/or the anastomosis. Mechanical thrombectomy is not advocated at the time of laparotomy because of the extensive clot burden.

The role of endovascular treatment for patients with mesenteric venous thrombosis is evolving, similar to the other causes of AMI. Transhepatic thrombolysis is an option for patients with progressive symptoms despite anticoagulation and those that are not surgical candidates.[105–108] Similar to the concerns with mechanical thrombectomy, the clot burden is very significant and usually extends from the small peripheral collaterals in the mesentery to the portal and mesenteric veins. Furthermore, the transhepatic approach is relatively complicated and associated with a significant bleeding risk in the setting of therapeutic anticoagulation.

Outcome

As noted earlier, the mortality rate (approximately 30%) for mesenteric venous thrombosis is significantly less than for the arterial causes of AMI.[81] Death has been associated with portal vein thrombosis, systemic venous thromboembolism, and obesity. The increased mortality rate associated with venous thromboembolism underscores the importance of early, adequate anticoagulation.

Aortic Dissection

Patients with acute aortic dissection can present with mesenteric malperfusion and AMI. The management of acute aortic dissection is beyond the scope of this chapter, but the topic is included to emphasize the importance of evaluating the status of the mesenteric vessels in all patients presenting with acute dissections. The presence of mesenteric malperfusion significantly increases the mortality rate.[109,110] A variety of endovascular approaches have been used to treat mesenteric malperfusion in this setting.[111,112] Endovascular revascularization is superior to the open approach, given the friability of an acutely dissected vessel wall, provided the patients are candidates from an anatomic and technical standpoint.

Protocols and Algorithms (Fig. 149.7)

Although patients frequently present with abdominal pain, their sensorium may be altered. The diagnosis should be considered in the critical care setting when patients decompensate acutely. The differential diagnosis should be framed within the appropriate clinical setting. A CT arteriogram is the diagnostic test of choice, although a catheter-based contrast arteriogram can be used. The CT findings are fairly characteristic for each of the diagnoses. Emergent revascularization is required in the setting of an embolus and in situ thrombosis; the bowel should be resected as necessary for ischemia/infarction. Preoperative evaluation should include broad-spectrum antibiotics, anticoagulation, and resuscitation. Medical management alone is usually adequate for patients with NOMI and mesenteric venous thrombosis. Intraarterial vasodilation may be required for persistent vasoconstriction in patients with NOMI. Lifetime anticoagulation is required for mesenteric venous thrombosis. Emergent endovascular revascularization is required for patients with acute aortic dissections and mesenteric malperfusion. Exploratory laparotomy and bowel resection should be reserved in patients with NOMI, mesenteric venous thrombosis, and aortic dissections for presumed bowel infarction.

Colon Ischemia

Isolated colon ischemia can occur after both open and endovascular aneurysm repair. Furthermore, it can develop as a complication of hemodynamic shock, similar to NOMI. Ischemic colitis has been reported to occur in approximately 2%–13% of open aneurysm repairs.[113] The reported incidence depends on the diagnostic algorithm and modality (routine sigmoidoscopy vs. selective sigmoidoscopy) and is dramatically increased after ruptured aneurysm repair. Indeed, the incidence of colonic ischemia after ruptured aneurysm repair in patients undergoing routine colonoscopy is approximately 25%–40%.[113,114] The sigmoid colon is affected most frequently, although all the sections of the colon may be involved. The ischemia may result from inadequate resuscitation, disruption of collaterals, and/or failure to revascularize a hemodynamically significant stenosis in the IMA. Interestingly, routine reimplantation of the IMA at the time of aortic reconstruction does not appear to prevent colon ischemia.[115] The ischemic colitis associated with endovascular aneurysm repair is more commonly related to atheroembolism than acute internal iliac artery occlusion, as might be suspected. The prognosis for ischemic colitis after endovascular aneurysm repair is worse than that for open repair.[116]

Patients with ischemic colitis usually present with bloody diarrhea in contrast to patients with AMI, who usually present with abdominal pain. In the most common scenario, patients develop bloody diarrhea on the first or second postoperative day after aortic reconstruction. However, the diagnosis should be considered after aortic reconstruction in the absence of bloody diarrhea in patients with thrombocytopenia, MODS, increasing abdominal pain/peritonitis, and generalized "failure to thrive." The diagnosis may be confirmed by endoscopy. Although sigmoidoscopy is used most frequently, a complete colonoscopy is likely optimal because of the potential involvement of the other colon segments.

Treatment depends on the endoscopic findings and clinical setting. The endoscopic findings range from mucosal ischemia to transmural necrosis. Unfortunately, it is often difficult to differentiate diffuse mucosal ischemia from transmural necrosis. Patients with mucosal ischemia alone should be treated with bowel rest, broad-spectrum antibiotics, fluid resuscitation, total parenteral nutrition, and serial endoscopic examinations. Many of these lesions resolve spontaneously

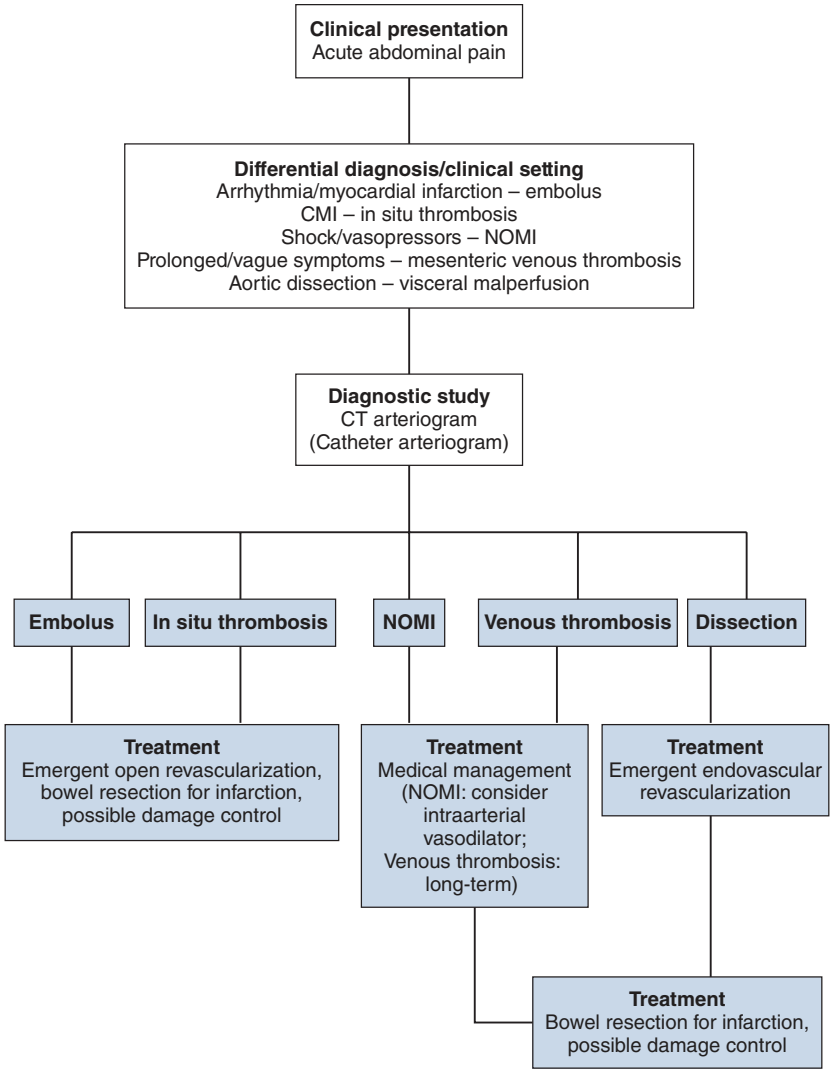

Fig. 149.7 Algorithm for the evaluation of patients with acute mesenteric ischemia. *CMI,* Chronic mesenteric ischemia; *CT,* computed tomography; *NOMI,* nonocclusive mesenteric ischemia .

without long-term sequelae, although colonic strictures may develop in a small subset of patients. Patients with transmural colonic necrosis should undergo laparotomy with resection of the involved segment, a proximal diverting colostomy, and a distal Hartmann pouch.

The reported mortality rate in patients with transmural colon necrosis after aortic reconstruction is approximately 85%.[113] Maintaining antegrade flow through the internal iliac vessels, routinely implanting the IMA, and preserving the colonic collateral circulation may reduce or prevent this adverse outcome. Evaluation of the patency of the mesenteric vessels should be part of the routine preoperative evaluation for aortic repair, and consideration should be given to staged or simultaneous revascularization for significant mesenteric stenoses.

KEY POINTS

Chronic Mesenteric Ischemia

- The underlying pathophysiology of CMI is the inability to achieve postprandial hyperemic intestinal blood flow.
- The symptoms of CMI usually do not occur unless two of the three mesenteric vessels are significantly diseased because of the rich collateral network.
- Patients presenting with abdominal pain and weight loss should initially undergo an expedited evaluation to rule out a gastrointestinal malignancy.
- The diagnosis of CMI is contingent upon the presence of the appropriate symptoms and the presence of significant mesenteric artery occlusive disease within the SMA and CA.
- CT arteriography has largely replaced catheter-based contrast arteriography as the diagnostic study of choice for patients with CMI.
- All patients with CMI require revascularization unless they are so debilitated that intervention is not warranted and/or they have opted for palliative care.
- Endovascular treatment with a covered intraluminal stent has emerged as the initial revascularization option, with open surgical revascularization reserved for patients with lesions nonamenable to endovascular treatment, endovascular failures, and select, younger patients.
- The immediate postoperative care for patients undergoing revascularization for CMI is frequently complicated by the development of MODS.
- The optimal management strategy for patients in the early postoperative period after mesenteric revascularization is to support the individual organ systems until the dysfunction resolves.

KEY POINTS—cont'd

- All patients who undergo revascularization for CMI require longer-term follow-up with duplex surveillance.

Acute Mesenteric Ischemia

- The impaired intestinal perfusion associated with AMI leads to mucosal compromise that can lead to the activation of the systemic inflammatory response and bowel infarction with perforation.
- The immediate clinical concern for patients with AMI is to reverse the underlying malperfusion to prevent bowel infarction.
- The etiology of AMI (i.e., embolus, in situ thrombosis, NOMI, mesenteric venous thrombosis, dissection) can usually be determined from the history and clinical setting.
- The emboli responsible for AMI usually lodge in the superior mesenteric artery and originate from the heart as a result of atrial fibrillation, an acute myocardial infarction, or a ventricular aneurysm.
- In patients with in situ thrombosis, the presentation of AMI is superimposed upon the symptoms of CMI in more than 50% of patients.
- NOMI represents an abnormal or paradoxical mesenteric vasoconstriction characterized by the loss of autoregulation.
- Mesenteric venous thrombosis is associated with a high incidence of hypercoagulable states and merits immediate and long-term anticoagulation, even in the absence of an identifiable condition.
- CT arteriography with 1- to 2-mm cuts has emerged as the diagnostic study of choice for most patients with AMI, whereas catheter-based arteriography remains the optimal imaging study for NOMI.
- Patients with AMI from an embolus or in situ thrombosis require emergent revascularization with inspection of the bowel viability.
- Operative treatment for patients with NOMI and mesenteric venous thrombosis is reserved for cases that have failed conventional therapy and when bowel infarction is suspected.
- The postprocedure course for patients undergoing treatment for AMI is oftentimes associated with the development of MODS, similar to the treatment of CMI.

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Abdominal Compartment Syndrome

Zsolt J. Balogh and Frederick A. Moore

HISTORICAL PERSPECTIVE

Pediatric surgeons closing omphaloceles have long recognized the lethal combination of pulmonary compromise and impaired renal function caused by increased intraabdominal pressure (IAP). Silo closure with gradual reduction of abdominal defect was recommended to prevent fulminant organ failure.[1] Concurrent improved survival of patients with ruptured abdominal aortic aneurysms (AAAs) increased awareness of the adverse consequences of high IAP. Vascular surgeons popularized the use of high IAP as a criterion for re-exploration.[2] In fact, the term *abdominal compartment syndrome* (ACS) was coined by vascular surgeons to describe the presentation of "increased ventilator pressure, increased central venous pressure (CVP), and decreased urinary output (UO) associated with massive abdominal distension not due to bleeding" in four early survivors after ruptured AAAs.[3] However, ACS did not become widely recognized until the mid-1990s, after an epidemic of ACS emerged in high-volume trauma centers as a result of fundamental advances in trauma care.[4–6] With the development of trauma systems, severely bleeding patients were triaged into level 1 trauma centers where the principles of the new Advanced Trauma Life Support course was being ingrained.[7] Early isotonic crystalloid resuscitation to achieve normal blood pressure became standard of care. It also became apparent that exploratory laparotomy with definitive repairs of all injuries resulted in a prohibitively high on-table operating room (OR) mortality from exsanguination.[8] Stone and colleagues introduced the concept of an abbreviated surgery for these patients with the aim of acute restoration of physiology and later staged definitive surgery.[9] This practice was exemplified by the widespread adoption of nonresectional management of major liver injuries with perihepatic packing and "towel clip" midline abdominal closure to enhance tamponade.[10] Survival notably improved, and this concept was extended to include all severely bleeding trauma patients, and the term *damage control laparotomy* gained popularity.[11,12] Finally, Kern and Shoemaker promoted the presumptive placement of pulmonary artery catheters (PACs) to guide supranormal oxygen delivery resuscitation to prevent occult hypoperfusion.[13] Because of these advances, more severely bleeding patients survived the first 24 hours. However, a substantial number of survivors progressed to develop ACS with organ dysfunctions. After repeat laparotomy to open the abdomen and decreased IAP, organ dysfunctions improved dramatically, but unfortunately, many of these patients would later deteriorate into a new predominant phenotype of fulminant multiorgan failure (MOF). This was a major challenge for trauma intensivists.[14]

This epidemic spurred research in the late 1990s and early 2000s to clarify the epidemiology and pathophysiology of ACS. The World Society of the Abdominal Compartment Syndrome (WSACS) was founded, which spurred international discussions and further research.[15,16] Definitions were standardized, monitoring of IAP was optimized, and consensus treatment guidelines were developed. ACS was recognized to be largely an iatrogenic problem. The abandonment of PAC-directed supranormal ICU resuscitation substantially decreased, but did not eliminate ACS.[17] Studies showed that the pathologic trajectory of ACS could be accurately predicted in the emergency department (ED).[18] Excessive crystalloids and failure to rapidly achieve hemorrhage were identified as the major contributing factors. This prompted the widespread adoption of the focused abdominal sonography of trauma (FAST) examination in the ED to ensure rapid triage to the OR for severe abdominal bleeding where liberal use of damage control and open abdomen surgery were used.[19] Protocols were implemented to rapidly identify major pelvic fractures and ensure appropriate use of pelvic binding, pelvic packing, interventional radiology embolization, and orthopedic external fixation.[20] Massive transfusion protocols (MTPs) enriched with fresh frozen plasma (FFP) were developed to ensure that transfusions were started as soon as possible after ED arrival and to minimize crystalloid use.[21] Hypotensive resuscitation was selectively used. Trauma-induced coagulopathy was recognized to be a distinct entity, and the resulting research supported early 1:1:1 ratios of FFP/platelets/packed red blood cells in MTPs and the use of fibrinogen and tranexamic acid. With these fundamental changes in initial management, ACS has become a relatively uncommon event in trauma ICUs.[22] With this focus to understand ACS as an acute event after trauma, ACS was described in a variety of other scenarios such as extreme constipation,[23] ovarian hyperstimulation,[24] noninvasive ventilation,[25] pancreatitis,[26] and severe burns.[27] With more timely diagnosis and treatment, more than 50% of afflicted patients are now surviving.

TERMINOLOGY

IAP is the pressure in the abdominal cavity. Clinical examination for monitoring IAP can provide inaccurate results.[28,29] The intravesical technique involving the use of a standard urinary catheter is the most reliable and least invasive method for monitoring IAP.[30] The intravesical technique has been shown to correlate well with IAP measured directly using a laparoscopic insufflator.[31] The vesical route is more accurate for monitoring IAP than rectal and gastric routes.[31] Animal studies have shown that the pressure in the inferior vena cava correlates well with the vesical pressure but is more invasive.[32,33] Several proprietary devices are available to intermittently monitor urinary bladder pressure. Unfortunately, IAP measurements are rarely obtained more often than every 4 hours because of logistic problems. These shortcomings have been overcome by developing and validating a continuous IAP measurement technique.[34] The mean value of IAP in hospitalized patients is 6.5 mm Hg (range, 0.2–16.2 mm Hg).[35] In critically ill patients, IAP is typically higher (12–16 mm Hg).[18]

Intraabdominal hypertension (IAH) is defined by abnormally high IAP and graded from I to IV based on IAP (grade I: 12–15 mm Hg;

TABLE 150.1 Classification of Abdominal Compartments

SYNDROME	
Basis of Classification	**Subcategories**
Time frame	Acute
	Chronic
Relation to peritoneal cavity	Primary
	Secondary
Etiology	Trauma
	Burn
	Postoperative
	Pancreatitis
	Bowel obstruction
	Ileus
	Abdominal aortic aneurysm
	Oncologic
	Gynecologic

grade II: 16–20 mm Hg; grade III: 21–25 mm Hg; and grade IV: above 25 mm Hg).[4]

ACS is defined by the presence of sustained IAP of greater than 20 mm Hg associated with attributable organ dysfunctions (described later). ACS can be classified based on its duration, presence or absence of intraperitoneal pathology, and cause of increased IAP (Table 150.1). Most of the available information related to ACS describes an acute syndrome in critically ill patients. However, ACS can be present in certain clinical conditions with chronic IAH, such as morbid obesity, chronic constipation, and pregnancy.[36]

Primary ACS is a condition associated with injuries or diseases in the abdominopelvic region. It typically develops after a damage-control surgery with temporary abdominal closure.[15] Intraperitoneal packing to tamponade bleeding increases intraabdominal contents, and when these packs are placed to control major liver injuries, they can partially occlude the portal vein, which promotes bowel edema. As time progresses, intraabdominal bleeding and worsening gut edema with ascites (secondary to resuscitation) cause further increases in the volume of the intraabdominal contents that significantly increase IAP, thus precipitating organ dysfunctions that characterize ACS. Primary ACS can also occur in patients who fail nonoperative management of liver and spleen injuries because of bleeding.[37]

Secondary ACS occurs after injuries or conditions that do not originate in the abdominopelvic region in the setting of massive resuscitation.[18] Secondary ACS is more elusive and unexpected, which delays its diagnosis.[38] It is typically associated with large-volume isotonic crystalloid resuscitation for ongoing bleeding related to mangled extremity injuries or penetrating chest injuries[39] and for severe burns or pancreatitis.[27,40]

DAMAGE CONTROL LAPAROTOMY

Patients undergoing laparotomy for major bleeding are at risk for entering the "bloody vicious circle" physiology of progressive acidosis, hypothermia, and coagulopathy, and this results in exsanguination from diffuse bleeding.[8] Prevention of this scenario is the rationale of damage control.[41] Damage control laparotomy has two goals: (1) quick control of bleeding to prevent the lethal spiral of the "bloody vicious cycle" and (2) prevent further contamination from hollow viscous perforations. After these goals are accomplished, the abdomen is temporarily closed without midline fascial approximation, and the patient is triaged to the intensive care unit (ICU) for resuscitation and correction of abnormal "bloody vicious circle" physiology. After this is accomplished, patients are returned to the OR (usually within 24 hours) for completion of the needed surgical interventions. The common use of damage control laparotomy necessitated the development of novel techniques of managing the open abdomen.

ABDOMINAL DECOMPRESSION

Traditionally, abdominal decompression has been achieved through a full midline laparotomy. Recently, other techniques such as transverse laparotomy and minimally invasive linea alba fasciotomy have been described as potentially useful methods in selected cases. Decompressive laparotomy can be performed in ICUs in extreme cases. However, it is generally preferred to be done in the OR, especially when further intraabdominal procedures or need to control bleeding is anticipated.

PATHOPHYSIOLOGY

IAP: The volume of the abdominal cavity is limited by its least tensile component, the fascia. Increased pressure can be caused by an increase in the volume of abdominal contents or because of a decrease in the volume of the "container" (Table 150.2). After IAP increases to greater than 20 mm Hg, the abdominal cavity is on the steep portion of its pressure-volume curve, and as a result, small increases in content volume or decreases in cavity volume can cause dramatic increases in IAP. This is when close monitoring of IAP (preferably continuously) and organ dysfunction is essential for timely intervention. In the 1990s it was popular to volume-load patients with impending ACS, but the result was a rapid increase in IAP with progression into full-blown ACS.

TABLE 150.2 Causes of Intraabdominal Hypertension and Abdominal Compartment Syndrome

Increased Abdominal Contents	Decreased Abdominal Volume
Ascites	Reduction of large, long-standing hernia
Hemoperitoneum	Direct closure of large, long-standing abdominal wall defect
Visceral edema	Circumferential abdominal wall burn
Abdominal packs	Continuous positive-pressure ventilation
Peritonitis	
Retroperitoneal edema (pancreatitis)	Retroperitoneal edema (pancreatitis)
Large pelvic and retroperitoneal hematoma	Large pelvic and retroperitoneal hematoma
Intestinal obstruction	
Ileus	
Gastric distention (esophageal ventilation)	
Abdominal aortic aneurysm	
Severe constipation	
Large abdominal tumor (chronic)	
Morbid obesity (chronic)	
Pregnancy (chronic)	

CEREBRAL PERFUSION

Increased IAP forces the diaphragm cephalad, thus increasing the intrathoracic pressure, which impedes venous return from the brain. This increases intracranial pressure (ICP) and consequently decreases cerebral perfusion.[42,43]

CARDIAC FUNCTION

Increased IAP impedes venous return to the heart, thus decreasing preload. However, high IAPs elevate CVP, falsely signifying euvolemia. Simultaneously, left ventricular afterload increases because of increased systemic vascular resistance. Increased intrathoracic pressure also increases right ventricular afterload, leading to right dilation with leftward displacement of the ventricular septum and impairment of left ventricular filling.[44–47] Low cardiac index (CI) is a typical finding associated with ACS. Contrary to traditional beliefs, low CI in the setting of increased IAP (and CVPs) usually does not respond to fluid challenges; moreover, ongoing volume loading can lead to the "futile crystalloid cycle" (described later; Fig. 150.1). An increase in CI in response to decompression is a predictor of improved outcome.[18]

Respiratory function: High-risk patients may develop acute lung injury, and ongoing crystalloid resuscitation worsens pulmonary edema. Increased IAP pushes the diaphragm into the thoracic cavity, thus decreasing thoracic compliance and lung volume. Therefore increased airway pressure is required to restore the lung functional residual capacity to improve oxygenation during mechanical ventilation.[47,48] Airway pressure promptly decreases in response to abdominal decompression. However, this cannot be used to differentiate between survivors and nonsurvivors.[18] Monitoring of airway pressure is important during attempted primary fascial closure after laparotomy, when ACS is a possible complication.

RENAL FUNCTION

In the early reports, oliguria or anuria was the typical presenting diagnostic sign of ACS. Mechanisms responsible for decreased renal function include direct compression of the renal parenchyma, decreased perfusion of the kidneys, and increased water and sodium retention because of activation of the renin-angiotensin system.[48–51] As high-volume crystalloid resuscitation became standard of care, low UO became a less reliable early sign of ACS.

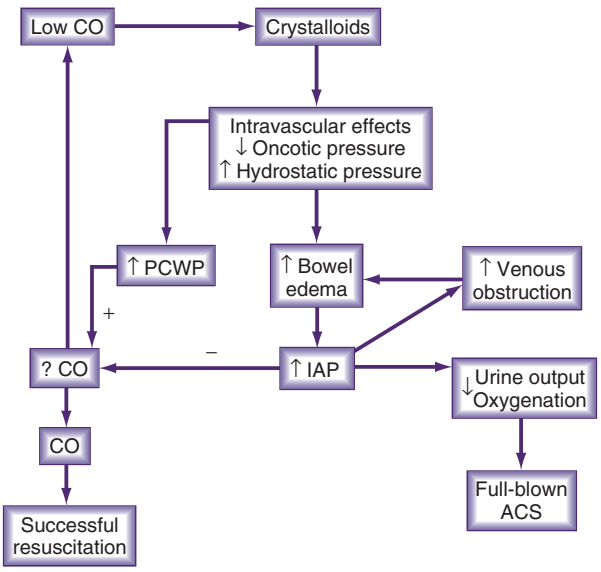

Fig. 150.1 Futile crystalloid preloading. *ACS,* Abdominal compartment syndrome; *CO,* cardiac output; *IAP,* intraabdominal pressure; *PCWP,* pulmonary capillary wedge pressure; ↑, increased; ↓, decreased; +, positive effect; −, negative effect.

GUT PERFUSION

Increased IAP impairs splanchnic perfusion by decreasing CI and by increasing splanchnic vascular resistance. Gut ischemia can occur in severe cases.[52–54] In the 1990s gastric tonometry was frequently used in the ICU, and increased gastric regional partial pressure of carbon dioxide ($PrCO_2$) or GAP_{CO_2} ($PrCO_2 - PaCO_2$) became accepted indicators of impaired intestinal perfusion. After damage control surgery to control major bleeding, $PrCO_2$ was frequently high because of ongoing hypovolemic shock. With effective resuscitation, $PrCO_2$ would decrease. However, with ongoing futile volume loading, IAP would increase because of progressive gut edema with increasing $PrCO_2$ into pathologic levels (>65 mm Hg) indicative of gut ischemia. Combined with concurrent IAP monitoring, tonometry to identify increasing $PrCO_2$ proved to be an excellent adjunct for identifying impending ACS.[16] Moreover, the physiologic response to effective decompression is a prompt decrease in $PrCO_2$, reflecting gut reperfusion.[18] Laboratory studies have shown that ACS induces gut ischemia and that decompression-induced gut reperfusion primes circulating neutrophils and releases cytokines into portal circulation. This causes acute lung injury, which is similar to that induced after hemorrhagic shock and resuscitation.[55,56] Therefore abdominal decompression in patients with very high IAPs can result in gut ischemia/reperfusion and serve as a "second hit" for early MOF.[57]

LOWER EXTREMITY PERFUSION

Increased IAP increases femoral venous pressure, increases peripheral vascular resistance, and decreases femoral artery blood flow by as much as 65%.[58] This can be an important contributing factor in the development of lower extremity compartment syndrome. ACS complicated by a lower extremity compartment syndrome is especially lethal.

PREDICTION

Potential risk factors of ACS include severe hemorrhagic shock, high-volume crystalloid resuscitation, damage-control laparotomy, high injury severity score, and markedly elevated $PrCO_2$ level.[59–61] Studies on secondary ACS have identified resuscitation fluid volume thresholds that warrant IAP monitoring. Maxwell and colleagues recommended that IAP be monitored when resuscitation volume exceeds 10 L of crystalloid fluid or 10 units of packed red blood cells.[62] Ivy and colleagues suggested that the trigger to initiate IAP monitoring should be greater than 0.25 L/kg of crystalloid resuscitation.[40,63] Biffl and colleagues reported that both these cutoffs are ineffective and recommended the following thresholds: 6 L of crystalloid fluid or ≥6 units of packed red blood cells in a 6-hour period in patients with a base deficit of greater than 10 mEq/L, especially when a vasopressor agent is required.[64]

Multiple logistic regression analysis was performed using a prospective database of patients who experienced a major torso trauma and who underwent standardized shock resuscitation.[18] An ED model (at 3 hours in patients discharged from the ED) and an ICU model (at 6 hours in patients admitted to the ICU) were developed. Table 150.3 lists independent risk factors of primary and secondary ACS that were determined using the ED and ICU models. A receiver operator characteristic curve of 0.88 was a predictor of ACS in the ED model and of 0.99 was a predictor of ACS in the ICU model.

TABLE 150.3 Independent Predictors of Postinjury Primary and Secondary Abdominal Compartment Syndrome

	ED MODEL	ICU MODEL
	Independent Predictors	Independent Predictors
Primary ACS	To OR <75 min	Temp ≤34°C
	Crystalloids ≥3 L	$GAPco_2$ ≥16
		Hb ≤8/dL
		BD ≥12 mEq/L
Secondary ACS	Crystalloids ≥3 L	$GAPco_2$ ≥16
	No urgent surgery	Crystalloids ≥.5 L
	PRBC ≥3 units	UO ≤150 mL

ACS, Abdominal compartment syndrome; *BD,* arterial base deficit; ED, emergency department; *$GAPco_2$,* carbon dioxide gap; *Hb,* hemoglobin concentration; *ICU,* intensive care unit; *OR,* operating room; *PRBC,* packed red blood cells; *Temp,* temperature; *UO,* urine output.

TREATMENT

Nonsurgical medical interventions: For patients with impending ACS, medical management should be initiated to reduce and prevent further increases in IAP.[3,65,66] These include (1) reduce abdominal distention (e.g., nasogastric or rectal tubes, reduce enteral feeding),(2) improve abdominal wall compliance (e.g., adequate pain/sedation followed by neuromuscular blockade), and (3) optimize fluid balance (e.g., minimize isotonic crystalloids, use hypertonic saline or colloids, start diuresis). Additionally, treatment of early organ dysfunction by traditional ICU interventions is often necessary; however, these interventions may aggravate the underlying pathophysiology. For example, ventilator strategies for increasing mean airway pressure to improve oxygenation directly increase IAH by pushing down the diaphragm. In addition, increased intrathoracic pressure impedes venous outflow from the abdominal cavity. This promotes gut edema with ongoing crystalloid resuscitation. Seminal studies performed in the mid-1990s advocated volume loading to improve low UO in patients with moderately high IAP. Increased IAP falsely elevates CVP, resulting in the underestimation of ventricular end-diastolic volume. Thus volume loading was recommended to increase preload for improving CI to increase renal and gut perfusion.[67] Although this makes physiologic sense, close monitoring in a standardized resuscitation protocol identified this to be ineffective in increasing CI, and if volume loading continued, it would precipitate full-blown ACS. This is referred to as the *futile crystalloid cycle* (see Fig. 150.1).[67,68]

PERCUTANEOUS METHODS

If ACS is caused by acute or chronic fluid collection, its symptoms can be relieved by initiating percutaneous drainage. Case reports have described successful drainage of abdominal fluid in burn patients with secondary ACS and drainage of blood in patients with nonoperatively managed liver injuries.[69–71]

SURGICAL DECOMPRESSION

Surgical decompression by opening the midline fascia along its full length remains the primary recommended intervention. Almost all reports have described a very good physiologic response to decompression. However, this does not necessarily translate into better outcomes. The best predictors of survival are postdecompression improvement in CI and urine output.[18,39] The decision to perform surgical decompression is a difficult one because it results in an open abdomen that is associated with numerous complications. This is especially true in patients with pancreatitis because delayed fascial closure is unlikely. These patients end up with a prolonged open abdomen and a large ventral hernia if they survive. On the other hand, case series in trauma patients have shown that early decompression is associated with better outcomes. However, patients with ACS are critically ill, and their intrahospital transfer can exert detrimental effects. Thus if no other intraabdominal surgical intervention is anticipated, bedside decompression can be performed in the ICU. More recently, alternatives to midline laparotomy, such as transverse laparotomy and linea alba fasciotomy, were described. These approaches were popularized in cases of severe acute pancreatitis.[72] The (subcutaneous) linea alba fasciotomy can prevent peritoneal contamination in selected pancreatitis cases where laparotomy is not required, only reduction of IAP.[73,74]

MANAGEMENT OF THE OPEN ABDOMEN

Decompressive laparotomy results in an open abdomen, and temporary abdominal closure is performed to keep the fascia open. Several methods (towel clips, Bogota bag, synthetic mesh, vacuum-assisted closure, Velcro patch, and zipper) are available. The key goals are to prevent evisceration, allow swelling of abdominal contents, control peritoneal fluids, prevent contamination, and preserve the fascia for a possible later closure. It is important to note that patients with open abdomens can develop recurrent ACS. This is especially true with temporary closure methods that decrease abdominal volume (e.g., vacuum-assisted closure, Velcro patch, and zipper) with the intention of promoting delayed fascia closure. Ongoing experience with a vacuum-assisted closure technique has provided very promising results. In trauma patients, rate of delayed primary fascial closure is greater than 85%. Moreover, use of the vacuum-assisted closure technique has dramatically improved the daily management of the open abdomen.[75–77]

KEY POINTS

- It is essential to distinguish between IAH and ACS through the early identification of organ dysfunction.
- IAP should be monitored during shock resuscitation requiring ongoing volume loading regardless of the cause of the shock (e.g., burn, sepsis, and trauma).
- Physical examination is unreliable at detecting ACS, and at present, the safest and most feasible method to monitor IAP is the intravesical technique.
- ACS can occur without abdominal pathology or injury (secondary ACS).
- To date, the best-characterized types of ACS are postinjury ACS, burn-associated ACS, and pancreatitis-associated ACS.
- Outcomes associated with ACS are very poor even after performing early decompression. Prevention, prediction, and surveillance are the keys to achieving successful management of ACS.
- Postinjury primary and secondary ACS can be accurately predicted 3–6 hours after hospital admission through adequate monitoring.
- Efforts to limit excessive crystalloids during shock resuscitation have decreased the incidence of ACS.
- Outcomes with open abdomen are improving with the use of vacuum-assisted closure techniques.

References for this chapter can be found at expertconsult.com.

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Extremity Compartment Syndromes

Roman Košir and Andrej Čretnik

EPIDEMIOLOGY

Extremity compartment syndrome occurs whenever the tissue pressure within a limited space of the body reaches the point where the circulation, nerve function, and muscle function of that space are compromised. For compartment syndrome to occur, the body compartment should be enveloped by fascia that prevents inner tissue expansion, and there should be at least one cause of increased tissue pressure present, either externally or internally.

The German physician Dr. Richard Von Volkmann first described the late sequelae of compartment syndrome in 1881.[1] He wrote: "The paralyses and contractures that follow tightly applied bandages, chiefly in the forearm and hand, and less often in the lower extremity, are to be viewed as ischemic. They arise from the arterial supply being interrupted for too long." Volkmann's ischemic muscle contractures of untreated forearm compartment syndrome are named after him (eFig. 151.1). Later, in 1912, Wilson first described exertional compartment syndrome,[2] and Mavor, in 1956, first reported chronic exertional compartment syndrome in a football player.[3] Since then, various cases of compartment syndrome have been reported in the literature, and the pathophysiology and treatment options have been discussed. Compartment syndrome has been reported in a wide variety of clinical conditions, including tetanus, meningococcemia, malignant hyperthermia, frostbite, horseback riding, and childbirth.[4–8] Typically, it occurs after traumatic events, most commonly those involving fractures or vascular trauma with subsequent ischemia-reperfusion injuries. The most commonly affected body compartments are lower extremity compartments. The literature describes an increasing incidence of around 2% in severely injured patients.[9–11] This occurs with developments in shock resuscitation in a population of patients with otherwise noninjured extremities. The incidence of compartment syndrome varies depending on the patient population studied and the etiology of the syndrome. In a group of patients with leg pain, according to Qvarfordt and colleagues, 14% were noted to have anterior compartment syndrome.[12] Compartment syndrome was also seen in 1%–9% of leg fractures.[13]

Common locations of compartment syndromes are in the upper and lower limbs. The most commonly affected are the four compartments of the lower extremity (anterior, lateral, superficial posterior, and deep posterior), followed by two compartments of the forearm (volar and dorsal). Other compartments that may be affected are the deltoid and biceps compartments of the arm; interosseous compartments of the hand; gluteal compartment of the buttock; quadriceps compartment of the thigh; and interosseous, medial, central, and lateral compartments of the foot.[14–17]

The etiology of compartment syndrome varies and can be divided into three major groups: decreased compartmental volume, increased compartmental content and therefore pressure, and externally applied pressure. There are probably more than 40 causes that fit into one of these groups. Common causes in critical care surgical cases are presented in Table 151.1.[18]

The most common causes of extremity compartment syndrome are categorized based on increased compartmental content. The pathophysiologic mechanism of bleeding is easy to understand. Most commonly, bleeding is caused by trauma, but recently, more reports of atraumatic bleeding caused by wide use of warfarin, low-molecular-weight heparins, or recombinant tissue plasminogen activator (rtPA) have been reported.[19–21]

Increasing volume of blood in a space limited by noncompliant fascia results in an exponential rise in intracompartmental pressure. Postischemic swelling or reperfusion injury is more complex because it causes the so-called *double ischemic insult.* Initial ischemic insult from any cause leads to abnormal function of all tissues, including nerves, muscles, and capillaries. This results in abnormalities of neuromuscular function; this is the *first insult.* Increased permeability after the relief of initial ischemia leads to postischemic swelling and subsequently increased compartmental volume and pressure. This leads to the development of compartment syndrome, which causes additional injury to neuromuscular function; this is the *second insult.* This process has clinical consequences. The classic physical examination in patients with reperfusion injury can be unreliable because of loss of motor and nerve function.[18,22,23]

CLINICAL PRESENTATION

Most extremity compartment syndromes in patients who are able to cooperate can be diagnosed by a clinical examination. The most common clinical signs found in the literature are the classic 5 Ps: pain (out of proportion), pulselessness (or weak pulse), pallor, paralysis (numbness and loss of motor function), and pressure (swelling and tenseness of compartment). Occasionally, poikilothermy (cold extremity) is also included (Fig. 151.1A). These signs are a consequence of increased intracompartmental pressure and loss of various tissue functions. Other signs include skin edema and blisters, swelling, and subcutaneous blood suffusions (see Fig. 151.1B).

To make the diagnosis, there must first be evidence of increased intracompartmental pressure. If so, these signs do not occur simultaneously but develop with time. One of the first signs is a swollen or tight compartment in combination with severe pain that is out of proportion to the injury and is not relieved by typical analgesia. Other signs present late and often, when present, represent irreversible damage to soft tissues. Numerous other pathophysiologic events can cause a similar clinical picture. In fact, a large meta-analysis of studies comparing clinical signs with the development of acute lower extremity compartment syndrome showed a sensitivity of

eFig. 151.1 Dr. Richard Volkmann. (Courtesy of the United States National Library of Medicine, Portrait no. 6859.)

TABLE 151.1 Most Common Etiology of Increased Compartment Pressure in Critical Care Surgery

Decreased compartmental volume	Application of excessive traction because of fracture immobilization Closure of fascial defects after trauma
Increased compartmental content	Intracompartmental bleeding caused by fractures, vascular injury, or bleeding disorders Increased capillary filtration in reperfusion after ischemia, embolectomy, soft tissue trauma, burns, fracture fixation
Externally applied pressure	Tight immobilization of fractures Lying on limb

Adapted from Matsen FA. *Compartmental Syndromes.* New York, NY: Grune & Stratton; 1980.

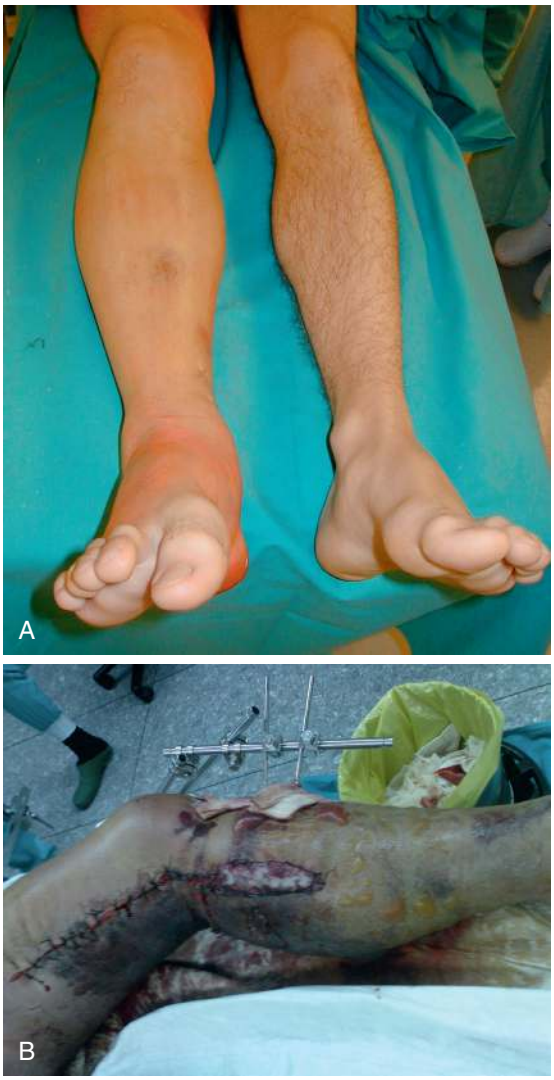


Fig. 151.1 A, A patient with right lower extremity compartment syndrome caused by isolated tibial fracture. On clinical presentation, pain, swelling, and inability of dorsal flexion of the toe were noted. **B,** Another patient with left lower extremity compartment syndrome after popliteal artery tear and revascularization in combination with proximal tibial fracture was treated with external fixation. A few hours later after initial treatment, there are obvious signs of developing compartment syndrome with swelling, skin discoloration, function loss, and fracture blisters.

13%–19%, specificity of 97%, positive predictive value of 11%–15%, and negative predictive value of 98%.[24] Thus the absence of this sign rules out compartment syndrome, but the presence rarely confirms the correct diagnosis.

Nevertheless, clinical observation of the suspected compartment is what is recommended because the progress of the symptoms over hours is what should be noted first before making a definitive diagnosis and initiating definitive treatment. In traumatic cases, careful observation is required in open fractures as well. Although early surgery is usually indicated in this group of patients, they can still present with compartment syndrome. One animal study has confirmed the necessity of careful monitoring of both open and closed tibial fractures.[25] A useful tool for such monitoring could be a simple sheet with notes about date, time, location, pain level, and motor and sensory testing. To do this, one must know the anatomic position of various compartments and their vascular and nerve content. A simple screening form of the most commonly observed acute lower extremity compartments is a useful tool for monitoring of the patient (eFig. 151.2).[26] To focus on this relatively rare syndrome and prevent missed diagnoses, more complex systems for monitoring and recognition have been developed in some institutions, with better recognition and outcomes.[27] In literature, special groups of patients with various etiology are described, where this condition occurs more often. Screening in these patients is highly recommended. In a large review study, stepwise logistic regression identified the presence of vascular injury, need for packed red blood cell (PRBC) transfusion, male gender, open fracture, elbow or knee dislocation, Gunshot Wounds (GSW), Injury Severity Score (ISS) greater than or equal to 16, and age less than 55 years as independent predictors for the need for extremity fasciotomy.[28] Several statistically significant predictors of relevant compartment syndromes after surgical reperfusion were found, including lactate, uric acid, transcutaneous oxygen pressure, bilirubin, intrafascial pressure, and serum myoglobin.[29]

DIAGNOSIS

To make a diagnosis of compartment syndrome, there must be evidence of increased tissue pressure, inadequate tissue perfusion, and loss of tissue function. When all three factors are present, the diagnosis may be made with assurance; when one or more of these factors are absent, the diagnosis is less accurate. Evidence of increased tissue pressure may include patient complaints of tightness or pressure in the involved area. By palpation, a physician may perceive tenseness of the compartmental envelope.[30]

Evidence of inadequate perfusion of local tissue pressure may include the symptom of pain out of proportion to what would be anticipated from the clinical situation. Increasing analgesia requirements in a properly immobilized leg should raise suspicion. Pain on a passive stretch of the intracompartmental muscles is another useful indication of increased pressure, especially if the muscles have not been injured. Reduced peripheral pulses are very late signs of compartment syndrome; in fact, studies have shown normal pulses with Doppler signals in otherwise severely elevated intracompartmental pressures. Arterial flow is rarely compromised in elevated tissue compartment pressures. On the other hand, diminished pulses could be a result of other causes (e.g., vascular lesions) and, in combination with reperfusion injury, could also lead to the development of compartment syndrome.[30]

Evidence of abnormal tissue function includes weakness of the intracompartmental muscles and nerves, including sensory branches, leading to hypoesthesia. Both nerve and muscle function may be altered by direct injury; therefore evidence of progressive loss of function over time may be a more reliable sign.[30]

Acute Lower Extremity Compartment Syndrome
Screening Form

Start Date: ___/___/___

Start Time: _____

CLINICAL DIAGNOSES

Increased tissue pressure / swelling — ***YES / NO***

Pain — *Assess according to scale from 1 to 10*

Calf Pain - Calf pain at rest

PPSF - Pain with passive stretch, foot in plantarflexion

PPSE - Pain with passive stretch, foot in extension/dorsiflexion

Vascular Exam	*Pulse*	*Scale*
DPA – Dorsal Pedal Artery	Palpable	4
	Diminished	3
PTA – Posterior Tibial Artery	Non-palpable, Doppler positive	2
	Non-palpable, Doppler negative	1

Neurologic Exam - Motor	*Strength*	*Scale*
DPN - Deep Peroneal Nerve **DPN-M** Foot dorsiflexion	Movement against gravity with full resistance	6
	Movement against gravity with some resistance	5
	Movement against gravity only	4
TN - Tibial Nerve **TN-M** Foot plantar flexion	Movement with gravity eliminated	3
	Visible/palpable muscle contraction	2
	Without movement, no contraction	1

Neurologic Exam - Sensory	*Touch Sensation*	*Scale*
DPN Deep Peroneal Nerve **DPN-S** 1st to 2nd toe web space	Normal	3
	Diminished	2
TN Tibial Nerve **TN-S** Sole	Absent	1

If unable to assess – write N/A

Left / Right	Initial exam	Exam 4h	Exam 8h	Exam 12h	Exam 16h	Exam 20h	Exam 24h	Exam 28h	Exam 32h	Exam 36h	Exam 40h	Exam 44h	Exam 48h
Date													
Time													
Swelling													
Calf Pain													
PPSF													
PPSE													
DPA													
PTA													
DPN-M													
DPN-S													
TN-M													
TN-S													

YOUR Hospital Name

Your Department Name

Acute Lower Extremity Compartment Syndrome Screening

Patient Sticker

eFig. 151.2 An example of a screening form for acute lower extremity compartment syndrome observation. (From Kosir R, Morre FA, Selby LH, et al. Acute lower extremity compartment syndrome (ALECS) screening protocol in critically ill trauma patients. *J Trauma*. 2007;63:268–275.)

To summarize, in awake and cooperative patients who can be reexamined frequently, the diagnosis of compartment syndrome is associated with the following findings:

- Pain out of proportion to what is anticipated from the clinical situation
- Weakness of the muscles in the compartment
- Pain on a passive stretch of the muscles in the compartment
- Hypoesthesia in the distribution of the nerves coursing through the compartment
- Tenseness of the compartmental envelope

Because some clinical signs progress over time, the clinical decision making can be challenging.[14,31–34] In addition, clinical symptoms and signs have well-documented poor sensitivity.[24,35] Especially in critically ill patients who are unable to cooperate because of head trauma, sedation, or even neuromuscular-blocking drugs, the diagnosis cannot be made based on the clinical examination alone.[26] In the pediatric population, compartment syndrome does not always present classically, making clinical diagnosis uniquely challenging.[33]

Although the clinical examination should be a cornerstone of the diagnosis of compartment syndrome, it has the disadvantage of being subjective and requiring patient cooperation.[14,24,34] Therefore tissue pressure measurement should be performed to assist in establishing a diagnosis so that immediate treatment can be initiated. The normal compartmental interstitial tissue pressure is around 5 mm Hg. Capillary blood flow becomes compromised at 20 mm Hg, and pain develops at pressures between 20 and 30 mm Hg. A tissue pressure of more than 45 mm Hg has been reported to be usually associated with compartment syndrome, and a pressure of more than 60 mm Hg can confirm the diagnosis.[36–38] However, the tolerance of tissues for increased pressure may be reduced by other factors, such as arterial occlusion, limb elevation, and shock.[37,39] In these conditions, compartment syndrome may occur at significantly lower interstitial pressures. According to the arteriovenous gradient theory, the local blood flow (LBF) depends on the pressure gradient between arteries (Pa) and veins (Pv) and local vascular resistance to flow (R). This is described by the following formula[40]:

$$LBF = (Pa - Pv)/R$$

LBF should be maintained to deliver enough oxygen to the tissues. According to the previous relationship, increased resistance that correlates with interstitial pressure is not the only factor that reduces LBF. The arterial pressure is also important, whereas venous pressure is somehow related to interstitial pressure. Increasing interstitial pressure also increases venous pressure and furthermore decreases blood flow.

Because tolerance of tissues to increased intracompartmental pressure varies among different individuals, and as there are more factors that influence LBF, only one isolated measurement of interstitial pressure may not be enough to diagnose compartment syndrome.[41] For example, higher compartment pressures may be necessary before injury occurs to peripheral nerves in patients with systemic hypertension,[37] whereas compartment syndrome may develop at lower pressures in those with hypotension and/or peripheral vascular disease.[39,42] It has been proposed that the difference between diastolic pressure and intracompartmental pressure is a better marker for compartment syndrome. ΔP is calculated as follows: ΔP = DBP (diastolic blood pressure) − IP (interstitial pressure), and values greater than 30–35 mm Hg suggest compartment syndrome, but a specific threshold does not exist.[43–46]

There are numerous methods of tissue pressure measurement.[47–50] The most commonly used are commercial handheld pressure monitors (e.g., the Stryker device); a simple needle manometer system (Whitesides technique); and the needle, wick, or slit catheter techniques. The question is accuracy because there are reports that an arterial line manometer is the most accurate device.[51] The slit catheter, side-ported bevel-tipped needle, or an 18-gauge needle, when appropriately used with current electronic transducer monitoring, may be used clinically with confidence.[52] The arterial line manometer device has an additional advantage of being able to monitor pressure continuously. This is reported to be useful in tibial diaphyseal fractures, where the estimated sensitivity and specificity of continuous pressure monitoring are high and continuous monitoring should be considered.[35,53] Independent of the method used to measure compartment pressures, accuracy depends on proper calibration of the measuring device and placement of the needle or pressure sensor at the level of the injured compartment. The principle of tissue pressure measurement in the case of acute lower extremity compartment syndrome is shown in Fig. 151.2.

Reported diagnostic performance characteristics of clinical symptoms and signs of acute compartment syndrome (ACS) and intracompartmental pressure monitoring are shown in Table 151.2.

Use of near-infrared spectroscopy (NIRS) for detection of low tissue oxygenation, and therefore the development of compartment syndrome, is controversial. It has been reported as a useful noninvasive tool in diagnosing compartment syndrome after surgical revascularization of lower limb ischemia and in traumatically injured patients. But some subsequent studies did not prove its utility in injuries because of severe edema of the soft tissues, and it cannot measure tissue hemoglobin oxygen saturation (StO_2) inside the muscle compartment.[31,45,54–61]

In a large review of studies, several noninvasive diagnostics for extremity compartment syndrome after traumatic injury have been analyzed, including tissue hardness, ultrasound for fascial displacement, magnetic resonance imaging (MRI) and microwave tomography for tissue imaging, B-mode ultrasound for displacement, pulse oximetry for peripheral SpO_2, infrared imaging for surface temperature, contrast-enhanced ultrasound for perfusion, Doppler ultrasound in

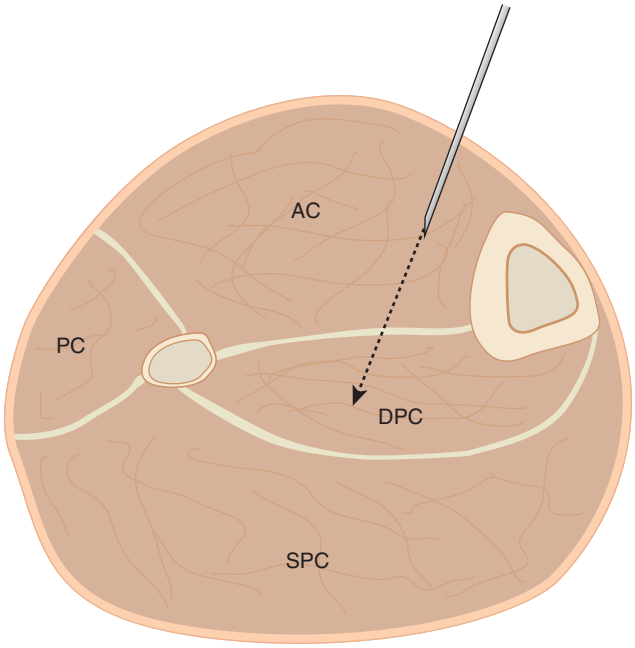


Fig. 151.2 Example of pressure measurement in the lower leg. Cross section shows anatomic compartments and needle placement first in the anterior compartment and then proceeding into the deep posterior compartment. *AC,* Anterior compartment; *DPC,* deep posterior compartment; *PC,* peroneal compartment; *SPC,* superficial posterior compartment.

TABLE 151.2 Reported Diagnostic Performance Characteristics of Clinical Symptoms and Signs of Acute Compartment Syndrome and Intracompartmental Pressure Monitoring

Symptom or Sign	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
Pain	19	97	14	98
Pain on passive stretch	19	97	14	98
Paralysis and motor changes	13	97	11	98
Paresthesia and sensory changes	13	98	15	98
Swelling	54	76	70	63
Intracompartmental pressure monitoring	94	98	93	99

From Duckworth AD, McQueen MM. The diagnosis of acute compartment syndrome: A critical analysis review. *JBJS Rev.* 2017;5(12):e1. doi:10.2106/JBJS.RVW.17.00016

brachial arterial flow, and NIRS for StO_2 detection. Although NIRS has shown the most promise, whether such technologies will be of diagnostic benefit await the completion of ongoing clinical trials.[62]

In animal research, the role of intramuscular glucose and partial pressure of oxygen for detecting compartment syndrome has been evaluated. Intramuscular glucose concentration and partial pressure of oxygen measured with commercially available probes rapidly identified muscle ischemia with a high sensitivity and specificity after an experimentally induced compartment syndrome in an animal model.[63]

Ultrasound shear wave elastography for measuring intracompartmental pressure of compartment syndrome has been used in another recent animal study, and this noninvasive technology can potentially help surgeons with early detection, monitoring, and prognosis of intracompartmental pressure.[64]

Another recent study described a noninvasive ultrasound compartment fascia flattening pressure measurement method in a cadaver model of anterior lower leg compartment syndrome. In this study ultrasound is coupled with pressure transducer and fascia flattening is visualized and pressure is recorded. This method is reported to be as an adjunct to clinical examination and includes evaluating injured and noninjured extremities, is noninvasive, is easily reproducible, and can be performed quickly without patient discomfort.[65]

In establishing a diagnosis of compartment syndrome, other causes of pain-producing symptoms have to be ruled out or confirmed or a cause of elevated intracompartmental pressure should be determined. When facing traumatic injuries, a workup for rhabdomyolysis (creatinine phosphokinase [CPK], renal function, urinalysis, and urine myoglobin) should be considered. In a group of patients with tibial fractures with or without compartment syndrome, a model combining maximal CPK level greater than 4000 U/L, maximal chloride level greater than 104 mg/dL, and minimal blood urea nitrogen (BUN) level less than 10 mg/dL had a 100% association with compartment syndrome.[66]

Moderate evidence supports that in patients with acute vascular ischemia, femoral vein lactate concentration samples during surgical embolectomy may assist in the diagnosis of ACS. On the other hand, there is little evidence supporting that serum troponin may assist in diagnosing ACS in patients with traumatic lower extremity injury.[67]

Extremity x-ray or computed tomography (CT) scans can confirm the presence of a fracture. MRI features of ACS include increased fascial and intramuscular T2 signal reflective of edema, and bulging of the fascia may also be present postcontrast, and fat-suppressed T1-weighted images demonstrate diffuse enhancement corresponding to the edema identified on the T2 sequences.[68] Ultrasonography can show muscle or any other tissue tears. Doppler ultrasonography or arteriography can detect vascular abnormalities.

MANAGEMENT

The objective of treatment of compartment syndrome is to minimize deficits in muscular and neurologic function by promptly restoring LBF. Certain nonoperative measures may be effective, such as eliminating external pressure and maintaining local arterial pressure. When there is external pressure that causes compartment syndrome, such as tight casts, it is essential to release the envelope immediately (remove and exchange for a noncircular splint) when only one symptom or sign is present. Usually, this is pain and is most often observed in patients with fracture splints several hours after treatment. Restoration of normal limb perfusion has priority over closed fracture treatment, and this can be postponed until perfusion returns to normal. Before resorting to operative methods for reducing tissue pressure, it is important to consider improvement of LBF if it has been reduced by shock, peripheral vascular disease, or elevation of the limb above the heart. All causes of systemic hypotension should be treated. Limb elevation should be avoided because it lowers local arterial pressure and does not help in reducing swelling.[69] Use of vasodilating drugs or sympathetic blockade appears to be ineffective because, in this condition, local maximal vasodilatation is already present. The use of phosphodiesterase inhibitors in experimental animal models caused modulation of compartmental pressures.[70] In a large study on trauma patients with isolated arterial injury, early anticoagulation with heparin was found to reduce the incidence of compartment syndrome without significant bleeding as a consequence.[71] Carbon monoxide–releasing molecule-3 displays a potent protective/antiinflammatory action in an experimental model of compartment syndrome, suggesting a potential therapeutic application for patients at risk of developing compartment syndrome.[72]

The primary goal of treating compartment syndrome is to decrease intracompartmental pressures. Surgical decompression of all limiting envelopes is the gold standard of treatment, indicated in the presence of a characteristic clinical picture of compartment syndrome in a cooperative patient. When the clinical examination is unreliable or difficult to obtain, pressure measurement should be obtained, where either pressure should not exceed 45 mm Hg or ΔP should not be below 30 mm Hg.

Standard treatment involves a long skin incision and fasciotomy of all involved compartments and debridement of obvious nonviable tissue. Usually, this procedure is performed under general or spinal anesthesia. Bedside fasciotomy under local anesthesia has been described in select cases to be feasible and reliable.[73] Fasciotomy should be performed without a tourniquet to avoid prolonging ischemia and to permit the surgeon to assess the degree of viability and restoration of blood flow. The skin is incised through the entire length of the involved compartment. Obvious muscle bulging is observed in true

compartment syndrome (Fig. 151.3). Only obvious necrotic muscle should be removed because the tissue may have the potential for reperfusion and recovery. The sign of contractility with electrostimulation should not be used initially. After fascial release, postischemic swelling should be anticipated; therefore the skin should be left open and the wound temporarily closed with a patch of compliant artificial temporary skin closures. If release of the compartment is not complete, "rebound" compartment syndrome may occur.

After surgical decompression and temporary skin closure, sterile dressings are applied and the extremity is usually splinted in a functional position. In the presence of fractures, one should consider fixation with external fixators, rarely with plates or intramedullary nails. This stabilization is performed immediately after fascial decompression and greatly facilitates later care of the wound, limb, and fracture. Passive stretching exercises are performed to maintain range of joint motion. Skin closure may usually be performed 3–5 days after surgical decompression, usually by a mesh graft and rarely by direct suturing (Fig. 151.4). At that time, additional debridement of nonviable tissue can be performed. Fascial closure is not recommended because this requires closure under tension and can lead to redevelopment of compartment syndrome. Muscle hernia is left behind and should be large enough to not cause additional late problems. When an optimal cosmetic result is desired, one may progressively approximate the wound edges over 7–14 days with sutures or commercial devices to achieve direct skin closure.

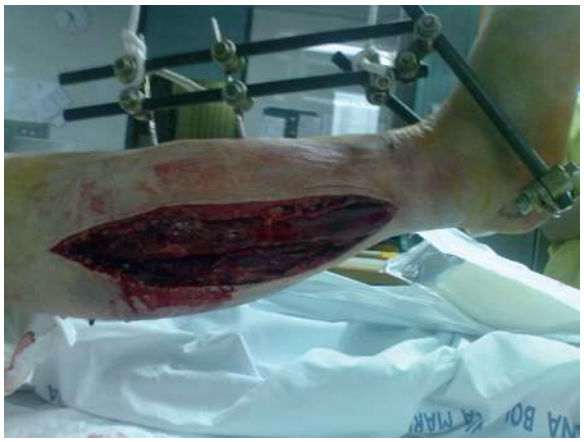


Fig. 151.3 The patient in Fig. 151.1A after fasciotomy of the anterior and peroneal compartment and external fixation of the tibial fracture. Note obvious muscle bulging after release of fascial compartments. Direct skin closure was not possible.

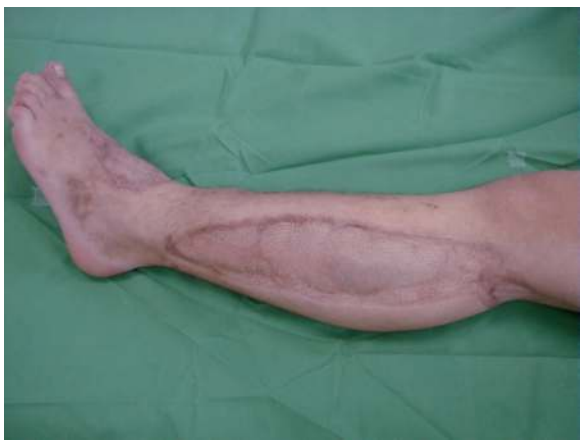


Fig. 151.4 Cosmetic result of the lower extremity compartment syndrome after mesh grafting of the lateral compartment.

Negative-pressure wound care closure devices can be useful in the management of fasciotomy wounds. Negative pressure decreases wound edema, facilitates approximation of the skin edges, enhances LBF, promotes granulation tissue, and decreases bacterial colonization. Conversely, in one animal study, negative pressure may be harmful to skeletal muscle after compartment syndrome.[74] One randomized study compared vacuum-assisted closure (VAC) with the shoelace technique. Both techniques were safe, reliable, and effective methods for closure of leg fasciotomy wounds. VAC required a longer time for definite wound closure and was reported to be far more expensive than the shoelace technique, especially when additional skin grafting was required.[75] In retrospective analyses, negative pressure led to significantly higher rates of complete skin closure and decreased time to skin closure.[76,77] In a recent large meta-analysis the highest success rate for closure of the wounds without skin grafting was observed with dynamic dermatotraction and gradual suture approximation, whereas VAC had the lowest complication rate.[78] Hyperbaric oxygen as an adjunct to management after fasciotomy is reported in some case reports and animal studies, but there is a lack of evidence suggesting that this is advantageous over current practices.[79–83]

FASCIOTOMY

Fasciotomy depends on the underlying condition or mechanism that caused compartment syndrome. The length of the lower extremity skin incisions has been debated for a long time. Minimal skin incisions with more extensive fascial incisions could place the patient at risk of recurrent compartment syndrome.[84–86] The degree of muscle swelling after reperfusion cannot be predicted, and peak edema occurs several hours after surgery.

An example of a treatment algorithm that includes both conscious and unconscious groups of patients helping in making a decision when to perform emergency fascia release is shown in Fig. 151.5.

FASCIOTOMY OF THE UPPER EXTREMITY

The upper extremity is anatomically divided into the brachium, antebrachium, and hand. Each of the anatomic segments has a different number of compartments with various muscle functions. Techniques for release of these compartments have to be discussed separately, and combined fasciotomy is shown in Fig. 151.6.

Fasciotomy of the Brachium

The arm has two compartments: anterior, which includes the biceps and brachioradialis muscles, and posterior with the triceps muscle. Fasciotomy includes a lateral skin incision from the deltoid insertion to the lateral epicondyle. Care must be taken to avoid damage to the larger cutaneous nerves. At the fascial level, the intermuscular septum between the anterior and posterior compartments is identified, and fascia overlying each compartment is released with longitudinal incisions. The radial nerve should be protected as it passes through the intermuscular septum from the posterior compartment to the anterior compartment just below the fascia (see Fig. 151.6).

Fasciotomy of the Antebrachium

The antebrachium has three muscular compartments: mobile wad proximally, volar compartment, and dorsal compartment. Fasciotomy consists of a longitudinal, centrally placed incision over the extensor compartment and a curvilinear incision on the flexor aspect beginning at the antecubital fossa (Fig. 151.7). A palmar incision is made between

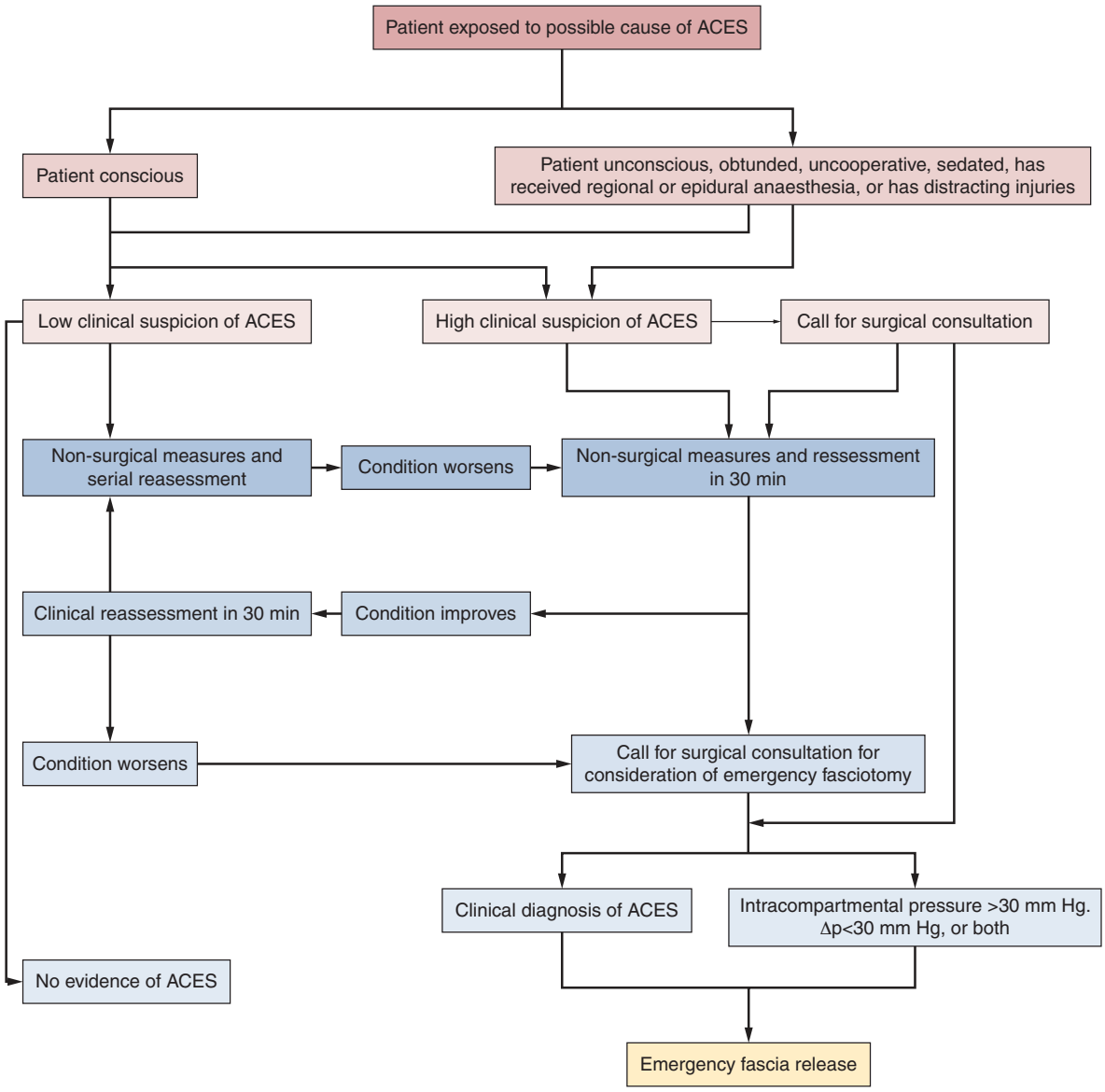


Fig. 151.5 An example of a management algorithm. *ACES,* Acute extremity compartment syndrome; Δp, diastolic blood pressure − intracompartmental pressure. (From Keudell AG, Weaver MJ, Appleton PT, et al. Emergency surgery 3. Diagnosis and treatment of acute extremity compartment syndrome. *Lancet.* 2015;386:1299–1310.)

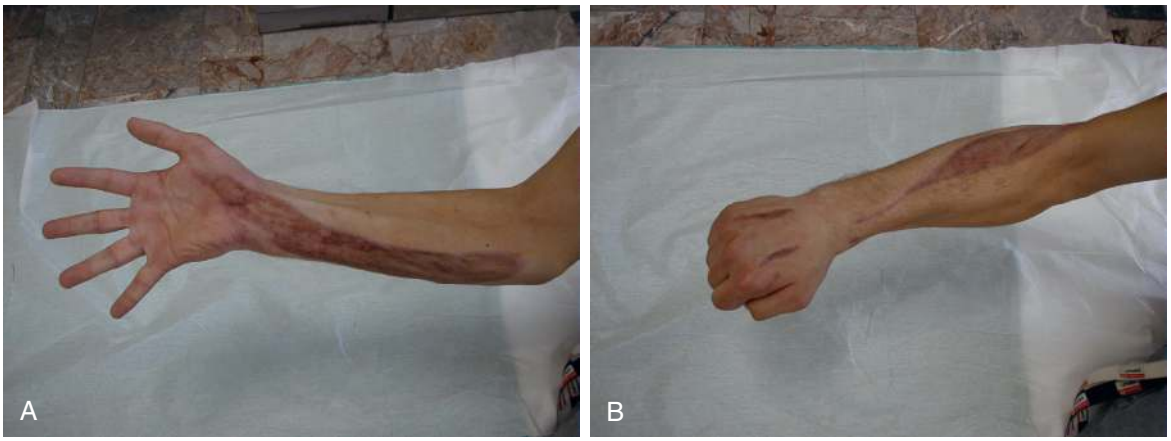


Fig. 151.6 Clinical photographs of combined fasciotomy of the upper extremity. Dorsal and volar aspects.

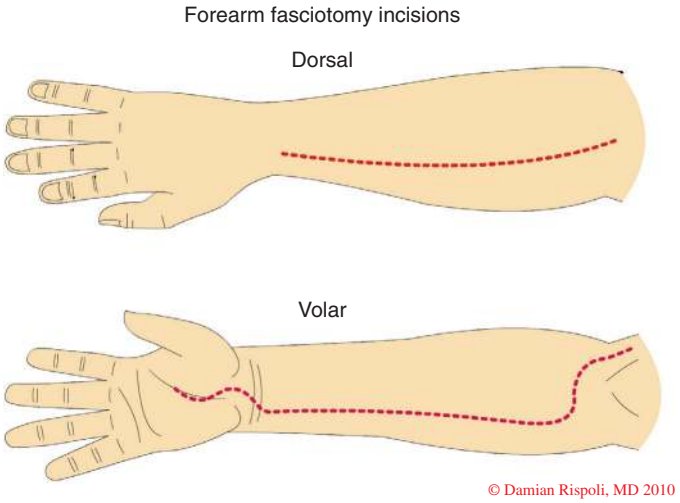


Fig. 151.7 Fasciotomy of antebrachium. Dorsal and volar aspects. (From Wheeless CR. *Wheeless' Textbook of Orthopaedics.* Towson, MD: Data Trace; 2014. © 2010, Damian Rispoli, MD.)

the thenar and hypothenar muscles in the palm, where the carpal tunnel can be released if needed. The incision is extended transversely across the wrist flexion crease to the ulnar side of the wrist and then arched across the volar forearm back to the ulnar side at the elbow. At the elbow, the incision is curved just radially to the medial epicondyle across the elbow flexion crease, and the deep fascia is released. At the antecubital fossa, a fibrous band overlying the brachial artery and median nerve is carefully released. This incision allows for soft tissue coverage of underlying neurovascular structures at the wrist and elbow and prevents soft tissue contractures from developing at flexion creases. A second straight dorsal incision can be made to release the mobile wad if necessary.

Fasciotomy of the Hand

The hand has a unique anatomy with 10 separate fascial compartments: 4 dorsal and 3 volar interossei, thenar muscles, hypothenar muscles, and the adductor pollicis muscle. Fasciotomy consists of four incisions (Fig. 151.8). One incision on the radial side of the thumb metacarpal releases the thenar compartment. A dorsal incision over the index finger metacarpal is used to release the first and second dorsal interossei, to reach the ulnar-to-index finger metacarpal, and to release the volar interossei and adductor pollicis muscle. A dorsal incision over the ring finger metacarpal is used to release the third and fourth dorsal interossei and to reach down along the radial aspect of the ring finger and small finger metatarsal to release volar interossei. An incision placed at the ulnar aspect of the small finger is used to release the hypothenar muscles.

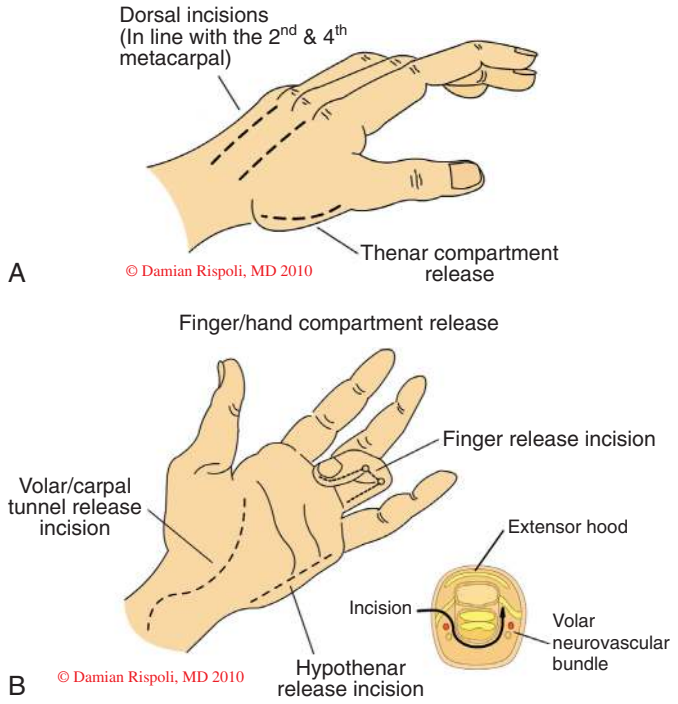


Fig. 151.8 Fasciotomy of the hand. Dorsal (**A**) and volar (**B**) aspects. (From Wheeless CR. *Wheeless' Textbook of Orthopaedics.* Towson, MD: Data Trace; 2014. © 2010, Damian Rispoli, MD.)

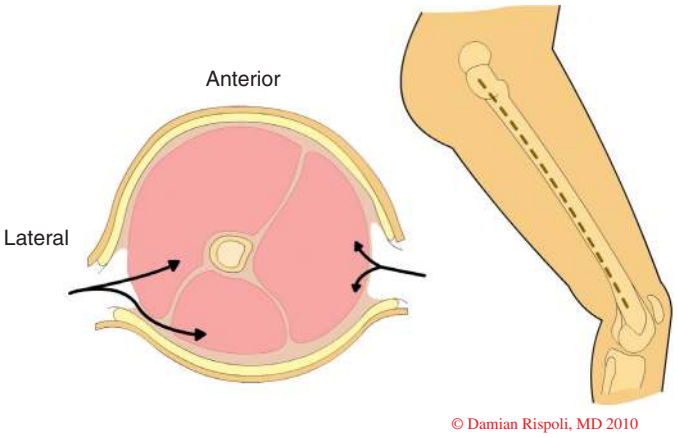


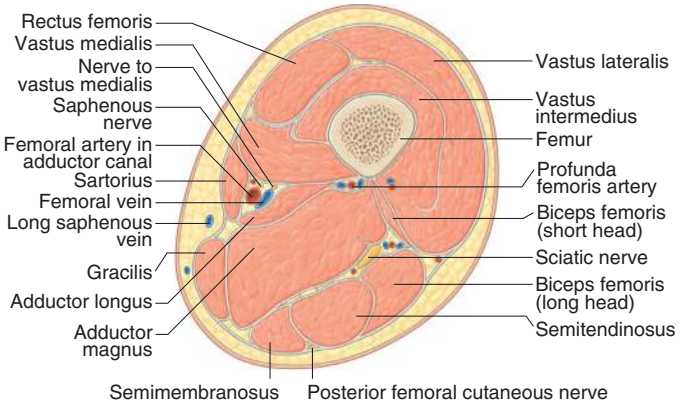
Fig. 151.9 Schematic presentation of fasciotomy of the thigh. (From Wheeless CR. Wheeless' Textbook of Orthopaedics. Towson, MD: Data Trace, 2014. © 2010, Damian Rispoli, MD.)

FASCIOTOMY OF THE LOWER EXTREMITY

The lower extremity is anatomically divided into three parts: thigh, lower leg, and foot. As in the upper extremity, each anatomic segment has a different number of compartments with various muscle functions. Techniques for release of these compartments are discussed separately as well.

Fasciotomy of the Thigh

The thigh has three compartments: anterior (quadriceps), medial (adductors), and posterior (hamstrings) (eFig. 151.3). Because of the large potential volume, compartment syndrome and blending of fascial compartments with the hip (allows extravasation of blood outside compartments) in the thigh are less likely to occur but can be seen especially in patients with high-energy femoral fractures or hip fractures. Fasciotomy consists of lateral incisions made from the greater trochanter to the lateral condyle of the femur. The iliotibial band is incised, and the vastus lateralis is reflected off the intermuscular septum bluntly, thereby releasing the anterior compartment. The intermuscular septum is then incised over the length of the incision, releasing the posterior compartment. This release should not be done close to the femur because a series of perforating vessels pass through the septum posteriorly to anteriorly near the bone. The medial compartment is released through separate anteromedial incisions (Fig. 151.9).



eFig. 151.3 Anatomy of the compartments of the thigh. (From Standring S, Borley NR, Gray H. *Gray's Anatomy,* 40th ed. Edinburgh, Scotland: Churchill Livingstone; 2008.)

Fasciotomy of the Lower Leg

Lower extremity compartment syndrome is the most common because of the unique anatomy of compartments. Most of the studies on compartment syndrome have been conducted on this part of the body, and most of the current knowledge about epidemiology and treatment is based on lower extremity compartment syndrome studies. Reported predictors for developing ACS of the lower leg are plateau fractures type Schatzker VI, especially when combined with shaft or fibular fractures, high energy mechanism, and fracture length.[87] The lower leg has four compartments: lateral (peroneal brevis and longus), anterior (extensor hallucis longus muscle, extensor digitorum longus muscle, tibialis anterior muscle, and peroneus tertius), superficial posterior (gastrocnemius and soleus), and deep posterior (flexor hallucis longus muscle, flexor digitorum longus muscle, and tibialis posterior muscle) (eFig. 151.4). The anterior compartment is the most commonly involved, followed by the deep posterior compartment. In the case of compartment syndrome of any of the compartments, release of all four is generally recommended. Some authors recommend selective fasciotomy of only the affected compartment as a less invasive and feasible treatment option, but recommend further comparative studies.[88]

There are two surgical techniques for release of all four compartments in the lower leg: the one-incision technique (Figs. 151.10 and 151.11) and two-incision technique (Fig. 151.12). There is no strong evidence on which technique has an advantage over the other. The only retrospective study in the setting of tibial fractures comparing the two methods found similar infection and nonunion rates.[89] The one-incision technique resulted in only one surgical wound and fewer related complications in one study.[90] It seems that the choice for fasciotomy can be based on surgeon experience, and, because of simplicity, the two-incision technique is more often used.

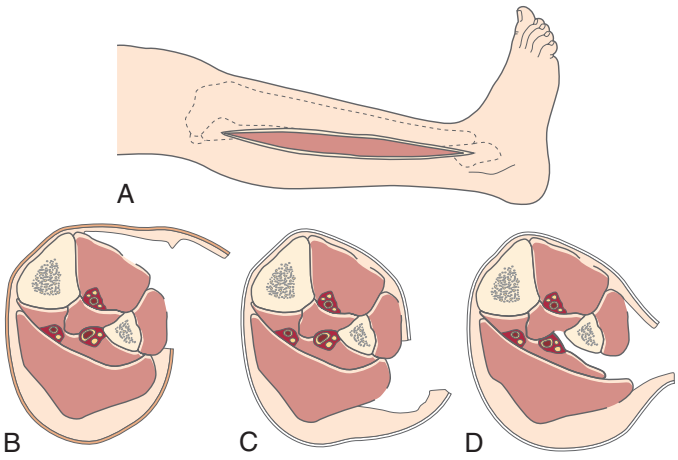


Fig. 151.10 Single-incision fasciotomy of the lower leg. **A,** Lateral skin incision from the fibular neck to 3–4 cm proximal to the lateral malleolus. **B,** The skin is undermined anteriorly, and a fasciotomy of the anterior and lateral compartments is performed. **C,** The skin is undermined posteriorly, and a fasciotomy of the superficial posterior compartment is performed. **D,** An interval between the superficial posterior and lateral compartments is developed. The flexor hallucis longus muscle is dissected subperiosteally off the fibula and retracted posteromedially. The fascial attachment of the posterior tibial muscle to the fibula is incised to decompress the muscle. (From Davey JR, Rorabeck CH, Fowler PJ. The tibialis posterior muscle compartment: An unrecognized cause of exertional compartment syndrome. *Am J Sports Med.* 1984;12:391–397.)

One-Incision Technique

The one-incision technique is technically more difficult, as it is difficult to visualize the deep posterior compartment, and therefore there is an increased risk of injury to the peroneal artery and nerve. The technique starts with a skin incision 1–2 cm anterior and parallel to the fibula, just inferior to the fibular head, and 3–4 cm proximal to the lateral malleolus. An anterior flap enables exposure of the anterior and lateral compartments. Longitudinal incisions are made in the fascia, and care must be taken to avoid damage to the common, superficial, and deep peroneal nerves at the fibular head. A lateral flap is exposed more posteriorly to visualize the superficial posterior compartment. The gastrocnemius muscle should be identified, and the fascia is incised longitudinally. The deep posterior compartment is identified later, after exposure of the posterior side of the fibula with dissection of the soleus muscle. Fasciotomy of the deep posterior compartment is performed at the medial border of the fibula. Here, peroneal vessels should be retracted and protected posteriorly to avoid injury (see Fig. 151.10).

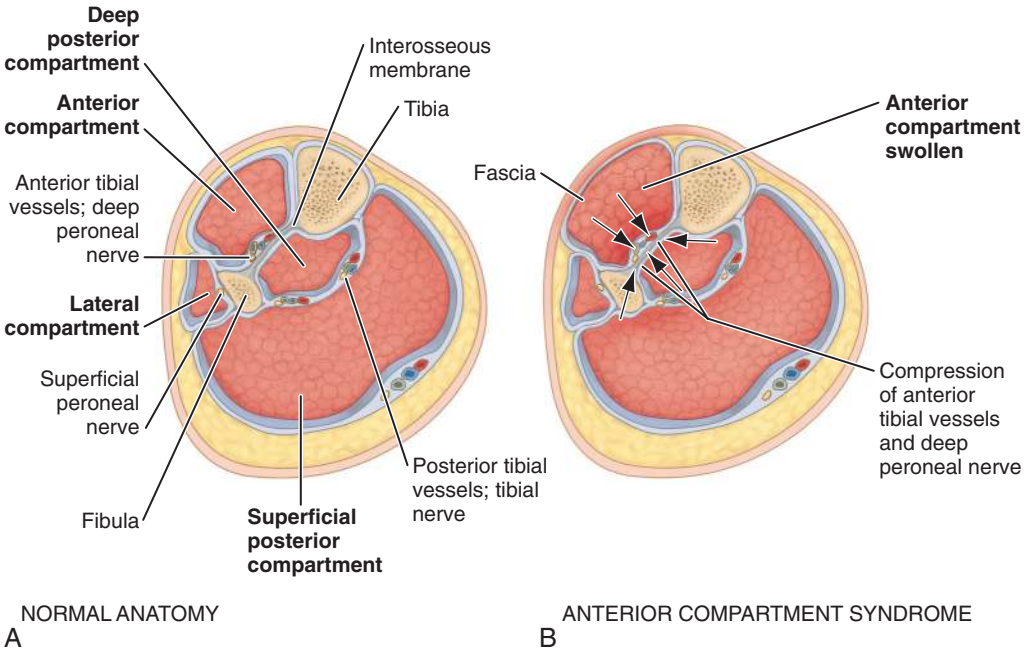
A recently described variant of the one-incision technique uses a paratibial route to release the deep posterior compartment rather than a transfibular or parafibular route (see Fig 151.11). This affords a faster fasciotomy with a smaller flap and avoids potential damage to the neurovascular bundle and lessens the risk of injury to the peroneal nerves, which could occur with dissection of the posterior aspect of the fibula.[91]

Two-Incision Technique

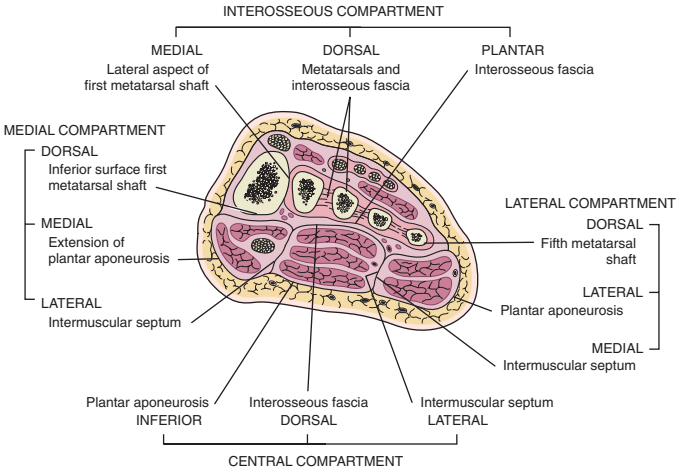
This technique uses medial and lateral longitudinal incisions that should be long enough to completely release all four compartments. In adults, incisions can be up to 30 cm long. The lateral incision starts about 5 cm lateral to the anterior border of the tibia. Underlying the incision are the fascial tissues of the anterior and peroneal compartments; these are identified and released. The intermuscular septum should be identified to ensure that both compartments are released. Care must be taken to not damage the common peroneal nerve proximally as it passes around the fibular head; therefore skin incisions should not reach the fibular head level. Distally, the skin incision ends about 5 cm above the lateral malleolus. The medial incision of the two-incision technique starts 2 cm medial to the tibial margin. It is used to release both posterior compartments. Care must be taken to avoid saphenous nerve and vein damage, and these structures should be identified before fasciotomy of these compartments. The superficial posterior compartment is decompressed by incising the gastrocnemius fascia in a longitudinal direction proximally to distally. The posterior compartment is decompressed by dividing the attachments of the soleus muscle to the tibia (see Fig. 151.12).

Fasciotomy of the Foot

Acute compartment syndrome of the foot most commonly occurs because of crush injury, and fasciotomy is rarely needed. There are four major compartments of the foot: intraosseus, lateral, central (calcaneal), and medial (eFig. 151.5). They are further divided into smaller muscle groups, so there are nine compartments in the foot, but this number is controversial (eFig. 151.5). Common needle insertion sites to measure the intracompartmental pressures of the foot are shown in Fig. 151.13. Whereas each of the compartments should generally be released, some debate exists whether the superficial compartment of the dorsal central compartment, which contains the flexor digitorum brevis muscle, should be included. A dorsal approach is most commonly used and requires less dissection than the other two. It begins with dual dorsal longitudinal incisions over the medial side of the second metatarsal bone and the lateral side of the fourth metatarsal bone. Each of the four interosseous compartments is released first between the metatarsal bones. The medial



eFig. 151.4 Anatomy of the compartments of the lower leg. (From Black JM, Hawks JH. *Medical-Surgical Nursing,* 8th ed. Philadelphia, PA: Saunders; 2009.)



eFig. 151.5 Compartments of the foot. (From Twaddle BC, Amendola A. Compartment syndromes. In Browner BD, Jupiter JB, Levine AM, et al., eds. *Skeletal Trauma,* 4th ed. Philadelphia, PA: Saunders; 2009.)

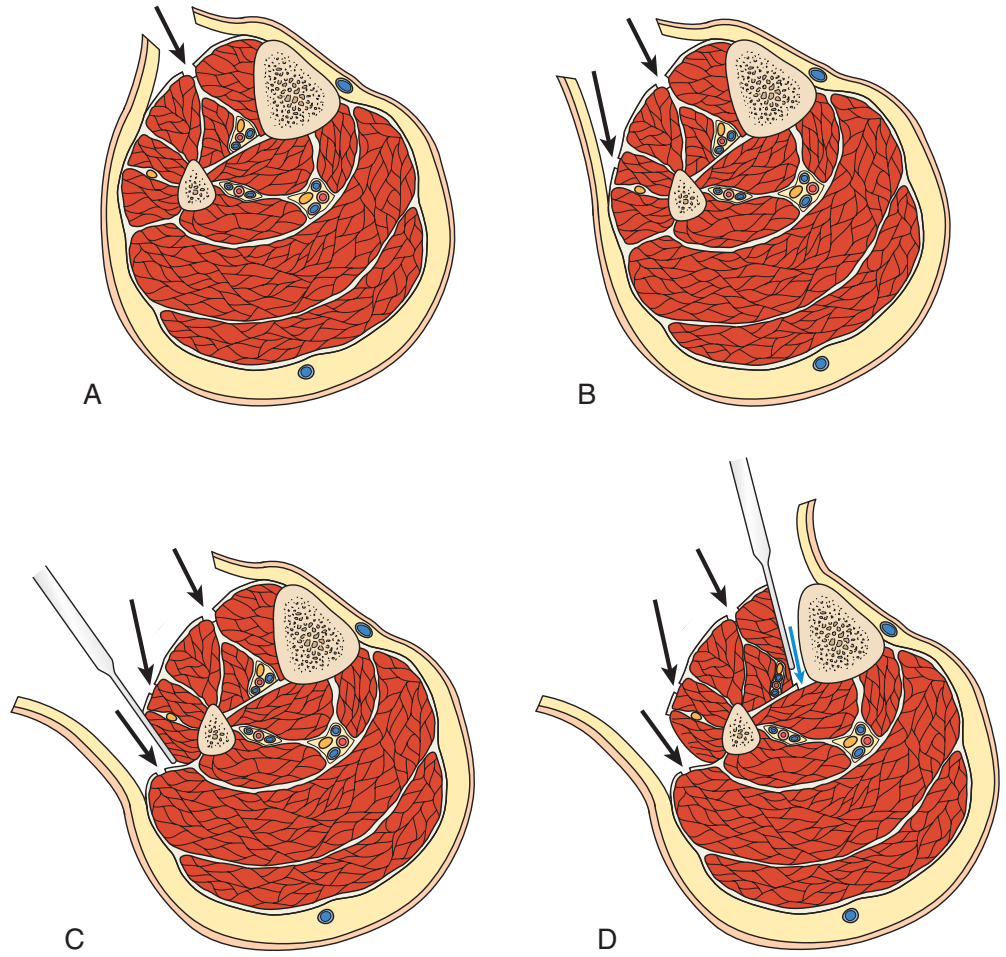


Fig. 151.11 A variant of the approach for the single-incision fasciotomy. **A,** The initial skin incision is made halfway between the tibia and fibula to release the anterior compartment. **B,** Release of the lateral compartment. **C,** The superficial posterior compartment is released after retracting the peroneals anteriorly. A Cobb may be used for this purpose. **D,** The deep posterior compartment is released by retracting the tibialis anterior laterally from the tibia and then incising the intraosseus membrane. (From Ebraheim NA, Siddiqui S, Raberding C. A single-incision fasciotomy for compartment syndrome of the lower leg. *J Orthop Trauma*. 2016;30:e252–e255.)

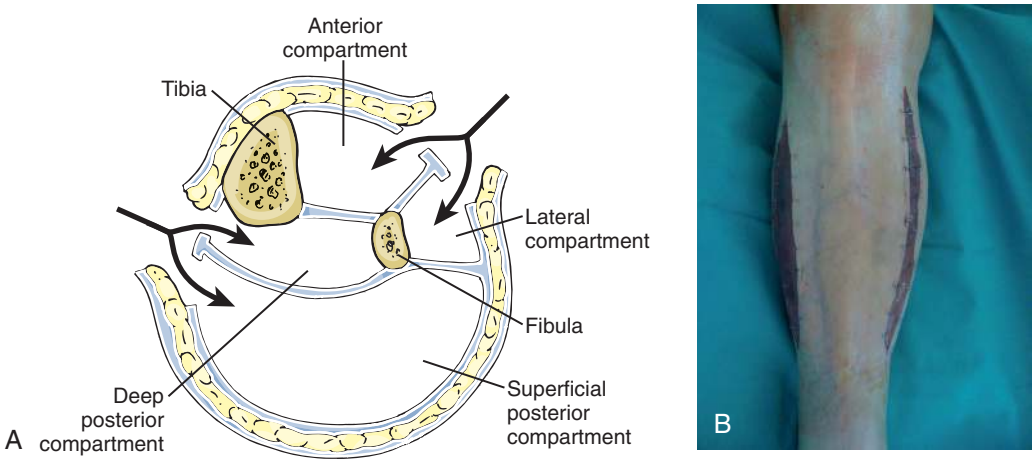


Fig. 151.12 Two-incision technique for fasciotomy of the lower leg. **A,** A cross sectional view and (**B**) position of skin incisions. Both wounds have been temporarily covered with an artificial skin graft. (**A,** from Cameron JL, Cameron AM. *Current Surgical Therapy,* 10th ed. Philadelphia, PA: Saunders; 2011.)

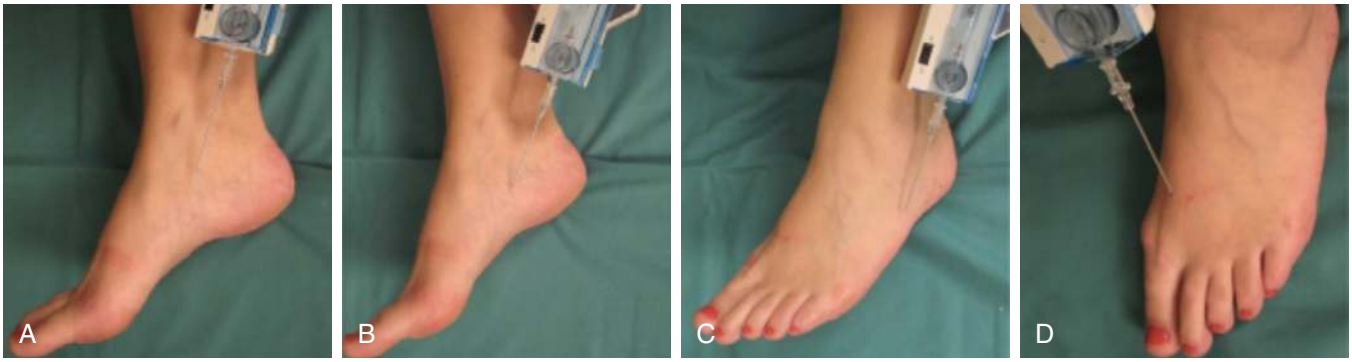


Fig. 151.13 **A,** Needle insertion site to measure the intracompartmental pressure of the medial and calcaneal compartments (4 cm distal to the medial malleolus). **B,** Needle insertion site to measure the intracompartmental pressure of the superficial compartment (ventral and plantar aspect; penetration of the flexor digitorum brevis muscle). **C,** Needle insertion site to measure the intracompartmental pressure of the lateral compartment (plantar to the fifth metatarsal). **D,** Needle insertion site to measure the intracompartmental pressure of the interosseous compartment. (From Lutter C, Schöffl V, Hotfiel T, et al. Compartment syndrome of the foot: An evidence-based review. *J Foot Ankle Surg.* 2019;58[4]:632–640.)

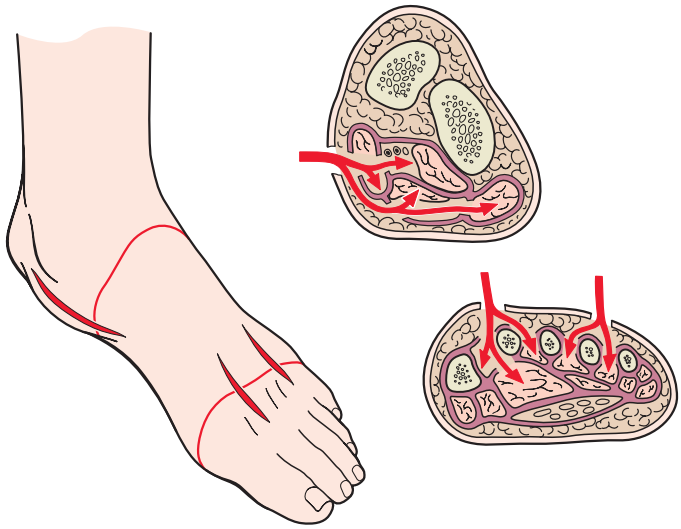


Fig. 151.14 **Fasciotomy of the foot. Medial and dorsal approaches.** (From Banerjee R, Nickisch F, Easley ME, et al. Foot injuries. In Browner BD, Jupiter JB, Levine AM, et al, eds. *Skeletal Trauma,* 4th ed. Philadelphia, PA: Saunders; 2009.)

compartment may be released by accessing a space medial to the second metatarsal; the lateral compartment is released by accessing a space lateral to the fourth metatarsal bone. The calcaneal compartment lies underneath the second interosseous space and can be released through a medial incision. The superficial compartment is accessed through the calcaneal compartment by blunt dissection of the adductor hallucis muscle. Sometimes release of this compartment is not required, because it contains predominantly tendons of the finger flexors and is not a "true" muscular compartment. Fasciotomy approaches to the foot compartments are shown in Fig. 151.14.

POTENTIAL COMPLICATIONS

Delay of treatment of compartment syndrome can lead to irreversible complications and, left untreated, can lead to death. The initial management should be focused not only on preservation of tissue viability in the compartment but also on the initial management of systemic complications of reperfusion injury. This requires restoration of intravascular volume, prevention of hyperkalemia, and treatment of metabolic acidosis and myoglobinuria, which may lead to acute kidney injury. Complications may also occur as a sequela of surgical procedures performed and wound management. Late sequelae of compartment syndrome include persistent hypoesthesia, dysesthesia, persistent motor weakness, infection, myoglobinuric renal failure, contractures, amputation, and death. In one study, persistent sequelae were reported to be associated with a higher number of operations, postfasciotomy complications, closures with skin grafting, and increased time to closure.[92]

Technical complications of fasciotomy are preventable when considering the anatomy of important structures. Persistent or recurrent compartment syndrome can occur if fascial incisions are not adequate to permit complete decompression of the compartment or if selective fasciotomy has been performed.[84]

Persistent neurologic deficits after fasciotomy are common. Nerve injury can occur because of the initial traumatic event, prolonged

ischemia, or as a consequence of fasciotomy dissection and tissue débridement. The most common neuropathic syndrome is altered sensation at the margins of the incision; chronic pain syndromes are also described.[93] Impaired neurologic function after lower extremity fasciotomy is described in 7%–36% of injured limbs.[94–96]

Wound complications after fasciotomy may occur immediately or be delayed for months to years. Early wound complications occur in up to 40% of patients after lower extremity fasciotomy.[94,97,98] Risk factors are related to the presence of vascular injury, lower extremity site, and premature or delayed closure of the wound.[98] Wound infection occurs in 4%–7% of extremity fasciotomies.[94,97] Prophylactic antibiotics should be given at the time of fasciotomy and discontinued after 24 hours. Repeated débridement of devitalized tissue may protect from severe wound infections and sepsis. Late wound complications are reported in 4%–38% of limbs.[93,94,97,98] Delayed wound complications include tethered scars and tendons, muscle hernias, and poor healing and ulceration, especially in patients with underlying vascular diseases. Venous insufficiency can predispose patients to chronic venous disease after fasciotomy. Tibial diaphyseal fracture healing in patients with compartment syndrome has been found to be delayed, and the rates of nonunion are reported to be higher compared with patients without compartment syndrome.[99]

Acute extremity compartment syndrome is associated with significant risk of limb loss.[100] Major amputation will be required in 5%–21% of limbs treated with fasciotomy.[94,95,97,98,100] Combined orthopedic and vascular injury, other severe injuries, and systemic factors may contribute to the need for amputation in severely injured patients. The highest amputation rate occurs in patients with severe vascular injuries with occlusion.[94] A large review of the National Trauma Data Bank for lower extremity vascular injury comparing early versus late fasciotomy findings suggests that appropriate implementation of early fasciotomy may reduce amputation rates.[101] Amputation of the upper extremity after fasciotomy is rare.

The most severe cases of compartment syndrome left untreated may cause death. Reported mortality ranges from 11% to 25% and depends on the epidemiology of the compartment syndrome.[84,95,97,102] Mortality is most often the result of massive trauma, severe hypovolemic shock, and multisystem organ failure and cannot be attributed only to the need for fasciotomy. This is especially true in severely injured patients with massive shock resuscitation where the mortality after fasciotomy in one study reached 67%.[26]

CONCLUSION

The patient who undergoes fasciotomy requires a physical therapy program to regain function. Postoperative care and rehabilitation are just as important as the procedure itself. During the immediate postoperative period, weight bearing is limited, and assistive devices (e.g., crutches) are needed. Within a few days, and with adequate pain control, the use of crutches can be discontinued. The rehabilitation program then involves range of motion (ROM) and flexibility exercises involving the muscles of the affected compartment. Adjacent joints need to be exercised to maintain their normal ROM.

Once the patient is able to ambulate with a normalized gait pattern, a program of graduated resistive exercises (depending on the patient's regular activities or work) is initiated. In the case of athletes, sports-specific exercises are started with the intention of returning to a regular athletic schedule. Cross training is also beneficial for these athletes. Activities such as swimming, pedal exercises, water jogging, or running help athletes regain muscle strength and flexibility without loading the affected compartment.

With surgical intervention for decompression, occupational therapy consultation should be considered early in the postoperative period. Appropriate treatment and assessment of the patient's deficits with regard to activities of daily living and for instruction in the use of any necessary assistive devices should be assessed.

KEY POINTS

- Compartment syndrome is a life-threatening condition and should be treated as soon as it is diagnosed.
- One of the first signs of compartment syndrome is a swollen extremity with pain out of proportion and increasing requirements for analgesia.
- Unfortunately, clinical signs alone are inadequate in the diagnosis of ACS because of well-documented poor sensivity.
- Critically ill patients, especially after severe trauma with massive fluid resuscitation, and youth patients with high energy mechanism and an associated underlying fracture, require special attention and frequent evaluation.
- Diagnosis of compartment syndrome is very likely when intracompartmental pressure reaches 45 mm Hg or the difference between diastolic blood pressure and intracompartmental pressure is less than 30 mm Hg for more than 2 hours.
- Treatment of compartment syndrome is primarily surgical with prompt release of all affected muscle compartments by fasciotomy.

References for this chapter can be found at expertconsult.com.

ANNOTATED REFERENCES

Duckworth AD, McQueen MM. The diagnosis of acute compartment syndrome. A critical analysis review. *JBJS Rev.* 2017;5(12):e1. doi:10.2106/JBJS.RVW.17.00016.
Although pain is characteristically the index sign associated with the development of acute compartment syndrome, clinical findings in isolation have been proven to have inadequate diagnostic performance characteristics, with sensitivity ranging from 13% to 54%.

Ebraheim NA, Abdelgawad AA, Ebraheim MA, et al. Bedside fasciotomy under local anesthesia for acute compartment syndrome: A feasible and reliable procedure in selected cases. *J Orthop Trauma.* 2012;13:153–157.
Standard compartment syndrome treatment involves a long skin incision and fasciotomy of all involved compartments and débridement of obvious nonviable tissue. Usually, this procedure is performed under general or spinal anesthesia. Various reasons can cause delay in performing the surgery. The authors of this study conclude that bedside fasciotomy under local anesthesia can be done safely and effectively to avoid delay in compartment release.

Hammerberg EM, Whitesides Jr. TE, Seiler III JG. The reliability of measurement of tissue pressure in compartment syndrome. *J Orthop Trauma.* 2012;26:24–31, discussion 32.
There are numerous commercially available methods of tissue pressure measurement (e.g., the Stryker device). To achieve adequate accuracy when measuring intracompartmental pressure without these devices, authors of this study concluded that the slit catheter, side-ported bevel-tipped needle, or an 18-gauge needle, when appropriately used with current electronic transducer monitoring, may be used clinically with confidence.

Jauregui JJ, Yarmis SJ, Tsai J, et al. Fasciotomy closure techniques: A meta-analysis. *J Orthop Surg.* 2017;25(1):2309499016684724.
The authors evaluated the risks and success rates of the three major techniques for compartment syndrome fasciotomy closure by reviewing all literature published to date. Success was defined as all wounds that could be closed without skin grafting, amputation, or death. The highest success rate was observed for dynamic dermatotraction and gradual suture approximation, whereas vacuum-assisted closure had the lowest complication rate.

Kosir R, Moore FA, Selby LH, et al. Acute lower extremity compartment syndrome (ALECS) screening protocol in critically ill trauma patients. *J Trauma.* 2007; 63:268–275.
In this study during a 6-month period, the incidence of acute lower extremity compartment syndrome (ALECS) in screened patients was surprisingly high

at 20% (nine patients). These were patients with severe injuries with an Injury Severity Score of 32.0 ± 12.5 who exhibited significant volume depletion, with a base deficit of 12.9 ± 5.9 mEq/L and a lactate level of 13.0 ± 5.2 mmol/L, requiring large-volume resuscitation. Acute lower extremity compartment syndrome was associated with an exceedingly high mortality rate at 67%. Mortality in severely injured patients is most often the result of massive trauma, severe hypovolemic shock, and multiple organ failure and cannot be attributed only to the need for fasciotomy.

Marchand LS, Working ZM, Rane AA, et al. Compartment syndrome in tibial plateau fractures: Do previously established predictors have external validity? *J Orthop Trauma*. 2020;34(5):238–243.

Injuries of the lower extremity are the most common cause of extremity compartment syndrome. In this retrospective review 513 patients with tibial plateau fractures treated operatively over a 10-year period (OTA/AO 41B1-3 & 41C1-3; Schatzker I-VI) were analyzed. This study confirms that several factors are associated with the development of ACS. Reported predictors for developing ACS of the lower leg are plateau fractures type Schatzker VI, especially when combined with shaft or fibular fractures, high energy mechanism, and fracture length. The presence of each independent predictor had a cumulative effect such that when more than one variable is present, the chance of ACS increases.

McQueen MM, Court-Brown CM. Compartment monitoring in tibial fractures. The pressure threshold for decompression. *J Bone Joint Surg Br.* 1996;78:99–104.

In this early prospective study of 116 patients with tibial diaphyseal fractures, continuous monitoring of anterior compartment pressure for 24 hours was studied. Three patients developed acute compartment syndrome (2.6%). In their series, the use of a differential pressure (ΔP) of 30 mm Hg as a threshold for fasciotomy led to no missed cases of acute compartment syndrome. The authors recommend that decompression be performed if the the differential pressure level drops to under 30 mm Hg.

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Thromboembolization and Thrombolytic Therapy

Anthony J. Lewis and Edith Tzeng

INTRODUCTION

Thrombolytic agents comprise a diverse group of compounds that indirectly initiate the lysis of a thrombus. After the initiation of the coagulation cascade, fibrinolytic mechanisms are concomitantly activated to prevent unconstrained thrombosis. Fibrinolysis begins with the cleavage of proenzyme plasminogen to plasmin, which hydrolyzes key bonds within a fibrin clot matrix, resulting in clot lysis (Fig. 152.1). Thrombolytic agents function by converting plasminogen to plasmin. Different thrombolytic agents vary in their specificity for plasminogen, metabolic half-life, and antigenicity (Table 152.1).

DRUGS

Streptokinase

Streptokinase, a protein produced by beta-hemolytic streptococci, was identified as having fibrinolytic properties in the 1930s and was the first compound to be used clinically as a thrombolytic drug.[1,2] Streptokinase complexes with plasminogen and converts it to plasmin. However, one of the major drawbacks of using streptokinase is its antigenicity, as streptococcal infection may induce antibody formation. Mild allergic reactions occur in 2%–5% patients; however, severe anaphylactic reactions may also occur.[3]

Urokinase

Urokinase is a thrombolytic protein that was initially isolated from human urine and has been used clinically for over 30 years. At present, it is isolated from human fetal renal tissue cultures. Unlike streptokinase, urokinase enzymatically cleaves plasminogen. In 1999 urokinase was removed from the U.S. market after concerns raised by the Food and Drug Administration (FDA) regarding its safety.[4] It was reintroduced in the United States in 2002 after rigorous testing showed that urokinase preparations were free of human pathogens. However, at present, it is only approved for treating pulmonary embolism (PE). Pro-urokinase, also known as single-chain urokinase-type plasminogen activator, is a single-chain precursor of urokinase that is converted into two-chain urokinase by hydrolysis.

Tissue Plasminogen Activator

Tissue plasminogen activator (tPA), which was first isolated in 1981, is a naturally occurring protein synthesized by human vascular endothelial cells.[5] Several recombinant variants of tPA are available, including alteplase (rtPA, approved by the FDA in 1987) and duteplase. Other forms of tissue-type tPAs include reteplase (rPA), tenecteplase (TNK-tPA), and lanoteplase (nPA). Recombinant tPAs are nonantigenic and show specificity for fibrin-bound plasminogen. They also avoid the infectious risks associated with products isolated from cultured human tissues. Newer recombinant tPAs have improved pharmacokinetics that enable their convenient administration, such as bolus dosage.

Other Agents

Other compounds that have been developed and investigated include vampire bat plasminogen activator (isolated from the saliva of vampire bat), fibrolase (isolated from the venom of southern copperhead snake), and staphylokinase (isolated from *Staphylococcus aureus*). However, data on these compounds are relatively limited; hence, they are rarely used clinically.

CLINICAL INDICATIONS

Myocardial Infarction

Acute myocardial infarction (AMI) is associated with a significant healthcare burden in industrialized countries. Modern management of AMI focuses on rapidly restoring perfusion to optimize myocardial salvage. Primary percutaneous coronary interventions are superior to thrombolytic therapy when employed as an early reperfusion strategy after AMI and are the first-line therapy.[6] However, logistic barriers hinder the access of patients with AMI who require interventional cardiology services to perform early percutaneous coronary intervention (PCI). On the other hand, fibrinolytics are administered in almost all hospitals.

Lytic therapy was first used for treating AMI in the 1950s.[7] The Fibrinolytic Therapy Trialists' Collaborative Group performed a meta-analysis by using results obtained from over 58,000 patients treated with thrombolytics.[8] This meta-analysis showed that treatment with thrombolytics resulted in approximately 25% reduction in mortality in patients with ST-segment elevation or bundle branch block. Since then, numerous studies have evaluated the efficacies, dosage strategies, administration routes, and adjunctive therapies with these agents for rapidly restoring blood flow in thrombosed coronary arteries.

Early studies such as ISIS-2 and GISSI focused on the use of streptokinase and showed 18% and 25% reduction in mortality after 3 and 5 weeks, respectively.[3,9] Similar results were obtained after 1- to 10-year follow-up.[10] The efficacy of tPA was studied in the GUSTO-1 trial, which examined four dosing regimens for the treatment of MI in 41,021 patients.[11] This study used "accelerated" tPA dosage in which two-thirds of the total dose were administered in the first 30 minutes rather than over a 3-hour period. This dosage regimen resulted in a modest but significant reduction in 30-day mortality (6.3%) compared with streptokinase (7.4%) or a combination of tPA and streptokinase (7.0%). The GUSTO angiographic substudy showed that differing patency rates among patients treated with either agent accounted for this difference in clinical efficacy. However, a subsequent meta-analysis of this approach failed to validate the survival advantage.[12]

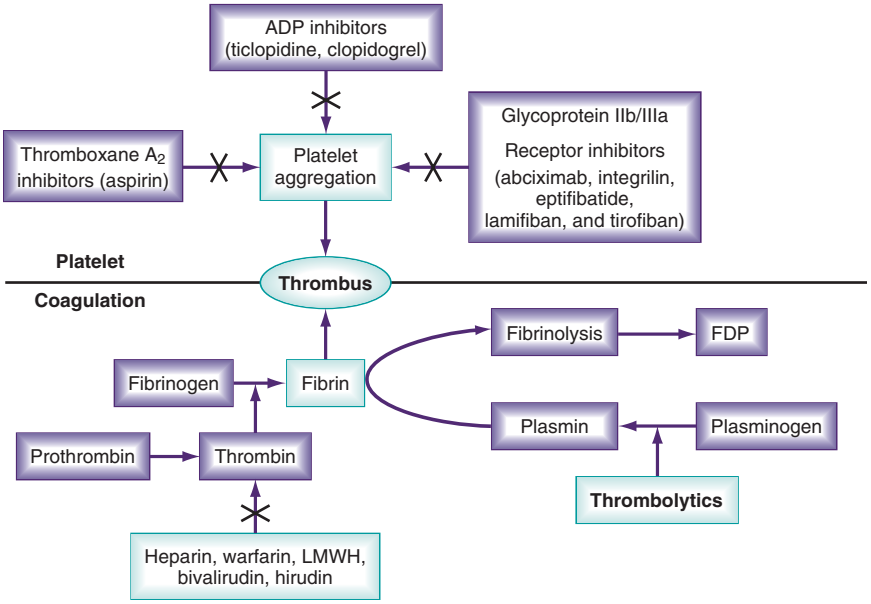

Fig. 152.1 Components of thrombus formation and effects of various antithrombotic and thrombolytic agents. *FDP,* Fibrin degradation products; *LMWH,* low-molecular-weight heparin.

TABLE 152.1 Properties of Commonly Used Thrombolytics

	Streptokinase	Urokinase	Tissue Plasminogen Activator (tPA)
Source	Group C *Streptococcus*	Human fetal kidney	Recombinant
Lytic	First	First (prourokinase: second)	Second (non-alteplase tPAs: third)
Generation	Anistreplase		
Available compounds	APSAC (half-life, 70–120 min)	Prourokinase	Alteplase, duteplase, reteplase (rPA), tenecteplase (TNK-tPA), and lanoteplase (nPA)
Molecular weight (kD)	47	35–55	63–70
Half-life (min)	18–23	14–20	3–4
Metabolism	Hepatic	Hepatic	Hepatic
Antigenicity	Yes	No	No
Fibrin specificity	Minimal	Moderate	Moderate
Plasminogen binding	Indirect	Direct	Direct

APSAC, Anisoylated plasminogen streptokinase activator complex.

Newer-generation tPAs such as r-PA and TNK-tPA can be used to administer a bolus dosage. The GUSTO III trial compared reteplase, the recombinant deletion mutant of tPA, with accelerated tPA in 15,059 patients. This trial did not detect any survival advantage with r-PA and showed that rates of intracranial hemorrhage (ICH) were similar after treatment with r-PA and tPA (0.91% and 0.87%, respectively).[13] The ASSENT-2 trial showed that 30-day mortality and ICH rates were identical in patients treated with TNK-tPA and those treated with accelerated tPA.[14] Although r-PA and TNK-tPA are not superior to tPA in terms of safety and efficacy, their pharmacokinetics allow simplified administration compared with that of accelerated tPA.

Adjunctive therapies such as aspirin, clopidogrel, and antithrombin agents improve the results of lytic therapy. Fibrinolysis strips fibrin from an occluding thrombus; the exposed thrombin then initiates platelet aggregation and subsequent rethrombosis.[15] Antiplatelet agents are essential to reducing this process. Heparin is typically used to maintain activated partial thromboplastin time (aPTT) between 50 and 70 seconds. If heparin-induced thrombocytopenia is suspected, direct thrombin inhibitors such as hirudin or bivalirudin are viable options.[16] Another development is the introduction of glycoprotein IIb/IIIa receptor blockers such as abciximab (ReoPro), eptifibatide (Integrilin), and tirofiban (Aggrastat).[17–19] Despite some promising early results, no randomized trial has yet to show a benefit of these agents on mortality.[20–23] A meta-analysis of 11 randomized trials assessing thrombolytic treatment with and without abciximab suggested a significantly increased risk of major bleeding events (5.2% vs. 3.1%, $P < 0.001$) with abciximab.[24]

The timing of diagnosis and institution of thrombolytic therapy is critical.[25,26] Patients with AMI who are treated with thrombolytic agents at more than 4 hours after symptom onset have twofold to threefold higher 30-day and 6-month mortality rates than patients treated within 2 hours of symptom onset.[27] The Late Assessment of Thrombolytic Efficacy study reported 1-year mortality rates of 17.6% and 15.8% in patients treated with rtPA at greater than 3 hours and less than 3 hours, respectively, after symptom onset.[28] Therefore prehospital administration of thrombolytics is recommended in select patients showing ST-segment elevation on electrocardiogram.[29,30]

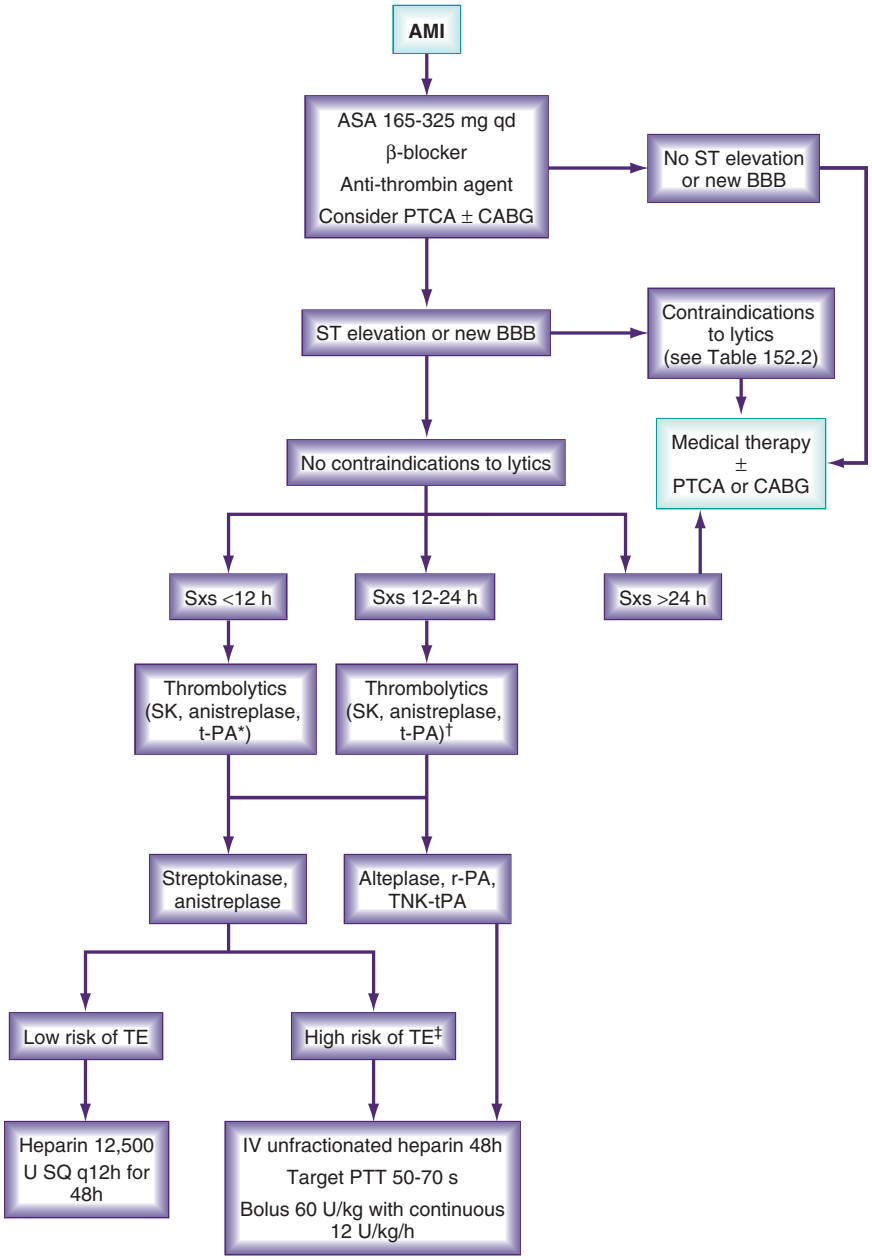

Fig. 152.2 Algorithm for treating acute myocardial infarction.*Preferred for symptom duration of <6 hours; †grade 2b data; ‡anterior myocardial infarction, existing heart failure, previous embolus, atrial fibrillation, and left ventricular thrombus. *AMI,* Acute myocardial infarction; *BBB,* bundle branch block; *CABG,* coronary artery bypass grafting; *PTCA,* percutaneous transluminal coronary angioplasty; *PTT,* partial thromboplastin time; *SK,* streptokinase; *SQ,* subcutaneous; *Sxs,* signs and symptoms; *TE,* thromboembolism. (Data from 1999/2002 ACC/AHA Guideline Update and 2001 ACCP Consensus Conference.)

The currently accepted guidelines for lytic therapy of AMI are outlined by the American College of Chest Physicians in the eighth edition (2008) of *Evidence-Based Clinical Practice Guidelines* and by the American College of Cardiology/American Heart Association in their 2013 guidelines.[31,32] A treatment algorithm for AMI is shown in Fig. 152.2. The established guidelines indicate that patients who are most likely to benefit from fibrinolytic therapy are those with ST-segment elevation, symptoms that began within 3 hours, anticipated delay in reaching a PCI facility, and low bleeding risk. However, the value of thrombolytic agents in the management of unstable angina remains unproven thus far. At present, lytic therapy is not used for treating acute coronary syndrome without ST-segment elevation in two or more contiguous leads or without new-onset bundle branch block. Contraindications to lytic therapy in the setting of AMI are summarized in Table 152.2.

Since the development of thrombolytics, coronary angioplasty has become the gold standard for treating myocardial infarction (MI) with ST-segment elevation. A large meta-analysis of 7739 patients with ST-segment elevation who were randomized to receive thrombolytic therapy (76% receiving fibrin-specific lytics) or primary percutaneous transluminal coronary angioplasty (PTCA) showed that short-term (4- to 6-week) mortality in patients in the PTCA group

TABLE 152.2 Contraindications to Thrombolytic Therapy in the Setting of Acute Myocardial Infarction (With ST-Segment Elevation and/or New Bundle Branch Block)

Absolute Contraindications	Relative Contraindications
>24 hours since symptom onset	12–24 hours since symptom onset
Prior intracranial hemorrhage	Age >75 years
Stroke within the past year	Systolic blood pressure of >180 mm Hg or diastolic blood pressure of >110 mm Hg
Intracranial neoplasm	Bleeding disorder
Active bleeding/bleeding diathesis	Prior allergic reaction to thrombolytics
Suspected aortic dissection	Pregnant or lactating
Significant closed-head or facial trauma within 3 months	Prolonged cardiopulmonary resuscitation (>10 min)
	Recent internal bleeding (less than 2–4 weeks)
	Active peptic ulcer

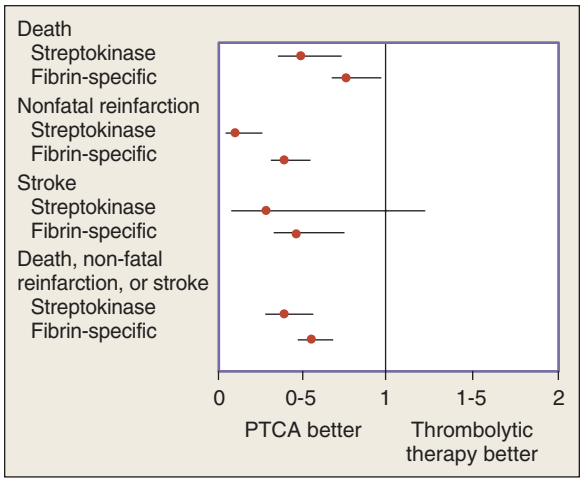

Fig. 152.3 Short-term clinical outcomes in patients treated with percutaneous transluminal coronary angioplasty and those treated with thrombolytic therapy. Odds ratios with 95% confidence intervals. (Reprinted with permission from Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: A quantitative review of 23 randomised trials. *Lancet*. 2003;361:13–20.)

was 7% compared with 9% in patients in the lytic therapy group ($P = 0.0003$).[6] Patients treated with primary PTCA showed lower rates of nonfatal reinfarction (3% vs. 7%) and stroke (1% vs. 2%) during follow-up in a smaller study.[33] Short-term results of this meta-analysis are summarized in Fig. 152.3.

Potential advantages of angioplasty over thrombolysis as the primary therapy for AMI are tempered by the recognition that results of angioplasty are highly dependent on the volume of cases at a given treatment center.[34–37] Moreover, many patients initially present to facilities where interventional cardiology services are not available for performing PCI, resulting in the use of thrombolytics before performing PCI. The Strategic Reperfusion Early After Myocardial infarction (STREAM) trial showed that fibrinolytic therapy, clopidogrel, and enoxaparin followed by PCI had improved outcomes as compared with primary PCI in patients with MI associated with ST-segment elevation who were unable to undergo PCI within 1 hour.[38] Moreover, the Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction (TRANSFER-AMI) trial showed a reduction in the composite endpoint of death, reinfarction, recurrent ischemia, new or worsened congestive heart failure, or cardiogenic shock within 30 days (11.0% vs. 17.2%; odds ratio [OR], 0.64; 95% confidence interval [CI], 0.47–0.87) in patients treated with early (<6 hours) PCI after thrombolytic therapy compared with those treated with standard therapy.[39] The ideal treatment for some patients may involve a combination of thrombolytic therapy, antithrombotic agents, antiplatelet agents, and PCI.

Stroke

Stroke is the third leading cause of death in the United States, affecting over 700,000 people per year. The majority of strokes are ischemic and result from sudden occlusion of the arteries that deliver blood to the brain. Traditional therapy for ischemic stroke includes anticoagulant and antiplatelet agents for medical support, followed by rehabilitation after the acute event. More recently, thrombolysis has emerged as a treatment for ischemic stroke. Similar to that for AMI, the efficacy of thrombolysis in the setting of stroke is highly time dependent because of the characteristics of the ischemic penumbra and is the highest when lytic treatment is initiated within 90 minutes after symptom onset.[40,41]

Use of thrombolytic therapies for ischemic stroke dates back to 1995 when the National Institute of Neurological Disorders and Stroke (NINDS) published a study on rtPA for treating acute ischemic stroke.[42] The trial examined the clinical efficacy of intravenous (IV) tPA administered within 3 hours of symptom onset. Administration of tPA did not improve neurologic function at 24 hours compared with administration of placebo. However, in the long term, patients who received tPA were 30% more likely to have minimal residual disability or were more likely to return to baseline functional status after 3, 6, and 12 months.[43] However, patients treated with tPA showed a higher incidence of intracerebral hemorrhage (6.4% vs. 0.6%, $P < 0.001$) at 36 hours. Nevertheless, mortality at 3 months was not significantly different (17% vs. 21%, $P = 0.30$). The results of this study led to FDA approval of IV tPA for the treatment of acute ischemic stroke when diagnosed within 3 hours of symptom onset.

Other early randomized trials on IV tPA for treating acute stroke were the European Cooperative Acute Stroke Study (ECASS-I), ECASS-II, and ATLANTIS trials.[40,44–46] Although these trials did not reach significance for their primary outcome measure, they did show a significant benefit of using tPA within 6 hours of symptom onset for improving alternative outcome measures, thus supporting its clinical use. More recently, the ECASS-III trial showed a significant but modest benefit of tPA compared with that of placebo when administered within 3–4.5 hours of symptom onset with no difference in mortality.[47] Based on the results of this trial, Lansberg and colleagues calculated the number of patients deriving benefit per 100 treated as 28, 23, and 17 for the 0- to 1.5-, 1.5- to 3-, and 3- to 4.5-hour windows, respectively.[48] As a result of the ECASS III trial, IV tPA for the treatment of stroke within 3–4.5 hours has been supported by the Scientific Advisory Committee from the American Heart Association Stroke Council. The European Medicines Agency has approved the use of IV tPA within 4.5 hours of symptom onset even though the FDA has not approved tPA use at this time interval.[49] The third International Stroke Trial evaluated whether tPA had beneficial effects in patients treated within 6 hours of symptom onset and in patients older than 80 years. The 18-month follow-up showed no improvement in mortality in those treated with alteplase versus standard care alone (34.9% vs.

35.1%, $P = 0.85$), but a modest statistically significant improvement was observed in patients with a low (0–2) Oxford handicap scale score (35.0% vs. 31.4%; OR, 1.28; 95% CI, 1.03–1.57; $P = 0.024$).[50]

At present, IV tPA is the only drug and route of administration approved by the FDA for treating ischemic stroke. However, intraarterial (IA) administration of thrombolytics has also been investigated. This method requires a neurointerventionalist to place a catheter into the thrombosed vessel to directly infuse a thrombolytic. The Prolyse in Acute Cerebral Thromboembolism (PROACT II) study[51] randomized 180 patients with middle cerebral artery occlusion to receive IA prourokinase plus heparin versus heparin alone. This study showed that over 40% of patients receiving IA prourokinase plus heparin had improved modified Rankin score of ≤2 compared with only 25% of the patients receiving heparin alone. The Japanese MELT trial on IA urokinase was halted early by the trial's independent monitoring committee after the approval of IV tPA for stroke in Japan, and thus did not reach significance for its primary endpoint.[52] Nevertheless, secondary analysis of this study and combined analyses with PROACT trials suggested a benefit of IA urokinase.[53]

Interventional Management of Stroke trialists conducted a phase III trial to compare a standard dose of IV tPA with that of an IV tPA bridge for endovascular treatment.[54] The trial was stopped early because of futility. Patients treated with tPA and endovascular therapy did not show significant differences in 90-day mortality (19.1% vs. 21.6%, $P = 0.52$) or modified Rankin score of ≤2 (40.8% vs. 38.7%, absolute adjusted difference, 1.5 percentage points; 95% CI, −6.1 to 9.1) when compared with patients treated with tPA alone. More recent data have demonstrated a benefit for endovascular therapy in anterior circulation ischemic stroke. A meta-analysis pooling patient-level data from five randomized controlled trials showed the benefit of mechanical thrombectomy in this population when performed within 6 hours of symptom onset.[55] Patients undergoing mechanical thrombectomy were more than twice as likely to have a modified Rankin score ≤2 at 90 days (OR 2.35; 95% CI, 1.85–2.98; $P < 0.0001$). There was no difference in patient mortality. The 2019 American Stroke Association guidelines recommend that patients eligible for IV tPA treatment receive the treatment even if endovascular therapy is being considered.[56] At centers without neurointerventionalist availability, IV tPA administration can be initiated before transfer to centers with endovascular capability. Standard contraindications for IV thrombolytic therapy in patients with acute ischemic stroke were included in the exclusion criteria used in the NINDS study (Table 152.3).

TABLE 152.3 Contraindications for Thrombolytic Therapy in Ischemic Stroke

Contraindications	Relative Contraindications
Symptom duration of >6 hours	Symptom duration of 3–6 hours
History of intracranial hemorrhage	Witnessed seizure
Evidence of active bleeding	Gastrointestinal or urinary
Platelet count of <100,000/mm^3	Hemorrhage within 3 weeks
	Recent lumbar puncture, noncompressible arterial puncture site
Prior stroke, head trauma, or intracranial surgery within 3 months	Systolic blood pressure of >185 mm Hg or diastolic blood pressure of >110 mm Hg
Rapidly improving or only minor symptoms Major surgery within 14 days	Mass effect or hypodensity of more than one-third of middle cerebral artery distribution on head computed tomography
Known arteriovenous malformation or intracranial aneurysm	Glucose level of <50 or >400 mg/dL Elevated partial thromboplastin time or international normalized ratio (>1.7)

Pulmonary Embolism

PE is a major source of morbidity and mortality in hospitalized patients, accounting for up to 15% of in-hospital deaths.[57] Anticoagulation has been the mainstay of treatment for PE since it was first shown to be beneficial in 1960.[58] This has been historically achieved with IV unfractionated heparin (UFH), although subcutaneous (SC) low-molecular-weight heparin (LMWH), SC fondaparinux, and monitored or fixed-dose SC UFH may also be used.[59] Despite the proven efficacy of anticoagulation for treating acute PE, a significant proportion of patients show incomplete resolution of their occlusion, with subsequent organization of the thrombus and obstruction of the involved pulmonary artery.[60–62] Therefore thrombolysis as a treatment for PE to initiate rapid and complete resolution of thrombus became a therapeutic approach.

The Urokinase Pulmonary Embolism Trial (UPET) was one of the initial studies to evaluate thrombolytic therapy for treating PE.[60] This prospective study did not show any improvement in mortality or perfusion rate after 5 days of lytic therapy. However, the UPET and the Urokinase-Streptokinase Embolism Trial showed improvements in small-vessel patency at 2 weeks and 1 year after thrombolytic therapy as compared with anticoagulation therapy alone.[63,64] A 7-year follow-up of this cohort of patients suggested that the risk of pulmonary hypertension decreased after thrombolytic therapy, presumably through clot dissolution.[65]

Current CHEST guidelines recommend thrombolytic therapy for the treatment of patients with massive PE with hemodynamic instability.[66] In addition, patients with right ventricular dysfunction or refractory hypoxemia in the setting of preserved systemic arterial blood pressure may benefit from thrombolytic therapy. Right heart strain is correlated with an intermediate risk of death.[67] Patients with submassive PE showed an improved clinical course after treatment with systemic IV thrombolytic therapy compared with anticoagulation alone; however, systemic thrombolysis did not improve long-term mortality.[68] Pulmonary Embolism Thrombolysis (PEITHO) investigators conducted a randomized trial involving 1006 patients with PE, right ventricular dysfunction, and cardiac enzyme elevation to compare TNK-tPA and heparin with placebo and heparin. The primary outcome of death or hemodynamic compromise within 7 days was reduced in patients treated with TNK-tPA as compared with anticoagulation alone (2.6% vs. 5.6%; OR, 0.44, 95% CI, 0.23–0.87; P = 0.02), although not without complications—patients receiving thrombolytic therapy had higher rates of stroke (2.4% vs. 0.2%, $P = 0.003$) and major bleeding (6.3% vs. 1.2%, $P < 0.001$). However, 30-day mortality was similar between the treatment arms (2.4% vs. 3.2%, $P = 0.42$).[69]

Although no significant differences exist among different thrombolytic regimens, IV tPA is preferred because of its short infusion time.[70,71] FDA-approved regimens for treating acute PE are listed in Table 152.4. Major hemorrhagic complications occur in approximately 12% of patients irrespective of the lytic agent used.[72] Fear of bleeding after thrombolytic administration has led some centers to investigate the use of "half-dose" thrombolysis, which has a low bleeding rate, although published series are small.[73] Propensity-matched comparison of 548 pairs of patients with PE undergoing half-dose versus standard-dose systemic thrombolysis revealed similar overall in-hospital mortality (13.0 vs. 15.1%, half-dose vs. full-dose, $P = 0.30$), but a higher percentage of patients receiving half-dose therapy required escalation

TABLE 152.4 Food and Drug Administration–Approved Regimens for Treating Pulmonary Embolism

Drug	Systemic Administration
Streptokinase	250,000 U over 30 minutes, followed by 100,000 U/hr for 24 hours
Urokinase	4400 U/kg over 10 minutes, followed by 4400 U/kg/hr for 12–24 hours
tPA (alteplase)	100 mg over 2 hours

of treatment in the form of secondary thrombolysis or catheter-based thrombectomy.[74] Costs were higher in the half-dose group as a result. Further, the theoretical benefit of lower intracranial bleeding risk was not realized in this series (0.5 vs. 0.4%, $P = 0.67$).

Verstraete and colleagues performed the first trial to compare direct pulmonary artery thrombolytic infusion with IV infusion.[75] However, this trial failed to show a benefit of pulmonary artery infusion. Other adjunctive techniques include use of ultrasound-producing catheters that may increase the permeability of tPA within a clot. A prospective randomized trial comparing the efficacy of ultrasound-assisted catheter-directed thrombolysis (USAT) with that of anticoagulation alone in patients with right heart strain showed the superiority of USAT in reversing heart strain within the first 24 hours.[76] Current guidelines do not support the use of catheter-directed thrombolysis (CDT) as a first-line therapy for PE because of the paucity of published trials addressing this question. The CHEST guidelines recommend catheter-directed therapies in patients who are at high risk for bleeding with systemic thrombolysis, patients who have failed systemic thrombolysis, and patients with impending cardiovascular collapse who may die before systemic thrombolytics can take effect.[66] Interest in catheter-directed therapy continues to rise. Catheter-based delivery of thrombolytics offers the potential to reduce hemorrhagic complications by dramatically reducing the total dose of tPA required—often 20% of systemic dosing.[77] Reported major hemorrhage rates were 1% or less.[77] A propensity-matched comparison of data from the National Inpatient Sample found an equivalent mortality rate between systemic and CDT among 1430 matched pairs, with a significantly reduced rate of intracranial hemorrhage in the catheter-directed lysis cohort (OR 0.47; 95% CI, 0.27–0.82; $P = 0.01$).[78] Randomized trials are necessary to compare systemic thrombolysis with catheter-directed therapy in a prospective fashion.

Deep Venous Thrombosis

The formation of deep venous thrombosis (DVT) is common in acutely ill patients, occurring in as many as 30% of intensive care unit patients despite prophylaxis.[79] Acute occlusion of the deep venous system leads to severe sequelae, such as venous gangrene (phlegmasia cerulea dolens), and long-term sequelae, including recurrent DVT and postthrombotic syndrome (PTS).[80–83] PTS is characterized by persistent pain, edema, discoloration, and ulceration. Patients with iliofemoral DVT experience a higher incidence and severity of postthrombotic morbidity than those with infrainguinal DVT. The standard therapy for DVT focuses on the prevention of thrombus propagation, stabilization of thrombus, and prevention of PE. This is achieved with anticoagulation. However, anticoagulation alone has limited efficacy in restoring venous patency and function. Thrombolytic therapy of DVT focuses on the dissolution of the clot to prevent PTS. The 2016 Cochrane review, which grouped both systemic and regional thrombolysis with anticoagulation versus anticoagulation alone, found that patients receiving lytic therapy showed more complete clot resolution (risk ratio [RR], 4.91; 95% CI, 1.66–14.53; $P = 0.004$) and lower incidence of PTS (RR, 0.66; 95% CI, 0.53–0.81; $P < 0.0001$). Thrombolysis carried a higher risk of bleeding complications (RR, 2.23; 95% CI, 1.41–3.52; $P = 0.0006$), but there was no significant difference in mortality.[84]

More recently, CDT and pharmacomechanical thrombolysis (PMT) have evolved as the first-line lytic therapies for DVT because they are theoretically associated with a reduced risk of bleeding complications. CDT involves catheter-directed infusion of thrombolytic agents into the affected venous bed and reduces the total dose of thrombolytic agent, which in turn decreases systemic side effects. The CaVenT study, a randomized controlled trial involving 209 patients, showed that patients with first-time iliofemoral DVT who were treated with CDT within 21 days of symptom onset showed improved iliofemoral patency at 6 months (65.9% vs. 47.4%, $P = 0.012$) and reduction in PTS at 2 years (41.1% vs. 55.6%, $P = 0.047$) compared with patients treated with anticoagulation alone. However, patients receiving thrombolytics also experienced 20 bleeding complications.[85] The ATTRACT multicenter randomized trial investigated the effect of PMT plus anticoagulation versus anticoagulation alone in patients with proximal DVT involving the femoral vein, common femoral vein, and/or iliac veins.[86] There was no significant difference in the development of PTS at 24 months of follow-up (47% PMT vs. 48% control, $P = 0.56$). Although representing the largest trial on CDT for DVT to date, this study has been criticized for grouping together patients with iliofemoral DVT and femoropopliteal DVT, the former of which are much more likely to develop PTS. This may have led to underestimation of the treatment effect of PMT on development of PTS in patients with iliofemoral DVT. Subsequent subgroup analysis of iliofemoral DVT patients in the ATTRACT trial did demonstrate a reduction in moderate-or-severe PTS in patients undergoing PMT (Villalta scale ≥10 or ulcer: 18% vs. 28%; RR, 0.65; 95% CI, 0.45–0.94; $P = 0.021$).[87]

The current guidelines put forth by the Society for Vascular Surgery and the American Venous Forum recommend CDT or PMT for treating patients with iliofemoral DVT diagnosed within 14 days of symptom onset, good functional capacity, acceptable life expectancy, and low bleeding risk.[88] The American College of Chest Physicians also recommended similar guidelines and reported that CDT was a more preferable approach than systemic thrombolysis.[66] CDT and/or PMT are also recommended for patients with phlegmasia cerulea dolens. In addition to treating patients with lower extremity disease, CDT has been used for treating young patients with primary upper extremity DVT resulting from effort thrombosis (Paget-Schroetter syndrome) or idiopathic factors.[89]

Acute Peripheral Arterial Occlusion

Acute peripheral arterial occlusion (APAO) is a potentially fatal condition that can lead to amputation in 10%–30% of cases and is associated with a mortality rate of 15% at 30 days.[90] Arterial occlusions arise from dissection, trauma, local thrombosis, or emboli. Various noninvasive methods have been developed for treating thromboembolic diseases.

Thrombolysis has become a popular means of treating acute arterial occlusion in certain settings, such as for those without an immediately threatened limb. This approach has been performed since the 1950s.[2] Initial attempts involved systemic delivery but were associated with high bleeding risks and poor clinical outcomes. Since the early 1970s, catheter-directed infusion has become the standard of care, which allows higher local thrombolytic concentrations while decreasing the systemic exposure to the medications.[91] Various infusion methods have been developed, including low-dose infusion regimens, high-dose infusion regimens, and high-pressure infusion (pulse spray).

However, none of these methods have shown genuine benefit in terms of clinical outcomes.[92,93]

Although streptokinase was the first agent used for treating APAO, multiple studies have indicated that urokinase and tPA are more effective for treating APAO than streptokinase with fewer bleeding complications.[94–96] Recently, tPA and its derivatives have supplanted urokinase as the agents of choice for treating APAO. The safety and efficacy profiles of low-dose (<2 mg/hr, usually beginning at 0.5 mg/hr) tPA regimens are similar to those of urokinase, with adjunctive heparin infusion to maintain the aPTT at 1.5 times of that at baseline. With this regimen, over 60% of patients have shown complete resolution and 30% of patients have shown partial resolution of thrombus within 24 hours of treatment initiation.[97] An advisory panel on CDT recommended weight-based dosing (0.001–0.02 mg/kg/hr) or non–weight-based dosing (0.12–2.0 mg/hr), with total doses not exceeding 40 mg.[98]

Use of thrombolytics for treating APAO is part of a multifaceted approach that often involves additional endovascular techniques and/or surgical interventions. The Rochester Trial compared initial surgery with urokinase treatment in 114 patients with severely threatened limbs.[99] Limb salvage rates in the two groups were identical (82%) at 12 months; however, mortality was significantly lower in patients treated with urokinase (16% vs. 42%). The Surgery or Thrombolysis for the Ischemic Lower Extremity (STILE) trial examined 393 patients randomized to surgery or one of two lytic therapies (rtPA or urokinase).[100] At 30 days, limb loss rates (5% with lysis vs. 6% with surgery) and mortality rates (4% vs. 5%, respectively) were similar between the two groups. Subgroup analyses performed in this study showed a higher benefit of thrombolytic therapy in patients with graft occlusion than in those with native vessel occlusion and acute ischemia of less than 2 weeks.[101,102] The TOPAS Trial compared recombinant urokinase therapy with surgery in 544 patients.[103,104] Although it failed to demonstrate an amputation-free survival benefit at 1 year (68% for urokinase, 69% for surgery), it did show that over 30% of the patients treated with urokinase were not only alive without amputation but also had nothing more than a percutaneous procedure at 6 months. Thus a significant number of patients presenting with APAO and treated with thrombolysis can avoid surgery. A contemporary series by Taha and colleagues comparing the effectiveness of endovascular (154 limbs) with surgical (326 limbs) revascularization for acute limb ischemia also showed similar amputation rates at 1 year (13.0% vs. 19.6%, $P = 0.074$). In this study, 1-year mortality was significantly lower in patients in the endovascular group (12.9% vs. 33.8%, $P < 0.001$).[105]

A 2018 Cochrane review identified five prospective, randomized trials from the 1990s that compared surgery with thrombolytic therapy for the management of acute limb ischemia. The review did not show any overall difference in limb salvage or mortality at 1 year. As expected, patients treated with thrombolysis showed a higher rate of major hemorrhage (OR 3.22, 95% CI 1.79–5.78; $P < 0.0001$) and stroke (OR 5.33, 95% CI 0.95–30.11; $P = 0.06$).[106] Therefore thrombolytic therapy is still not considered the standard of care for treating APAO. However, it is useful for treating patients who are poor candidates for surgery and may be best regarded as an adjunct to surgical therapy rather than a competing modality. In some cases, thrombolysis can aid in recanalization of distal vessels that are not patent at treatment initiation, thus permitting subsequent revascularization through bypass surgery. Moreover, it may be the best approach for treating patients with occluded bypass grafts (Fig. 152.4).[100,101] A recent review of available published data affirm the high rate of technical success for CDT in APAO, approaching 80%, and a pooled 30-day amputation-free survival of 88.5%.[107] Use of thrombolysis is contraindicated in patients with early postoperative thrombosis, thrombosis after penetrating or multiple trauma, or irreversible ischemia in the limbs.

Other Applications

In addition to the previously listed indications for thrombolytic therapy, another common application is the treatment of thrombosed dialysis grafts or central venous catheters. Although the ultimate goal is to recognize and treat a graft before it fails, thrombolytic treatment can play an important role once the graft is occluded. Several techniques have been used for treating acutely thrombosed grafts, including mechanical thrombectomy, surgical revision, and pharmacologic thrombolysis. A meta-analysis indicated that surgical thrombectomy remains the standard of care and is associated with superior patency, presumably because of anastomotic revision, which is performed concurrently.[108] In patients with occluded central venous catheters, the instillation of 2-mg (1 mg/mL) aliquot of alteplase into each lumen for 2 hours may be used to restore patency of the catheters.[109] Multiple studies have shown this regimen to be both safe (≤1% bleeding risk) and efficacious (<90% patency after two treatments).[109,110]

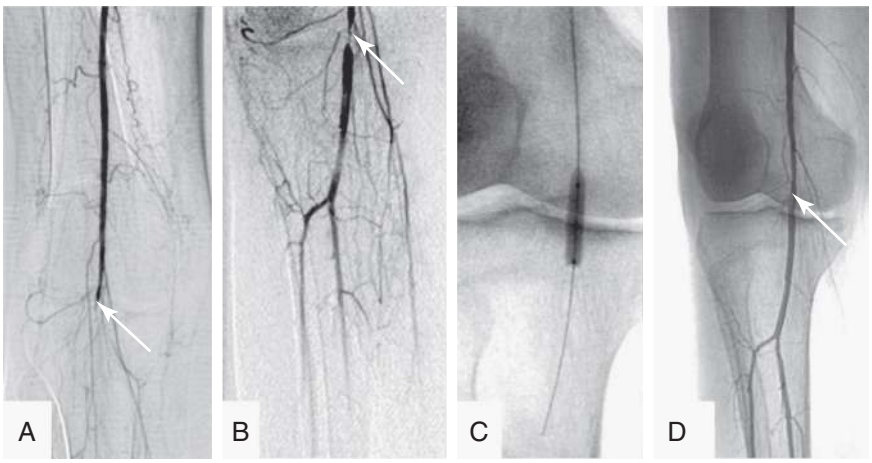

Fig. 152.4 Successive angiograms showing occluded popliteal artery (*arrow*, **A**) treated with thrombolytics. After thrombolysis, a focal popliteal artery stenosis is observed (*arrow*, **B**) along with patent distal vessels. This area was subsequently treated by performing balloon angioplasty **(C)**. Thrombolysis and angioplasty resulted in a patent popliteal artery (*arrow*, **D**), with good distal arterial flow.

MANAGEMENT/LABORATORY VALUES

Administration of thrombolytic agents decreases the circulating levels of plasminogen and fibrinogen. Fibrinogen is degraded during fibrinolysis, reaching nadir values between 5 and 7 hours after the initiation of therapy.[111] In most patients, these values return to baseline within 48 hours after lysis. Fibrin degradation products are a reliable indicator of fibrinolytic activity because degradation of fibrinogen or fibrin by plasmin is the only source of these products in humans.

Monitoring of fibrinogen levels every 6–8 hours is recommended during lytic therapy, with a decrease in dose or discontinuation of infusion if levels decrease to below 100 mg/dL. In addition, platelet counts should be monitored daily. Thrombocytopenia occurs in as many as 10% of patients receiving rtPA compared with less than 1% patients receiving streptokinase.[112–114] If bleeding occurs, thrombolysis should be discontinued and blood products—namely, fresh frozen plasma or cryoprecipitate—should be administered to correct the patient's coagulopathic state.

CONCLUSION

Although evidence strongly supports the use of thrombolytic agents for the treatment of various occlusive vascular disorders, this therapy is administered in relatively few patients. Increasing data support the safety and efficacy of thrombolytic therapy for a variety of disorders, which has substantially increased its use over the past two decades. One of the challenges in the coming years will be to more clearly define the patients who will benefit the most in terms of improved outcomes of the underlying disorder, decreased mortality, and prevention of hemorrhagic complications. Evolution of technology, including diagnostic modalities, mechanical thrombectomy devices, and adjunctive therapies, will continue to expand the indications for thrombolytic therapy.

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KEY POINTS

- Thrombolytics comprise a diverse group of compounds that convert plasminogen to plasmin.
- Thrombolytic therapy is indicated within 6 hours of the onset of AMI, especially in patients who are not eligible for primary angioplasty.
- Patients with acute ischemic stroke receive the greatest long-term benefit from thrombolytic therapy when performed within 4.5 hours of symptom onset, and thrombolytic therapy may serve as a pharmacologic bridge to CDT in appropriate patients.
- The role of thrombolytic therapy in PE is primarily limited to patients with hemodynamic instability based on currently available data. The choice of systemic versus catheter-directed therapy must be made based on patient bleeding risk, previous lysis attempts, hemodynamic status, and available local expertise.
- Thrombolysis in deep venous thrombosis is controversial outside of cases of phlegmasia. Proponents of catheter-directed techniques cite lower rates of post-thrombotic syndrome morbidity.
- Urokinase and tissue plasminogen activator are commonly used for managing acute peripheral arterial occlusion. Highest benefit is observed in patients with occlusions for less than 14 days duration and in those with previous extremity bypasses.
- Thrombolytic therapy requires intensive monitoring and follow-up radiography. Fibrinogen levels should be monitored every 6 to 8 hours, and patients should be closely monitored for signs of major hemorrhage.

References for this chapter can be found at expertconsult.com.

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Hilleman DE, Tsikouris JP, Seals AA, et al. Fibrinolytic agents for the management of ST-segment elevation myocardial infarction. *Pharmacotherapy.* 2007;11:1558-1570.
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Randomized, multicenter trial examining intraarterial urokinase versus surgery for acute (<14 days) arterial occlusion. This trial, along with the Rochester and STILE trials, provides the cornerstone for the argument supporting the use of lytics in acute peripheral arterial occlusion.

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Atheroembolization

Cristian Baeza and Yasir Abu-Omar

Atherosclerosis and its thromboembolic complications are leading causes of mortality and morbidity. This progressive disorder usually remains clinically silent until it causes end-organ damage resulting in stroke, ischemic heart disease, and/or peripheral vascular insufficiency. Atherosclerosis characteristically affects the aorta, with the abdominal aorta more widely involved than the thoracic aorta. Lower limb vessels are more frequently affected than upper limb vessels, whereas renal, pulmonary, and mesenteric vessels are the least susceptible.

Nearly half of all strokes were thought to result from cerebral vasospasm until the 1950s, when Fisher stressed the etiologic importance of emboli from carotid artery atherosclerotic plaques.[1] Although embolization from the heart and major vessels accounts for a large number of ischemic cerebrovascular accidents, the cause of a significant proportion (40%) remains undetermined; nevertheless, after appropriate imaging studies, about 20% of them could be reclassified as embolic in origin.[2] The following account will focus on the pathophysiology, clinical consequences, detection, prevention, and management of atheromatous embolization.

PATHOPHYSIOLOGY

Atherosclerosis

The process of atherosclerosis may begin as early as childhood, developing slowly with effects rarely manifesting before the fourth or fifth decades of life. Traditional risk factors include hypertension, diabetes, smoking, and hypercholesterolemia.

Atherosclerosis can affect any artery, but the most frequently affected are the large and medium-sized arteries. Intravascular sites of blood turbulence, such as bifurcations, favor the development of atherosclerotic lesions. Initial changes in arterial wall morphology result in the formation of fatty streaks that consist of lipid-engorged macrophages in the arterial intima. Progression of such precursor lesions occurs secondary to an inflammatory process initiated by endothelial injury and dysfunction.[3] Insufficient nitric oxide production results in increased adhesion and aggregation of platelets. Up-regulation of the expression of endothelial adhesion molecules and selectins leads to the accumulation of monocytes and T lymphocytes. These cells become activated and produce growth factors, cytokines, and chemokines. Smooth muscle cells migrate from the media into the intima and proliferate. In time, these lesions develop into raised, fibrous plaques consisting of a fibrous cap covering a core containing necrotic material, lipids, and cholesteryl esters. This advanced plaque forms the base onto which the complex plaque develops, consisting of fissures, erosions, or ulceration. Interest has increased in the role of monocytes and macrophages in the pathogenesis of plaque progression and rupture,[4] processes that are related to thrombosis, embolism, and clinical manifestations.

Atheromatous Embolization

Atheromatous embolization is a descriptive term for embolization of any atheromatous material. *Atheroembolization* refers to the dislodgment of vascular plaque material that contains cholesterol crystals, red blood cells, and fibrin.[5] This "cholesterol emboli" syndrome comprises renal failure, skin lesions, blue toes, and neurologic manifestations. It can develop spontaneously (because of plaque rupture) or after the use of thrombolytics or anticoagulants,[6] or result from arterial manipulation (during surgical procedures, cardiac catheterization, insertion of an intraaortic balloon pump [IABP], percutaneous aortic valve replacements [transcatheter aortic valve implantation (TAVI)], and aortic endo-stent placements [thoracic endovascular aortic repair/endovascular aortic repair (TEVAR/EVAR)]).[7] Disruption of a vascular plaque results in the release of cholesterol crystals with subsequent downstream vascular obstruction and initiation of an inflammatory process with lymphocytic and mononuclear cell infiltration. Biopsy specimens of affected organs such as skin or kidneys are usually diagnostic.

Plaque Morphology and Embolic Risk

Severe atherosclerosis of the ascending aorta appears to be the most important morphologic indicator of an increased risk of atheromatous embolization. The French Aortic Plaque in Stroke group identified a plaque thickness of 4 mm or greater on transesophageal echocardiogram (TEE) as an independent predictor of recurrent embolization.[8,9] Plaque ulceration and morphology may contribute to an increased risk of embolic events, with evidence of pedunculated, mobile plaques and the absence of calcium conferring a higher risk.[10,11] The cerebral embolic risk is also influenced by plaque location; as complex plaques are more frequent distal to the ascending aorta, there is increased risk to the left cerebral hemisphere and the peripheral circulation.[10]

Macroembolization and Microembolization

Emboli can be divided into macroemboli and microemboli, also described as *thromboembolism* and *atheroembolism.* Despite sharing the same underlying pathophysiology, clinical manifestations differ. Thromboemboli affect arteries larger than 200 μm in diameter, whereas atheroemboli affect smaller arteries, arterioles, and capillaries.[12] Macroemboli may cause overt clinical presentations (e.g., stroke or peripheral ischemia), whereas microemboli tend to be more occult in their manifestations of end-organ injury or dysfunction (e.g., renal injury, neuropsychological impairment). Embolization may arise spontaneously or be related to vascular interventions and cardiovascular surgery. The complex aortic plaque–related 3-year mortality is reported to be as high as 20%.[13]

CLINICAL CONSEQUENCES OF ATHEROMATOUS EMBOLIZATION

Cerebral

As the prevalence of aortic atherosclerotic disease increases with age, so does the rate of atheromatous embolization. Postmortem studies indicate that it affects 20% of patients in their fifth decade, increasing to 80% in those in their eighth decade.[14] Emboli from the atherosclerotic thoracic aorta commonly result in stroke (50%) and transient ischemic attack (35%),[13] with the middle cerebral artery being the most frequent site of arterial embolism. Stroke has profound effects; outcomes from acute stroke are measured in terms of survival, functional independence, and financial cost. Survival after stroke is significantly poorer than after myocardial infarction (MI) or most cancers and is the leading cause of disability in developed countries.[15]

Cholesterol emboli (atheroembolization) are an important and frequently unrecognized cause of stroke.[16] Microembolization is a recognized cause of more subtle, sometimes subclinical neurologic injury.[17,18] This injury is manifested by subtle changes in cognitive function that may only be evident on detailed neuropsychological testing[19,20] and include amaurosis fugax, transient ischemic attack, and confusional state. Rarely, embolization to the spinal cord can lead to lower extremity paralysis. The importance of microembolization has increased over recent years, particularly in patients undergoing coronary artery bypass surgery (CABG); nevertheless, the evidence suggests that the late cognitive decline between 1 and 5 years after surgery may be secondary to high rates of cerebrovascular disease among patients who need CABG. A history of hypertension and other cardiovascular risk factors are known to be associated with increased risk for long-term cognitive decline.[21]

Cardiac

Atherosclerotic disease is the leading cause of death in developed countries. Every year it results in over 19 million deaths worldwide, and coronary heart disease accounts for the majority of those.[22] Most acute coronary syndromes are caused by plaque rupture. Distal embolization of cholesterol and atheromatous material may be important in the pathogenesis of some acute coronary syndromes.[23] The occurrence of distal coronary embolization in the setting of acute coronary syndromes has been followed using serum levels of cardiac troponins to detect small degrees of myocardial necrosis. Embolization after percutaneous coronary interventions is well recognized, and elevated troponins are seen in up to 44% of patients.[24,25]

Peripheral

Peripheral emboli most frequently lodge in the lower extremities. Cholesterol atheroembolization may be subclinical or result in systemic effects. Although renal, neurologic, and cutaneous manifestations tend to dominate the clinical picture, involvement of most organs has been reported.

Cholesterol embolization frequently manifests as acute kidney injury[26,27] and can even lead to renal failure.[26,27] In those cases, renal biopsy is diagnostic.[28] Cutaneous manifestations, including livedo reticularis and "blue-toe" syndrome, are the most common signs of atheroembolism, occurring in up to 34% of cases.[29] Atheroemboli from the carotid vessels give rise to retinal emboli,[30] resulting in visual symptoms. The mesenteric circulation may also be affected, resulting in small bowel bleeding[31] and intestinal infarction. The pancreas, spleen, liver, and gallbladder may also be involved.[32] More rarely, involvement of transplanted viscera such as the kidney may result in renal failure.[33]

DIAGNOSIS AND SCREENING

Full clinical assessment and screening of patients presenting with embolic complications are essential in guiding management and prevention strategies. Diagnosis of cholesterol embolization syndrome relies on clinical findings in patients with atherosclerotic disease and a history of recent vascular intervention. As different organs can be involved, a high index of clinical suspicion is vital. It is important to differentiate between atheroembolism and thromboembolism, as the treatment may be guided accordingly.

Many imaging modalities have been used to visualize atherosclerotic plaques—some in routine clinical practice and others reserved for research. Technologic advances in imaging have provided tools that allow primary prevention by identifying those at highest risk, enabling appropriate disease-modifying treatment to be initiated.

X-ray Angiography

X-ray angiography is an invasive procedure that allows assessment of the vascular lumen. However, it is not as sensitive in plaque detection as other imaging modalities and also confers an additional risk of plaque disruption secondary to instrumentation. Despite these limitations, angiography is still regarded as the gold standard for imaging coronary, carotid, and peripheral arterial disease.[34]

Surface and Transesophageal Ultrasonography

Measurement of carotid and aortic wall thickness in addition to qualitative and quantitative assessment of atherosclerotic plaques can be determined using ultrasonography. The North American Symptomatic Carotid Endarterectomy Trial and the Asymptomatic Carotid Artery Stenosis Study have shown that the degree of stenosis and its hemodynamic consequences are important in the development of stroke.[35,36] High-resolution, real-time B-mode ultrasound with Doppler flow imaging is currently considered the modality of choice in imaging the carotid arteries.[37]

With respect to screening, carotid intima-medial thickness (CIMT) measured by B-mode ultrasound is assessed as a risk factor and a marker for vascular disease risk. This marker most accurately represents subclinical vascular disease, but not plaque formation or atherosclerosis per se. Epidemiologic and clinical trial evidence, digitization, and standardization have made CIMT a validated and accepted marker for generalized atherosclerosis burden and vascular disease risk.[38] CIMT is a predictor of coronary events and stroke, in addition to all-cause mortality.[39,40] The American Society of Echocardiography Carotid Intima-Media Thickness Task Force recommends the use of CIMT measurement by ultrasound in intermediate-risk asymptomatic patients, with a goal of predicting future coronary heart disease events.[41]

TEE is a quick and safe procedure with widespread use ranging from the operating theater to the bedside.[42] TEE is the procedure of choice for the detection, assessment, and characterization of thoracic aortic atherosclerosis. TEE can reliably detect intimal thickening, ulceration, calcification, and the presence of mobile components within the aortic plaque (Fig. 153.1). The French Aortic Plaque in Stroke investigators used TEE to assess aortic plaque thickness in patients with stroke, reporting that increased plaque thickness imparted a significant increase in stroke risk.[8,9] Katz and colleagues used the following five-grade ranking system to indicate the severity of aortic atherosclerosis as assessed using TEE in 130 patients undergoing cardiac surgery with cardiopulmonary bypass: grade 1, normal aorta; grade 2, flat intimal thickening; grade 3, protruding atheroma in the aortic lumen (<5 mm); grade 4, protruding atheroma (>5 mm); and grade 5, atheroma with a mobile thrombus.[43] Patients with grade 5 lesions were at highest risk of stroke. Logistic regression identified aortic arch atheroma

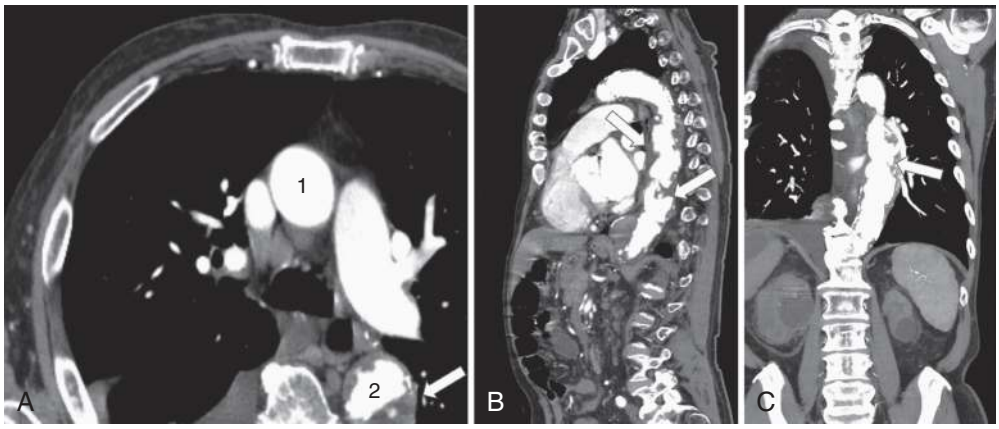

Fig. 153.1 CT angiography demonstrating heavily diseased thoracic aorta ("shaggy aorta"). The arrows show atherosclerotic plaques. The difference between a normal vessel and a severely atherosclerotic one can be appreciated here in ***A,*** between the ascending aorta (1) and the descending aorta (2). ***A,*** Transversal view; ***B,*** sagittal view; ***C,*** coronal view.

as the only variable that was predictive of stroke, with an odds ratio of 5.8. Another study of 315 CABG patients undergoing intraoperative TEE also reported a significant increase in the risk of stroke in patients with aortic arch intimal thickening of greater than 5 mm.[44]

It is no surprise that patients with the highest-risk carotid lesions also have high-risk aortic plaques. Assessment of the carotid arteries and the aorta is prudent in the investigation of atherosclerotic patients who have suffered embolic events.

Intraoperative Epiaortic Ultrasound

Epiaortic ultrasonography involves intraoperative imaging of the ascending aorta using a sterile-sheathed transducer. This technique is noninvasive and has been used in the context of cardiac surgery to detect areas of ascending aortic atherosclerosis,[45] thus allowing modification of the surgical technique in an attempt to reduce potential embolic complications.[46] The main disadvantage of this technique is suboptimal imaging of the aortic arch. Intraoperative epiaortic ultrasound can therefore be used to complement the information on the aortic arch obtained by TEE.

Transcranial Doppler

Transcranial Doppler (TCD) ultrasonography can be used to detect and quantify cerebral microemboli. Ultrasound probes are placed bilaterally on the temple, overlying the middle cerebral vessels. Emboli cause an increase in the reflected ultrasound, causing high-intensity transient signals (HITS). These HITS are the footprints of microemboli, which may consist of air, fat, atheromatous material, or platelet-fibrin emboli. In addition to detecting cerebral microemboli, TCD can be reliably used to assess cerebral vasomotor reactivity and autoregulation; to document the circle of Willis functional status; and to identify cerebral hypoperfusion and hyperperfusion, recanalization, and reocclusion.[47]

TCD can reliably detect HITS intraoperatively and has been used extensively in the context of cardiac and carotid surgery. During cardiac surgery, microemboli can be detected after intraoperative aortic manipulation (aortic cannulation and application and removal of aortic cross-clamp) and during cardiopulmonary bypass; nevertheless, this study and others showed that advanced age is still the strongest predictor of postoperative neurocognitive impairment after surgery.[48] HITS have also been identified in patients with symptomatic carotid artery stenosis,[49] patients with prosthetic heart valves,[50] and those with aortic atherosclerosis.[51] Their presence is a significant independent predictor of early recurrence of stroke.[52]

A major limitation is an inadequate acoustic window in 5%–20% of individuals.[53] With multirange, multifrequency Doppler systems, automatic artifact rejection and differentiation between solid and gaseous microemboli have become possible with high sensitivity and specificity.[54,55] A significant reduction in intraoperative cerebral microembolism and a reduction in the proportion of solid microemboli have been reported with TCD, with avoidance of cardiopulmonary bypass and minimizing manipulation of the ascending aorta during cardiac surgery.[48,56]

An exciting recent development with TCD ultrasonography is its therapeutic use in the treatment of stroke. This procedure involves the use of TCD ultrasound to augment the effect of fibrinolysis and has been shown to at least double the chance of early complete arterial recanalization.[57]

Computed Tomography

Computed tomography (CT) can be used for imaging the aorta and quantifying aortic wall calcification. Contrast-enhanced CT has been proposed as a valuable method for following the progression and regression of atherosclerotic disease.[58] The main advantage over TEE is the ability to completely image the thoracic and abdominal aorta. Disadvantages include radiation and contrast exposure with potential for renal damage, limiting its use in asymptomatic populations.

Coronary multidetector CT angiography (MDCTA) can be used in identifying patients at a particularly high risk of dying suddenly or suffering a nonfatal MI. It provides information on coronary artery stenosis and an estimate of calcification: coronary artery calcium (CAC). The latter is related to multiple risk factors of coronary artery disease. The importance of CAC screening lies in its potential to increase the predictive power of testing for future events.[40,59]

Magnetic Resonance Imaging Techniques

Magnetic resonance imaging (MRI) has emerged as a leading noninvasive imaging modality for atherosclerotic disease. MRI can be used to image atherosclerotic plaques in aortic, carotid, peripheral, and coronary arterial disease.[60,61] Its major strengths rest in its ability to determine plaque morphology. Using a range of techniques, MRI can provide valuable information on the composition of the atherosclerotic plaque by identifying the three main factors that determine plaque stability: (1) presence of a lipid core, (2) thickness of the fibrous cap, and (3) inflammation within the cap. MRI allows identification of

high-risk unstable plaques and thus guides intervention and therapy[62] in addition to monitoring response to therapy with statins.[63] Magnetic resonance angiography has a high sensitivity and specificity and can be used to image the aorta, carotid, renal, and other peripheral vessels. Evolving magnetic resonance techniques include intravascular[64] and transesophageal[65] MRI.

Tissue Diagnosis

Cholesterol embolization can only be confirmed with biopsy, as the clinical manifestations are often subtle and nonspecific compared with those of thromboembolism. Cholesterol clefts in arterioles are evidence of cholesterol crystal emboli that have dissolved during the process of fixation of the specimen. Intimal proliferation of the arterial vascular bed after cholesterol crystal embolization may be responsible for the end-organ malperfusion.[66]

VASCULAR MANIPULATION AND EMBOLIC EVENTS

Cardiac Surgery

Stroke, transient ischemic attack, and peripheral embolization are potential complications after cardiac surgery. Atheroembolism results in a variety of clinical manifestations and can be fatal in about 20% of patients.[67] Stroke affects less than 2% of CABG patients and is higher in those undergoing open heart procedures.[68] The risk of perioperative stroke increases with advancing age, and those with concomitant cardiovascular risk factors are at highest risk.[69] Additionally, female sex is independently associated with a significantly higher risk of perioperative stroke.[70] Embolization from the atheromatous aorta is the single most important etiologic factor for stroke. This risk arises during intraoperative manipulation of the aorta, including cannulation for cardiopulmonary bypass, application and removal of an aortic cross-clamp for administration of cardioplegia, and the use of side-clamps for anastomosis of the proximal end of the graft to the aorta. Special approaches such as single-clamp or touchless aortic techniques significantly reduce this risk.[71] Patients undergoing cardiac surgery with aortic plaque greater than or equal to 5 mm had a higher incidence of stroke.[72] As previously mentioned, mobile plaques confer a greater risk of stroke. This effect was seen in an analysis of 130 patients undergoing CABG, with a higher incidence of stroke in the cohort in whom mobile plaques were identified.[73] Roach and colleagues showed that atherosclerosis of the ascending aorta is the strongest independent predictor of perioperative stroke, with an odds ratio of 4.5.[74]

Cardiac Catheterization and Peripheral Vascular Intervention

Aortic manipulation during cardiac catheterization procedures or IABP insertion may cause embolization from aortic atheroma. In a report comparing 59 patients with atherosclerotic aortic debris undergoing transfemoral cardiac catheterization, an embolic event occurred in 17% of the patients with atherosclerotic aortas compared with 3% of controls.[75] In the proportion of patients requiring IABP, 5 out of 10 patients with atherosclerotic aortas had an embolic event compared with none of the 12 patients with IABP in the control group. When a transbrachial approach was used in patients with atherosclerotic aortas, none of the 11 patients suffered an embolic event. Patients with mobile aortic atheromas on TEE are at the highest risk of catheter-related embolization.[75] A recent study reported the rate of clinically significant distal embolization in 2.4% of patients undergoing peripheral arterial intervention.[76]

Cholesterol embolization can complicate cardiac catheterization. Because it is commonly asymptomatic, the exact incidence is uncertain and mainly depends on the detection criteria used (clinical or pathologic). Cholesterol can be identified in the lumen of affected arterioles in up to 12% of patients after cardiac catheterization.[77] A prospective multicenter study reported cholesterol embolization in 1.4% of patients after cardiac catheterization based on evidence of peripheral cutaneous involvement or renal dysfunction.[78] The syndrome occurred more frequently in patients with generalized atherosclerosis.

PREVENTION AND MANAGEMENT

Treatment of atheromatous embolization depends on the clinical manifestation. However, evidence of atherosclerotic disease with plaque should be considered a cardiovascular risk factor, and preventive measures should be taken despite the symptomatic status of the individual. General measures include identification and modification of risk factors. Patients with the clinical syndrome of cholesterol embolization have a generally poor prognosis, particularly when there is evidence of visceral and renal involvement. Supportive management with blood pressure control and, if necessary, renal replacement therapy is indicated. Strategies for the general prevention and management of atheromatous embolization are discussed here.

Antiplatelet Agents and Anticoagulants

As thrombi can develop on and embolize from atherosclerotic plaques, it seems logical to use antiplatelet agents or anticoagulants to prevent these thromboembolic complications. Three studies have reported a reduction in the risk of stroke with anticoagulation.[79–81] These studies, however, were not randomized and did not include long-term follow-up. A randomized trial reported that in patients with stroke, large aortic plaques remain associated with an increased risk of recurrent stroke and death at 2 years despite treatment with warfarin or aspirin.[82]

The Aortic Arch Related Cerebral Hazard (ARCH) trial was an open-label trial where patients with aortic arch atheroma (4 mm or greater) and nondisabling stroke were assigned to warfarin (target international normalized ratio [INR], 2.0–3.0) versus aspirin (75 mg/d) plus clopidogrel (75 mg/d) and followed longitudinally to determine which treatment was superior for secondary stroke prevention. Unfortunately, the trial was stopped prematurely and was underpowered to determine a difference in the primary endpoints of cerebral infarction, MI, peripheral embolism, and intracranial hemorrhage, although vascular death was significantly lower in the dual-antiplatelet cohort.[83] The main concern with anticoagulation is the risk of plaque hemorrhage and atheroembolization.[84] However, the risk of clinical atheroemboli syndrome during warfarin therapy in such patients appears to be low (only 1 episode in 134 patients according to the Stroke Prevention in Atrial Fibrillation trial).[79]

In patients with atherosclerosis, acute ischemic events are usually precipitated by thrombosis, and antiplatelet agents play a fundamental role in thrombosis prevention. Routine use of aspirin in high-risk patients is universally recommended.[85] The Antithrombotic Trialists' Collaboration published a major meta-analysis with over 200,000 patients assessing the effect of antiplatelet therapy in patients with various manifestations of atherosclerosis. This study reported a significant reduction in the rate of stroke, MI, or vascular death in those on antiplatelet therapy.[86]

Aspirin is the most commonly used antiplatelet agent. It inhibits thromboxane-dependent platelet aggregation. Thienopyridines, including clopidogrel and ticlopidine, act by blocking adenosine diphosphate (ADP)–dependent activation of platelets. There is evidence that thienopyridine derivatives are modestly but significantly more effective than aspirin in preventing serious vascular events in patients at high risk, but there is uncertainty about the size of the additional benefit.[86] The thienopyridines are also associated with less gastrointestinal

hemorrhage and upper gastrointestinal upset compared with aspirin but with an excess of rash and diarrhea.[87] In the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, a long-term benefit was observed with the use of clopidogrel in addition to aspirin in high-risk patients (unstable angina and non–Q-wave MI).[88]

Platelet activation leads to a conformational change in glycoprotein IIb/IIIa, the major fibrinogen receptor on platelets. Intravenous glycoprotein IIb/IIIa inhibitors (e.g., abciximab) are generally reserved for the high-risk setting of percutaneous coronary intervention.

Dextran has antiplatelet and intravascular volume expansion effects. Postoperative or perioperative administration of 10% dextran 40 reduces the rate of TCD-detected microembolic signals after carotid endarterectomy.[89,90] Dextran, however, may interfere with crossmatching blood and cause bleeding, renal failure, or (occasionally) acute allergic reactions.

The *Guidelines for the Diagnosis and Management of Patients with Thoracic Aortic Disease* have been published by the American College of Cardiology Foundation/American Heart Association (ACCF/AHA). Oral anticoagulation therapy with warfarin (INR, 2.0–3.0) or antiplatelet therapy in stroke patients with aortic arch atheroma 4.0 mm or greater to prevent recurrent stroke was a class IIb recommendation (level of evidence, C).[91] However, American College of Clinical Pharmacy (ACCP) guidelines from 2012 recommend that patients with aortic disease with no previous neurologic event have no indication for anticoagulation.[92]

Statins

There is a clear association between elevated levels of plasma cholesterol and atherosclerotic disease. Statins or 3-hydroxy-3-methylglutaryl coenzyme-A (HMG Co-A) reductase inhibitors reduce the hepatocyte cholesterol content and increase expression of low-density lipoprotein (LDL) cholesterol receptors, resulting in a drop in serum LDL cholesterol. In addition, it has become evident in recent years that statins possess cholesterol-independent or pleiotropic effects. These include improvement of endothelial function by improving the bioavailability of nitric oxide, decreasing vascular inflammation, and stabilizing plaques.[93] Statins are widely used in primary and secondary prevention of ischemic heart disease. A meta-analysis of randomized placebo-controlled double-blind trials with statins reported a 30% reduction in stroke risk with statin therapy.[94] Another meta-analysis of data pooled from over 49,000 patients treated with statins in 28 trials reported a relative risk of stroke of 0.76 in statin-treated patients.[95] Tunick and colleagues showed that statin therapy was independently and significantly protective against the occurrence of embolic events (risk ratio, 0.39) in patients with severe thoracic aortic plaque.[13]

Plaque size reduction, stabilization, and prevention of plaque thrombosis may be the mechanisms leading to a reduction in atheromatous embolization. Two randomized studies of low-dose and higher-dose statins in patients with aortic and/or carotid plaques showed significant regression in plaques seen on MRI.[96,97]

Minimal Aortic Manipulation

The use of smaller arterial catheters during cardiac catheterization may help reduce the risk of embolization.[98] Reduction of embolization during cardiac surgery is possible with modifications to the operative technique. Avoidance of aortic manipulation intraoperatively is most important.[71] This can be achieved in patients undergoing CABG by avoidance of cardiopulmonary bypass, which obviates the need for aortic cannulation and cross-clamping.[99,100] For those patients where cardiopulmonary bypass and aortic cross-clamp cannot be avoided, there are some options using arterial cannulas with incorporated filter devices—the results using these kinds of devices have been promising in highly selected patients with preoperatively determined high risk for embolization.[101] The use of composite arterial grafts (bilateral internal thoracic artery grafts with the radial artery anastomosed to the internal thoracic artery) avoids the need for proximal aortic anastomosis requiring a side-clamp.[102] Off-pump surgery has been shown to offer a reduction in the risk of stroke in patients with atheromatous aortas.[103] We have reported a significant reduction in cerebral microembolization by avoiding cardiopulmonary bypass and aortic manipulation.[48,56] A strategy for potential prevention of embolization in cardiac surgery is summarized in Box 153.1.

BOX 153.1 Prevention of Embolization During Cardiac Surgery in Patients With Atherosclerosis

- Establish the patient's preoperative risk factors.
- Image the ascending aorta and arch preoperatively.
- Assess the carotid arteries.
- Assess the ascending aorta using intraoperative epiaortic ultrasound.
- Use evidence-based decisions to reflect the operative technique.
- Decide the site and risk of cannulation.
- Avoid repeated aortic clamping.
- Consider no-touch aortic techniques.
- Perform off-pump surgery with composite arterial grafting where possible.

Surgical Treatment

Treatment of patients with symptomatic carotid atherosclerosis is well established. The European Carotid Surgery Trial (ECST) and North American Symptomatic Carotid Endarterectomy Trial (NASCET) investigators reported a clear benefit of carotid endarterectomy in the prevention of stroke in patients with high-grade, recently symptomatic carotid stenosis.[35,104] This benefit is offset by the surgical risk of the procedure. The perioperative stroke and death rate for patients with high-grade stenosis was 8% at 30 days in ECST and 6% in NASCET. These rates are acceptable, given the absolute risk reduction by surgery of 10% and 17%, respectively. However, for patients with asymptomatic carotid disease, the risk-to-benefit ratio is narrower, and carotid endarterectomy is currently only recommended for high-grade carotid stenosis (70%–99%).

The International Carotid Stenting Study looked at angioplasty and stenting of the carotid vessels as an alternative to endarterectomy. However, they reported higher rates of stroke and mortality with carotid stenting compared with endarterectomy and therefore recommended that carotid endarterectomy should remain the treatment of choice.[105]

Management of patients with recurrent embolic events caused by aortic atherosclerotic disease can be problematic. Aortic arch endarterectomy in patients with severe aortic atherosclerosis has been reported.[106–108] This procedure is performed using deep hypothermic circulatory arrest and is associated with significant perioperative morbidity and mortality. When performed during cardiac surgical procedures using cardiopulmonary bypass, it resulted in a significantly higher rate of stroke and mortality. Therefore there is insufficient evidence to recommend this mode of treatment for stroke prevention. In the context of cardiac surgery, replacement of the ascending aorta can be performed with acceptable mortality and morbidity,[109] particularly in the intraoperative management of patients with so-called *porcelain aorta*[110] (severe diffuse atherosclerosis and calcification of the ascending aorta that causes an eggshell appearance on x-ray or CT). Systematic use of preoperative noncontrast CT of the chest in all patients

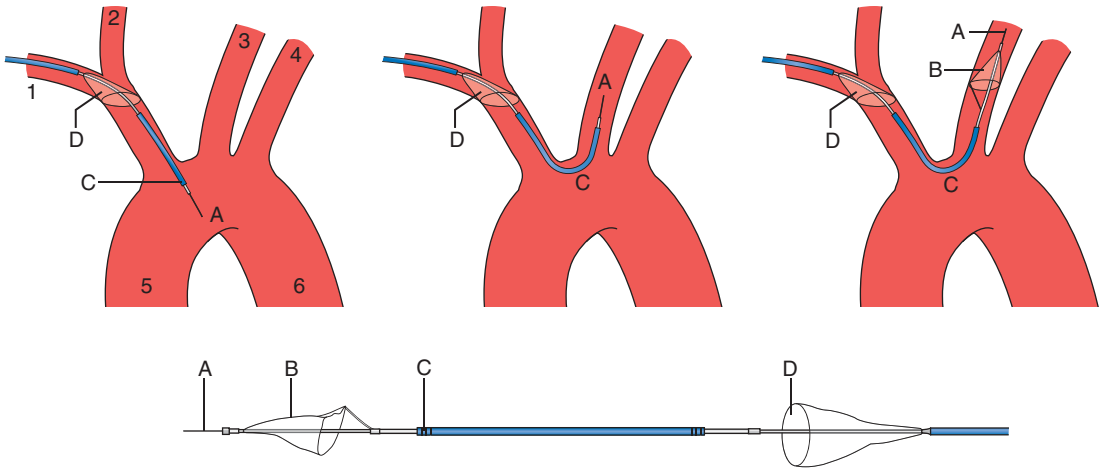

Fig. 153.2 Percutaneous antegrade cerebral filter protection device. The system is delivered through right radial artery percutaneous access and floated, under fluoroscopy guidance, to the desired position: with the proximal filter (D) deployed at the innominate trunk entrance and the distal filter (B), through a connecting sheath (C) into the proximal left common carotid artery. *1,* Right subclavian artery; *2,* right common carotid artery; *3,* left common carotid artery; *4,* left subclavian artery; *5,* ascending aorta; *6,* descending aorta; *A,* guidewire; *B,* distal filter; *C,* articulating sheath; *D,* proximal filter.

70 years of age and older who undergo open heart surgery increases the chance of identifying aortic disease and accordingly allows for planning of operative strategies and risk stratification related to perioperative stroke.[111]

With increasing interest, dedicated endovascular procedures to treat atherosclerotic aortas with stents as a means of preventing subsequent embolization from aortic plaque have been explored with some success. This involves the use of covered stents to exclude the plaque disease. This minimally invasive approach may offer a treatment strategy for patients who are unfit for conventional surgery despite its inherent risk of embolization secondary to instrumentation.[112,113]

Endovascular procedures to treat cardiac valve pathology, aortic aneurysms, dissection, hematomas, and so on have gained a leading role within the therapeutic armamentarium and open a whole new area of potential thromboembolic complications.

The presence of aortic wall thrombus (AWT) or its most aggressive entity better known as *shaggy aorta syndrome* can affect suitability to endovascular repair. A qualitative score classification system (0–10 AWT) has been used.[114] With aortic CT angiographic assessment, the number of affected aortic segments, thrombus type, thickness, area, and circumference can be identified and have a better quantification of the atherothrombotic burden (see Fig. 153.1). Modification of the surgical technique and use of filter devices can help to minimize potentially devastating complications.[114]

Transcatheter Aortic Valve Replacement

Transcatheter aortic valve replacement (TAVR) has become the leading therapeutic strategy for the treatment of patients with aortic valve disease. Since the PARTNER trial results, TAVR became the procedure of choice not just for high-risk and intermediate-risk patients but also for low-risk patients with severe aortic stenosis. Stroke remains a concerning complication and is associated with increased mortality and morbidity.[115–123] Data from MRI post-TAVR has showed the presence of clinically "silent" brain embolic lesions that could be associated with neurocognitive disorders after the procedure.[124–126] These perfusion defects can occur in up to 80% of patients after TAVR.[127–130] It is a multifactorial problem; nevertheless, the presence of perfusion defect on MRI is proof of embolization of debris from the aorta or the aortic valve during the procedure.[131–132] Previous exploratory studies attempted to minimize procedural embolization by using either transcatheter filters or deflection devices.[133–140] A randomized trial was designed to assess the safety of transcatheter cerebral embolic protection (TCEP) during TAVR and the efficacy of TCEP in reducing the effects of cerebral embolization (Fig. 153.2). As we continue to operate on patients who are increasingly older and sicker and increase application of percutaneous techniques in the treatment of vascular diseases, the continued development of strategies to minimize atheroembolization continues to be of huge importance.

KEY POINTS

- Atherosclerosis and its thromboembolic complications are a leading cause of death in the Western world.
- The risk of atheromatous embolization increases significantly with increasing plaque thickness (>4 mm) and the presence of ulceration.
- Ultrasonography (transesophageal and surface) is one of the most frequently used investigative techniques. CT provides information on coronary artery atherosclerosis and the degree of calcification. MRI provides very high resolution in imaging plaque morphology.
- The risk of embolization increases significantly during cardiac surgery and vascular interventions.
- The use of antiplatelet agents and statins is recommended in all patients with significant atherosclerotic disease.
- Perioperative aortic screening allied with minimal aortic manipulation during cardiac surgery in high-risk patients may be associated with a significant reduction in the rate of atheromatous embolization.
- The role of novel protective devices continues to evolve. Their benefits have been demonstrated in a selected group of high-risk patients

References for this chapter can be found at expertconsult.com.

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This large meta-analysis with more than 200,000 patients reported that aspirin is protective in most patients at increased risk of occlusive vascular events, including those with an acute MI or ischemic stroke; unstable or stable angina; previous MI, stroke, or cerebral ischemia; peripheral arterial disease; or atrial fibrillation.

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This study of 334 patients aged 60 years and above reported that in patients with brain infarction, the risk associated with aortic plaque thickness (≥4 mm) is markedly increased by the absence of plaque calcifications.

Evered LA, Silbert BS, Scott DA. Postoperative cognitive dysfunction and aortic atheroma. *Ann Thorac Surg.* 2010;89(4):1091–1097.
In over 300 patients undergoing cardiac surgery, the incidence of early postoperative cognitive decline was directly related to aortic atheroma burden (imaged using TEE and epiaortic ultrasound).

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In a retrospective, single-center analysis,604 patients were used for a qualitative 0–10 Aortic Wall Thrombus (AWT) score classification system. Severe and irregular thrombus of the descending thoracic and abdominal aorta has been strongly associated with acute respiratory failure and peri-interventional stroke in transfemoral aortic valve implantation.

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A novel device: transcatheter cerebral embolic protection (TCEP). *Nineteen centers randomized 363 patients undergoing TAVR to a safety arm (n = 123), device imaging (n = 121), and control imaging (n = 119). TCEP was safe, captured embolic debris in 99% of patients, and did not change neurocognitive function.*

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Pressure Ulcers

Laura J. Moore

EPIDEMIOLOGY

A *pressure ulcer* is any wound that develops in the upper, outer layers of the skin as a result of sustained, external pressure.[1] Pressure ulcers are serious complications among hospitalized patients. They increase healthcare costs, decrease patient quality of life, and often result in prolonged hospital stays. Hospital-acquired pressure ulcers are generally considered to be preventable, and if allowed to progress to full-thickness skin loss must be reported as "never events" to the Centers for Medicare & Medicaid Services. Current estimates of the prevalence of pressure ulcers among hospital patients are highly variable but have been decreasing across the United States.[2] In the largest investigation to date, the incidence of hospital-acquired pressure ulcers is 4.5% and the prevalence of pressure ulcers on admission is 5.8%. More significantly, in those admitted with a previously acquired pressure ulcer, almost one in five patients developed an additional pressure ulcer at a different site during their hospital stay.[3,4] The prevalence of pressure ulcers is even higher among residents of long-term geriatric facilities, occurring in up to 30% of patients. Whereas the majority of the ulcers (50%) in hospitalized patients are stage I, the prevalence of stage III and IV ulcers is estimated to be as high as 4% in patients who reside in long-term care facilities.

Pressure ulcers result in a substantial financial burden, with an estimated cost ranging from $3.3 billion to $11 billion per year.[5,6] The Centers for Medicare & Medicaid Services has reduced the reimbursement for hospital-acquired pressure ulcers, with a single episode costing hospitals $500 up to $70,000.[7]

RISK FACTORS

There are multiple risk factors for the development of pressure ulcers; they can be categorized as intrinsic and extrinsic. Intrinsic risk factors are those related to the patient's preexisting medical condition. Extrinsic factors are those related to the patient's environment. Intrinsic risk factors include neurologic disease, motor impairment, cognitive impairment, sensory deficits, malnutrition, and hypoperfusion caused by peripheral vascular disease or congestive heart failure. Extrinsic risk factors include inadequate mobilization by care providers, trauma, sedation, application of physical restraints, improper positioning (especially among patients under general anesthesia), moisture, and shearing forces. Among these risk factors, failure to frequently change position is thought to be the biggest contributor to pressure ulcer formation. The combination of improper positioning and moisture at the skin surface is a frequent cause of pressure ulcer formation in critically ill patients.

Because of the underlying pathophysiology of pressure ulcer formation, there are several high-risk areas for the development of pressure ulcers. Pressure ulcers are more prone to develop in bony or cartilaginous areas. These include any area of the body that has limited soft tissue coverage such as the coccyx, spinous processes, heels, elbows, and ankles. In patients who are frequently positioned on their side, the iliac crest and trochanters are considered high-risk areas. Additionally, patients with malnutrition and subsequent cachexia have significant loss of soft tissue and are more prone to the development of pressure ulcers at any location. Medical devices can also be associated with the development of pressure ulcers. Examples include masks for noninvasive positive-pressure ventilation, cervical collars, endotracheal tubes, nasogastric tubes, and nasal cannula tubing.

PATHOPHYSIOLOGY

Pressure ulcers form as a result of hypoperfusion to an area. The basic principle of pressure ulcer development is simple. When externally applied pressure exceeds the capillary perfusion pressure, flow becomes impaired and tissue ischemia occurs. If the hypoperfusion and ischemia are not reversed, necrosis of the involved tissue layers will occur. Ischemia to the area will initially present with erythema and induration. If this progresses to necrosis, tissue loss will occur. The critical duration of ischemia varies from patient to patient. However, it is generally accepted that pressure injury typically occurs between 30 and 240 minutes of hypoperfusion. In patients with preexisting peripheral vascular disease, the time to critical ischemia is shorter. Because of impaired arterial inflow, these patients experience significant delays in restoration of perfusion and reversal of tissue hypoxia after the external pressure has been removed. In addition, because of poor underlying tissue perfusion, these patients will experience longer healing times once pressure ulcers develop.

CLASSIFICATION

All pressure ulcers begin in the outer layers of the skin. With ongoing pressure, the ischemia progressively extends to deeper layers of the skin. Therefore the classification of pressure ulcers is based on the depth of skin involvement. Pressure ulcers are classified as stage I through IV, with stage I being the most superficial and stage IV being the deepest. The classification of pressure ulcers is listed in Table 154.1. Having a uniform, well-defined classification system for pressure ulcers is critical. It not only allows for standardization of wounds for research purposes but also allows for accurate communication of wound staging among healthcare providers. Once a pressure ulcer develops, it is important to classify the wound and monitor the progress of the wound bed. Having a standard grading system allows for continuity of care and objective monitoring of the progression of the wound.

PREVENTION

Prevention of pressure ulcer formation should be standard practice. This is of particular importance when caring for critically ill patients, because they often possess multiple risk factors for pressure ulcer formation.

TABLE 154.1 Pressure Ulcer Staging

National Pressure Ulcer Staging System	
Stage I	Nonblanching erythema of intact skin.
Stage II	Partial-thickness skin loss involving the epidermis and/or dermis. The ulcer is superficial and presents clinically as an abrasion, blister, or shallow crater.
Stage III	Full-thickness skin loss with damage and/or necrosis of the subcutaneous tissue. The wound extends down to, but not through, the underlying fascia.
Stage IV	Full-thickness skin loss with extensive destruction and necrosis of overlying structures, including muscles, bone, or tendon

Risk Assessment

Prevention programs should include an initial risk assessment of the individual patient. This assessment should include questioning about previous or preexisting pressure ulcers; a thorough skin inspection; evaluating the patient's mobility/activity level, continence, and nutritional status; and a review of comorbid conditions that may contribute to the development of pressure ulcers. Assessment of these risk factors should be standardized and documented on all patients. Several tools have been developed for pressure ulcer risk assessment. The Braden Scale (Fig. 154.1) assesses external pressure forces and skin-related factors in a standardized fashion.[8] The scores on the Braden Scale range from 6 to 23, with a score of 15–18 indicating mild risk, a score of 13–14 indicating moderate risk, a score of 10–12 indicating high risk, and a score ≤9 indicating very high risk. The Norton Scale assesses patient-specific risk factors (age, cognitive impairment, mobility, incontinence) for pressure ulcer development.[9] The Waterlow Scale assesses both intrinsic and extrinsic risk factors and was initially developed for use in the pediatric population.[10] However, studies to date have shown little efficacy in reducing the incidence of pressure ulcers with these tools compared with nonstructured risk assessment.[11]

Prevention Plan

Once the individual patient risk assessment has been addressed, a plan for pressure ulcer prevention should be implemented. Regardless of the plan used, a frequent assessment of its efficacy must be performed and any necessary adjustments made. The key elements of prevention include patient mobilization, patient positioning to prevent/remove pressure, and the use of positioning aids to redistribute pressure. Among critically ill patients, this requires vigilance and team effort, particularly among those patients who are sedated for prolonged periods. Prevention also includes avoidance of skin damage by shearing forces and avoidance of maceration of the skin as a result of moisture from incontinence and heat accumulation. A variety of support services are available to help decrease the risk of pressure ulcer formation. These pressure-reducing surfaces include static support surfaces (mattresses, mattress overlays) and dynamic support surfaces that mechanically alter the amount of pressure applied to the patient's skin. Examples of dynamic support surfaces include low-air-loss beds, air-fluidized mattresses, and alternating pressure mattresses. The use of foam mattress overlays can reduce the risk of pressure ulcer development in high-risk populations.[12] Although associated with higher costs, dynamic mattresses have not consistently been shown to be superior to static support surfaces. However, dynamic mattresses are better than standard hospital mattresses in preventing pressure ulcer formation.

TREATMENT

A variety of treatment options and products are available for the management of pressure ulcers. Very few of the currently available treatment options have been rigorously evaluated in randomized controlled trials.[13,14] An in-depth discussion of all the currently available products is beyond the scope of this text, so general classes of treatment options are discussed rather than specific products.

Wound Débridement

Débridement of the wound bed is a critical step in the healing process of pressure ulcers. The purpose of débridement is to remove foreign material and devitalized tissue from the wound. After débridement, a wound bed of healthy tissue should be visible. Débridement of the wound bed reduces the production of inflammatory mediators that inhibit wound healing. A variety of techniques are used for wound débridement. These include surgical débridement, hydrotherapy, larval therapy, and application of topical enzymatic débridement solutions. The choice of débridement techniques used depends on multiple factors, including the size of the wound, comorbid conditions, and the presence of infection. Surgical débridement is most often required in large-volume wounds when extensive tissue débridement is needed. However, surgical débridement requires the patient be a suitable candidate for general anesthesia. The risk of subjecting a critically ill patient to general anesthesia and a trip to the operating room must be weighed against the benefits of sharp surgical débridement of a pressure ulcer. Hydrotherapy, although commonly practiced, has not been rigorously evaluated in the setting of a large randomized controlled trial. However, some small studies of patients with stage III or IV pressure ulcers have demonstrated faster wound healing among patients receiving hydrotherapy as compared with those who did not receive hydrotherapy.[15,16]

Larval therapy, also referred to as *biosurgery,* has been used for débridement of pressure ulcers. The basic concept is that application of larvae to wounds results in rapid débridement of necrotic tissues, with avoidance of the potential complications of surgical débridement such as pain and bleeding. Currently, there is evidence that compared with topical enzymatics, larval therapy significantly reduces the time to débridement of necrotic tissue. However, the use of larval therapy did not appear to have any effect on time to wound healing.[17]

A variety of topical enzymatic débridement products are commercially available. These can be used alone or in conjunction with other débridement techniques. These agents are applied directly to the wound bed once or twice a day. Multiple randomized controlled trials have validated the efficacy of topical enzymatic débridement products for the removal of necrotic tissue from the wound bed.[18] Before applying these agents, the wound bed should be cleansed with normal saline. The presence of any topical wound products containing metal will diminish the efficacy of topical enzymatics, and removing these agents from the wound bed is critical for the success of the enzymatics. In the event an eschar is overlying the wound bed, it is recommended that the eschar be cross-hatched with a surgical blade to allow for penetration of the topical enzymatic agent. Once applied, the wound bed should be covered with gauze. These agents are a viable and valuable therapy, particularly in those patients who are not candidates for alternative débridement methods.

Hydrocolloids

Hydrocolloid dressings are widely used in the management of pressure ulcers; their purpose is to absorb wound exudates. Typical hydrocolloid dressings contain some type of gel-forming agent placed in contact with the wound bed, and this is covered with a membrane that

BRADEN SCALE FOR PREDICTING PRESSURE SORE RISK

Patient's Name _____ Evaluator's Name _____ Date of Assessment

SENSORY PERCEPTION Ability to respond meaningfully to pressure-related discomfort	**1. Completely Limited** Unresponsive (does not moan, flinch, or grasp) to painful stimuli, due to diminished level of consciousness or sedation OR limited ability to feel pain over most of body.	**2. Very Limited** Responds only to painful stimuli. Cannot communicate discomfort except by moaning or restlessness OR has a sensory impairment which limits the ability to feel pain or discomfort over ½ of body.	**3. Slightly Limited** Responds to verbal commands, but cannot always communicate discomfort or the need to be turned OR has some sensory impairment which limits ability to feel pain or discomfort in 1 or 2 extremities.	**4. No Impairment** Responds to verbal commands. Has no sensory deficit which would limit ability to feel or voice pain or discomfort.				
MOISTURE Degree to which skin is exposed to moisture	**1. Constantly Moist** Skin is kept moist almost constantly by perspiration, urine, etc. Dampness is detected every time patient is moved or turned.	**2. Very Moist** Skin is often, but not always moist. Linen must be changed at least once a shift.	**3. Occasionally Moist** Skin is occasionally moist, requiring an extra linen change approximately once a day.	**4. Rarely Moist** Skin is usually dry, linen only requires changing at routine intervals.				
ACTIVITY Degree of physical activity	**1. Bedfast** Confined to bed.	**2. Chairfast** Ability to walk severely limited or non-existent. Cannot bear own weight and/or must be assisted into chair or wheelchair.	**3. Walks Occasionally** Walks occasionally during day, but for very short distances, with or without assistance. Spends majority of each shift in bed or chair.	**4. Walks Frequently** Walks outside room at least twice a day and inside room at least once every two hours during waking hours.				
MOBILITY Ability to change and control body position	**1. Completely Immobile** Does not make even slight changes in body or extremity position without assistance.	**2. Very Limited** Makes occasional slight changes in body or extremity position but unable to make frequent or significant changes independently.	**3. Slightly Limited** Makes frequent though slight changes in body or extremity position independently.	**4. No Limitation** Makes major and frequent changes in position without assistance.				
NUTRITION Usual food intake pattern	**1. Very Poor** Never eats a complete meal. Rarely eats more than ½ of any food offered. Eats 2 servings or less of protein (meat or dairy products) per day. Takes fluids poorly. Does not take a liquid dietary supplement OR is NPO and/or maintained on clear liquids or IVs for more than 5 days.	**2. Probably Inadequate** Rarely eats a complete meal and generally eats only about ½ of any food offered. Protein intake includes only 3 servings of meat or dairy products per day. Occasionally will take a dietary supplement OR receives less than optimum amount of liquid diet or tube feeding.	**3. Adequate** Eats over half of most meals. Eats a total of 4 servings of protein (meat, dairy products) per day. Occasionally will refuse a meal, but will usually take a supplement when offered OR is on a tube feeding or TPN regimen which probably meets most of nutritional needs.	**4. Excellent** Eats most of every meal. Never refuses a meal. Usually eats a total of 4 or more servings of meat and dairy products. Occasionally eats between meals. Does not require supplementation.				
FRICTION & SHEAR	**1. Problem** Requires moderate to maximum assistance in moving. Complete lifting without sliding against sheets is impossible. Frequently slides down in bed or chair, requiring frequent repositioning with maximum assistance. Spasticity, contractures or agitation leads to almost constant friction.	**2. Potential Problem** Moves feebly or requires minimum assistance. During a move skin probably slides to some extent against sheets, chair, restraints or other devices. Maintains relatively good position in chair or bed most of the time but occasionally slides down.	**3. No Apparent Problem** Moves in bed and in chair independently and has sufficient muscle strength to lift up completely during move. Maintains good position in bed or chair.					
				Total Score				

Fig. 154.1 Braden Risk Assessment Scale.

protects the wound against external contamination but allows for water evaporation.[18] Hydrocolloid dressings are typically applied every 3–5 days, depending on the amount of exudates being produced by the wound. When compared with standard gauze dressings, hydrocolloids have been shown to be more absorptive and less painful.[18]

Negative-Pressure Therapy

The use of negative-pressure therapy for wound healing has become increasingly common in the past decade. The basic concept behind this therapy is that applying negative pressure to the wound bed both removes edema fluid and increases blood flow to the area. Increased blood flow results in delivery of oxygen and nutrients, which promote wound healing. In addition, the application of negative pressure to the wound results in wound contracture. Compared with standard wet-to-dry dressings, another benefit to patients of negative-pressure therapy is decreased frequency of dressing changes. The use of negative-pressure therapy for pressure ulcers has been associated with improved wound healing and decreased length of hospital stay.[19] Traditionally, negative-pressure therapy has been applied to clean wounds that had very little slough or necrotic tissue. However, there is some evidence that the application of negative-pressure therapy to wounds that are covered with soft necrotic tissue is a viable option.[20]

Nutritional Support

The presence of malnutrition has a significant impact on wound healing. In fact, its mere presence results in weakening of the skin and increases the risk of pressure ulcer development. Unfortunately, nutritional assessment is often neglected, particularly in chronically institutionalized patients. Establishing nutritional assessment protocols and treating malnutrition are essential in preventing and healing pressure ulcers. This is best accomplished by a multidisciplinary team that includes physicians, dieticians, and nursing staff.[21]

An initial nutritional assessment should be performed. Any recent weight loss, the current weight, and the patient's dietary intake should all be evaluated. After the initial assessment is completed, a nutrition plan should be created and implemented to address any issues identified. Weekly monitoring of the patient's nutritional status should occur to determine if the nutritional intervention is having the desired effect. Monitoring should include the patient's weight and assessment of functional status. The use of biochemical tests, including serum prealbumin, transferrin, and nitrogen balance, is also helpful.

CONCLUSION

Pressure ulcers continue to be a common problem among critically ill patients. Constant vigilance and education of care providers are essential components of pressure ulcer prevention. When pressure ulcers do occur, a multidisciplinary approach is needed to manage these debilitating wounds. Management should include objective assessment of the scope of the wound, a multimodality treatment program specifically adapted to the patient's needs, and optimization of nutritional status to promote wound healing.

KEY POINTS

- Prevention is critical. The key elements of prevention include patient mobilization, patient positioning to prevent/remove pressure, and the use of positioning aids to redistribute pressure. Among critically ill patients, this requires vigilance and team effort, particularly among those patients who are sedated for prolonged periods. Avoidance of skin damage by shearing forces and avoidance of maceration of the skin because of moisture from incontinence and heat accumulation are also essential.
- Perform a structured risk assessment to identify high-risk individuals upon admission. High-risk factors include difficulty with mobilization, improper positioning, moisture, and hypoperfusion. Repeat risk assessment at regular intervals.
- Develop a plan for prevention and care. This should include regular repositioning and use of dynamic support surfaces to relieve skin pressure.

References for this chapter can be found at expertconsult.com.

ANNOTATED REFERENCES

Anders J, Heinemann A, Leffmann C, et al. Decubitus ulcers: Pathophysiology and primary prevention. *Dtsch Arztbl Int.* 2010;107(21):371–382.
In this article the authors performed a systematic review of the literature related to the pathophysiology and prevention of pressure ulcers. They identified age, presence of comorbid conditions, and immobility to be the highest risk factors for development of pressure ulcers. They found that the most useful means for prevention and treatment of pressure ulcers is avoidance of excessive pressure by encouraging mobility. In addition malnutrition, tissue hypoperfusion, and impaired mobility must be recognized and addressed as part of a comprehensive strategy to prevent pressure ulcer development.

Baharestani MM, Houliston-Otto DB, Barnes S. Early versus late initiation of negative pressure wound therapy: Examining the impact on home care length of stay. *Ostomy Wound Manage.* 2008;54(11):48–53.
In this retrospective analysis of over 500 patients the authors evaluated the impact of early vs. late application of negative-pressure wound therapy to stage III and stage IV pressure ulcers. They found that earlier application of negative-pressure wound therapy was associated with shorter lengths of stay. In addition, for each day in delaying the application of negative-pressure wound therapy, almost 1 day was added to the total length of stay.

Barrett R, Tuttle V, Whalen E, et al. Pressure ulcers and nutritional support: A partnership to improve patient outcomes. *J Nurs Care Qual.* 2010;25(2):145–150.
This article describes the implementation of a targeted strategy to improve the provision of nutritional support for patients at risk of developing pressure ulcers. They identified three key lessons. First, pressure ulcer risk assessments can be used as an opportunity to trigger evaluation by a dietician for recommendations to optimize nutritional status. Second, visual triggers and educational initiatives to increase staff awareness about the importance of nutrition and pressure ulcer assessment contribute to quality patient care. Third, interdisciplinary partnerships are an effective way to implement evidence-based care.

Reddy M, Gill SS, Rochon PA. Preventing pressure ulcers: A systematic review. *JAMA.* 2006;296(8):974–984.
This systematic review discusses interventions for pressure ulcer prevention. A total of 59 randomized control trials were included. Studies were grouped into three categories: mobility, nutrition, and skin health. The strategies found to be most useful for impaired mobility included use of support surfaces, mattress overlays on operating room tables, and specialized foam or sheepskin overlays. For nutritional deficiency, dietary supplements were found to be beneficial. Finally, no clear benefit could be found for any specific topical agent for skin health.

Rondinelli J, Zuniga S, Kipnis P, et al. Hospital-acquired pressure injury. *Nurs Res.* 2018;67(1):16–25.
In this article the authors describe the incidence, risk factors, and risk-adjusted variation in hospital-acquired pressure ulcers within Kaiser Permanente, an integrated healthcare delivery system in California. They analyzed over 1600 inpatients with hospital-acquired pressure ulcers and determined that age, severity of illness, comorbid conditions, and Braden Scale scores were all important predictors for pressure ulcer risk. They also demonstrated that female gender appeared to be protective against the development of pressure ulcers.

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Burns, Including Inhalation Injury

Ian R. Driscoll and Julie A. Rizzo

INTRODUCTION

Patients with severe burns today are more likely to survive compared with those injured decades ago. Advances in early source control of deep burns, antimicrobial strategies, and critical care medicine are largely responsible, buoyed by translational research in burn-induced inflammation, hypermetabolism, and the wound environment. As survival rates improve, burn clinicians are challenged to address the sequelae of critical illness after recovery.

Designated burn centers and units are resource-intensive initiatives that thrive in a collaborative model of care. A wide variety of personnel provide specific expertise to ensure the survival and functional recovery of injured patients. The burn team consists of surgeons, intensivists, anesthesiologists, nurses, physical and occupational therapists, respiratory therapists, nutritionists, psychiatrists and psychologists, chaplains, and child-life therapists, among others.[1]

Disasters, both natural and those caused by humans, repeatedly highlight the need for nonburn and nontrauma centers to develop plans for managing large numbers of casualties. In this setting, intensivists and surgeons must have some familiarity with the acute resuscitation and stabilization of burn patients until safe transfer can occur.

INITIAL CARE OF THE BURN PATIENT

Although most burn patients encountered in the intensive care unit (ICU) arrive having been screened by a trauma team, simultaneous transfer of multiple casualties and other factors may curtail the attention these patients receive. Burn patients may have other injuries, and it is important for critical care clinicians to not be distracted by the visual appearance of the skin. Injuries noted on primary and secondary surveys causing hemorrhage, airway compromise, or other threats to life should be addressed before beginning burn-specific resuscitation. Removal of contaminants, including fuel, should occur before transfer. Patients must be protected from hypothermia.

Early and serial assessments of the airway are critical. Smoke inhalation injury is familiar as a risk for airway compromise. However, mucosal and soft tissue edema from burns to the face or over large surface areas alone may cause progressive airway narrowing, when volume resuscitation is superimposed.[2] Patients likely to require endotracheal intubation include those with symptomatic smoke inhalation injury, deep facial burns, or second- and third-degree injuries greater than 40% total body surface area (TBSA) (Box 155.1). Supraglottic devices fail in the setting of oral and laryngeal edema. Using as large an endotracheal tube as practical facilitates pulmonary toilet. Endotracheal tubes should be secured with cotton twill ties, which are adjusted as edema progresses during resuscitation; many standard airway device holders do not adhere to burned skin (Fig. 155.1). Frequently reassess the depth of the tube during the acute resuscitation period. Urgent tracheotomy is not indicated.

Volume resuscitation can be reliably conducted via peripheral intravenous (IV) or intraosseous (IO) catheters, but soft tissue edema often leads to early failure of such devices. Consider transitioning to central venous access in burns >40% TBSA. Likewise, deep burn eschar and soft tissue edema make noninvasive blood pressure measurements less reliable. For large burns, invasive arterial blood pressure measurement is recommended.

It is difficult to provide an early definitive visual diagnosis of burn depth. Soot and other debris may mask important visual cues, and progression of edema and cell death continue for hours.[3] Clinicians should make their best estimate of burn depth upon initial survey and reassess periodically. Superficial burns (first degree) do not form blisters and appear red and blanchable. Partial-thickness burns (second degree) form blisters and remain moist and sensate and are often quite painful. Not all second-degree injuries are created equal, however. Slow capillary refill in second-degree injuries may indicate deeper dermal damage. These deeper partial-thickness injuries often act more like full-thickness injuries in their healing trajectory and contribution to inflammation.[4] Full-thickness burns (third degree) are insensate and form leathery eschar and thrombosed vessels.

Make an initial estimate using the rule of nines or Lund-Browder Burn Estimate and Diagram by adding the areas of all second- and third-degree burns (Fig. 155.2). Thus the percentage of TBSA reflects only second-degree and third-degree areas. For irregularly shaped areas, the patient's hand (palm and fingers included) roughly estimates 1% TBSA. Once wounds are cleansed, recalculate the injury size.

Antihypothermia measures such as a warm room, warm fluid infusions, and convective forced-air blankets should take priority over antimicrobial dressings initially. Extremity escharotomy for circumferential burns, discussed later, is ideally completed by the most experienced clinician in the warmest, best-equipped, and best-lit location, often the operating room (OR) or dedicated burn ICU. This procedure may be deferred in patients with evidence of intact distal extremity perfusion until trauma surveys are completed. Thoracic escharotomy, however, can be a lifesaving procedure in a patient with deep circumferential torso burns who cannot be ventilated.

ACUTE BURN RESUSCITATION

Fluid resuscitation after acute burn injury remains challenging. At TBSA ≥20%, the intense inflammatory response at the injury sites becomes a global cytokine storm, resulting in profound capillary leak and severe hypovolemia. Burn shock is caused by hypovolemia coupled with depression in cardiac function and low systemic vascular resistance.[5] Resuscitation strategies during burn shock must restore intravascular preload with only as much fluid as is needed to reduce the risk of edema formation and resuscitation morbidity from capillary leak. The pathophysiology of edema involves disruption of the

BOX 155.1 Endotracheal Intubation and Inhalation Injury Signs

Indications for Endotracheal Intubation
Symptomatic smoke inhalation injury
Deep facial burns
>40% TBSA

Inhalation Injury Signs
Deep facial burns
Stridor
Soot in nares and mouth
Carbonaceous sputum
Patient rescued from enclosed space

TBSA, Total body surface area.

Fig. 155.1 Cotton twill-tie endotracheal tube. A twill-tie harness is a reliable way of securing the endotracheal tube. Protective pads may reduce injury to oral commissures. Tube security should be regularly assessed because reintubation can be very difficult in this setting.

interstitial scaffold and loss of the oncotic gradient.[6] The amount and type of fluid given during burn resuscitation continue to be debated.[7]

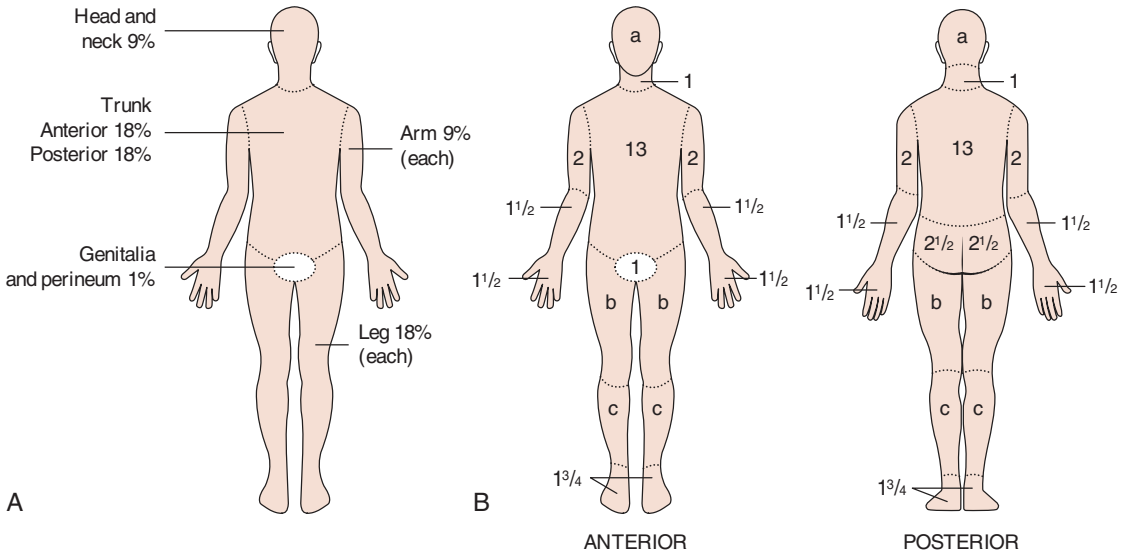
Many developments in burn resuscitation occurred in the 20th century after large urban fires resulted in mass burn casualties. After the 1921 Rialto Theatre fire in New Haven, Connecticut, Underhill noted the composition of burn blister fluid was similar to plasma, suggesting fluid losses be replaced with infusions containing protein.[8] Fluid replacement strategies based on percentage TBSA were introduced after the 1942 Cocoanut Grove nightclub fire. Refined by Evans in 1952, early strategies included both colloids (plasma) and crystalloids as resuscitation fluids in addition to dextrose-containing crystalloids as maintenance fluids.[9] A modification decreasing the amount of colloid fluid required became known as the *Brooke formula*.[10] In the 1960s Baxter and Shires used both human and canine data to generate an estimated fluid requirement of 3.5–4.5 mL per percentage TBSA per kilogram in the first 24 hours after injury, which became known as the *Parkland formula*.[11] The Parkland formula and Modified Brooke formula, two of the most widely cited strategies, provide lactated Ringer's solution (LR) as the resuscitation crystalloid, use no colloid in the first 24 hours after injury, and do not provide additional maintenance fluid.[12] The previously discussed burn formulae rely on intravenously administered fluid. However, the enteral route may allow early initiation of resuscitation fluids, especially in resource-constrained environments, and warrants further study.[13]

All resuscitation formulae require an accurate estimation of second- and third-degree burn size. Resuscitations of patients with ≥20% TBSA should be guided by one of the formulae, but clinicians must recognize that these formulae are initial estimates only.[14] Typically, isotonic crystalloid fluid rates are increased or decreased each hour in response to urine output without boluses. The fluid volume a burn patient actually requires will vary widely based on many factors, including time from injury, the ratio of second-degree to third-degree burns, age, medical comorbidities, and presence of inhalation injury, among others.[15,16] Administered fluid significantly outpaced recommended estimates in burned casualties during the wars in Afghanistan and Iraq.[17] The rule of 10 was developed in order to simplify the initial fluid rate calculation.[18] The percentage TBSA is multiplied by 10, and the result is the initial crystalloid fluid rate in mL/h. For example, a patient with 40% TBSA would be initially given isotonic crystalloid at $40 \times 10 = 400$ mL/h. The rule of 10 applies to patients between 40 and 80 kg. For patients greater than 80 kg, 10 mL/h is added to the initial calculation for every 1 kg over 80 kg. The fluid rate is adjusted up or down by 20%–25% each hour to maintain normal urine output (0.5 mL/kg/h for adults). The rule of 10 does not give a 24-hour fluid estimate, but rather forces the clinician to monitor and adjust the resuscitation for the individual patient. A suggested algorithm for burn resuscitation is given in Fig. 155.3. Other endpoints of resuscitation are discussed later, although urine remains the standard method of titrating resuscitative fluids in burn patients (Table 155.1).

Balanced crystalloid solutions such as LR continue to be recommended.[19,20] The introduction of colloid should reduce the crystalloid fluid totals and subsequent tissue water deposition. The use, timing, and duration of the colloid fluid adjunct continue to be debated, and prospective observational trials are currently underway.[21] Patients who would benefit from early colloid use are those at risk of overresuscitation morbidities—historically burn size ≥30% TBSA. Common colloids include 5% or 25% human albumin solutions and fresh frozen plasma (FFP), with each choice reducing fluid totals, although conclusions on mortality require further study.[22–25]

Vitamin C (ascorbic acid) is a pharmacologic adjunct thought to reduce resuscitation-related complications. As an antioxidant, it regenerates vitamin E, which scavenges reactive oxygen species (ROS) in the cell membrane. ROS are plentiful during burn shock and contribute to endothelial injury.[26] Preclinical studies and limited clinical data have shown that a high-dose vitamin C infusion during the early hours of burn resuscitation reduces the isotonic crystalloid requirement, decreases tissue water deposition, and improves respiratory function. The vitamin C dose (66 mg/kg/h) is infused in an LR solution and its rate calculated as part of the total LR resuscitation volume. This adjunct performs best when started early (within 6 hours of injury) for burns >30% TBSA. Counterintuitively, increases in IV fluid rate may be required for a portion of the first 24 hours because of the diuretic effect of high-dose vitamin C. Savings in tissue water deposition result from the *net* 24-hour volume and reduction in oxidative stress.[27,28]

Other adjuncts to resuscitation include vasoactive medications, renal replacement therapy (RRT), and total plasma exchange (TPE). Vasoactive medications lack a clearly defined role, as the primary mechanism behind shock in these patients is hypovolemia. However, vasopressin (at 0.04 unit/min) and other vasoactive medications are useful for maintaining mean arterial pressure (MAP) >65 mm Hg in patients who appear to be receiving adequate volume.[29] Vasopressors allow focused treatment of the vasodilatory component of burn shock. Crystalloid boluses in this setting contribute to overresuscitation morbidity. Patients who demonstrate persistently decreased cardiac function also may benefit from cardiac inotropic support during



Relative percentage of body surface areas (% BSA) affected by growth

	0 yr	*1 yr*	*5 yr*	*10 yr*	*15 yr*
a–½ of head	9½	8½	6½	5½	4½
b–½ of 1 thigh	2¾	3¼	4	4¼	4½
c–½ of 1 lower leg	2½	2½	2¾	3	3¼

Fig. 155.2 Burn area diagrams. The rule of nines (A) and Lund-Browder Burn Estimate and Diagram (B) graphically display second- and third-degree burn burden and allow burn formula calculations. (From Artz CP, Moncrief JA. *The Treatment of Burns,* 2nd ed. Philadelphia, PA: Saunders; 1969.)

RESUSCITATION OF MAJOR BURNS

PATIENT ARRIVAL

- Establish vascular access
- Establish definitive endotracheal airway if needed
- Prevent hypothermia
- Place urinary catheter
- Estimate patient weight (kg)
- Estimate % TBSA (2nd- and 3rd-degree burns)
- Screen for other injuries

INITIAL FLUID RESUSCITATION RATE CALCULATION (Lactated Ringer's Solution, LR)

For **ADULT** burns>20% TBSA
Calculate initial fluid resuscitation rate (mL/h) using the Rule of 10:
(10 x %TBSA for 40–80 kg) + (10 x kg for>80 kg)
Increase or decrease fluid rate each hour by 20%–25% to maintain urine output 0.5 mL/kg/hr

For **PEDIATRIC** burns>15% TBSA
Calculate initial fluid resuscitation rate using Modified Brooke Formula:
3 mL/kg/24 h estimate ½ in first 8 hours and ½ in second 16 hours
Increase or decrease fluid rate each hour by 20%–25% to maintain urine output 0.5–1 mL/kg/h
Add maintenance fluid containing dextrose according to the 4:2:1 rule
(1–10 kg x 4) + (11–20 kg x 2) + (>20 kg x 1) mL/h

COMPLICATED BURN RESUSCITATION

Do not bolus IV fluids
At 12 hours post-injury, estimate 24-hour fluid total assuming stable fluid rate
Warning signs: >250 mL/kg over 24 hours
Persistent oliguria
Hypotension (MAP<65 mmHg) refractory to fluid titration
Evaluate intravascular volume status
Begin vasopressin 0.04 unit/min, then norepinephrine 2–20 µg/min (goal MAP>65 mmHg)
For **adults**, begin colloid fluid (5% albumin or fresh frozen plasma) at the following rates:

% TBSA burn	30%–49% TBSA	50%–69% TBSA	>70% TBSA
Colloid infusion rate (mL/h)	50	100	150

SHOCK REFRACTORY TO FLUID TITRATION OR ADJUNCTS

Evaluate for missed injury
Treat acidemia (ventilation, bicarbonate, RRT)
Replace calcium
Treat adrenal insufficiency with hydrocortisone

Fig. 155.3 Burn resuscitation algorithm. A sample algorithm is provided to guide initial resuscitation fluid titration and the use of adjuncts in difficult cases. *IV,* Intravenous; *MAP,* mean arterial pressure; *RRT,* renal replacement therapy; *TBSA,* total body surface area.

TABLE 155.1 Burn Resuscitation Endpoints

Endpoint	Target Range
Urine output	Adults: 0.5 mL/kg/h Children: 0.5–1 mL/kg/h Infants: 1 mL/kg/h
Mental status	Follows commands, purposeful age-appropriate activity
Heart rate	Adults: <130 bpm Children: <140 bpm Infants: <160 bpm
Systolic blood pressure	Adults: >90 mm Hg Children: 70–90 + (twice age in years) mm Hg Infants: 60–70 mm Hg
Central venous pressure	6–10 mm Hg
Stroke volume variation	<13%
Lactate	<2
Base deficit	Trend toward zero
Hematocrit	Gradual dilution

resuscitation. The use of vasoactive medications and inotropes must be guided by both invasive hemodynamic and laboratory monitoring. Failure to correct hypovolemia before using these agents often leads to worsening of the shock state. RRT and TPE have both been used during burn resuscitation. They are believed to facilitate resuscitation by cytokine removal, thus blunting the proinflammatory "cytokine storm" of early burn shock.[30,31]

Monitoring a burn resuscitation requires serially evaluating a constellation of physical examination findings, vital signs, laboratory data, and invasive monitors. Urine output remains the primary monitor, with a goal of 0.5 mL/kg/h (30–50 mL/h for most adults).[32] However, confounding factors such as early oliguric acute kidney injury, prior dehydration, alcohol intoxication, use of diuretics, and glycosuria can make urine output an unreliable indicator of resuscitation progress. The vital sign derangements typically encountered in burn shock are caused by a massive release of catecholamines, which increase the heart rate to 130 bpm or greater. This effect can persist for months without intervention (see Table 155.1).[33] Controversy remains over the most useful laboratory values during burn resuscitation. Serum lactate and base deficit have correlated with mortality and morbidity.[34,35] Central venous oxygen saturation has crossed over from sepsis resuscitation into burn shock management.[36] Hemoconcentration is observed early after burn injury and is late to correct. Titrating crystalloid fluid resuscitation to endpoints other than urine output is quite difficult, and no one endpoint should take precedence. Instead, the trends of as much data as possible should be examined to determine if volume resuscitation should be augmented versus other interventions such as vasopressors to address vasodilation.

Examining the impact of burn resuscitation on cardiac function requires advanced monitoring. Although the pulmonary artery (PA) catheter has largely been replaced by other technologies such as echocardiography and arterial waveform monitoring (stroke volume variation [SVV]), it may be required in patients with a history of heart failure or who require inotrope use.[37] The hyperdynamic response to burn injury and poor correlation of preload and cardiac output estimations with ultimate fluid requirements have challenged the universal adoption of these technologies in the burn ICU.[38] Clinicians must take as many variables into consideration as possible when determining the adequacy of resuscitation.

The judicial use of fluid and accurate monitoring is essential to avoid overresuscitation morbidities, including extremity compartment syndrome, acute respiratory distress syndrome (ARDS), abdominal compartment syndrome (ACS), orbital compartment syndrome, and cerebral edema. These complications are associated with severe morbidity or mortality. Patients at risk of receiving large resuscitation fluid volumes should be identified. One assessment is the "Ivy Index," which associates patients who receive >250 mL/kg in the first 24 hours postburn with increased risk of ACS.[39] Recognizing this trajectory allows initiation of fluid-sparing adjuncts, including colloids, vasopressin, RRT, or surgical intervention such as decompressive laparotomy.

INHALATION INJURY

Clinical evidence of inhalation injury includes deep facial burns, stridor, soot about the nares and mouth, or carbonaceous sputum. Patients evacuated from enclosed spaces (vehicles and buildings) are most at risk. Fiberoptic bronchoscopy in the intubated patient may confirm subglottic inhalation injury, although the visual grade of inhalation injury does not necessarily correlate with common sequelae, including increased resuscitative fluid requirements, airway obstruction, bronchospasm, pneumonia, and ARDS.[40] The burden of carbonaceous debris and epithelial sloughing are managed with aggressive pulmonary toilet. Nebulized adjuncts include unfractionated heparin (antiinflammatory and anticoagulant), N-acetylcysteine (antioxidant), and beta-adrenergic agonists (antiinflammatory and treats bronchospasm).[41,42] Prophylactic antibiotics are not recommended, but as pneumonia is common, clinicians should have a low threshold for obtaining cultures, including bronchoalveolar lavage samples, and starting antibiotic therapy in patients with new-onset fever and worsening respiratory function in the days after injury.

Adherence to lung-protective ventilation strategies is standard in most ICUs and should be extrapolated to most patients with burns and inhalation injury.[43] However, hypercatabolism or inhalation injury may cause severe gas exchange derangements, necessitating higher-than-expected mean airway pressures. Inverse ratio modes may not allow adequate expiratory time in the setting of hypercarbia. Specialized strategies, including high-frequency percussive ventilation (HFPV), have been used to obtain early bronchial clearance of debris, lower mean airway pressures, and provide tidal breaths and have found a niche in the burn population.[44] Timing of tracheotomy in burn patients unable to liberate from mechanical ventilation varies among centers.[45] Injury location, respiratory dysfunction, metabolic demands of large injuries, and refractory delirium all play a role in the decision and should become clear within 2 weeks of injury.

Patients with severe ARDS after inhalation injury are typically supported by lung-protective ventilation and adjuncts including reduction of excess fluids, early use of diuretics, neuromuscular blockade, prone positioning, and use of pulmonary vasodilators. Extracorporeal membrane oxygenation (ECMO), long avoided in adult burn patients, is now applied more regularly. ECMO strategies without systemic anticoagulation have seen successful use in burn patients requiring excision and grafting. Mortality in burn patients requiring ECMO is similar to nonburn patients.[46]

All patients with suspected inhalation injury should also be suspected to have carbon monoxide (CO) exposure. Co-oximetry via arterial blood gas is used to measure CO-hemoglobin levels. Symptoms of CO toxicity include confusion, stupor, coma, seizures, and cardiac ischemia. Administer 100% oxygen. Hyperbaric oxygen therapy may reduce the CO-hemoglobin half-life, but this therapy is cumbersome, particularly in the critically ill patient.[47]

Cyanide (CN) toxicity after smoke inhalation causes failure of oxygen utilization. Severe lactic acidosis is noted, although underresuscitated

burn patients present in similar fashion.[48] In addition to 100% oxygen, the antidote hydroxocobalamin should be administered.[49] Sodium thiosulfate may be given via the intramuscular injection route.[50]

CIRCUMFERENTIAL EXTREMITY BURNS

Escharotomy may be required for circumferential full-thickness burns to extremities with evidence of distal ischemia. If the burn is partial thickness or not circumferential, first rule out hypovolemic or hemorrhagic shock. Burned extremities should be elevated 30–45 degrees to decrease edema. Repeat the vascular examination at least every hour. The requirement for escharotomy usually presents in the first 24 hours. If available, use a handheld Doppler probe to assess the palmar arch, dorsalis pedis, and posterior tibialis for a normal triphasic signal. Consider performing escharotomy early, based on the vascular examination.

Escharotomy is performed by incising full-thickness burns just into the subcutaneous fat to allow the incision to visibly spring open. Patients will require analgesia, sedation, and usually intubation. Even though the eschar is insensate, deeper structures are not. Electrocautery is recommended because blood loss can be significant. Although this procedure can be performed in the ICU or emergency department, the OR, with its lighting and equipment, may be the better option. Extend escharotomy incisions the entire length of the circumferential portion of full-thickness burn, crossing all affected joints (Fig. 155.4). Reassess circulation after performing each incision. Once perfusion is restored, control bleeding, perform dressing care, and elevate the extremity once again. Continue regular vascular assessments. Be prepared for late bleeding as the tourniquet effect of circumferential burns is released. Fasciotomies on burned extremities are rarely required. Patients at risk for requiring a fasciotomy often have associated vessel injury with delayed revascularization, massive transfusion, or crush injury.[51]

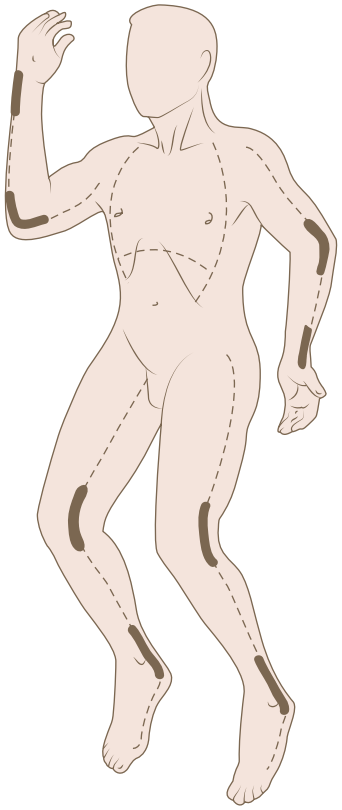


Fig. 155.4 Escharotomy. Properly performed escharotomy will result in immediate improvement in extremity blood flow. (From Steurer M, Chang T, Lancman B. Anesthesia for trauma. In Pardo MC, Miller RD, eds. *Basics of Anesthesia,* 7th ed. Philadelphia, PA: Elsevier; 2018:715–723.e2, Fig. 56.7.)

PERIOPERATIVE MANAGEMENT OF THE BURN PATIENT

Burn wound management is central to burn patient care, and the OR should be considered an extension of the ICU. A formal communication process between intensivists, surgeons, anesthesiologists, nurses, and OR staff is required. Continuation of ICU mechanical ventilators and continuous RRT should be strongly considered in the most critically ill patients to allow adequate surgical source control without interrupting needed therapy.

Hypothermia and intravascular volume depletion can occur rapidly via exposed surfaces. In addition to warming the OR air, convective warming blankets, IV fluid warmers, and esophageal warming devices should be used liberally.[52,53] IV fluid replacement should be guided by hemodynamic monitoring, urine output, and serial laboratory data.

Blood loss during tangential excision of large burn surface areas can be enormous. Adequate crossmatched blood products should be available before the start of the case. Replacement of large volume losses should approximate a 1:1:1 ratio of packed red blood cells, FFP, and platelets. Burn patients should be monitored intraoperatively for coagulopathy by standard assays and thromboelastography (TEG) if available.[54]

WOUND COVERAGE

Early excision, within 1 week of injury, is fairly standard for deep burns today.[55] Although wound care protocols vary widely, antimicrobials and grafts delay microbial recolonization while wounds close. An autograft (split-thickness skin graft) is used for definitive closure of deep burns. It survives via diffused oxygen and nutrients from wound fluid. The autograft is usually meshed to expand the area each graft covers and to allow evacuation of fluid. Mesh ratios >2:1 require a second skin substitute layer to protect the autograft while its interstices (spaces in the mesh) close. Silver-impregnated dressings are gaining in popularity, allowing for less frequent manipulation. The wound is considered "closed" once interstices are filled with a layer of epidermal cells. Although a grafted wound may close within a week, appearance and functionality continue to evolve over many months.

Much research effort is devoted to wound coverage, including spray-on autologous epithelial cells, laboratory-grown keratinocytes, and artificial skin substitutes.[56–58] Common skin substitutes remain biologic ones. An allograft (split-thickness deceased donor skin) is used if the wound bed is not conducive to autograft survival. Although eventually rejected by the host, it buys precious time during periods of instability or while awaiting healing of donor sites.

ANALGESIA AND SEDATION

Pain, anxiety, and sedation are discussed daily. The largest burn injuries lead to lengthy hospital stays and medication tolerance. Patients should be normalized as much as possible while providing adequate analgesia to accomplish procedures, therapy, and sleep. Continuous titratable analgesic and sedative infusions are used during periods of resuscitation and organ dysfunction. The use of ketamine as both procedural and maintenance sedation in adults has increased in recent years and is recommended during the hemodynamic instability of

acute postburn resuscitation.[59] De-escalation to intermittent dosing and the addition of oral analgesic formulations and multimodal strategies are used as patients become less critically ill and wound coverage progresses.[60] Management of behavioral health (e.g., depression, anxiety, and psychoses) is linked to adequate pain control. Have a low threshold to consult specialists in psychiatry and psychology, especially in the setting of preexisting disorders.

INFECTION IN THE BURN PATIENT

Prophylactic systemic antibiotics are not indicated for cutaneous burns alone. Early excision of deep burns and topical antimicrobials are the mainstays of infection prevention. However, associated traumatic injuries such as penetrating wounds, soiled lacerations, or open fractures do warrant systemic antibiotics. The choice and duration of this therapy should be selected according to institutional guidelines. Tetanus prophylaxis is given to all burn patients.

Deep, unexcised burn wounds are particularly susceptible to gram-negative colonization and wound sepsis. A wide variety of topical antimicrobials exist to cleanse wounds and act as barriers to colonization (Table 155.2). These agents, however, do not replace prompt surgical excision of deep wounds followed by immediate coverage with autologous skin or temporary skin substitutes. All topical agents have advantages and disadvantages. Although several topical agents allow for continuous use over many days, new-onset fever or organ dysfunction should prompt dressing removal and a complete wound examination.

The expected hyperdynamic response to major burns can be prolonged even months after injury, causing elevated thresholds for hyperthermia, tachycardia, and tachypnea.[61] Suspected systemic infection should trigger a complete physical examination, including of all wounds and grafts. Antibiotics should be started while awaiting culture data if new organ dysfunction occurs.

Burn wound infection is a clinical diagnosis. Signs include cellulitis (expanding induration and tenderness), foul odor, purulent drainage, graft necrosis, and previously healing partial-thickness injuries that now appear full thickness. Diagnosis may be augmented by quantitative cultures or wound histology showing invasion of organisms into viable tissue.[62] These efforts are merely adjuncts, however, and wound biopsy is less frequently employed today. Swab cultures of wound sites are of little benefit, as they cannot differentiate between infection and colonization.

Once a wound infection is diagnosed, empiric systemic antibiotic therapy and topical antimicrobials should be directed against both gram-positive and gram-negative bacteria using known institutional susceptibilities. *Pseudomonas* species, including resistant strains, are common. The best prevention of burn wound sepsis is early excision of deep burns and autologous tissue coverage. If wound infection is diagnosed in previously excised wound beds, re-excision may be required. With hyperdynamic physiology and increasing use of extracorporeal organ support, serum levels of systemic antibiotics should be monitored closely to ensure adequate therapeutic ranges.

The inflammatory response after burn injury alters electrolyte homeostasis. Hypocalcemia, hypomagnesemia, and hypophosphatemia are frequently encountered and are often severe. Tissue water deposition and insensible losses contribute to hypernatremia early after the acute resuscitation period, and liberal free water replacement is required. Later in the course of the hospitalization, hyponatremia is routinely noted.[63]

TABLE 155.2 Topical Antimicrobials

Agent	Characteristics
Antibiotic ointments	Oily preparations for partial-thickness burns, limited antibacterial activity, Bactroban (mupirocin) active against MRSA
Ionic silver dressings	May be left for several days, broad-spectrum antibacterial
Dakin solution	Dilute sodium hypochlorite, used in soiled wounds, broad spectrum, toxic to keratinocytes at strengths >0.0025%
Silver sulfadiazine	Well tolerated and widely available, does not penetrate eschar
0.5% Silver nitrate	Often used for SJS/TEN, stains black, causes hyponatremia
Mafenide acetate	Used as a cream or dilute solution, penetrates eschar, can be painful, causes metabolic acidosis

MRSA, Methicillin-resistant *Staphylococcus aureus; SJS,* Stevens-Johnson syndrome; *TEN,* toxic epidermal necrolysis.

GASTROINTESTINAL STRESS ULCERATION

Historically, gastric acid–reducing medications have been associated with decreased incidence of Curling ulcer (burn-specific stress ulceration) and mortality from gastrointestinal bleeding in patients with large burns.[64] Hemodynamic support, nutrition interventions, and wound sepsis prevention have also likely contributed to the low modern incidence of significant gastrointestinal hemorrhage. Patients with injuries ≥20% TBSA should receive stress ulceration prophylaxis with a proton pump inhibitor or other gastric-reducing agent.[65] Advancing enteral nutrition as soon as practicable is recommended.

NUTRITION

It is challenging to provide adequate nutrition during the hypercatabolic response to large surface area burns. Early (even during resuscitation) enteral feeding has become standard in many centers. Calculated calorie and macronutrient goals vary in the literature. Adult burn patient consensus guidelines suggest approximately 1.5–2 g/kg/day of protein, which many American Burn Association (ABA)–verified burn centers consider inadequate to meet the nutritional needs of the hypermetabolic burn patient. Nonprotein caloric load goals are no longer recommended.[66] Indirect calorimetry repeated at intervals can provide metabolic data to assist with nutritional interventions. Ultimately, the quality and rate of wound closure reflect the adequacy of nutrition. Admission screening of weight, HbA_{1c}, vitamin D, calcium, and albumin levels provide important information about preinjury nutrition status. Micronutrients such as vitamin C, zinc, copper, and selenium play important roles in wound healing in the largest burns.[67] Anabolic steroids and beta-adrenergic blockade are routinely used to reduce the effect of hypercatabolism.[68,69]

Patients able to swallow effectively should receive a high-protein, high-calorie diet. Patients with ≥30% TBSA burns are often unable to attain adequate nutrition via oral intake alone. These and patients with dysphagia should have nasoenteric access. Percutaneous placement of gastric tubes (PEG tubes) must be weighed against the risks of site complications, particularly if torso burns are present.[70] Enteral feeding should be continued in patients who are not exhibiting worsening shock. Meeting nutritional goals can be challenging when enteral infusions are interrupted for frequent procedures. Postpyloric access is not necessary but may decrease perioperative interruptions in formula infusion. An increasing number of centers continue uninterrupted

TABLE 155.3 Splinting Recommendations

Location	Positioning	Splinting
Neck/face	Anterior neck burns: extension Posterior neck burns: neutral Ear burns: no pillows	Soft neck collar
Shoulder/axilla	Keep arm elevated	Abduction wedge
Chest	Shoulder abduction, arms elevated	Abduction wedge or pillows
Elbows	Elevate arms above heart	Extension splint
Hands	Elevate hands and arms above heart	Intrinsic plus splints: MCP joint flexion and PIP/DIP joint extension Splints are worn at all times when not performing therapy
Hips	Hips are extended and abducted; avoid hip flexion	
Legs	Elevate legs above heart level Check for Achilles and heel wound breakdown Avoid pillows behind knees	Elevate legs above level of heart Ankle dorsiflexion splint Knee extension splints (knee immobilizer)

DIP, Distal interphalangeal; *MCP,* metacarpophalangeal; *PIP,* proximal interphalangeal.

enteral feeding during operative cases.[71] The enteral route is preferred for provision of nutrition, but supplemental parenteral nutrition should be considered in patients who are unable to reach a significant proportion of their estimated needs after 1 week.[72,73]

REHABILITATION IN THE BURN ICU

Physical and occupational therapists are essential members of the multidisciplinary team and inform daily ICU goals. Generally, injured extremities are elevated above the level of the heart to reduce edema. Check for skin and wound breakdown caused by pressure (e.g., sacrum, heels, elbows, and occiput). Splints are used to prevent flexion contractures (Table 155.3). Extremities with unexcised burns or those covered with temporary skin substitutes should be allowed full active and passive range of motion. Extremities receiving a split-thickness autograft, particularly over joints, may receive range-of-motion limitations for several days, but these restrictions are increasingly being liberalized at many centers.[74] Patients should be given liberal access to sunlight, outdoor spaces, and even the gym.

PEDIATRIC PATIENTS

Although pediatric burn injuries are most associated with the need to screen for abuse or neglect, clinicians are reminded that *all* burn-injured patients are potentially victims and should be alert to other traumatic injuries and evidence of malnutrition.

The smaller airways of pediatric patients are at risk for faster compromise.[75] As with adults, IV and IO access can be used for resuscitation, but central venous catheters are generally required for the largest burns. The relative surface areas of extremities, trunk, and head vary with age. Percentage TBSA may be estimated using the Pediatric Lund-Browder Burn Estimate and Diagram (see Fig. 155.2), which has both infant and child estimates.

For burn sizes ≤15% TBSA, children may be given 1.5 times their expected maintenance rate while monitoring urine output and vital signs. Maintenance fluid needs may be estimated with the "4:2:1 rule." For each kilogram in the range of 1–10 kg, provide 4 mL/h; for each kilogram in the range of 11–20 kg, provide 2 mL/h; and for each kilogram >20 kg, provide 1 mL/h.[76] The enteral route should be used for at least some hydration if possible. Infants may be given breast milk or bottle feeds, and older children may be given nasoenteric infusions of oral rehydration formulas, such as the World Health Organization (WHO) Oral Rehydration Solution (ORS).[77]

For burn sizes >15% TBSA, place an appropriately sized urinary catheter. Anticipate volume requirements with the Pediatric Modified Brooke formula (3 mL/kg/%TBSA LR or other isotonic fluid divided over 24 hours, with one-half given during the first 8 hours). As with adults, the formula only provides a resuscitation starting point. Increase or decrease the IV isotonic fluid infusion rate by 20%–25% each hour to attain goal urine output: 0.5–1 mL/kg/h for children. Young children <20 kg with large burns will require additional dextrose-containing maintenance fluid (LR containing 5% dextrose) according to the 4:2:1 rule to compensate for inadequate glycogen stores. Unlike the isotonic fluid given for resuscitation, this maintenance infusion is not titrated.

To reduce the risk of overresuscitation, colloid fluid in the form of 5% albumin should be added for children with burns >30% TBSA. Starting at 12 hours postinjury, give 5% albumin at the calculated maintenance rate using the 4:2:1 rule. Subtract this volume from the hourly isotonic fluid rate. This albumin infusion is not titrated. Continue the albumin infusion until 48 hours postinjury. Pediatric burn resuscitations are monitored using urine output, vital signs, and laboratory data, which must be compared with age-related norms.

High-quality burn care in the pediatric population is particularly resource-intensive. Access to experienced consultants in addition to pediatric psychosocial support and physical and occupational therapists is critical. Malnutrition is poorly tolerated in children, and enteral feeding with a pediatric formula should be given to all hemodynamically stable patients.[78] Tolerance to sedative and analgesic medications is common and monitored procedural sedation is standard for dressing care and other manipulations that cause pain and anxiety.[79]

OPHTHALMIC INJURY

Patients with facial burns or exposure to blasts, flash fires, or chemicals may also have ophthalmic injuries. Eye examinations should be completed before significant facial edema occurs. Examination with the Wood's lamp screens for corneal injury, which should prompt early ophthalmology specialist consultation. At a minimum, if no eye injuries are identified, intubated patients should receive frequent lubricating eye drops. Lateral canthotomy should be considered in those patients demonstrating intraocular hypertension during resuscitation.

CHEMICAL BURNS

Patients with known or suspected chemical exposure should be cleansed with low-pressure water for at least 30 minutes. Litmus paper may be applied to affected areas to track the progress of decontamination. Obtain as much information about the exposure as possible to anticipate potential systemic effects. Fluid resuscitation of chemical burn casualties proceeds as for a similar area of flame burns. Visual declaration of wound depth may be delayed. Cement causes alkali contact burns after extended exposure, and patients often present in delayed fashion.[80] Hydrofluoric acid exposure may result in severe systemic hypocalcemia and require subeschar injection of 10%

calcium gluconate as a bridge to urgent excision.[81] Tar used for paving and other applications causes very high-temperature contact burns, and the material quickly solidifies. Cool water irrigation is followed by lipophilic solvent application and then operative excision.[82]

Chemicals and certain munitions may be encountered during periods of armed conflict or acts of terrorism. Medical providers must protect themselves from exposure to the very agents they are treating. Institutional protocols for decontamination of chemical exposure casualties should be developed and practiced. White phosphorus is an incendiary and antipersonnel compound that ignites in the presence of oxygen. Wounds should be covered with soaking wet cloth to prevent reignition of retained fragments. Urgent operative exploration addresses particles buried deeply in soft tissues, and copper sulfate may aid in their identification.[83] Vesicant compounds such as sulfur mustard, phosgene, and lewisite are used as chemical weapons and cause contact injuries to skin and epithelial surfaces.[84] Respiratory compromise may occur early, but skin lesions may take days to fully develop, depending on the agent. Patients are prone to ARDS, early pulmonary infection, wound sepsis, and pancytopenia. Fluid resuscitation needs are often less than those predicted by burn formulae.

ELECTRICAL INJURY

Electrical injuries are defined as "low-voltage" (110–220 volts) and "high-voltage" (>1000 volts) exposures. The distinction can be misleading, however. Even low-voltage exposures may result in dysrhythmias, wound complications, and neurologic sequelae.[85] In addition to these problems, high-voltage exposures have the potential to cause even more widespread tissue injury and secondary effects such as rhabdomyolysis, flame burns, corneal injury, and blunt trauma. Patients presenting after significant electrical contact should have a full trauma evaluation.

Admission criteria after electrical exposure are not universal, but it is reasonable to observe patients with high-voltage exposures and no obvious injuries for 24 hours. A 12-lead electrocardiogram should be obtained to screen for cardiac dysrhythmias, even after low-voltage contact. Admitted patients will typically have evidence of cutaneous burns or other injury. Fluid resuscitation should proceed as for thermal burns, but be prepared to increase the rate of isotonic crystalloid fluid in response to urine output and other indicators of perfusion. Urine output should be examined for gross pigmenturia (the color of red wine). If this is present, the crystalloid rate should be increased to target a urine output of 1 mL/kg/h. Acute kidney injury is common in this setting, and continuous RRT is an important adjunct to management.[86] Rhabdomyolysis usually indicates deep tissue injury. Suspected compartment syndrome in affected extremities should prompt urgent fasciotomy and excision of burns. In this setting, definitive coverage is best deferred until tissue necrosis is absent after several OR trips.

COLD INJURY

Cold injuries, often referred to burn centers, are classified as freezing or nonfreezing. Freezing injury, including frostbite, occurs in tissues exposed to below-freezing temperatures (≤0°C). Nonfreezing injury, such as trench foot, results from prolonged exposure to wet and cold conditions (>0°C).[87] Patients with comorbid conditions such as advanced age, dehydration, peripheral vascular disease, diabetes, and a history of alcohol overuse or nicotine dependence are at increased risk of cold injury. Hypothermia is managed by providing a warm environment, convective heating, and warm fluid infusions. Avoid lactated and potassium-containing fluids. Cardiac arrest in the hypothermic patient should be treated by external cardiac massage, warm fluid infusion (including lavage through gastric and rectal tubes), and correction of acidosis and hyperkalemia. As core temperature rises, defibrillation may be attempted.[88]

Frostbite occurs when tissue water crystallizes. Areas affected by frostbite may be warmed in a water bath of 40°C. Hemorrhagic bullae should be left intact.[89] It is difficult to predict the extent of tissue loss; thus early débridement or amputation is discouraged until full demarcation of necrosis occurs, often over weeks to months. Multimodal analgesia is recommended. Given the high levels of prostaglandin $F_{2\alpha}$ and thromboxane A_2 in blister fluid, nonsteroidal antiinflammatory drugs (NSAIDs) are used routinely.[90] Other adjuncts such as thrombolytic therapy may be considered on an individual basis.[91] Wounds are covered with loose antimicrobial dressings. Early physical and occupational therapy is required.

RADIATION INJURY

Exposure to ionizing radiation can occur during industrial accidents and armed conflict. Localized radiation injury from high-dose exposure > 8–10 Gy causes burns with similar visual appearance to thermal burns. Erythema appears quickly and usually subsides only to reappear weeks later. This may be accompanied by hair loss and blistering. Skin necrosis may be significantly delayed from the index injury.[92] Treatment of partial-thickness burns is conservative and relies on moist antimicrobial dressings and skin substitutes until epidermal healing occurs. Full-thickness injuries are excised, followed by skin grafting only when granulation tissue appears adequate.

Whole-body radiation exposure results in critical illness after prodromal and latent phases. The higher the cumulative radiation dose, the faster the onset of pancytopenia, gastrointestinal mucosal sloughing, neurologic deterioration, and cardiovascular collapse.[93] Decontamination protocols are necessary to protect clinicians from secondary exposure. The need for prolonged supportive care should be factored into triage decisions.[94]

DESQUAMATIVE DISORDERS

Burn centers are often asked to evaluate patients with desquamative disorders (severe cutaneous adverse reactions [SCARs]). Stewardship of limited burn beds mandates accurate diagnosis. The Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) continuum are T-cell immune reactions classified by extent of epidermal detachment. Many triggers have been reported, including anticonvulsant medications, antibiotics, and viral illnesses, among others. Often, a prodromal phase of fever, lethargy, and dysphagia is followed by sloughing of the epidermis, tracheobronchial tree, gastrointestinal tract, vaginal mucosa, cornea, and oropharynx. Clinical suspicion should be corroborated by cutaneous punch biopsies.[95,96]

Stop all potential offending agents. Although the capillary leak is not as severe as for thermal burns, patients' fluid status must be closely monitored. Comorbid organ dysfunction often worsens in the setting of the inflammatory response to SJS/TEN. Blisters may be left in place. Exfoliated areas may be covered with silver-based dressings while awaiting re-epithelialization, which should occur within 2–3 weeks. Specialist consultation in ophthalmology, dermatology, and gynecology is recommended for affected structures. Early administration of immune adjuncts may benefit select patients and should be guided by experienced clinicians. This includes the use of intravenous immunoglobulin (IVIg), corticosteroids, cyclosporin A, and granulocyte colony-stimulating factor (G-CSF).[97,98]

CONCLUSION

Patients with major burn injuries rely on aggressive management of their wounds combined with multidisciplinary critical care to increase their odds of a good outcome. Although resource-intensive, quality burn care is an investment that returns precious time to patients in their most productive years.

KEY POINTS

- Do not become distracted by the cutaneous injuries of burn patients; screen for other traumatic injuries per advanced trauma life support (ATLS) guidelines.
- Fluid resuscitation and hypothermia prevention are early priorities after burn patient arrival.
- Establish a definitive endotracheal airway in patients with symptomatic smoke inhalation injury, deep facial burns, and burns >40% TBSA; secure with cotton twill ties.
- Suture all IV and central venous and arterial catheters in place.
- Perform frequent neurovascular assessments of deep circumferential extremity burns and perform escharotomy early if required.
- All burn formulae provide starting points only; titrate isotonic crystalloid rates hourly to attain urine output and other resuscitation endpoints.
- Increased urine output should be targeted in the setting of electrical injury with gross pigmenturia.
- The hypercatabolic state after burn injury may last months.
- Early nutrition without frequent interruptions is required to heal large burns.
- Physical and occupational therapy must begin early in the hospital course.

References for this chapter can be found at expertconsult.com.

ANNOTATED REFERENCES

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Thoracic Trauma

Frank Z. Zhao and Walter L. Biffl

Thoracic trauma is responsible for approximately 20% of all trauma-related deaths and is second only to central nervous system injury as the primary cause of death at the scene. For patients arriving at the emergency department (ED) alive, rapid diagnosis and treatment of potentially life-threatening injuries are required to prevent death during the "golden hour" of initial resuscitation. However, many thoracic injuries that are not immediately life-threatening still have the potential for significant morbidity and mortality. The following is an overview of the diagnosis and management of thoracic trauma.

INITIAL ASSESSMENT

Primary Survey

The Advanced Trauma Life Support (ATLS) course of the American College of Surgeons Committee on Trauma[1] provides basic tenets for the management of injured patients. The process begins with the primary survey, a stepwise evaluation of the "ABCs": airway, breathing, and circulation.

Airway patency may be compromised by neurologic injury, facial injury, or obstruction (e.g., by the tongue, blood, vomitus, or tooth or bone fragments). Trauma to the larynx, trachea, or bronchus may also complicate or preclude airway control. Thoracic trauma may also cause life-threatening breathing (e.g., pneumothorax [PTX], pulmonary contusion) and circulation (e.g., tension PTX, pericardial tamponade, massive hemothorax) problems. These must be identified and treated rapidly.

Resuscitative Thoracotomy

Resuscitative thoracotomy (RT) is indicated for traumatic cardiac arrest or persistent severe hypotension (e.g., systolic blood pressure [SBP] <60 mm Hg). The primary objectives of RT are to (1) release pericardial tamponade and repair cardiac injuries, (2) control intrathoracic hemorrhage, (3) control bronchovenous air embolism or bronchial injury, (4) perform open cardiac massage, and (5) attenuate subdiaphragmatic hemorrhage and redistribute blood flow to the brain and myocardium.[2] The critical determinants of survival after this procedure are the mechanism of injury and the patient's condition. The best outcomes are seen in adult patients with isolated penetrating cardiac injuries who present with detectable SBP; survival averages 35% in one large series. In contrast, RT is least beneficial in the treatment of blunt injury without signs of life, with only 0.7% of patients surviving.[3]

An algorithm for resuscitation of moribund trauma patients is presented in Fig. 156.1.[2] Patients arriving in extremis after blunt injury undergo thoracotomy if they have had less than 10 minutes of cardiopulmonary resuscitation (CPR). Penetrating trauma victims undergo thoracotomy if they have had less than 15 minutes (for torso injuries) or 5 minutes (nontorso injuries) of CPR. The pericardium is opened; if there is no organized cardiac activity and no blood in the pericardium, the patient is pronounced dead. Otherwise, the descending thoracic aorta is occluded to limit subdiaphragmatic hemorrhage and redistribute perfusion to the myocardium and brain. Patients who do not respond with SBP >70 mm Hg are pronounced dead on the basis of futility. The value of thoracotomy in the resuscitation of a patient in profound shock is unquestioned. Its indiscriminate use, however, is not appropriate. Although the performance of RT only "costs" the price of a scalpel and sterilization of the instrument tray, it is critical to recognize futility and avoid initiating massive transfusion or transferring the patient to the operating room (OR). These costly resources should be reserved for potential survivors. Furthermore, although no cases have been specifically reported, there is a potential risk of transmission of bloodborne disease to the healthcare team. An alternative approach to selective RT involves the use of focused ultrasonography to evaluate for meaningful cardiac activity. Inaba and colleagues showed in a prospective study of 187 patients that cardiac motion seen on focused assessment with sonography in trauma (FAST) examination was 100% sensitive for identification of survivors and organ donors. Thus the performance of RT was deemed futile to both overall survival and survival to organ donation in patients without cardiac motion.[4]

Recently, the use of resuscitative endovascular balloon occlusion of the aorta (REBOA) has been proposed for traumatic cardiac arrest.[5] This has not been studied in adequately controlled prospective trials—it takes precious time to deploy, and major thoracic hemorrhage is considered an absolute contraindication to its use.[6] The patient presenting in extremis secondary to subdiaphragmatic hemorrhage is most likely to benefit from REBOA if it can be deployed rapidly.[5] For the patient presenting in cardiac arrest resulting from exsanguination or pericardial tamponade, open-chest CPR has proven superior to closed-chest CPR, and thus RT remains our recommendation in this setting.[7]

PLEURAL SPACE

Pneumothorax

PTX is common in thoracic trauma. Clinical diagnosis based on decreased breath sounds and hyperresonance to percussion is not accurate, especially in the noisy trauma resuscitation bay. Chest x-ray (CXR) has long been considered the diagnostic standard, but ultrasonography performed as part of the extended focused assessment with sonography for trauma (E-FAST) has potentially greater sensitivity for a small PTX in the supine patient.[8] An untreated PTX may progress to tension PTX, especially if the patient is receiving positive-pressure ventilation. In this setting, the mediastinal structures are shifted away from the affected side. Once venous return to the heart is impaired, cardiovascular collapse ensues. Immediate decompression of tension

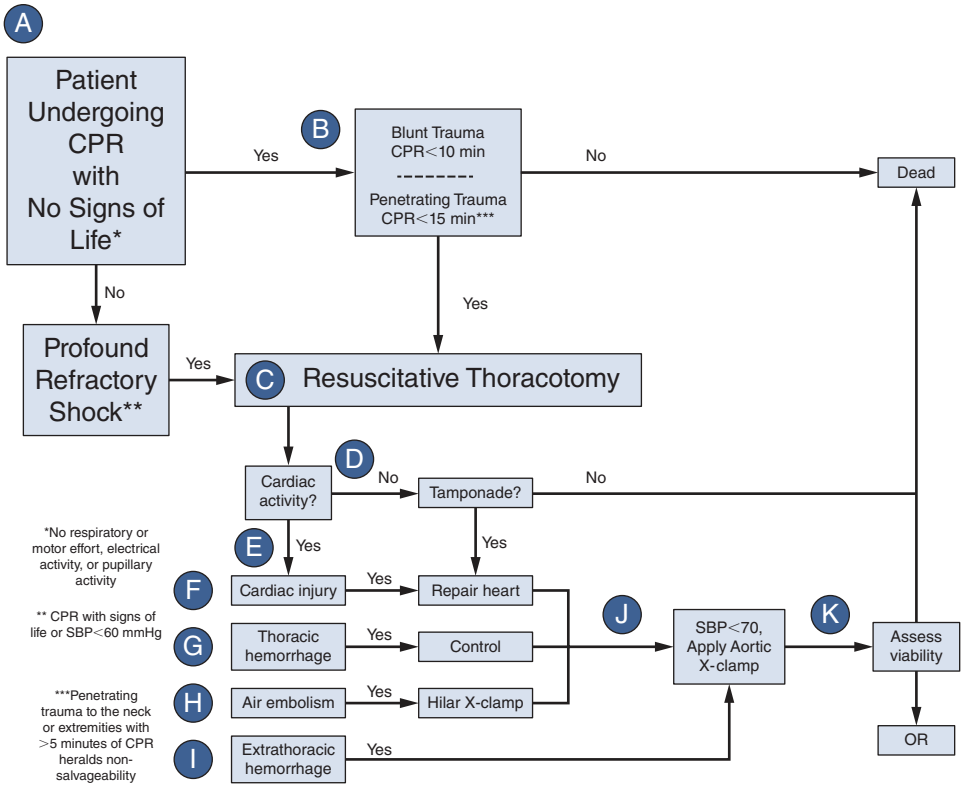

Fig. 156.1 Algorithm for resuscitative thoracotomy. *CPR*, Cardiopulmonary resuscitation; *OR*, operating room; *SBP*, systolic blood pressure. (From Burlew CC, Moore EE, Moore FA, et al. Western Trauma Association critical decisions in trauma: Tesuscitative thoracotomy. *J Trauma Acute Care Surg.* 2012;73[6]:1359–1363.)

PTX is imperative. If a patient arrives in extremis and has evidence of chest trauma (e.g., penetrating wound, subcutaneous crepitance, tenderness consistent with rib fractures), empiric tube thoracostomy for presumed hemopneumothorax is recommended.

An open PTX (aka "sucking chest wound") results from a full-thickness chest wall wound. If the wound diameter exceeds two-thirds of the tracheal diameter, negative intrapleural pressure associated with inspiratory effort results in air entering the pleural space preferentially through the wound. Because of the large hole, there is little chance of tension. However, this can be life-threatening because it prevents pulmonary gas exchange. It is managed by an occlusive dressing secured on three sides to prevent sucking of more air but allowing decompression of the PTX until definitive wound closure, and tube thoracostomy should be performed.

With the growing use of thoracic computed tomography (CT), small PTXs are often discovered that are not seen on CXR. These "occult PTXs" generally do not require treatment but should be monitored for progression. A prospective multicenter study of the American Association for the Surgery of Trauma (AAST) found that only 6% of patients with occult PTX ultimately required a chest tube. Moreover, consistent with earlier studies, fewer than 20% receiving positive-pressure ventilation required chest tubes, and none of them had tension.[9] Another recent study of small traumatic PTXs from both blunt and penetrating injuries found that a distance of ≤35 mm between the visceral and parietal pleura was a safe cutoff for observation.[10]

Tube Thoracostomy

Tube thoracostomy is the definitive treatment for PTX and hemothorax. The procedure is not difficult and can be performed rapidly, but care must be taken to avoid malpositioning. The optimal position is posterior to facilitate dependent drainage of blood and is directed to the apex of the pleural cavity. The current trend is to place smaller-diameter tubes (28–32F), as they cause less discomfort for the patient and are adequate to drain most nonclotted hemothoraces.[11]

In the setting of tension PTX, if tube thoracostomy is not immediately available, the chest can be quickly decompressed with finger thoracostomy or needle decompression. Although many authors previously promoted needle thoracostomy via the second intercostal space in the midclavicular line, it has been recognized repeatedly that catheters may be kinked in the pectoralis major muscle or breast tissue, rendering them ineffective—often unbeknownst to the clinician. Recent literature has documented that the chest wall is, on average, 10–12 mm thinner in the anterior axillary line at the fifth intercostal space. This site allows rapid, reliable, safe entry into the pleural space and is currently promoted by ATLS.[12]

A recent meta-analysis of 12 randomized trials concluded that prophylactic administration of antibiotics was associated with significantly less risk of empyema and pneumonia. We thus recommend preprocedural administration of a first-generation cephalosporin with duration no longer than 24 hours.[13]

Pneumothoraces and air leaks should be resolved before removal of the tube, and ideally, drainage should be less than 2–3 mL/kg/day. After 12–24 hours without an air leak, the tube may be removed while on suction. However, a 6- to 12-hour trial of water seal drainage is generally warranted to observe for an occult air leak.[14] It has been recommended that tubes be removed at maximal deep inspiration with a Valsalva maneuver, but recurrent PTX may occur in 6%–8% of patients regardless of respiratory phase. More than 20% of patients require longer than 3 days to resolve an air leak, in which case their hospital course may be expedited by the use of thoracoscopy.[15]

Hemothorax

Blunting of the costophrenic angle on upright CXR requires 200–250 mL of blood, and in a supine patient, there may be only subtle haziness of the affected hemithorax. Whereas small, asymptomatic hemothoraces may be managed expectantly, it is currently recommended that hemothoraces greater than 300 mL be drained by tube thoracostomy.[16] A massive hemothorax is usually the result of a major vascular injury and is life-threatening. Indications for thoracotomy include the immediate return of 1500 mL of blood via tube thoracostomy or continued output of more than 200 mL/h for 2–3 consecutive hours. The clinician should be wary of an initial high-volume chest tube output (>10 mL/kg) that is followed by an abrupt decrease in volume. If there is clinical suspicion of ongoing bleeding, a repeat CXR should be obtained to rule out a retained hemothorax. This can occur because of a malpositioned, kinked, or clotted chest tube and should prompt a second chest tube. If the hemothorax remains significant, thoracoscopy or thoracotomy is indicated.[17] Occasionally, in penetrating trauma there will be a "caked hemothorax" where the original chest tube is well positioned, but there is ongoing arterial bleeding that is too rapid to be evacuated. The result is retained "tension" hemothorax with a mediastinal shift and mandates immediate thoracotomy. Additionally, hemothoraces associated with massive blunt chest wall trauma can pose special challenges. Ongoing bleeding suggests the need for thoracotomy, but a large incision may compound the bleeding, and diffuse bleeding from bone and soft tissue disruption may prove difficult to control. In this setting, angioembolization of the intercostal vessels can be considered in the hemodynamically stable patient.

Rib Fractures

Rib fractures are present in 10% of trauma patients admitted to the hospital. Elderly patients are especially susceptible to diminished pulmonary function and complications. Patients over the age of 65 have twofold to fivefold increases in morbidity and mortality compared with younger patients with similar injuries.[18] In addition, it is important to identify patients who are at risk for respiratory decompensation and admit them to units with closer monitoring. Fig. 156.2 shows our institutional algorithm for initial triage and management of rib fracture patients.

Another key factor in the management of these patients is protocolized multimodal pain management. This allows facilitation of pulmonary physiotherapy to avoid atelectasis and improve clearance of secretions. Epidural catheters have proved to be efficacious and superior to patient-controlled analgesia in this regard and may also modify the immune response.[18] Often the polytrauma patient has contraindications to epidural catheters, such as spinal fractures and coagulopathy.[19] In these patients, intercostal nerve/rib blocks may provide immediate relief in the ED or intensive care unit (ICU) while awaiting further therapy. Alternatively, paravertebral catheter infusion of bupivacaine can provide significant relief of rib fracture pain and may be equivalent to epidural catheters in terms of efficacy. These catheters can also be used in patients who have contraindications to epidural catheters.[20,21]

Although pain and morbidity from rib fractures are often emphasized for hospitalized patients, there is a growing body of literature detailing the presence of prolonged pain and physical incapacity 2–12 months after hospital discharge.[22,23] Recently, the technique of

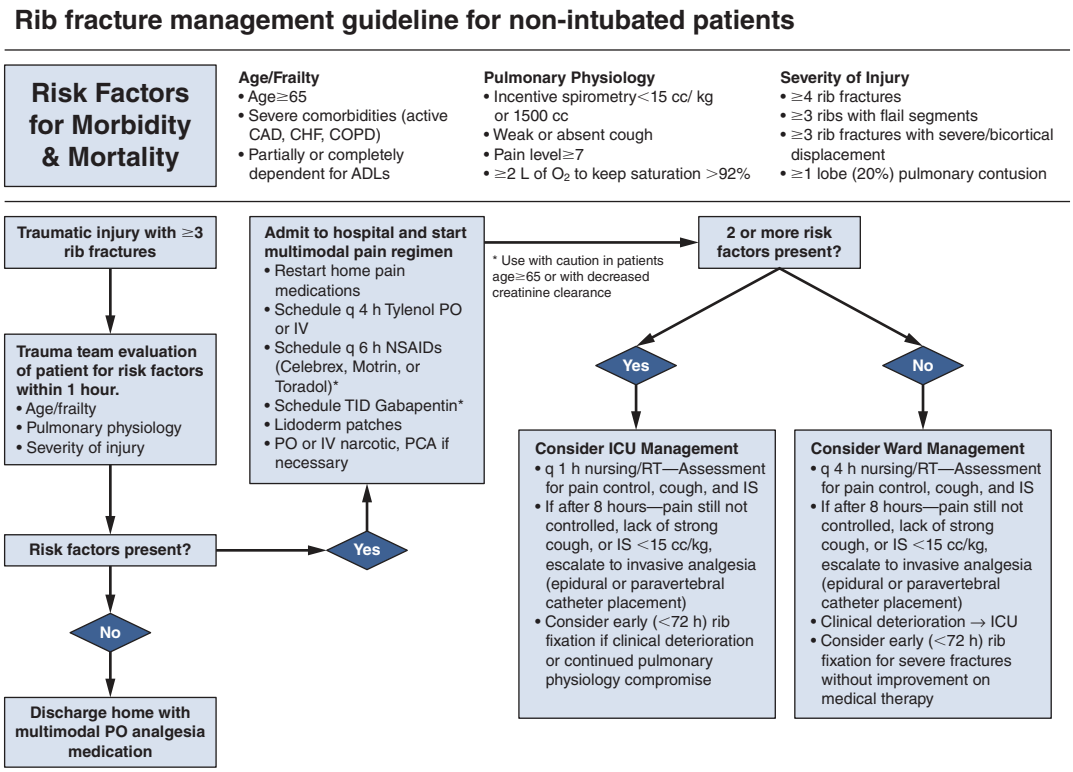

Fig. 156.2 Institutional rib fracture triage and management guideline. (Data from Witt CE, Bulger EM. Comprehensive approach to the management of the patient with multiple rib fractures: A review and introduction of a bundled rib fracture management protocol. *Trauma Surg Acute Care Open*. 2017;2[1]:e000064; and Brasel KJ, Moore EE, Albrecht RA, et al. Western Trauma Association Critical Decisions in Trauma: Management of rib fractures. *J Trauma Acute Care Surg*. 2017;82[1]:200–203.)

intercostal nerve cryoablation has become a topic of interest for pain management secondary to severe rib fractures, given its ability to provide longer-lasting (8–12 weeks) analgesia. The technique causes axonotmesis but leaves the perineural structures intact. In this manner the nerve regenerates and provides reinnervation over time in anatomic fashion. Preliminary studies in trauma patients have shown a significant decrease in postoperative numerical pain levels.[24] In addition, pediatric surgeons performing chest wall reconstruction have been able to show decreases in opioid use, pain levels, and hospital length of stay using this technique.[25]

Flail Chest

Three or more ribs fractured in two or more places produce a flail segment of the chest wall. In the nonventilated patient, this segment may move paradoxically—inward during inspiration, outward during expiration—and consequently impair ventilation. Additionally, flail chest is often accompanied by pulmonary contusion, which compounds the degree of pathophysiology, as contused lung tissue cannot function in oxygenation. Treatment for pulmonary contusions is supportive, including supplemental oxygen, analgesia, and pulmonary toilet. See further details in this chapter.

Surgical Stabilization of Rib Fractures

Although surgical stabilization of rib fractures (SSRF) has been undertaken since the early 20th century, the wider adoption of the technique has only occurred in the past 20 years. As technology has improved with chest wall–specific tools and systems, muscle sparing and minimally invasive techniques have replaced older thoracotomy incisions and associated morbidities. Although not definitive, the physiologic and functional benefits of SSRF have gained more acceptance in the past 10 years. A systematic review was performed by the Eastern Association for the Surgery of Trauma (EAST) showing decreased ICU length of stay, time on ventilator, pneumonia rates, tracheostomy rates, and mortality for patients with flail chest.[26] For patients who have severely displaced rib fractures without flail chest, a recent multicenter prospective randomized trial of the Chest Wall Injury Society (CWIS) demonstrated decreased numeric pain scores, pleural space complications, and narcotic consumption and improved quality of life.[27] Overall indications for SSRF have been codified in recent CWIS consensus guidelines[28] and can be summarized as a patient with either flail chest or severely displaced rib fractures, especially one who is concurrently experiencing physiologic deficits.

Sternal Fracture

An early series of sternal fractures described the "steering wheel syndrome" (rapid deceleration, with impact of the sternum on the steering wheel) as the most common cause of sternal fractures. Associated blunt cardiac injury was common, so sternal fractures were thought to be harbingers of significant thoracic injury. More recently, however, sternal fractures have been reported more commonly with the "seat belt syndrome" (in conjunction with three-point or bandolier seat belts). Associated injuries are less frequent, so stable patients without electrocardiogram (ECG) abnormalities can be safely discharged from the ED. For hospitalized patients with severely displaced sternal fractures, surgical fixation can be a consideration; however, the body of scientific literature remains weak and requires more robust studies in the future.[29]

BLUNT LUNG INJURY

The spectrum of lung parenchymal injury after blunt chest trauma ranges from simple contusions to frank lacerations. Pulmonary contusion is by far the most common and is merely a bruise of the lung. The pathophysiologic changes fundamentally include alveolar hemorrhage with surrounding edema, with a broad range of severity. The clinical result is hypoxia and increased work of breathing because of ventilation/perfusion mismatching and decreased pulmonary compliance. Pulmonary contusions may not appear on initial chest radiographs, although they are usually seen by 6 hours after the injury; chest CT is more sensitive at diagnosing early pulmonary contusions. Treatment is supportive, including supplemental oxygen, pain control, pulmonary toilet, and judicious fluid management. There is no role for either routine antibiotics or steroid therapy.[30] Intubation and mechanical ventilation are employed only as necessary. The degree of pulmonary dysfunction can peak at 72 hours and generally resolves in the absence of associated nosocomial pneumonia.

Posttraumatic pulmonary pseudocysts (PPPs) are cavitary lesions that occur in approximately 3% of lung parenchymal injuries after blunt trauma.[31] They are seen more often in children as an incident CXR finding after relatively minor trauma (e.g., fall from bicycle) and are more likely to occur because of their more compliant chest walls. The clinical course is benign (with occasional minimal hemoptysis and fever). In adults, however, PPPs occur after more severe blunt mechanisms, appear as a dense pulmonary contusion on CXR, and most resolve spontaneously as a nonspecific infiltrate. However, occasionally, they will become infected, leading to an abscess that will be resistant to antibiotic therapy and require interventional radiologic drainage or surgical resection.[32] In patients with previous severe chest trauma who develop delayed nonresolving sepsis, a CT scan of the chest should be obtained to rule out an infected PPP. A blunt pulmonary laceration is rare and typically presents as a major hemopneumothorax. The initial tube thoracostomy reveals severe bleeding with a significant air leak, and this often requires an emergency thoracotomy.

PENETRATING LUNG INJURY

After penetrating trauma, a laceration likewise presents as a hemopneumothorax but with less severe bleeding that is usually self-limited. The vast majority are definitively managed by tube thoracostomy alone. Of the 10% of patients requiring thoracotomy, approximately 20% need lung resection. Historically, anatomic resection patients experienced high morbidity and mortality, with mortality after pneumonectomy approaching 100%. In 1998, Wall and colleagues introduced the concept of pulmonary tractotomy as a nonresectional means of managing penetrating lung injuries.[33] It is indicated for deep through-and-through injuries that do not involve central hilar vessels or airways. The wound tract is exposed by passing clamps (as originally described) or a stapling device (our preference) through the wound and dividing the bridge of lung tissue. Air leaks and bleeding points are sutured, and the wound tract is left open. Morbidity and mortality compare favorably with anatomic resections.[34]

In patients with multiple anatomic sites with active hemorrhage, including the thorax, the concept of damage control thoracotomy (DCT) has been described.[35] Although this pertains to the minority of patients requiring thoracotomies (4%), the idea of lung clamping, tractotomy, and/or thoracic packing with temporary skin closure followed by a second-look thoracotomy is a reasonable course of treatment rather than immediate pulmonary resection.

MEDIASTINAL INJURIES

Pneumomediastinum

Pneumomediastinum has classically been considered a sign of aerodigestive injury, particularly when seen on CXR; however, with expanding use of chest CT, pneumomediastinum is seen with increasing

frequency. Recent analyses have found that pneumomediastinum is present on approximately 5% of chest CT scans after trauma but that only 10% of these patients actually have aerodigestive injuries.[36,37] In the absence of signs or symptoms or additional suspicious findings on CT scan, further investigation is not necessary.

TRACHEOBRONCHIAL INJURY

Tracheobronchial injuries are uncommon but should be excluded in the presence of cervical subcutaneous emphysema, pneumomediastinum, or PTX with a persistent air leak. The definitive diagnostic test is bronchoscopy. Cervical injuries are approached via cervical incisions, with partial or complete sternotomy as needed. Blunt injuries often occur in the distal trachea or right mainstem bronchus and are approached via right thoracotomy. Tracheal injuries can usually be repaired primarily or by resection and reanastomosis without tracheostomy; late stenosis is uncommon. On the other hand, laryngotracheal injuries often require tracheostomy as an adjunct to repair, and tracheal stenosis is a common late complication. Absorbable monofilament sutures are preferred. Bronchial injuries may be repaired, but severe disruptions or associated vascular injuries may necessitate pneumonectomy or lobectomy. Positive end-expiratory pressure is avoided postoperatively.[38]

ESOPHAGEAL INJURY

Esophageal perforation from blunt force trauma is a rare event caused by a sudden rise in intraluminal pressure or by the upper esophagus being crushed between the trachea and a vertebral body. More commonly, esophageal injury is the result of penetrating trauma. Early signs and symptoms of injury can be subtle. Pneumomediastinum should prompt consideration of this injury. Barium esophagography is considered the diagnostic study of choice and can be readily obtained in a stable, awake patient. However, video endoscopy can be done at the bedside virtually anywhere in the hospital and has excellent accuracy. Thus it is preferred in critically ill or unstable patients in the ICU or operating room.[39]

If the injury is identified within 24 hours, it can usually be treated with debridement, primary repair, and drainage. If a tension-free repair is not possible, it is best managed with débridement and drainage, cervical esophagostomy, and feeding tube placement.[39]

CARDIAC INJURY

Blunt Cardiac Injury

Blunt cardiac injury (BCI) represents a wide spectrum of cardiac injuries, ranging from occult and inconsequential to lethal dysrhythmias, pump failure, or cardiac rupture. It can occur after virtually any trauma to the chest.

The diagnostic criteria for BCI are not standardized; no test is 100% predictive of the uncommon but life-threatening complications of ventricular dysrhythmias and cardiac pump failure—the so-called "*significant BCI*." The pivotal issue is to identify patients at risk and have them in a setting where the complication can be identified and treated promptly.

The initial evaluation for BCI screening should include 12-lead ECG. The utility of routine cardiac enzyme testing has been an area of debate.[36] Although a 2012 EAST practice management guideline[40] made a level 3 recommendation for routine troponin as a screening test, troponin levels have not been demonstrated to independently predict significant BCI. Their primary value is in identifying a patient with potential BCI who has a normal ECG, prompting a period of monitoring. We do not recommend serial troponin testing or routine echocardiography in the patient with suspected BCI. Patients with shock, ischemic changes on the ECG, or significant dysrhythmias are admitted to the ICU. If angina or ischemic ECG changes are noted, the diagnosis of acute coronary syndrome should be pursued. Patients with significant blunt chest trauma and nonspecific ECG findings (e.g., sinus tachycardia) who are being admitted for associated injuries should have cardiac monitoring for 24 hours.[41] A subset of patients may not require admission for other injuries. These patients can be safely discharged from the ED if ECG normalizes and if a troponin-I level at 8 hours is less than 1.5 ng/mL.[42]

Dysrhythmias are treated by pharmacologic suppression. The management of cardiogenic shock from cardiac pump failure may include early placement of a pulmonary artery catheter to optimize fluid administration and inotropic support. An echocardiogram may be indicated to exclude septal or free wall rupture, valvular disruption, or pericardial tamponade. Patients with refractory cardiogenic shock may require placement of an intraaortic balloon pump to decrease myocardial work and enhance coronary perfusion.

Commotio cordis is a rare but well-described cause of sudden cardiac death in young patients with sudden traumatic impact to the chest. This impact profoundly alters the electrical stability of the myocardium, resulting in ventricular fibrillation.[43] In a series of 70 cases, Maron and colleagues reported a 90% mortality rate in a young (mean age 12 years) population of patients.[44] An experimental model demonstrated that ventricular fibrillation is reproducibly triggered by a precisely timed blow during a narrow window within the repolarization phase of the cardiac cycle (15–30 ms before the peak of the T wave). The management of this pathology is primarily prevention, centered around adequate protective equipment and prompt defibrillation using readily available automated external defibrillators (AEDs).[43]

Pericardial Injury

Pericardial tears may result from direct thoracic impact or from an acute increase in intraabdominal pressure. Herniation of the heart through a large tear may be associated with significant cardiac dysfunction. A pericardial rub may be detected on physical examination. The CXR may demonstrate pneumopericardium, displacement of the heart, or bowel gas in the chest. Echocardiography or CT may be required to confirm the injury. In a stable patient, a subxiphoid pericardial window should be performed, followed by sternotomy in the presence of large hemopericardium or a visible pericardial tear. An unstable patient may require RT. Pericardial lacerations should be repaired, but large holes that cannot be closed primarily should be left widely open to prevent future cardiac herniation. A late complication is the post-pericardiotomy syndrome, manifested by fever, chest pain, pericardial effusion, a pericardial rub, and ECG abnormalities; this is adequately treated with antiinflammatory agents.

Valvular Injury

Valve injuries are rare. Even in lethal cardiac trauma, the valves are injured in approximately 5% of patients. The most commonly injured valve is the aortic, followed by the mitral, tricuspid, and pulmonary. Aortic valve disruption may result in acute severe cardiac failure, but a mild injury may present with syncope or anginal symptoms. Mitral valve leaflet tears, or more commonly, rupture of papillary muscles or chordae tendineae, may also result in acute heart failure. A heart murmur will generally be present, and echocardiography and/or cardiac catheterization are used to confirm the diagnosis. Most valve injuries are amenable to supportive care until other injuries have been stabilized. Valve repair is generally preferred over valve replacement when feasible.[45]

Septal Injury

Septal injuries are found in 5%–7% of patients dying from blunt trauma. Ventricular septal ruptures are much more common than atrial septal injuries; they usually occur in the muscular portion near the apex. Characteristic physical findings include a systolic thrill and a harsh holosystolic murmur heard best at the left sternal edge and radiating to the right, but the symptoms may be delayed for hours or days as the defect enlarges. Atrioventricular conduction abnormalities may also be present, simulating myocardial ischemia, and severe hypoxemia may result from an acute left-to-right shunt. Prompt echocardiography is indicated to establish the diagnosis; cardiac catheterization may be needed.

Small septal defects may heal primarily, allowing expectant management with periodic follow-up. Surgical repair—either primary or with a patch graft—is indicated if the patient is hemodynamically compromised or has a left-to-right shunt with a shunt ratio of 2:1 or greater. Repair of the defect is delayed for several weeks if possible.[46]

Coronary Artery Injury

Direct injuries to coronary arteries are rare. The left anterior descending artery is the most susceptible (76% of cases), followed by the right coronary artery (12%) and the circumflex coronary artery (6%). Surgical revascularization or repair of delayed complications related to infarction, such as ventricular pseudoaneurysms, may be indicated.

Penetrating Cardiac Injury

Cardiac penetration is rapidly lethal in 90% of gunshot wounds and up to 50% of stab wounds. All patients in shock with penetrating chest injuries between the right midclavicular line and left anterior axillary line, in addition to the posterior left chest, should be considered to have a cardiac injury until proven otherwise.[47] The right ventricle, with its maximal anterior exposure, is at greatest risk, followed by the left ventricle, right atrium, and left atrium. Multiple cardiac structures are involved in a third of patients. Stab wounds are more commonly associated with tamponade, whereas gunshot wounds often result in exsanguination through a large pericardial defect.

Repair of cardiac injuries can be accomplished through either a median sternotomy or anterolateral thoracotomy incision. In a hemodynamically compromised patient, left anterior thoracotomy with transsternal extension is used for definitive repair. In a hemodynamically stable patient, sternotomy is generally preferred. A limitation of sternotomy is access to posterior mediastinal injuries. Satinsky clamps are useful in isolating atrial or caval injuries, whereas small ventricular lacerations are controlled digitally. Larger wounds may be stapled. Wounds that are very large are occasionally reparable using temporary caval inflow occlusion.[48]

Pericardial Tamponade

Potential pericardial tamponade should be suspected in all patients sustaining penetrating injuries to the anterior chest wall. Pericardial tamponade can be a two-edged sword: although it may limit initial blood loss, it can prove fatal by restricting diastolic filling of the heart.[49] Because the pericardium is not acutely distensible, as blood accumulates, the pressure in the pericardial sac rises to match that of the injured chamber. When the pressure approaches that of the right atrium, right atrial filling is impaired and right ventricular preload is reduced; ultimately, this leads to decreased right ventricular output. Increased intrapericardial pressure also impedes myocardial blood flow, which leads to subendocardial and later subepicardial ischemia, with a further reduction of cardiac output. This vicious cycle may progress insidiously with injury to low-pressure conduits, or it may occur precipitously with a ventricular wound. Acute tamponade of as little as 100 mL of blood within the pericardial sac can produce life-threatening hemodynamic compromise.

Early diagnosis is key, as the ultimate cardiovascular collapse can be abrupt. Compensatory responses, including tachycardia and vasoconstriction, can transiently stabilize the hemodynamic status of the patient. Similarly, vigorous fluid administration may improve the patient's vital signs. The classic findings of the Beck triad (hypotension, distended neck veins, and muffled heart sounds) are present in less than 10% of patients; furthermore, Kussmaul sign (neck vein swelling with inspiration) and pulsus paradoxus (SBP drop with inspiration) are not reliable indicators of acute tamponade. In fact, neck veins may not become distended until hypovolemia is corrected.

In the setting of suspected pericardial tamponade, ultrasonography using subxiphoid and parasternal views (or formal echocardiography if immediately available) is extremely helpful if the findings are positive, although a negative ultrasonographic examination may be misleading if there is a pericardial laceration.[50] If pericardial fluid is demonstrated, the patient should be transported immediately to the OR for exploration. However, if ultrasonography is equivocal, a central venous pressure line should be inserted promptly. Persistently elevated central venous pressure in a patient with thoracic trauma should prompt consideration of a subxiphoid pericardial window. If the pericardial ultrasonography is positive and there will be any delay in getting to the OR, pericardiocentesis should be done if there is any suggestion of cardiac compromise, because subclinical endocardial ischemia can lead to recalcitrant lethal dysrhythmias. The pericardial tap should be performed with a pigtail catheter to allow repeated aspiration during preparation for thoracotomy. In the setting of shock, evacuation of as little as 15 mL of blood may dramatically improve the patient's hemodynamic profile. Pericardiocentesis is successful in decompressing tamponade in approximately 80% of cases; most failures are caused by clotted blood within the pericardium. If pericardiocentesis is unsuccessful and the patient remains severely hypotensive (SBP $<$70 mm Hg), RT should be performed. Recently, several studies have questioned the mandate for a sternotomy in patients who are hemodynamically stable. If, after irrigating the pericardium, there is no reaccumulation of blood and the patient remains stable, it appears reasonable and safe to forego the sternotomy. A drain should be placed, and the patient should have intensive postoperative monitoring. One potential pitfall is the presence of a posterior pericardial wound, so accumulation of blood in the plural space should be assessed. The pericardial drain is removed once output is minimal and clear.[51,52]

TRANSMEDIASTINAL PENETRATING TRAUMA

Transmediastinal trajectory of a bullet should be considered in the setting of (1) entry and exit wounds on opposite sides of the thorax, (2) a single entry wound with the bullet ending up on the opposite side of the thoracic cavity or in close proximity to the mediastinum, or (3) multiple gunshot wounds to the thorax. Significant injury, especially to the heart or great vessels, often results in prehospital death or hemodynamic instability. There is little controversy regarding the management of unstable patients: they should have emergent thoracotomy. However, stable patients may harbor occult injuries to critical mediastinal structures (heart, great vessels, trachea, or esophagus). Helical CT angiography (CTA) of the chest has proved useful in demonstrating the trajectory of missiles in the thorax.[53] In the setting of a potential transmediastinal gunshot wound, a CT scan may confirm a trajectory remote from the mediastinum, obviating further testing. A proven transmediastinal trajectory mandates further evaluation, tailored to the specific structures at risk. Our current approach to evaluating these patients is outlined in Fig. 156.3.

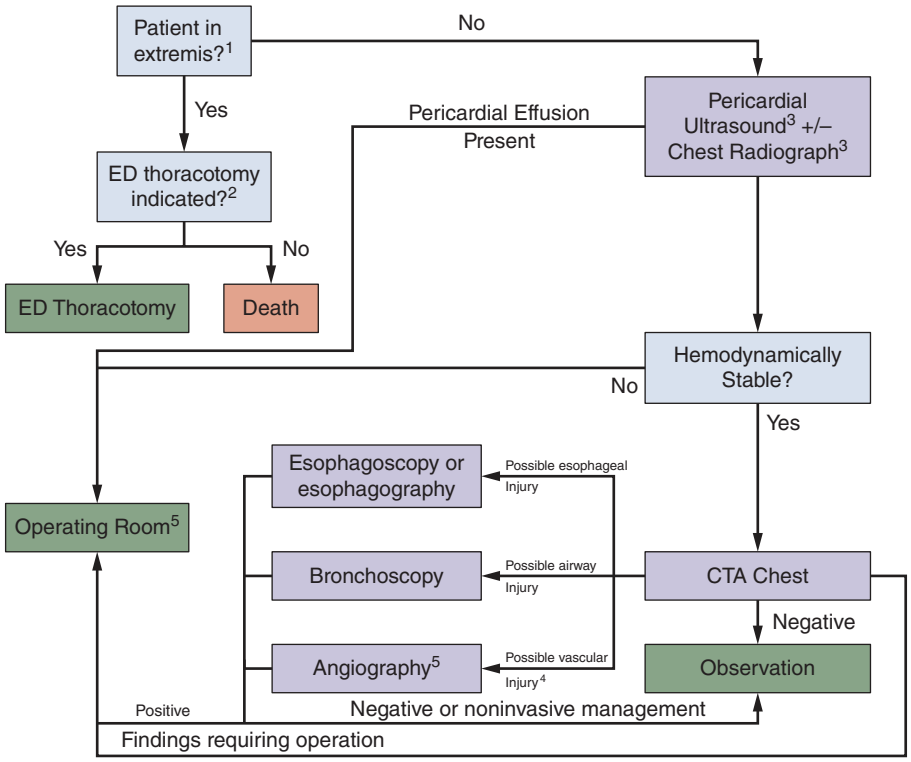

Fig. 156.3 Evaluation of suspected transmediastinal gunshot wounds (TMGSWs).[54] Transmediastinal injuries should be suspected in the presence of entry and exit wounds on opposite sides of the thorax, a single entry wound with the bullet located in the contralateral hemithorax or adjacent to the mediastinum, or multiple gunshot wounds to the thorax. *CTA*, Computed tomography angiography; *ED*, emergency department. (From Gunn ML, Clark RT, Sadro CT, et al. Current concepts in imaging evaluation of penetrating transmediastinal injury. *Radiographics*. 2014;34[7]:1824–1841.)

THORACIC GREAT VESSEL INJURY

Patients with penetrating injuries to extrapericardial thoracic great vessels often succumb in the field; however, patients can arrive with a contained hematoma. Early CXR is critical to identify hemothorax, in addition to a widened mediastinum or apical capping. Patients who are hemodynamically unstable should be taken directly to the OR; those in extremis should undergo RT. A reasonable approach can be inferred from the CXR and the location of the wounds. If the patient has a left hemothorax, a left anterolateral thoracotomy in the third or fourth intercostal space should be performed. Patients with a right hemothorax should likewise be approached via a right anterolateral thoracotomy. Unstable patients with injuries near the sternal notch may have large mediastinal hematomas or may have lost blood externally. These patients should be explored via a median sternotomy with cervical extension. Hemorrhage should be controlled digitally until the vascular injury is delineated. In a hemodynamically stable patient, CTA can facilitate a more directed approach. In the setting of pericla-vicular trajectory, it must be remembered that collateral flow around the shoulder girdle can result in palpable pulses, even in the presence of a significant subclavian artery injury.

A median sternotomy, with appropriate extension, is used for exposure of the aortic arch branch vessels. In patients who have undergone RT, the left anterolateral thoracotomy incision may have to be extended to a bilateral anterolateral thoracotomy ("clamshell"). In exposing the proximal left subclavian artery, it may be necessary to create a full-thickness flap of the upper chest wall. This is accomplished with a partial sternotomy and supraclavicular extension. If necessary, the ribs can be transected laterally, allowing the flap to be folded laterally, but this is rarely required. This incision has been referred to as an *open-book* or *trapdoor thoracotomy*. The midportion of the subclavian artery is accessible via a supraclavicular skin incision.

The great vessels are rather fragile and can be easily torn during dissection or crushed with a clamp. For this reason, injuries adjacent to the aortic arch are oversewn, and a graft is inserted onto a new location on the arch. The graft is then sewn (without tension) to the distal artery. Nonoperative management of nonocclusive peripheral arterial injuries has proved successful, and there are limited data supporting similar management within the thorax for certain patients. Similarly, lesions associated with severe neurologic injuries are usually managed nonoperatively. Experience with endovascular stenting is growing, although long-term outcomes have not been reported.[55] Clearly unstable patients require operative control and repair; however, it appears that stent graft treatment of subclavian artery injuries is preferred in stable patients and results in fewer morbidities.[56]

BLUNT THORACIC AORTIC INJURY

Blunt thoracic aortic injury (BTAI) typically results from sudden deceleration and shearing force resulting in varying degrees of aortic disruption. The injury usually occurs just distal to the left subclavian artery where the aorta is tethered by the ligamentum arteriosum. In 5% of cases, the tear occurs in the ascending aorta, in the transverse arch, or at the diaphragm. An estimated 85% of thoracic aortic injuries are fatal at the injury scene.

CXR is considered the initial screening tool of choice for determining whether further investigation is needed for BTAI. Commonly associated radiographic findings include mediastinal widening, obscured

aortic knob, deviation of the left mainstem bronchus (downward) or nasogastric tube (rightward), and opacification of the aortopulmonary window. In a AAST multicenter study, widening of the mediastinum on the anteroposterior chest radiograph was present in 85% of cases. However, 7% of patients with aortic tears had normal chest radiographs.[57] Thus additional investigations are warranted in the setting of significant energy transfer. CTA of the chest has supplanted thoracic angiography as the primary diagnostic test. When hematoma adjacent to the thoracic aorta is considered a positive finding, the sensitivity of CT for aortic injury is 100%.

Over the past decade, the surgical treatment and medical management of BTAIs have become more uniform and clearer. The Society of Vascular Surgery has classified BTAIs into four grades in increasing severity: I, minimal intimal injury; II, intramural hematoma; III, pseudoaneurysm; and IV, aortic rupture.[58] A suggested treatment algorithm based on grade is shown in Fig. 156.4. For grade I and II injuries, the mainstay of therapy is blood pressure control (<120 mm Hg), heart rate control (<90 bpm), antiplatelet therapy, and follow-up surveillance imaging to assess for either resolution or progression. Grade IV injuries should undergo surgical repair, with endovascular technique preferred over traditional open thoracotomy. Grade III injuries represent a gray area that could be managed based on the risk of rupture. Smaller pseudoaneurysms in patients who are high-risk surgical candidates may be managed medically, whereas larger pseudoaneurysms with increased risk for rupture should undergo endovascular repair. In addition, patients who are contraindicated for blood pressure control (i.e., traumatic brain injuries with intracranial hypertension) should undergo surgical repair.[59] Despite the lack of level 1 evidence, the choice of endovascular repair over open repair is now well accepted. Systematic reviews of 37 comparative studies favor endovascular repair with lower mortality (8% vs. 19%) and paraplegia rates (0.5% vs. 3%). The endovascular group did have a higher stroke rate (2.5% vs. 1%).[60]

Some debate remains regarding immediate versus delayed repair of BTAIs. Until the 1990s, BTAI was thought to require urgent repair to avoid early rupture. Recognizing significant morbidity and mortality in patients with severe associated injuries and comorbid medical conditions, the concept of immediate repair was challenged. In fact, an AAST prospective multicenter trial found that delayed repair is associated with significant survival benefit.[61] Although patients with major associated injuries are most likely to benefit, the study supported delayed repair in all patients, irrespective of risk factors. A current practice guideline by the EAST recommends delayed repair to reduce mortality and paraplegia.[60]

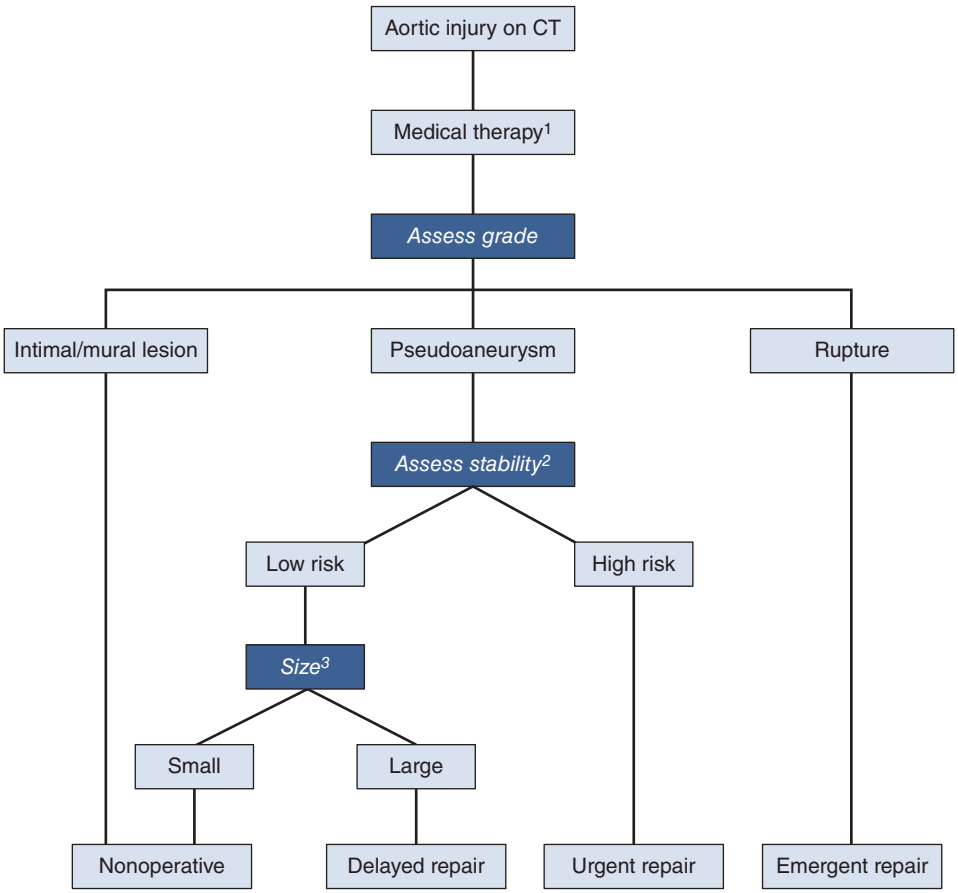

Fig. 156.4 Lesion-Specific Management for Blunt Thoracic Aortic Injury. [1]Antiplatelet therapy and beta-blockade targeting a systolic blood pressure of 100–120 mm Hg and heart rate of 60–90 bpm with additional antihypertensive agents as required for blood pressure control; repeated computed tomography (*CT*) within 48–72 hours for patients managed nonoperatively or by delayed repair to assess stability. [2]High-risk factors include two or more of the following: signs of hypotension, large pseudoaneurysm, and extensive mediastinal hematoma (refer to Table II). [3]Small defined as <50% aortic circumference or <1 cm in maximal dimension.[58] (From Harris DG, Rabin J, Starnes BW, et al. Evolution of lesion-specific management of blunt thoracic aortic injury. *J Vasc Surg.* 2016;64[2]:500–505.)

KEY POINTS

- Resuscitative thoracotomy will not yield productive survival when patients (1) sustain blunt trauma and require more than 10 minutes of prehospital CPR without response, (2) have penetrating wounds and undergo more than 15 minutes of prehospital CPR without response, or (3) manifest asystole without pericardial tamponade.
- Management of rib fractures include early triage based on risk factors for respiratory decompensation. Higher-risk patients should be initially observed in the ICU setting.
- Surgical stabilization of rib fractures can reduce patient morbidity and mortality and should be considered in patients with flail chest and severely displaced rib fractures with physiologic deficits.
- In patients with a penetrating pulmonary laceration, pulmonary tractotomy results in favorable morbidity and mortality rates compared with lung resection for trauma. Damage control thoracotomy can be considered in patients with multicompartmental hemorrhage.
- Bronchoscopy should be performed for cervical subcutaneous emphysema, pneumomediastinum, or pneumothorax with a persistent air leak to rule out tracheobronchial injuries. For esophageal injuries, contrast esophagography is the preferred diagnostic study, but video endoscopy can also be performed at the bedside in intubated patients and is superior in the pharyngeal area.
- Echocardiography is most useful in identifying pericardial tamponade or intracardiac injuries. Ultrasonography and central venous pressure monitoring are critical adjuncts in diagnosing pericardial tamponade, as the classic findings of Beck triad are present in very few patients.
- Helical CT scanning is useful in delineating the trajectory of potential transmediastinal gunshot wounds, allowing a truncated and cost-effective workup in stable, asymptomatic patients.
- In blunt thoracic aortic injury, helical CT is an excellent screening test and should be considered even in the face of a normal chest radiograph if there is severe energy transfer.
- Medical versus surgical treatment of BTAI is based on grade of severity. Medical management consists of SBP and heart rate control with a rapidly reversible beta-blocking agent. Surgical treatment should be performed endovascularly in a delayed fashion for optimum results.

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Abdominal Trauma

Nicole C. Toscano and Andrew B. Peitzman

INTRODUCTION

Trauma is the leading cause of death in patients between 1 and 44 years of age.[1] The trauma patient requires rapid and systematic evaluation by a multidisciplinary team using principles defined by Advanced Trauma Life Support (ATLS).[2] These principles allow the effective transition of care from the prehospital to hospital environment. External signs of abdominal injury can be absent; effective diagnosis relies heavily on recognizing patterns of injury and maintaining a high suspicion of injury to minimize the risk of morbidity and mortality. This chapter focuses on the evaluation, diagnosis, management, and complications associated with abdominal injuries. Patients with abdominal injury will be admitted to the intensive care unit (ICU) for management of concomitant brain or spine injury, chest wall injury/pulmonary contusion, extremes of age, and nonoperative management of high-grade solid organ injury or after damage-control laparotomy.

ETIOLOGY OF INJURY

Abdominal trauma can be broadly categorized into blunt force or penetrating mechanism of injury. Each mechanism produces different injury patterns. A thorough understanding and early recognition of these patterns aid in rapid diagnosis and treatment, minimizing risk of morbidity and mortality from abdominal injury. It is important to understand that the early critical decision in management is recognizing that the trauma patient requires emergent laparotomy. Time spent on diagnostic evaluation, most often computed tomography (CT), or failure to recognize signs of abdominal injury delays definitive treatment, increasing morbidity and mortality. The priority is to detect and correct abnormal physiology, not to define the specific anatomic injuries.

Blunt Abdominal Injury

Blunt abdominal trauma accounts for 80% of abdominal injuries. These injuries result from an external force that causes direct compression, shearing, rapid change in intraluminal pressure, or deceleration forces. These forces can cause injury to solid organs, hollow organs, or vascular injury within the abdominal cavity. Blunt trauma can be associated with single-organ injury or multisystem trauma, significantly increasing patient risk of morbidity and mortality. Common mechanisms of injury include motor vehicle crash, motorcycle crash, bicycle crash, fall, pedestrian-automobile impact, abuse, and assault.

Evaluation

Clinical Evaluation. The initial resuscitation of an injured trauma patient begins with identification of the mechanism of injury and establishing patient stability. A proper handoff from emergency medical services quickly provides information regarding the mechanism of injury to guide assessment. Patients are further classified based on stability, with unstable patients exhibiting hypotension or tachycardia. Initial assessment of all patients, as defined by ATLS, begins with the primary survey to ensure a patent airway, breathing, and circulation (perfusion). The secondary survey is a head-to-toe examination, with special care taken to evaluate the abdomen. Although physical examination is often unreliable to identify abdominal injury, certain findings raise the suspicion for injury. Abdominal distention suggests massive hemoperitoneum from solid organ or vascular injury. Peritonitis is not typically associated with hemoperitoneum, but can be present with hollow viscus organ injury. Bruising across the lower abdomen or chest (seatbelt sign) suggests the presence of a hollow viscus injury or lumbar vertebral body spine (Chance) fracture. Physical examination is unreliable in the diagnosis of blunt abdominal trauma because of altered mental status or distracting injury. However, repeated abdominal examination helps identify missed injuries. The liver or spleen is the most common solid organ injured after blunt injury. As 85% of splenic and hepatic injuries are grades I to III, the vast majority of these patients are hemodynamically stable and managed nonoperatively. On the other hand, high-grade injury to the spleen or liver often produces active bleeding and a hemodynamically unstable patient. More details on specific organ injuries are discussed later in the chapter.

Diagnostic Tests. Limitations of the physical examination require appropriate use of adjunct testing for rapid diagnosis. These diagnostic tests include focused abdominal sonography for trauma (FAST), diagnostic peritoneal lavage/aspiration (DPL/DPA), plain radiography, and CT. Use of these modalities is ultimately dependent on patient stability.

Focused Abdominal Sonography for Trauma. FAST should be used in the assessment of all patients with blunt abdominal trauma. FAST both has bedside availability and is noninvasive, allowing detection of hemoperitoneum within minutes.[3–7] However, FAST has a false-negative rate as high as 40%, often missing injury to the diaphragm, hollow viscus, or retroperitoneum.[7] A positive FAST in a hemodynamically unstable patient has the highest utility to allow prompt transfer to the operating room for definitive care. However, a negative FAST does not exclude abdominal injury and often requires further assessment with CT or DPL/DPA.

Diagnostic Peritoneal Lavage or Aspiration. Patients with a negative FAST, hemodynamic instability, and ongoing suspicion for intraabdominal hemorrhage are assessed with DPL/DPA. Of note, FAST and DPA have largely replaced DPL. Similar to FAST examination, DPL/DPA is limited in its ability to assess retroperitoneal or diaphragm injury. Although this procedure is invasive, risks of complications are low in experienced hands. A positive DPA is defined by return of blood on aspiration. A positive DPL is defined by the presence of 10 cc gross blood on aspiration, >100,000 red blood cells/mm^3, >500 white blood cells/mm^3, bile, or food particles. A positive DPL/DPA in the unstable patient requires immediate laparotomy.

Computed Tomography. CT should be performed in the hemodynamically stable patient who has sustained significant blunt abdominal trauma. Modern helical CT scanners have significantly reduced imaging time and improved imaging quality. CT identifies and grades solid organ injuries and the presence of retroperitoneal injuries. However, CT is less reliable in the identification of hollow viscus, diaphragm, or pancreatic injury. Perform CT with intravenous contrast, with both arterial and portal venous phase images. Special care should be taken in the patient with known contrast dye allergy or chronic kidney disease. Patients with contrast dye allergy will require premedication to minimize the risk of allergic reaction or noncontrast studies. Oral contrast is not routinely used, as it may cause delay or place patients at risk for aspiration.

Laboratory Testing. Laboratory testing is routinely obtained on initial presentation to the trauma bay. The acutely hemorrhaging patient will rarely demonstrate anemia, as whole blood has been lost. A global assessment of perfusion is important, as patients in hemorrhagic shock may demonstrate a metabolic acidosis with an elevated base deficit or lactate level. Urinalysis with the presence of red blood cells suggests urologic injury. Although initial laboratory testing is unreliable for diagnosis, trending values can aid in resuscitation or identification of missed injury. Patients with pancreatic or hollow viscus injury may initially have normal serum amylase levels, which later become elevated. Thromboelastogram (TEG) assesses hemostasis and whole blood coagulation. It has been more routinely used in identifying trauma-induced coagulopathy and guiding resuscitation.

Penetrating Abdominal Injury

A penetrating abdominal injury (PAI) is defined as a perforating injury that violates the abdominal cavity. Anatomically, injury from the nipple line to the groins anteriorly or scapula tip posteriorly to the buttocks posteriorly should raise suspicion for possible thoracic and abdominal injury. These injuries result from high-velocity projectiles such as firearms or other mechanisms such as stabbings or impalement. A thorough understanding of missile or wound trajectory is imperative in diagnosis and management. Penetrating trauma from high-velocity weapons with significant kinetic energy produces extensive injury and tissue damage, some of which may progress over the first 24–48 hours postinjury.

Evaluation

Clinical Evaluation. Similar to the evaluation of patients sustaining blunt abdominal trauma, patients with PAI require rapid evaluation and assessment following the principles of ATLS. Initial identification of the mechanism of injury and patient stability further defines the diagnostic algorithm. Upon ensuring an intact primary survey, a patient should be examined head to toe to identify all injuries to help approximate missile trajectory. Take special care to examine the axilla, perineum, gluteal folds, rectum, and body creases to ensure no injuries are missed. Wounds should be counted, and an odd number of wounds suggests a retained foreign body (generally a bullet). Wounds are marked with radiographic markers or paperclips secured with tape. Plain radiographs of the chest, abdomen, and pelvis and cross-table lateral abdominal films then aid in determining the trajectory of missiles. Physical examination should also assess for abdominal distention and the presence of peritonitis. Identification of visceral or omental evisceration, peritonitis, or hypotension is an indication for immediate exploratory laparotomy. Stable patients selected for nonoperative management (NOM) who can provide a reliable examination should undergo serial examination for a minimum of 24 hours. Those patients who develop a change in vital signs (fever or tachycardia), peritonitis, or leukocytosis should undergo surgical exploration.

Diagnostic Tests.

FAST. FAST should be used in both stable and unstable patients who have sustained PAI. FAST may identify hemoperitoneum in PAI and, more importantly, hemopericardium in patients where the trajectory puts the heart at risk. FAST remains unreliable in the diagnosis of hollow viscus injury, which is common with penetrating injury.

Computed Tomography. Patients who remain hemodynamically stable can be assessed by CT with intravenous and oral contrast. Rectal contrast is generally not recommended currently. Cross-sectional imaging can define the trajectory of injury and violation of the peritoneal cavity. However, evaluation of violation of the peritoneal cavity with CT is limited in patients who are thin.

SURGICAL EXPLORATION

Surgical exploration can be achieved by exploratory laparotomy or diagnostic laparoscopy (in selected patients). The hemodynamically unstable patient with concerning trajectory should undergo immediate exploratory laparotomy after assessment for hemopericardium via FAST. The exploratory laparotomy in the trauma patient is a systematic evaluation of abdominal injuries. The primary goals of the trauma laparotomy are to (1) control hemorrhage, (2) stop gastrointestinal contamination, (3) define all injuries, and (4) resect/repair injuries with consideration for damage control (discussed later). Diagnostic laparoscopy should only be considered in the hemodynamically stable patient and has largely replaced DPL to exclude intraabdominal injury. It can be helpful in the assessment of diaphragmatic injuries and violation of the peritoneal cavity, especially with PAI. However, its utility to detect retroperitoneal or hollow viscus injury is limited by surgeon experience.

ORGAN-SPECIFIC INJURY

General Principles

As mentioned earlier, the essential decision in the management of abdominal injury is recognizing the need for emergent laparotomy. The initial management of patients with suspected abdominal injury begins with appropriate triage and resuscitation. Ultimately, evaluation depends on the mechanism of injury and hemodynamic stability of the patient. In the hemodynamically stable blunt trauma patient, CT with intravenous contrast is the diagnostic test of choice to determine the extent of injury (grade), presence of associated intraabdominal injuries and hemoperitoneum, and active extravasation. The majority of patients with blunt injury to the liver, spleen, or kidney are hemodynamically normal, and appropriate management will be observation.

Hemodynamically unstable patients or those with evidence of peritonitis on examination require immediate laparotomy. FAST and plain radiography of the chest and pelvis are used in the unstable patient to detect hemoperitoneum and assess the chest as a site of blood loss.

Successful NOM requires appropriate patient selection; high-quality CT; and the availability of an effective multidisciplinary team of intensive care physicians, experienced surgeons, and interventional radiologists. Institutions should have well-established protocols and consistent practice patterns to minimize risk of failure of NOM. Frequent evaluation upon admission to the ICU is necessary to monitor for complications, including bleeding, abscess, or bile peritonitis.

Hepatic Injury

With its anatomic position anteriorly in the right upper quadrant, the liver is the largest and one of the most commonly injured intraabdominal organs.[8] The highest incidence of these injuries is secondary to blunt abdominal trauma from motor vehicle crashes.[9] More than

85% of blunt hepatic injuries are low-grade injuries (American Association for the Surgery of Trauma [AAST] grade I–III) and 15% represent high-grade injuries (AAST grade IV–V). Mortality in patients with hepatic injury is dependent on the grade of injury and ranges from 10% in the low-grade injuries (AAST grade I–II) to greater than 50% in high-grade injuries.[10] Patients who present with hepatic injury are at high risk for concomitant injuries of the spleen (21%), kidney (9%), and bowel (4%).[11]

Measure serum transaminases, lactate dehydrogenase, and gamma-glutamyl transferase (GGT) on admission and trend throughout the patient's hospitalization. Abnormalities of these values have been associated with grade of hepatic injury and can serve as screening tests.[12–14]

NOM of hepatic injury in hemodynamically stable patients without peritonitis is now routine.[15,16] With appropriate patient selection, more than 85% of patients with liver injury can be managed successfully with NOM. Patients requiring immediate laparotomy for hemodynamic instability typically have AAST grade IV or V injury. Hemodynamic status remains the most important factor in predicting success of NOM. Other predictors of failed NOM in high-grade liver injuries include age, male gender, higher Injury Severity Scale (ISS), lower Glasgow Coma Scale, hypotension, and the presence of associated intraabdominal injuries.[17,18]

Frequent evaluation upon admission to the ICU is necessary to monitor for complications including bleeding, abscess, or bile peritonitis. Observation should include frequent physical examination, hemodynamic monitoring, and serial hemoglobin levels. It is of the utmost importance to prevent hypothermia and reverse coagulopathy in these patients.

Although NOM of hepatic injury has resulted in lower mortality rates, reduced transfusion requirements, and reduced length of stay, 12%–24% will develop complications. These include early (<24 hour) and late (>24 hour) bleeding, bile leak, hepatic necrosis, gallbladder necrosis, abscess, biliary-venous fistula, hemobilia, and thrombosis or pseudoaneurysm of the hepatic vasculature. Increasing liver grade is associated with a higher complication rate. Complications can be recognized by the development of a variety of symptoms, including increasing abdominal pain, change in vital signs, leukocytosis, or abnormalities of liver function tests. Patients with these symptoms and laboratory abnormalities require definitive imaging to establish the appropriate diagnosis and treatment modality. CT with intravenous contrast is effective to assess for hepatic or gallbladder necrosis, abscess, and pseudoaneurysm formation. Suspicion for bile leak can be confirmed with hepatobiliary iminodiacetic acid (HIDA) scan. Patients with hematemesis, melena, or jaundice should undergo angiography for suspicion of hemobilia.

Management of complications associated with NOM of liver injury varies and can range from observation to surgical intervention. Only 15% of complications will require operation. Small bilomas can typically be managed with observation. Bile leaks require endoscopic retrograde cholangiography and stenting. Large bilomas and abscesses can be managed with percutaneous drainage. Approximately 2%–7% of patients will develop recurrent/late bleeding or ongoing transfusion requirements, typically managed with angiography and embolization. Angiography/embolization enhances the success of NOM but should only be used in patients who are hemodynamically stable without other indications for operative intervention. Complications associated with angioembolization include hepatic necrosis, gallbladder necrosis, bile leak, and abscess formation with rates ranging anywhere from 29% to 80% (Fig. 157.1). Patients with active extravasation on CT are more likely to fail NOM and should undergo early angioembolization. Operative intervention is reserved for resection of devitalized or necrotic liver, control of large bile leaks in the setting of biliary peritonitis, and drainage.

Splenic Injury

The spleen is the intraabdominal organ secondary to blunt abdominal trauma most likely to require operation. Patients may report left upper quadrant fullness or pain and left shoulder pain (Kehr sign). Left lower rib fractures have been associated with splenic injury in 25%. However, physical examination is largely unreliable for the diagnosis of splenic injury.

Ultimate management of splenic trauma depends on the hemodynamic status of the patient. NOM of splenic trauma has become routine in the hemodynamically stable patient.[19,20] Immediate laparotomy should be undertaken in hemodynamically unstable patients or those with evidence of peritonitis.[21,22]

Patients managed nonoperatively require close observation in hospital or the ICU for high-grade injuries (AAST grade >III) with frequent physical examination, serial hemoglobin measurements, and a

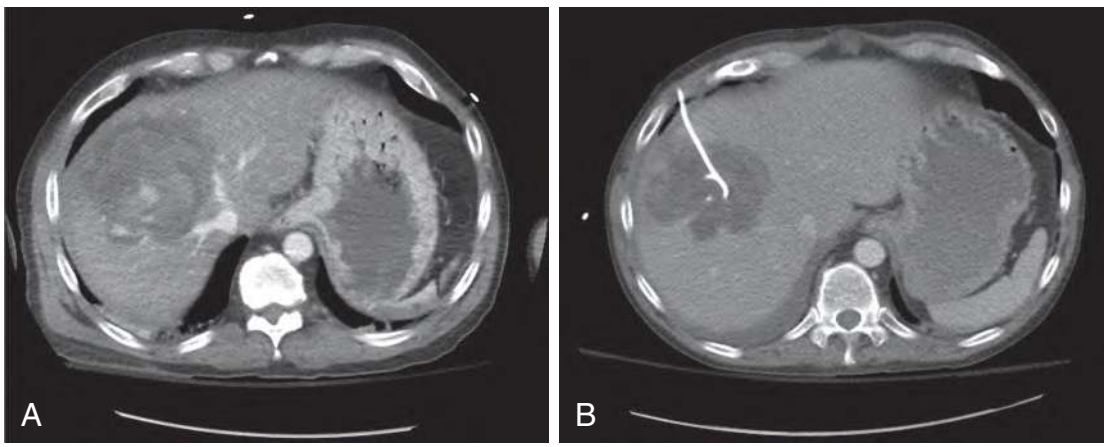

Fig. 157.1 A 52-year-old-male, motor vehicle crash, hemodynamically normal. **A,** C with contrast shows large active extravasation and clot in the right lobe of the liver. The right hepatic artery was embolized. The patient was managed nonoperatively and discharged from the hospital. **B,** The patient re-presented 2 weeks later with an elevated white blood cell count. A liver abscess was drained percutaneously.

period of immobility. Failure of NOM of splenic injuries in patients with blunt splenic trauma ranges from 3% to 38%, but generally under 10%.[23–32] Patients with high-grade injuries (AAST grade IV–V), high ISS, presence of pseudoaneurysm, arteriovenous fistula, active extravasation, moderate to large amounts of hemoperitoneum, or subcapsular hematoma are at highest risk for failure of NOM.[26,27] Ninety percent of patients who fail NOM will do so in the first 3 days after injury and 60% in the first 24 hours. Patients who undergo successful NOM with high-grade injuries should undergo interval CT (generally 48 hours post initial CT) with intravenous contrast to evaluate for the development of pseudoaneurysm, which will require angioembolization. Chemical deep vein thrombosis (DVT) prophylaxis is initiated within 48 hours and has not been shown to increase the risk of failure of NOM.[33,34]

Angiographic embolization is an adjunct in the management of splenic injuries and can enhance the salvage rate of NOM. However, this should only be considered in the hemodynamically stable patient. Patients with contrast extravasation on CT, high-grade injury (grades IV and V) even without active extravasation, moderate hemoperitoneum, or concern for ongoing bleeding should be considered for proximal or selective angioembolization.[25,29–31] Complications of angioembolization include femoral access issues, pleural effusions, contrast-induced acute kidney injury, splenic infarction, splenic rebleeding requiring splenectomy, and splenic abscesses or cysts[32] (Fig. 157.2).

After splenectomy, patients are at risk for overwhelming postsplenectomy infection (OPSI) secondary to encapsulated organisms, including meningococcus, *Haemophilus influenza, Streptococcus pneumoniae, Staphylococcus aureus,* and *Escherichia coli.* This risk is highest in the pediatric population. However, both adult and pediatric patients require immunization within 2 weeks of splenectomy or before discharge with Pneumovax, *H. influenza,* and meningococcal vaccines. Patients should be educated regarding revaccination schedules to ensure proper follow-up. Immune function in patients with high-grade injuries or after splenic artery embolization seems to be preserved. The need for vaccination after angioembolization remains controversial.

Pancreatic Injury

The retroperitoneal location of the pancreas makes injury uncommon, ranging in frequency from 0.2% to 12% in patients with abdominal trauma.[35–38] These injuries typically occur from a crushing force to the abdomen that compresses the pancreas against the vertebral column or a gunshot wound. When pancreatic injury occurs, there is a high rate of associated intraabdominal injuries of solid organs, hollow organs, and vascular structures.

Early identification of pancreatic injury remains a diagnostic challenge, especially in the injured patient who does not require immediate laparotomy. Given the retroperitoneal location of the pancreas, FAST and DPL are unreliable in the detection of injury.[39] Physical examination may reveal abdominal tenderness, ecchymosis, or no signs or symptoms and remains insensitive for the diagnosis of pancreatic injury. Laboratory studies may reveal elevated serum amylase or lipase on admission. However, this is neither sensitive nor specific for the presence of a pancreatic injury.

Operative exploration of the pancreas with visual inspection and bimanual palpation is the most sensitive method to diagnose injury. CT remains the imaging modality of choice in the hemodynamically stable patient. However, the sensitivity of CT in identification of injury remains variable, ranging from 47% to 79%.[40,41] Patients with normal pancreas architecture and without peripancreatic edema on CT should be closely observed with serial physical examination. Development of abdominal pain, leukocytosis, or change in vital signs should prompt immediate evaluation with repeat CT using a pancreatic protocol or laparotomy.

Endoscopic retrograde cholangiography (ERCP) may be used to diagnose and, at times, treat pancreatic ductal injury in the stable trauma patient with suspicion of pancreatic injury. Magnetic resonance cholangiography (MRCP) may also be used for diagnosis, but does not offer the therapeutic advantages available during ERCP. Performing an ERCP on the acutely injured patient can be challenging and can exacerbate inflammation of the pancreas.[42]

The status of the pancreatic duct, the location of injury (proximal versus distal), and the overall status of the patient determine the most appropriate management. Given the high incidence of concomitant injuries, patients with pancreatic injury generally require laparotomy. Pancreatic injury without evidence of ductal injury (AAST grade I and II) is managed with débridement and external drainage alone. Distal pancreatic injury (AAST grade III) is managed with distal pancreatectomy and drainage. Proximal pancreatic ductal injuries and disruption of the pancreatic head (AAST grade IV and V) are difficult to manage.

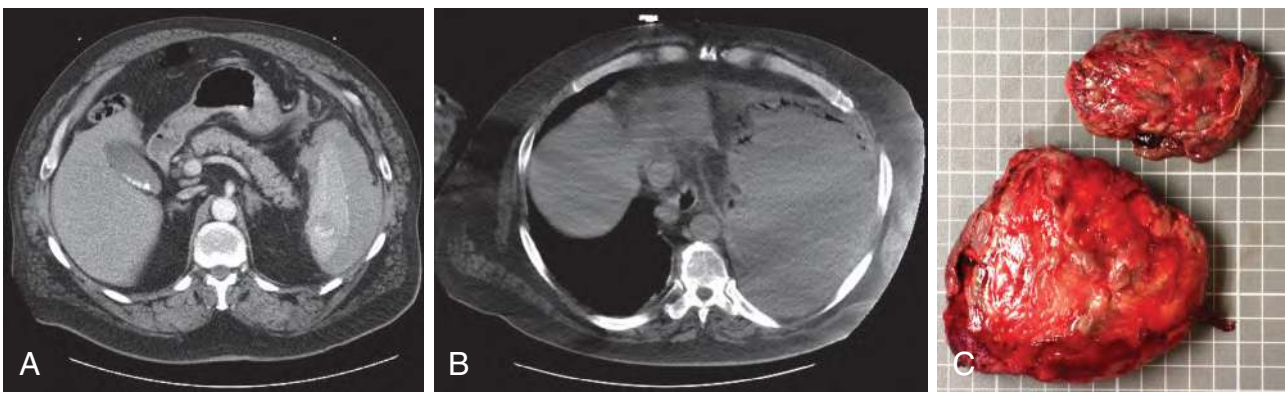

Fig. 157.2 A 54-year-old male presented 2 days after falling with abdominal pain and hemodynamically normal and benign examination. **A,** His computed tomography (CT) shows a splenic laceration with active bleeding. The splenic artery was embolized and the patient discharged from the hospital a week later. **B,** The patient re-presented 1 month later with fever, malaise, and mental status changes. White blood cell (WBC) was 35,000/mm^3. CT showed extensive splenic infection. **C,** The patient was promptly taken for splenectomy. Gross pathology of the spleen. Microscopy revealed diffuse and chronic inflammation. Cultures grew heavy *Propionibacterium granulosum* and moderate *Peptostreptococcus* species. He did well postoperatively.

Recommendations range from simple drainage to complex procedures, including pancreaticoduodenectomy or on-lay pancreaticojejunostomy. Pancreaticoduodenectomy is rarely required.[43,44]

Mortality from pancreatic injury ranges from 9% to 24%.[43] Early mortality after pancreatic trauma is primarily associated with vascular injuries. Sepsis, multiple-organ failure, respiratory failure, and delay in the diagnosis of pancreatic injury account for late mortality.[44] Complications related to pancreatic injury are dependent on the presence of ductal injury and the grade of injury or concomitant duodenal injury. Patients are at risk for developing pancreatic fistula, abscess, posttraumatic pancreatitis, pseudocysts, and hemorrhage of adjacent retroperitoneal vessels. Postoperative hemorrhage can be appropriately managed with angioembolization or laparotomy in the unstable patient. Pancreatic fistulae are typically managed conservatively and resolve spontaneously. Evidence regarding the use of somatostatin analogues for fistula prevention and management is variable. Abscesses are managed with percutaneous drainage and intravenous antibiotics. These rarely require surgical intervention. Patients with traumatic pancreatitis will need enteral nutritional support with nasojejunal feeding access or parenteral nutrition if this is unable to be obtained.

Hollow Viscus Injury

Hollow viscus injuries, including stomach, small bowel, duodenum, colon, and rectum, are most commonly secondary to penetrating trauma. Small bowel followed by the stomach have the highest incidence of injury secondary to penetrating trauma. High-velocity penetrating injury can cause a significant degree of tissue destruction, making management of these injuries challenging. Blunt trauma accounts for only a fraction of hollow viscus injury and usually results from a sudden increase in intraluminal pressure and distention or deceleration forces that cause contusion, serosal injury, or hematoma.

Patients who have sustained penetrating trauma often require surgical exploration via diagnostic laparoscopic or laparotomy to exclude hollow viscus injury. Blunt trauma poses a more difficult diagnostic challenge when assessing for hollow viscus injury. These challenges can result in a delay in diagnosis and significantly increase morbidity and mortality. Physical examination may reveal tenderness, seatbelt sign, or peritoneal signs. However, this is unreliable in the early diagnosis of injury, as definitive signs and symptoms of injury may not be present until later. Digital rectal examination should be performed if there is a high suspicion for rectal injury. The presence of blood on digital rectal examination is concerning for the presence of a rectal injury and should be interrogated in the operating room with proctosigmoidoscopy at a minimum. However, the absence of blood does not exclude injury. Plain radiography of the chest or abdomen may reveal free air, which should prompt immediate exploration. However, the absence of free air on plain radiography does not exclude injury.[45,46]

The presence of free air and oral contrast extravasation on CT is highly suggestive of injury and requires surgical exploration. CT findings of free fluid without evidence of solid organ injury, mesenteric hematoma or stranding, mesenteric blush, bowel wall thickening, or edema suggest injury. Intestinal injury may be present despite normal findings by CT. Should a high suspicion for hollow viscus injury remain, diagnostic laparoscopy can be used as an adjunct to CT. The sensitivity of diagnostic laparoscopy depends on surgeon skill, and injuries can be missed. Some authors suggest repeat abdominal CT scan with oral contrast in this setting.

Hollow viscus injury is managed with surgical exploration. Management strategies depend on the degree of destruction and range from primary repair, resection with primary anastomosis or proximal diversion, and wide drainage for rectal injuries. Antibiotics are administered in the perioperative period.

Postoperative complications after the management of hollow viscus injury include leak, abscess formation, and wound infection. Patients who develop increasing abdominal pain, tachycardia, or leukocytosis warrant evaluation with CT with oral and intravenous contrast to detect leak or abscess formation. Tachycardia and abdominal pain in the early postoperative period are suggestive of leak.

Diaphragmatic Injury

Traumatic diaphragm injuries have an incidence of less than 1% with more than two-thirds of these injuries secondary to penetrating trauma.[47] Blunt diaphragm injuries are more common on the left, as the liver offers a protective advantage on the right.

Diagnosis of diaphragm injuries is challenging. Chest radiograph is normal in 25% of all patients with a diaphragm injury.[48] Occasionally, chest radiography may demonstrate a hollow viscus or a coiled nasogastric tube in the left hemithorax, which is diagnostic for a diaphragm injury and requires surgical exploration. CT similarly is insensitive in the diagnosis of diaphragm injuries. Surgical exploration via diagnostic laparoscopy or laparotomy remains the most sensitive method for evaluation. Patients who have sustained a penetrating thoracoabdominal injury are at high risk for diaphragm injury and should undergo surgical exploration, generally laparoscopy in the stable patient. Diaphragm injuries can be missed at a patient's initial presentation and may present years later with herniation of and entrapment of intraabdominal organs. Posterior diaphragm injuries can be particularly challenging to diagnose and can be missed even during surgical exploration.

Management of diaphragm injuries requires surgical repair either through the chest or abdomen. In the acute setting, repair is performed through the abdomen, as there is a high risk of associated injuries to the spleen, stomach, small intestine, and colon. Injuries are repaired primarily with nonabsorbable sutures. Uncommonly, synthetic, nonabsorbable mesh or biologic grafts are required for large defects. Patients with concomitant hollow viscus injury and gross contamination of the abdominal and thoracic cavity are at risk for abscess formation. Development of fevers and leukocytosis postoperatively warrants imaging with CT with intravenous contrast to evaluate for abscess formation.

Genitourinary Injury

Genitourinary trauma occurs in 10% of all injured patients, with the kidney representing the majority of these injuries. More than 80% of renal injuries are secondary to blunt trauma.

Hematuria is the hallmark sign of injury to the genitourinary system and can be classified as macroscopic or microscopic. Gross hematuria is highly suspicious for genitourinary tract injury and warrants evaluation of the upper and lower urinary tract. Patients with microscopic hematuria warrant further evaluation in the setting of blunt trauma, hypotension, lower rib fractures, flank tenderness or ecchymosis, spine fractures, or high ISS.[49,50] Patients with pelvic fractures, difficulty voiding, perineal hematoma, high-riding prostate, or blood at the urinary meatus should be evaluated for the presence of urethral injury.

Selection of the appropriate imaging modality depends on the area of the genitourinary tract injured. Male patients with suspected urethral injury should undergo retrograde urethrogram (RUG) before Foley catheter placement. Upper genitourinary tract injuries, including the kidney and ureters, are most effectively evaluated with CT of the abdomen/pelvis with excretory imaging. CT allows staging of renal injuries, evaluation of the collecting system, presence of contrast extravasation, and confirmation of a normal contralateral kidney. One-shot intravenous pyelography can be performed intraoperatively in the patient who requires emergent laparotomy for evaluation of renal or ureteral injury. Retrograde cystography or CT cystogram are the diagnostic modalities to evaluate intraperitoneal and extraperitoneal bladder injuries.

Renal preservation is the goal when managing genitourinary trauma. NOM has become routine in hemodynamically stable patients with blunt renal trauma regardless of injury grade. Angioembolization can be used as an adjunct to NOM in select cases. Patients with renal trauma who undergo NOM successfully should undergo interval CT imaging at 48–96 hours to evaluate for urinoma or pseudoaneurysm. When operative exploration is required, renal salvage is attempted with renal reconstruction and renorrhaphy. However, hemodynamically unstable patients with high-grade injuries not amendable to repair will require nephrectomy. After renal trauma, patients are at risk for development of urinomas and perinephric abscesses, especially in high-grade injuries. Persistent urine leaks from collecting systems can be managed with stenting or percutaneous nephrostomy tube placement. Abscesses are best managed with percutaneous drainage. Postinjury hypertension can develop months after injury and often requires antihypertensive therapy. In rare instances, refractory cases of hypertension require nephrectomy.

Definitive management of bladder injuries depends on the location of the injury. Extraperitoneal bladder injuries are managed with bladder decompression with Foley catheter placement for a minimum of 7–10 days. Intraperitoneal bladder injuries require surgical repair. These injuries are frequently associated with hollow viscus injury and have a higher degree of morbidity and mortality. A follow-up cystogram is performed for both intraperitoneal and extraperitoneal bladder rupture before Foley catheter removal. Complications related to bladder injury include persistent bladder leak resulting in urinoma, abscess, and osteomyelitis. Furthermore, patients are at risk for incontinence and urinary retention.

Ureteral injuries are rare, with the majority secondary to penetrating trauma. Ureteral injuries require surgical repair if patient stability allows. Postoperatively patients can develop persistent urine leak, stricture, and fistula formation. Urethral injury is more common in men in the setting of pelvic fracture or direct crushing of the urethra from a straddle injury. Urethral injury requires surgical repair in a delayed fashion with bladder decompression via suprapubic tube. Patients who undergo early surgical repair are at high risk for incontinence, impotence, and stricture formation.

Abdominal Vascular Injury

Major abdominal vascular injury typically occurs secondary to penetrating trauma. However, blunt trauma can produce avulsion or thrombotic injury to vasculature. Patients require prompt recognition of injuries and urgent intervention to minimize the morbidity and mortality associated with these injuries. Patients with penetrating major abdominal vascular injury are generally unstable on presentation. On occasion, hemodynamically stable patients can be evaluated with CT with intravenous contrast.

Intraoperatively, patients may undergo aortic cross-clamping or ligation of major venous structures. Operative time is kept to a minimum, and damage control laparotomy performed. Recognition of these intraoperative proceedings significantly affects patients postoperatively. Patients with prolonged aortic cross-clamping are at high risk for end-organ dysfunction, particularly acute kidney injury. These patients may require early initiation of continuous renal replacement therapy. Similarly, combined arterial and venous injuries affecting perfusion to the lower extremities can result in extremity compartment syndrome. Frequent compartment checks and trending creatine phosphokinase can ensure early recognition of extremity compartment syndrome and need for lower extremity fasciotomies. These patients often develop profound trauma-induced coagulopathy and should be kept warm with correction of coagulopathy.

Damage Control

Damage control refers to a truncated surgical operation to control immediate life-threatening problems, including hemorrhage and gastrointestinal contamination.[51] Prolonged efforts in the operating room for definitive repair of injuries subjects patients to a lethal triad of acidosis, hypothermia, and coagulopathy.[51–53]

Damage control laparotomy involves a truncated operation with placement of temporary abdominal closure, often performed in 1 hour or less, with coordinated resuscitative efforts by a multidisciplinary team before return to the operating room. The patient is subsequently scheduled to return to the operating room within 24–48 hours, unless the patient requires intervention more urgently. Reoperation involves removal of packs, resection of devitalized tissue, and definitive repair of injuries.

The postoperative management of a patient after damage control requires coordinated efforts between the intensivists and surgical team. The goal of this resuscitative period is to prevent the lethal triad by rewarming, reversing coagulopathy, and restoring adequate tissue perfusion. These patients are at high risk for missed injury. Thorough initial assessment upon arrival to the ICU includes a thorough physical examination and full laboratory studies to assess acid-base status, oxygenation, hemoglobin, and coagulation profile. Bedside radiographs should be used to assess line and tube positions that may have been placed under emergent conditions. If patient stability allows, central lines placed emergently under potentially unsterile conditions should be replaced. These patients often have not undergone complete radiographic imaging to determine the extent of their injuries. Extremity injuries can be assessed with bedside radiographs. Patients should be kept in strict spine precautions and a cervical collar maintained. These patients are often too unstable for transport, and trips outside of the ICU should be minimized at all costs. These patients often require massive transfusion and ongoing resuscitation that places them at high risk for acute lung injury and acute respiratory distress syndrome. As a result, lung-protective ventilation strategies should be employed. Attempt to minimize crystalloid infusion. Use whole blood or 1:1:1 transfusion of blood products. Patients should undergo frequent reassessment. Failure to correct persistent acidosis, increasing vasopressor requirements, ongoing laboratory derangements, persistent transfusion requirements, and changes in drain output should be immediately communicated to the surgical team. These changes may indicate the need for immediate return to the operating room. After damage control surgery, patients are at risk for abdominal compartment syndrome, even when the abdomen is managed with a temporary abdominal closure. The bladder pressure should be measured at least every 4–6 hours. A tertiary survey, involving a head-to-toe examination, should be performed, again looking for missed injuries. This examination should be repeated once the patient can participate in the examination without distracting injuries.

Patients who have undergone damage control present to the ICU with an open abdomen with placement of a temporary abdominal closure device. The abdominal wall fascia is left unapproximated to allow swelling and edema of the abdominal viscera and to minimize risk of development of abdominal compartment syndrome. These temporary closure devices are negative-pressure vacuum seal dressings that create a protective layer over the bowel and minimize fascial retraction (Fig. 157.3). Although this technique minimizes operative time and simplifies re-exploration, ultimate closure can prove to be challenging. Patients with an open abdomen are at risk for development of enterocutaneous fistula, enteroatmospheric fistula, and ventral hernia. Attempts should be made at abdominal closure as soon as patient condition allows. Often closure is complicated by massive resuscitation and

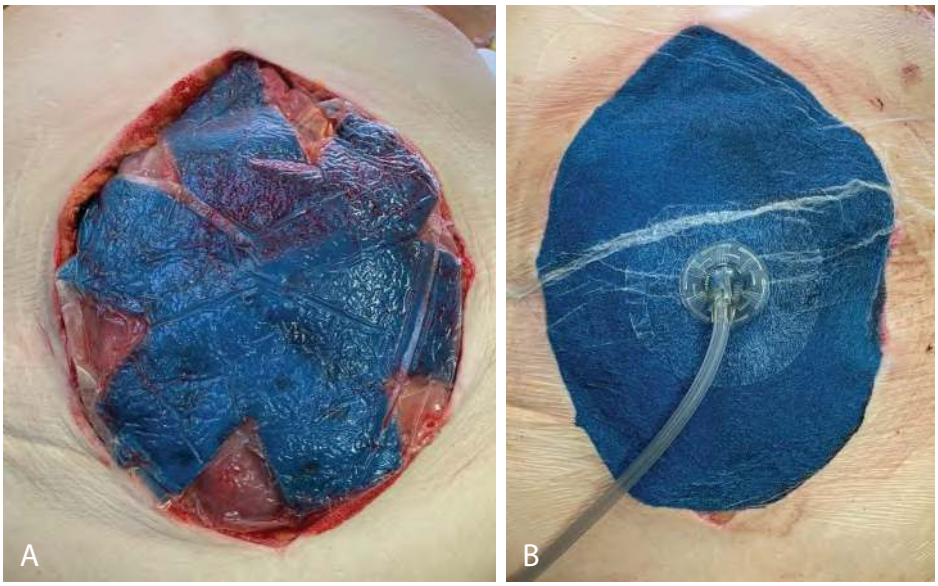

Fig. 157.3 **A,** This picture shows the inner visceral protective layer of the ABThera open abdomen negative-pressure system (KCI, San Antonio, TX). **B,** Completed VAC dressing with the outer sponge seen and external suction system.

shock state, which results in abdominal wall and visceral edema. Diuresis when patient hemodynamics allow may improve attempts at fascial closure. Patients may require staged abdominal closure with multiple trips to the operating room, placement of mesh, and even complex abdominal reconstruction.[53]

KEY POINTS

- Abdominal injury can result in significant morbidity and mortality. These patients remain susceptible to delay in diagnosis and missed injury.
- Prompt evaluation, resuscitation, and recognition of injuries help minimize the risk of avoidable morbidity and mortality.
- Coordinated efforts with clear lines of communication between a multidisciplinary team of intensivists and surgeons ensure patient safety and improve outcomes.
- Eighty percent of abdominal injuries are produced by a blunt mechanism of injury. The most common penetrating mechanisms are gunshot wounds and stab wounds.
- Trauma patients with abdominal injury will be admitted to the ICU for management of chest wall injury/pulmonary contusion, extremes of age, nonoperative management of high-grade organ injury, after damage control laparotomy, or management of concomitant brain or spine injury.

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Pelvic Fractures and Long Bone Fractures

Sumeet V. Jain and Nicholas Namias

INTRODUCTION

Pelvic and long bone fractures are found frequently in trauma patients, especially in blunt polytrauma patients with significant injury burden. Initial intensive care management of severe pelvic fractures or long bone injury is similar: damage control resuscitation, hemorrhage control, antibiotic prophylaxis for open fractures, identification and treatment of concomitant injuries, early nutrition, and supportive care for known complications like pulmonary embolism and fat embolism syndrome. In this chapter, we will examine overall management and specific considerations for pelvic and long bone fractures.

INITIAL MANAGEMENT

Damage Control Resuscitation

The most common manifestation of pelvic and long bone fracture in the intensive care unit (ICU) is hemorrhage. It is well established that severely injured trauma patients arrive at the hospital with coagulopathy already present, and this is an independent predictor of mortality.[1,2] The development of coagulopathy is a multifactorial process, theorized to stem from humoral activation of the coagulation cascade with consumption, systemic inflammation, and fibrinolysis. Acquired traumatic coagulopathy develops independent of resuscitation strategy, but it is believed that subsequent resuscitation with crystalloid or packed red cells alone further exacerbates coagulopathy. Therefore management of hemorrhagic shock from trauma has shifted from liberal administration of early crystalloid and red blood cells (RBCs) to the concept of "damage control resuscitation," or balanced resuscitation with more plasma and platelet administration.[3]

Early data from military and civilian trauma centers demonstrates that increased plasma:RBC ratios are associated with survival to hospital discharge.[4,5] Subsequent clinical trials have validated the use of balanced resuscitation strategies on mortality and hemostasis in multitrauma patients. The Prospective, Observational, Multicenter, Major Trauma Transfusion study (PROMMTT) is a landmark study that demonstrated reduced mortality with early administration of plasma and platelets and higher plasma:platelet:RBC ratios in the early resuscitation period.[6] Further, the Pragmatic, Randomized Optimal Platelet and Plasma Ratios trial (PROPPR) assessed the efficacy of a 1:1:1 ratio of blood product administration vs. a 1:1:2 ratio; the trial found no difference in mortality between these two groups at 24 hours or 30 days, but did find increased hemostasis and less death because of hemorrhage.[7] Importantly, there was also no difference in rates of acute respiratory distress syndrome, multiple organ failure, venous thromboembolism, sepsis, or transfusion-associated complications. Overall, damage control resuscitation with a 1:1:1 ratio of platelets:plasma:RBC administration in patients suffering hemorrhagic shock decreased mortality and overall volume of resuscitation and has become the accepted standard for the resuscitation of trauma patients.[5] Further resuscitation in the ICU consists of correction of coagulopathy as needed, with the aid of coagulation studies or viscoelastic testing if available.[8]

Another factor to consider during damage control resuscitation is the presence of hyperfibrinolysis. Initially, there was much excitement over the use of tranexamic acid (TXA)—an antifibrinolytic agent—because of the Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage 2 (CRASH-2) study. This study examined adult trauma patients with hemorrhagic shock and found reduced mortality with administration of TXA within 3 hours.[9,10] A subgroup analysis of the PROPPR trial also showed improved 6-hour mortality in patients with hyperfibrinolysis on admission who were given TXA without an increase in venous thromboembolism.[11] However, there have been conflicting data regarding dosing TXA universally in trauma patients with hemorrhagic shock, with evidence that there may be an increase in mortality and venous thromboembolic phenomenon in a subset of patients who required operative intervention and presented early to a level 1 trauma center.[12,13] It also appears late administration of TXA offers no mortality benefit compared with administration within 3 hours of injury.[10] Viscoelastic testing, such as thromboelastography if available, may help stratify hemorrhaging patients into those that do and do not have hyperfibrinolysis based on the LY30 value. LY30 greater than 3% identifies hyperfibrinolysis, and this patient population appears to benefit from TXA administration.[14,15] The use of TXA and thromboelastography in trauma, however, is controversial; at present both are tools available to the ICU physician and must be used based on clinical judgment while more research is performed.

Open Fractures

Whether a fracture is open or closed is an important distinction and should be a component of the initial assessment of any fracture. There are significant implications on the risk of wound infections, osteomyelitis, fracture nonunion, morbidity, and mortality depending on the presence of an open fracture and the degree of contamination.[16–18] An open fracture is defined as any fracture with an overlying soft tissue defect that tracks to the fracture site. Open fractures can be further subclassified into grades, with higher grades associated with increased infectious complications and mortality. Broadly, grade I and II involve simple, clean lacerations without a crushing component or degloving injury, whereas grade III fractures involve much more complex and contaminated wounds and special cases such as farming accidents or arterial injury requiring surgical intervention.[19] Infections typically involve gram-negative rods and gram-positive cocci.[20] Though multidrug-resistant organisms have been implicated in some outbreaks of open fracture infections in the hospital, this is relatively uncommon

and not prevented by broader prophylactic antibiotic coverage. Antibiotics should be started within 3 hours of presentation. The use of a first-generation cephalosporin (e.g., cefazolin—or clindamycin if anaphylactic to penicillin) for 48–72 hours is adequate antibiotic prophylaxis for grade I–II fractures, and an aminoglycoside should be added for grade III fractures.[21] In farm-related accidents, penicillin G or clindamycin should be added to the antibiotic regimen because of the higher risk of infection by *Clostridium* species. In addition to antibiotics, open fractures require early operative exploration to wash out the tissues, stabilize the fracture, and cover the fracture with soft tissue to reduce the risk of infection.

Nutrition

After severe injury, patients frequently enter a state of hypermetabolism that progresses to catabolism that progresses rapidly to malnutrition. When evaluating all geriatric patients with hip fractures, an increasingly common patient population both in and out of the ICU, there is a significant practice pattern variation with regard to nutritional supplementation. Specifically, there is a tendency to underfeed this population.[22] Underfeeding occurs despite evidence that in that patient population, malnutrition increases mortality, whereas adequate nutrition supplementation leads to greater functional recovery.[23] When evaluating the subset of critically ill trauma patients, inadequate nutrition has been shown to increase morbidity and mortality.[24] Early enteral nutrition has been shown to have numerous benefits in the ICU setting. It promotes gut mucosal integrity, motility, and immunity and reduces nosocomial infections.[25] Furthermore, in trauma patients specifically, early enteral nutrition has clearly been shown to decrease mortality.[26] If enteral nutrition cannot be administered, parenteral nutrition should be considered. A recent meta-analysis by the Cochrane Collaboration demonstrated no difference between enteral and parenteral routes with regard to mortality, aspiration, and pneumonia, although the enteral route may be associated with decreased incidence of sepsis.[27,28]

The 2016 American Society for Parenteral and Enteral Nutrition Guidelines (ASPEN) and the 2019 European Society guidelines recommend early initiation of enteral feeding (i.e., within 24–48 hours), provided the patient does not have any known bowel injury and is hemodynamically stable.[29,30] The ASPEN guidelines recommend administration of immune-modulating formulas containing arginine and glutamine in the trauma population because of decreased infection rates. These enteral formulas can be used in patients with open abdomens as well, provided they have intestinal continuity. Protein delivery is an especially important element of nutrition supplementation in this population; multitrauma patients will be on the upper end of the 1.2–2 g/kg/day protein that is recommended in the ICU. If enteral nutrition cannot be safely provided, or if it will not be able to meet the caloric needs of the patient, then parenteral nutrition should be initiated early in this high-risk population. Current guidelines recommend hypocaloric parenteral feeding initially at 80% basal energy expenditure, or <20 kcal/kg/day, while still maintaining adequate protein feeding at 1.2–2 g/kg/day, increasing gradually to cover full basal energy expenditure with frequent clinical reassessment. A full discussion regarding nutrition for ICU and trauma patients is outside of the scope of this chapter.

COMPLICATIONS OF PELVIC AND LONG BONE FRACTURES

Pulmonary Embolism

Trauma patients are known to be at increased risk of deep venous thrombosis (DVT) and pulmonary embolism (PE) because of intrinsic hypercoagulability, with an incidence of approximately 12% and 1.5%, respectively, and higher in patients who do not receive prophylaxis.[31] PE in particular has a high associated mortality rate at 17%–26%.[32] Pelvic and long bone fractures are independent risk factors for increased risk of venous thromboembolism (VTE) because of associated trauma-induced hypercoagulability, immobility, venous stasis, and the need for major surgical procedures; these events often occur early in the hospital course, within 72 hours.[32–35] Interestingly, it is unclear if VTE is the only cause for PE in trauma patients. For one, Allen and colleagues demonstrated that DVT surveillance in high-risk trauma patients—with either therapeutic anticoagulation or inferior vena cava (IVC) filter if DVT was present—decreased the rate of VTE.[36] At the same time, studies examining DVT surveillance after diagnosis of PE demonstrated that >20% of patients did not have concomitant lower extremity or pelvic DVT.[37,38] It is unknown why, with the theory being either complete VTE without residual clot or de novo formation of pulmonary artery thrombus instead of VTE. Regardless of the method, balancing the need for blood products in the hemorrhaging fractured trauma patient and the bleeding risk with VTE pharmacologic prophylaxis versus the high risk of VTE or de novo PE in a patient with a known hypercoagulable state represents a significant management challenge for the ICU physician.

The preferred method of VTE prophylaxis is pharmacologic with subcutaneous heparinoids. The current body of evidence, including a Cochrane review by Barrera and colleagues, has demonstrated that subcutaneous low-molecular-weight heparin specifically is better at reducing VTE than subcutaneous heparin and mechanical prophylaxis.[39,40] In a trauma patient without significant bleeding risk or renal dysfunction, the most effective dosing for DVT prophylaxis is enoxaparin 30 mg twice daily. Unlike standard 40 mg once-daily dosing used in other settings, in a trauma patient without significant bleeding risk or renal dysfunction enoxaparin 30 mg twice daily is used, though there is evolving evidence that suggests a benefit from higher doses. Subcutaneous heparin can be used in the presence of renal dysfunction. In a patient who develops VTE, therapeutic anticoagulation should be initiated if there is no contraindication. Our preference is to start with a heparin drip, as this is easily reversed with protamine if the patient does develop a bleeding complication, unlike therapeutic Lovenox or direct oral anticoagulants (DOACs). If the patient tolerates a heparin drip without bleeding, they can be bridged with a heparin drip or therapeutic Lovenox to destination oral anticoagulation with warfarin or a DOAC such as apixaban.

What remains more controversial is the role of prophylactic IVC filters in a trauma patient with a high bleeding risk. It is established that placing IVC filters in all hospital patients who are on anticoagulation does not reduce mortality.[41,42] Further, in the trauma population there is no high-quality evidence that shows a benefit to IVC filters, and more recent evidence has shown no decrease in mortality when using prophylactic IVC filters.[43–47] Despite the fact that modern IVC filters are retrievable, the fact remains that the majority of filters are not retrieved, and there is associated morbidity with the long-term placement of IVC filters, including erosion and DVT. Currently, there is no strong recommendation for prophylactic IVC filter placement because of the lack of benefit and increased morbidity. Current American College of Chest Physicians guidelines recommend against IVC filters in patients on anticoagulation, but recommend IVC filter placement in patients with an established diagnosis of DVT or PE with contraindications to anticoagulation.[41,48] Once a patient is able to receive therapeutic anticoagulation, however, it should be initiated even with an IVC filter in place. Ideally, an IVC filter should also be retrieved at a later point when it is no longer needed.

The latest technology for the prevention of VTE is the Angel catheter. The Angel catheter is a vena cava filter permanently attached to a central venous line. Its intended use is for short-term (<30 days) VTE prophylaxis in high-risk patients. The thought is that the catheter can

Fig. 158.1 Angel catheter. (Courtesy Mermaid Medical, Stenløse, Denmark.)

be placed quickly via femoral access without fluoroscopy, and once the central line is removed, the vena cava filter is removed with it. Currently it is indicated for patients with PE with contraindications to anticoagulation or critically ill patients at high risk for VTE with increased bleeding risk. The catheter has been primarily tested in all critically ill patients, though there are case reports in trauma patients.[49] Efficacy has been inferred from studies showing reduced in-hospital mortality in noncancer patients with acute PE and contraindication to anticoagulation.[50,51] Feasibility studies have shown no increase in adverse events with the use of the Angel catheter (Figure 158.1); however, at this stage more evidence is needed to support whether early use of the Angel catheter decreases mortality and VTE in high-risk patients with contraindications to anticoagulation.[52–54]

Fat Embolism Syndrome

Fat embolism after trauma was well described by Dr. Zenker in 1862.[55] It has been a relatively common finding at autopsy of posttraumatic patients, especially those with pelvic or lower extremity long bone fractures. The presence of fat embolism should not be confused with fat embolism syndrome (FES); pulmonary fat embolism occurs regularly in patients with fractures—as high as 90%–100% on autopsy studies—but FES is relatively rare, with an incidence of less than 2%.[56,57] Diagnosis is based primarily on clinical examination, and it remains a diagnosis of exclusion. Signs and symptoms typically occur 24–72 hours after injury. The classic triad for FES is petechial rash of the mucous membranes, conjunctiva, anterior neck, and/or thorax; hypoxemia with pulmonary edema; and mental status changes unrelated to head injury. However, petechial rash occurs in less than 50% of FES patients, and so it is not a reliable physical examination finding. Other associated findings include tachycardia greater than 110 beats per minute, fever greater than 38.5°C, retinal emboli, lipuria, or an unexplained drop in hemoglobin.[58,59] Originally, it was suggested that patients with FES manifest with petechial rash and neurologic signs because of a patent foramen ovale leading to fat embolization into the systemic circulation.[60,61] More recent evidence suggests, however, that these findings occur even in patients with a sealed foramen ovale, suggesting either a biochemical explanation for fat embolism or microembolization of fat particles through the capillary network into the systemic circulation.[62]

If there is suspicion for FES, initial testing involves exclusion of other causes. Patients with hypoxia will invariably get chest imaging, whether computed tomography (CT) or plain films, to evaluate for consolidation, effusion, or pneumothorax. Because of the neurologic symptoms, a CT brain is often done to rule out a missed head injury or stroke. CT angiography of the chest is not needed to diagnose FES but may help exclude thrombotic PE. Other invasive testing is not routinely indicated—such as bronchoscopy, transesophageal echocardiogram, or pulmonary artery catheter—unless being done to exclude another diagnosis. Treatment consists of supportive care, primarily with fluid resuscitation, circulatory support, oxygenation, and mechanical ventilation if needed. Early femur fracture fixation has also been shown in multiple studies to decrease the rate of pulmonary complications, including FES.[63,64] If the patient has profound hypoxia despite maximal ventilatory support, venovenous extracorporeal membrane oxygenation has also been described and should be considered.[65] There is evidence that corticosteroids may improve symptoms from FES, and possibly even prevent it; unfortunately, no reduction in mortality has been demonstrated, and the dosing required is unclear, varying from 6 to 90 mg/kg of methylprednisolone over 48 hours.[66–68] Furthermore, there are known risks of even short-term steroid use, including immune suppression leading to increased risk of sepsis, VTE, and impaired wound healing.[69] With current evidence, we cannot recommend routine steroids in patients with multiple long bone or pelvic fractures for prevention of FES.

PELVIC FRACTURE

In blunt trauma, pelvic fractures have an estimated incidence of 9%, with another 10% of those being classified as severe.[70] Mortality in patients with pelvic fracture early on stems from hemorrhage, often from several sources and not just the pelvis. Deaths outside of 6 hours typically occur from other causes, such as head injury and multiple organ failure.[71,72] The force required to fracture the pelvis has a high chance of causing other injuries that contribute to the morbidity and mortality of patients. Concomitant intraabdominal or urogenital injury occurs in 11%–20% of patients with pelvic fractures, with a higher incidence in patients with more severe injury. Blunt trauma leading to combined pelvic fracture and thoracic trauma or head injury is also common.[73] Specific considerations for management of pelvic fractures in the ICU are control of pelvic hemorrhage and the diagnosis and management of associated intrapelvic injuries. The management of thoracic, abdominal, and head trauma must also be carefully considered, but is outside the scope of this chapter.

Pelvic Hemorrhage Control

Pelvic ring disruptions, the so-called *"open book" pelvic fracture,* can cause significant venous plexus bleeding or internal iliac branch arterial bleeding. Although a minority of pelvic fractures involve unstable ring disruptions, patients with this injury pattern have an estimated mortality of 34%–50%.[74,75] The majority of mortalities from pelvic fractures is related to early hemorrhage, from both pelvic and extrapelvic sources, and this has been the case for decades.[71,72,76,77] Damage control resuscitation, as described earlier, and control of pelvic bleeding points are critical in reducing morbidity and mortality in this population. One reason for profound hemorrhage in severe pelvic fracture is that the extraperitoneal pelvic space expands in size dramatically with pelvic ring disruption. A 5-cm diastasis, for example, increases the pelvic space by more than 20%, allowing a significant volume of blood to extravasate into the pelvic space without tamponade.[78] Initial maneuvers for pelvic hemorrhage control involve reducing the size of the potential retroperitoneal space to tamponade the bleeding via pelvic binding, extraperitoneal pelvic packing, or external fixation. This section will discuss these techniques and two additional supplementary techniques: resuscitative endovascular balloon occlusion of the aorta (REBOA) and pelvic angiography.

The easiest early maneuver is placement of a pelvic binder or tying a sheet around the pelvis to externally close the pelvic space.[79,80] It is important to place the binder in the proper position at the level of the acetabulum; the goal is to reduce the pubic symphysis and close the pelvic ring. Placing the binder higher on the pelvis, such as at the anterior superior iliac spine, will not reduce the fracture, and may even

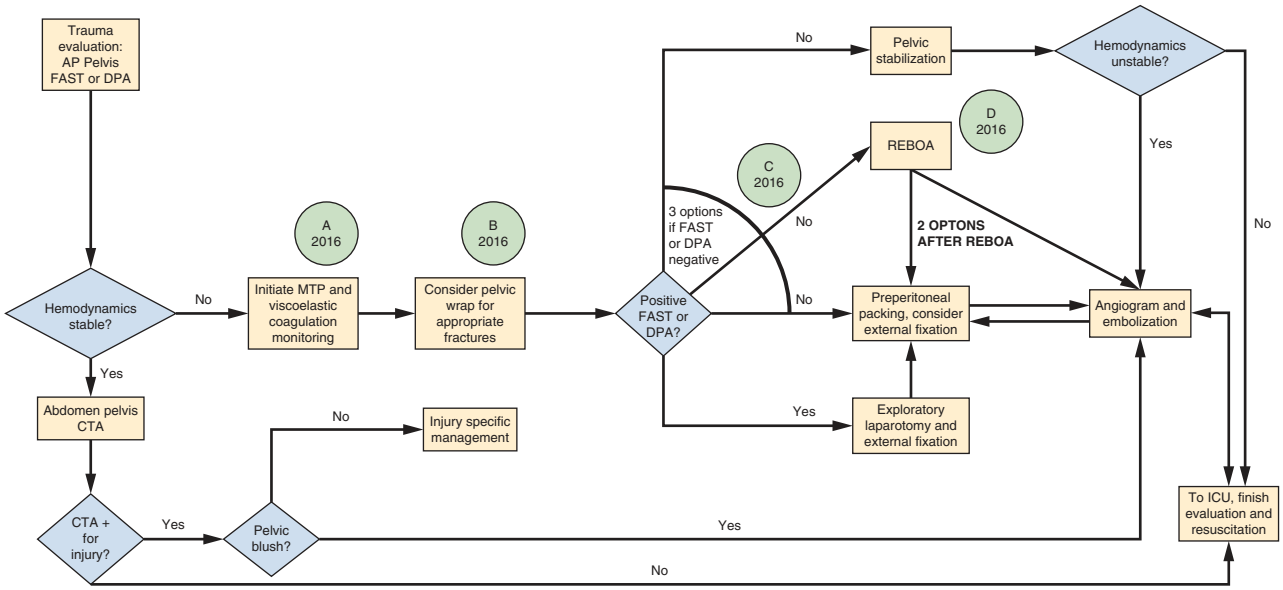

Fig. 158.2 Pelvic hemorrhage control algorithm.

worsen the fracture and associated hemorrhage. Correct binder placement may be enough to tamponade pelvic venous bleeding and allow time for adequate resuscitation. If the patient continues to have signs of hemorrhagic shock despite this maneuver, more invasive means of hemorrhage control may be necessary. Early evaluation by a multidisciplinary team consisting of trauma and orthopedic surgeons is critical to quickly and decisively intervene in the hemorrhaging patient with an unstable pelvic fracture. The Western Trauma Association also has a published algorithm for hemodynamically unstable pelvic trauma that serves as a useful guide in this case.[81] After pelvic binder placement or sheet stabilization, a focused abdominal ultrasound or direct peritoneal aspiration is performed to rule out abdominal trauma. If this is positive, the patient must go for laparotomy to control intraabdominal sources of hemorrhage. Alternatively, if there is no evidence of intraabdominal hemorrhage, then three options may be considered: preperitoneal pelvic packing in the operating room, external fixation, and REBOA, all of which can be done in conjunction with angiographic embolization.

Extraperitoneal packing is an operative technique that involves direct surgical packing of the pelvis to exert pressure and limit the size of the retroperitoneal space.[82] It has been shown to be expeditious and efficacious in limiting hemorrhage when used by an experienced team as part of a pelvic hemorrhage algorithm.[83,84] Another advantage is the ability to use this technique as a bridge to other adjuncts, namely external fixation and pelvic angiography. This is important because unstable pelvic fractures have a significant risk of arterial hemorrhage for which extraperitoneal pelvic packing alone is insufficient.[85,86] The pelvic packs should be removed within 48 hours when the patient is stabilized; otherwise, there is a risk of infectious complications.

One newer technique for pelvic hemorrhage management is REBOA. Originally described for noncompressible intraabdominal hemorrhage, REBOA is a technique that shows promise as a bridge to angioembolization in the hemorrhaging pelvic fracture patient with arterial bleeding.[81] To perform REBOA, arterial access is obtained in the common femoral artery with ultrasound guidance. The catheter is then guided into the infrarenal aorta and the balloon inflated. This raises the systolic blood pressure and diminishes flow to the pelvic arteries in addition to the bilateral lower extremities. Because of the ischemia caused

Fig. 158.3 REBOA catheter. (Courtesy Prytime Medical, Boerne, Texas.)

by REBOA, it is paramount that the patient be taken for further intervention as soon as possible, with the goal of removing the REBOA as soon as a more definitive method of repair is performed, whether that is angioembolization or packing and fixation.[87] Whether REBOA truly reduces mortality and morbidity requires further inquiry.

The goal of external fixation is fracture reduction to reduce the potential pelvic space and allow for bony alignment on a temporary or definitive basis to reduce bleeding from the cancellous bone.[88] The benefit to external fixation, whether posterior fixation with a C-clamp or an anterior fixation device, is that it is more quickly applied than definitive internal fixation and has greater pelvic stability than a pelvic binder or preperitoneal packing because of the immobility of the device.[89] Further, it decreases pain levels, reduces deformity, and improves functional outcome in the long term.[90] However, it is more time consuming than either pelvic binder placement or extraperitoneal

packing; the decision of when and how to proceed with external fixation depends entirely on the patient's condition. Again, using a binder or extraperitoneal pelvic packing may serve as a bridge to external fixation. In the hypotensive, bleeding unstable pelvic fracture patient, it is prudent to proceed with extraperitoneal pelvic packing, REBOA, and angiography before external fixation.

Pelvic angiography is the most effective way to manage arterial bleeding. Most pelvic arterial bleeding comes from branches of the internal iliac arteries, branches which are difficult to find and ligate surgically. Angiography allows for control of these vessels to staunch bleeding in patients in hemorrhagic shock, often after the adjuncts mentioned. If there is no intrabdominal bleeding suspected based on ultrasound or direct peritoneal aspiration, then angiography is indicated and should be performed after one of the adjuncts.[76,81,91] Furthermore, if the patient is stable enough for a CT scan and is found to have intravenous (IV) contrast extravasation in the pelvis, this is another indication for angioembolization regardless of hemodynamic stability, as this patient population has a high chance of continued bleeding.[92] Angioembolization is effective between 85% and 99% of the time; if a patient continues to show signs of hemorrhage after embolization and nonpelvic sources have been ruled out, repeat angioembolization should be performed.[93]

Treatment of unstable pelvic fracture hemorrhage requires a multidisciplinary algorithm because of the numerous options available. Damage control resuscitation and early intervention to control hemorrhage are critical to mortality reduction. Often, patients will come into the ICU after many of these interventions have taken place, such as pelvic packing and angiographic embolization. It is at this point that continued reassessment and awareness of management strategies is important to ensure hemodynamic stability to move onto further management.

Urinary Tract and Rectal Injuries

Pelvic fracture patterns can be associated with specific injuries to organs in the general vicinity, namely the lower urinary tract and rectum. Lower urinary tract injury is relatively rare—approximately 3%–6% of patients with pelvic fractures—and more commonly occurs in severe anterior pelvic ring disruptions.[94,95] Rectal injuries are even more rare and are more likely to occur with penetrating pelvic trauma than blunt trauma.[96] Neither of these injuries are immediately life threatening, so the management priorities still focus on pelvic stabilization and hemorrhage control first. However, after stabilization, identification can allow for early intervention by the appropriate surgical team and limit morbidity.

The lower urinary tract consists of the bladder and urethra, and each has a different series of findings on physical examination and imaging. Bladder injuries are commonly identified on CT imaging, especially on a delayed phase when IV contrast enters the urinary collecting system and can be seen in the bladder. On physical examination, hematuria is also suggestive of injury to either the bladder or kidneys. If there is any concern for bladder rupture, then CT cystography should be performed.[97] Bladder ruptures may occur in the extraperitoneal or intraperitoneal space. Intraperitoneal bladder ruptures require repair in the operating room. Extraperitoneal bladder ruptures often can be treated with Foley decompression, with the rupture site healing on its own with time. However, in an unstable pelvis where definitive repair will involve hardware insertion, there is some evidence that operative repair may reduce the risk of morbidity, such as hardware infection.[98,99] Urethral injuries are much more common in men than in women, and classic signs are perineal bruising or hematoma, displaced pubic ramus fracture, blood at the urethral meatus, and a high riding or impalpable prostate.[100] If perineal bruising or blood at the urethral meatus is found, Foley should not be attempted and instead a retrograde urethrogram should be performed.[101] If this is positive, a Foley catheter should not be placed and a urologist called to evaluate the patient. Depending on the degree and type of urethral injury found, treatment can range from catheterization and time to complex surgical approaches.[102]

Rectal injuries are more common in penetrating trauma, which accounts for greater than 70% of all rectal injuries. The remainder are associated with less than 5% of pelvic fracture patients.[96] On physical examination, typically rectal injuries are found by the presence of rectal bleeding and a high index of suspicion. If one is found, regardless of whether it is intraperitoneal or extraperitoneal, surgical consultation is indicated for diverting colostomy and rectal repair; missed rectal injuries in this setting can lead to disastrous pelvic sepsis, including abscess formation and osteomyelitis.

LONG BONE FRACTURE

Initial priorities in the management of long bone fractures are like pelvic fractures: hemorrhage control and identification of associated injuries. Extremity fractures can lead to significant hematoma and hemorrhage from the bone itself in addition to concomitant vascular injury, which may require damage control resuscitation as mentioned earlier. In addition, limb viability must be assessed continuously because of complications related to vascular injury and compartment syndrome. Patients with long bone fractures are also at risk for rhabdomyolysis, particularly if they suffer a crush injury or reperfusion injury.

Hemorrhage Control Adjuncts, Vascular Injury, and Limb Viability

Hemorrhage control for long bone fractures ultimately depends on the source. The bony break itself and associated soft tissue damage are the most common sources and can lead to a surprising amount of bleeding. Femoral fractures, for example, can have a significant amount of bleeding into the soft tissue space. In addition, long bone fractures can lacerate or crush major arteries and veins that travel alongside them. Key steps first involve assessment for external compressible hemorrhage, for which control often can be obtained by applying direct pressure above the bleeding point.[103] If this maneuver fails, hemostatic agents and/or a tourniquet can be safely applied in the prehospital setting to increase limb salvage and reduce mortality.[104–106] This could theoretically be extended to the ICU in an emergency with the understanding that quick action must be taken afterwards to definitively control bleeding; tourniquets cannot be left on indefinitely without consequence, and early surgical involvement is paramount to assess limb viability and reduce morbidity. Improperly placed tourniquets can cause major harm: placement for longer than 6 hours leads to profound ischemia and reperfusion injury, and a venous tourniquet, with intact arterial flow, promotes compartment syndrome and amputation. It cannot be overemphasized that tourniquet placement is a bridge to operative interventions that are primarily helpful in the prehospital setting and should be removed as soon as possible; tourniquets should not be used for long-term hemorrhage control.

Assessment of limb viability starts with looking for "hard signs" of vascular injury and performing a complete pulse examination. If a tourniquet is present, this should be loosened for evaluation and tightened again if the patient begins to hemorrhage. "Hard signs" of vascular injury include a rapidly expanding hematoma, obvious arterial bleeding, thrill from a traumatic arteriovenous fistula, or a pulseless extremity. The presence of any of these signs warrants operative exploration without any imaging required.[107] If these signs are not present, the patient should be evaluated for "soft signs" of vascular injury. "Soft signs"

include neurologic deficit, a nonexpanding hematoma, and wound proximity to an artery.[108] If "soft signs" are present or pulses feel diminished, noninvasive vascular testing should be performed (i.e., ankle-brachial index or brachial-brachial index). An ankle-brachial index or brachial-brachial index <0.9 is an excellent noninvasive test that has a sensitivity and specificity of more than 95% for major arterial injury.[109] If the patient is hemodynamically normal and the patient's noninvasive testing is consistent with vascular injury without "hard signs," CT angiogram of the affected extremity should be done as part of the workup. Blunt trauma patients are less likely to have vascular injury, but when present, they often are seen with crush or stretch injury, dissection, or even arterial compression from fracture fragments.[110–112] In these cases, fracture reduction and splinting may allow return of flow, and perfusion should be reassessed afterwards. In penetrating trauma, the likelihood of a direct arterial injury is higher, but in select cases minimally invasive methods may be more appropriate. Additionally, CT angiogram is less invasive than traditional angiography, with sensitivity and specificity approaching 100%. In the setting of combined fracture and vascular injury, management can prove particularly challenging because patients need urgent fracture fixation and vascular repair. This often will involve temporary vascular shunting and external fixation, with subsequent definitive vascular repair.[113,114] Postoperatively after vascular repair for trauma, we do not recommend routine heparinization for these patients, as the risk of bleeding must be carefully weighed against the risk of graft thrombosis.

After assessing for vascular injury, fracture stabilization should be performed. Plain films should be performed of the suspected fracture site in addition to a joint above and below the injury to assess for occult fractures. If significantly displaced, reduction should be attempted by an experienced practitioner, with subsequent splinting. This may require sedation, but reduction can help reduce hemorrhage in addition to pain. Depending on the extremity, other techniques may be indicated, such as traction in femur fractures. Traction has previously been used extensively throughout history to reduce fractures, with the thought that it can reduce pain and bleeding from fracture sites. Displaced femur fractures, in particular, can bleed substantially into the thigh compartment. There have not been sufficient clinical data in favor of or against traction, and so it should be performed on a case-by-case basis in the hands of an experienced practitioner. Early fixation of long bone fractures, especially femur fractures in the elderly, is particularly important, as there is reduced morbidity compared with delayed repair.[63,115–117]

Acute Compartment Syndrome and Rhabdomyolysis

All extremity fractures need to be continuously assessed for limb viability and compartment syndrome, whether in a preoperative splint or after temporary or definitive fixation postoperatively. The most common site is the lower leg, though thigh and arm compartment syndromes can occur. Acute compartment syndrome of the extremity requires a high index of suspicion and frequent evaluation to detect.[118] Crush injury, limb ischemia, vascular reperfusion, open fractures, and even overly tight dressings are at particular risk for progressive edema of the leg. This increases compartment pressures and reduces perfusion leading to tissue hypoxia and, ultimately, myonecrosis and rhabdomyolysis.[119] Acute compartment syndrome is notoriously difficult to diagnose. The classic symptoms are the "five Ps": pain, pallor, paresthesia, pulselessness, and poikilothermia, with pain often described as occurring with passive stretch. Unfortunately, although these signs may be specific, they are not particularly sensitive for the diagnosis.[120] In an obtunded ICU patient, compartment syndrome can be particularly difficult to diagnose, as these clinical signs cannot be assessed easily, and pulselessness is known to be a very late sign of compartment syndrome. There also are no specific biomarkers that can be checked for compartment syndrome. In this situation, compartment pressure measurements may be indicated with appropriate clinical suspicion. Unfortunately, an "elevated" compartment pressure is ill defined, though accepted values are an absolute pressure >30 mm Hg or a perfusion pressure (i.e., diastolic blood pressure minus compartment pressure) <20 mm Hg. Compartment syndrome is a surgical emergency requiring fasciotomy, and the more delay there is in recognition, the higher the morbidity and rate of limb loss, highlighting the need for continuous limb assessment in this patient population.

Rhabdomyolysis is related to myonecrosis resulting in the release of myoglobin in the blood. It is often associated with compartment syndrome, though it may also occur in ischemia-reperfusion from vascular injury and from severe crush or burn injuries. It is thought that rhabdomyolysis is primarily propagated by oxygen-free radicals with subsequent release of myoglobin.[121] The circulating myoglobin then causes renal toxicity by tubular obstruction, vasoconstriction, or direct toxic effects.[122] This may be exacerbated by prerenal azotemia secondary to hypovolemia in the bleeding or severely injured trauma patient. Numerous therapies have been suggested: mannitol for oxygen free radical scavenging and osmotic effects, loop diuretics to dilute the urine, and sodium bicarbonate to alkalinize the urine with the hope of preventing tubular obstruction. However, to date the only therapy that appears to reduce the incidence of kidney injury from myoglobinuria is early and aggressive fluid resuscitation with isotonic fluid.[123] Patients with rhabdomyolysis will also have hyperkalemia because of the release of intracellular potassium with myonecrosis. Hyperkalemia combined with associated kidney injury may necessitate the use of renal replacement therapy. Continuous renal replacement therapy does not offer any advantage over intermittent hemodialysis but may be more appropriate in the hypotensive severely injured trauma patient, depending on the clinical picture.[124]

CONCLUSION

Pelvic and long bone fractures are common injuries in the trauma population, particularly in the blunt polytrauma patient. The first management consideration is evaluation for shock and the necessity for damage control resuscitation and hemorrhage control. Hemorrhage control may require numerous adjunctive therapies, such as a binder for pelvic fractures or a tourniquet for lower extremity fractures, and even interventional or operative intervention. Additionally, these fracture patterns can have numerous associated injuries that must be diagnosed and addressed once the patient is stabilized. Finally, there are several complications that one must be vigilant in diagnosing: PE, FES, and acute extremity compartment syndrome.

KEY POINTS

- "Damage control resuscitation" using a 1:1:1 ratio of plasma:platelets:packed red blood cells should be initiated for hemorrhage related to pelvic or long bone fractures. Early blood product use is favored over crystalloid administration.
- Fractures should be assessed for overlying soft tissue defects and contamination. Open fractures should be treated with prophylactic antibiotics for 48–72 hours.
- When possible, early enteral nutrition should be initiated to reduce the risk of nosocomial infections, promote intestinal mucosal integrity and immunity, and prevent catabolism.
- Major trauma patients, especially those with pelvic and/or long bone fractures, are at high risk for VTE and should be started on chemical prophylaxis as soon as it is possible and safe.
- FES is a rare but potentially deadly complication of major orthopedic trauma that presents with tachycardia, hypoxia, and altered mental status. Treatment is supportive care.
- Pelvic fracture hemorrhage requires multidisciplinary management. Adjuncts to controlling hemorrhage include short-term binder or sheet stabilization, preperitoneal pelvic packing, angioembolization, REBOA, and external fixation.
- Pelvic fracture patients should be assessed for associated injuries, including the lower urinary tract and rectum.
- Assessment of major long bone fractures starts with assessment of vascular injury and limb viability first, followed by early fracture stabilization.
- Clinicians should assess patients with extremity fractures for compartment syndrome and rhabdomyolysis to prevent morbidity.

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Determination of Brain Death and Management of the Brain-Dead Organ Donor

Helen I. Opdam, Rohit L. D'Costa, Dale Gardiner, and Sam D. Shemie

INTRODUCTION

The diagnosis of death using neurologic criteria is recognized as the complete and irreversible loss of capacity for consciousness and all brain function as a consequence of catastrophic brain injury.[1]

Historically and in many countries, this diagnosis is called "brain death." Some countries and academic papers have moved away from this term, which can be a source of confusion, especially in the media.[2–4] Although supportive of this move, for the purposes of this chapter, the historic and shorthand "brain death" is used.

The pathophysiologic sequelae of brain death include hemodynamic changes, activation of inflammatory and coagulation pathways, metabolic and endocrine effects, and loss of autoregulatory brain functions, all of which can affect multiple organ systems.

The physiologic care and management of the patient with brain death are important for optimizing donation and transplantation outcomes. Approximately 80% of worldwide organ donation after death occurs in individuals determined deceased using neurologic criteria.[5]

DETERMINATION OF BRAIN DEATH

The Concept and Definition of Brain Death

Brain death is accepted as death throughout most of the world, although there exists international variability in both the definition and process of determining brain death.[6] There is general consensus regarding brain death as the complete and irreversible loss of brain function resulting from a devastating brain injury with the features of unresponsive coma, brainstem areflexia, and apnea.[4]

Before the 1950s, catastrophic brain injury would inevitably lead to inadequate spontaneous respiration and rapid cardiorespiratory arrest. The advent of mechanical ventilation and cardiopulmonary resuscitation disrupted the interdependent linkage between these three functions. Complete cessation of brain function could occur and yet by intensive care support, respiration and circulation could be maintained.

Published case series from France in the 1950s first described ventilator-dependent patients in an irreversible state of apneic coma with absent brainstem reflexes and absence of electroencephalographic (EEG) activity, and the term "le coma dépassé" (a state beyond coma) was used.[7,8] In 1968 a committee of Harvard University faculty proposed criteria to diagnose this state, which they called "irreversible coma," and asserted that despite the presence of mechanically supported respiration, and consequent circulation and organ function, people with permanent loss of all functions of the entire brain were dead.[9] The Harvard report heralded the successive worldwide acceptance of brain death and the clinical approach to its determination.

The Harvard report described the requirement for "whole brain death," inclusive of the cerebral hemispheres, cerebellum, and brainstem, and this approach was accepted within the United States and most other countries. At a similar time in the United Kingdom (UK) the "brainstem death" concept was evolving, with a focus on the vital role of the brainstem in consciousness and respiration.[10] This became the legally accepted standard in the UK and in some other countries with historical colonial links.[11] Despite these differences, in practice, the occurrence and process for determining death are very similar in both circumstances.[4,12]

Recent publications have sought to move from an historical and anatomic focused view of brain death to definitions that attempt to unify all diagnoses of human death (both neurologic and circulatory) around a concept of the permanent loss of brain function.[1,13,14]

The vast majority of brain death arises from severe cerebral injury culminating in increased intracranial pressure (ICP), rostral-caudal herniation, reduced cerebral perfusion pressure, and finally the absence of brain blood flow. The loss of brainstem function is caused by ischemia and compression through uncal herniation.

The most common etiologies are hemorrhage (e.g., subarachnoid or intracerebral hemorrhage), ischemic stroke, traumatic brain injury, and hypoxic-ischemic brain injury after a resuscitated cardiac arrest. Other causes include central nervous system infection (e.g., bacterial meningitis, viral encephalitis, brain abscesses); neoplasms (primary brain tumors or metastases); obstructive hydrocephalus; and cerebral edema from hyponatremia, liver failure, or other metabolic conditions. The pathophysiology of raised ICP with loss of brain blood flow and perfusion is facilitated by the rigid nonexpanding nature of the skull and thus can be less likely or slower in onset in patients post-craniectomy and children younger than 2 years with nonfused skull sutures.

In the uncommon circumstance of an isolated brainstem or cerebellar injury, jurisdictions that require whole brain death need to ensure loss of supratentorial blood flow, as it cannot be presumed that "whole brain" death criteria have been met through clinical examination alone. Of note the majority of patients with posterior fossa lesions will with time go on to lose cerebral blood flow through the development of hydrocephalus or by other mechanisms.[15]

Given the linkage between brain and cardiorespiratory function, with cessation of the latter in the setting of devastating brain injury, the development of brain death requires, at a minimum, the provision of mechanical ventilatory support. The setting for brain death is therefore almost exclusively in-hospital and usually within intensive care units.

The fundamentals of the clinical examination for brain death are relatively consistent throughout the world. Most variability in the process of brain death determination relates to aspects such as the qualifications of the examiners and number of examinations; time intervals

between examinations; and the prerequisites for blood pressure, temperature, and drug levels, in addition to the indications and recommended techniques for ancillary testing. Healthcare providers should be knowledgeable about jurisdictional laws and guidelines and ensure their practice is consistent with local requirements.

Making a diagnosis of brain death has benefits irrespective of the potential for organ donation, as it establishes whether a patient is alive or dead. This can eradicate doubt for the family and hospital staff and allow futile and/or inappropriate treatment to cease.[16] Brain death should therefore be determined whenever it has occurred and regardless of whether donation is being considered.

Process for Determining Brain Death

Although individual jurisdictional requirements may vary, the general principles outlined here do not.

The consideration of brain death requires there to be definite clinical and neuroimaging evidence of acute brain pathology sufficient to result in the complete and irreversible loss of brain function. In countries that require "whole brain death," evidence of sufficient cerebral pathology to cause loss of *all* brain function must be present.

The patient must have observed unresponsive coma, brainstem areflexia, and lack of spontaneous breathing effort in the absence of reversible conditions. Some conditions other than a devastating brain injury may result in reversible loss of brain function mimicking brain death, such as severe Guillain-Barré syndrome, snake bite, and botulism. The diagnosis of brain death must not be entertained in such situations.

Even in jurisdictions that require ancillary investigations, the diagnosis of brain death requires a clinical examination to demonstrate the absence of brainstem function.

Preconditions to Clinical Examination

The absence of confounders is important to ensure that the clinical examination accurately reflects the absence or presence of brainstem function. If confounding factors are present (e.g., inability to exclude sedative effects), or if a portion of the examination cannot be adequately undertaken (e.g., inability to adequately examine all brainstem reflexes or perform apnea testing), a clinical examination that is as complete as possible should be conducted, as evidence of residual brain function will exclude the presence of brain death. Where confounders exist, ancillary testing will be necessary in addition to the clinical examination to determine brain death (see later).

The following preconditions should be met before and throughout the clinical examination:

- Exclusion of hypothermia (e.g., temperature ≥35°C).
- Exclusion of hypotension (e.g., mean arterial pressure [MAP] 70–100 mm Hg in an adult and age-appropriate blood pressure in children).
- Exclusion of effects of sedative medications (self-administered or otherwise). The time taken for plasma concentrations of sedative medications to fall below levels with clinically significant effects depends on the dose and pharmacokinetics of medications used and on hepatic and renal function, especially in the case of barbiturates, which take many days to metabolize. Measurement of blood levels to ensure they are below that of clinically significant effects may be necessary. Particular care should be taken to ensure the absence of continued sedative medication effect in patients who have been hypothermic (e.g., therapeutic hypothermia post cardiac arrest). If there is any doubt about the persisting effects of opioids or benzodiazepines, an appropriate medication antagonist should be administered at the time of examination, or ancillary investigations must be carried out.
- Absence of severe electrolyte, metabolic, or endocrine disturbances. These include marked derangements in plasma concentrations of glucose, sodium, phosphate, magnesium, and urea and severe endocrine dysfunction (e.g., severe hypothyroidism or hypoadrenalism).
- Absence of acute liver failure or decompensated chronic liver disease.
- Absence of neuromuscular-blocking drugs. A peripheral nerve stimulator should be used to confirm that neuromuscular conduction is normal unless it is certain that neuromuscular-blocking medications have not been administered.
- Ability to adequately examine the brainstem reflexes (e.g., may not be possible if major facial trauma prevents eye and/or ear examination).
- Absence of a cervical spinal cord injury. This may preclude apnea testing that is reflective of brainstem function.
- Absence of severe cardiopulmonary injury or disease, which may preclude the safe undertaking of apnea testing.

Observation Period and Establishing Irreversibility

It must be established that the loss of brain function is constant over time and irreversible. This is achieved by knowledge of the mechanism and natural history of the devastating brain injury and a period of observation (e.g., a minimum of 4–6 hours of features consistent with brain death). When brain death is suspected after a resuscitated cardiac arrest, a longer period of 24 hours observation is recommended before brain death testing, as there can be slow recovery of brainstem function after successful resuscitation. Similarly, after prolonged hypothermia, such as therapeutic cooling post cardiac arrest, a period of 24 hours post-rewarming is recommended because of the effects of hypothermia on neurologic function and the impact cooling may have on drug metabolism, as demonstrated by case reports that support a more conservative approach in such circumstances.[17,18]

In patients who are unresponsive with nonreactive pupils but appear to be spontaneously breathing, care must be taken that the ventilator is not autocycling/autotriggering on a spontaneous mode secondary to cardiac pulsations.

Situations Requiring Extra Caution

The UK has identified "red flag" categories where additional diagnostic caution is advised[19]:

1. Testing <6 hours of the loss of the last brainstem reflex
2. Testing <24 hours of the loss of the last brainstem reflex, where the etiology is primarily anoxic damage
3. Hypothermia—24-hour observation period after rewarming to normothermia recommended
4. Patients with any neuromuscular disorders
5. Steroids given in space-occupying lesions such as abscesses
6. Prolonged fentanyl infusions
7. Etiology primarily located to the brainstem or posterior fossa
8. Therapeutic decompressive craniectomy.

Clinical Examination

The following three clinical criteria need to be established for the neurologic determination of death:

- Unresponsive coma
- Absent brainstem reflexes
- Apnea (absence of spontaneous breathing)

A generic process for undertaking the clinical examination is suggested in Table 159.1. A number of countries have published education videos to assist clinicians.[20–22]

Protocols vary in the requirement of whether it must be possible to reliably test each of the brainstem reflexes bilaterally, or at a minimum unilaterally. Ancillary testing is required if it is not possible to meet the

TABLE 159.1 Process for the Clinical Examination in the Determination of Brain Death

Test	Response Consistent With Brain Death	Considerations
Responsiveness		
There should be unresponsive coma with no evidence of arousal or movement after noxious stimulation, other than spinal-mediated reflexes.		
Noxious stimuli should be applied in the cranial nerve distribution and all four limbs and trunk, observing for centrally mediated motor responses (e.g., pressure over the supraorbital nerve, sternal rub, and deep nail bed pressure).	There should be no motor response within the cranial nerve distribution or any response in the limbs secondary to cranial nerve stimulation. This equates to a Glasgow Coma Score (GCS) of 3.	Spinal reflexes may be present in patients with brain death (see later) and are not to be confused with a pathologic flexion or extension response.
Brainstem Reflexes **The cranial nerves should be examined sequentially and bilaterally**. **All testable brainstem reflexes must be absent for brain death to be determined**. **The presence of a brainstem reflex means brain death is not present and testing is then ceased.**		
Pupillary light reflex—cranial nerves II and III Shine a bright light into the eye and look for a pupillary constrictor response.	There should be absence of ipsilateral and contralateral pupillary response, with pupils fixed in a midsize or dilated position (~4–6 mm), in both eyes.	Constricted pupils are not consistent with brain death and suggest the possibility of drug intoxication or locked-in syndrome. Pupils can be any shape (round/oval/irregular). Ancillary testing is recommended if eye trauma or anophthalmia limits examination.
Corneal reflex—cranial nerves V and VII Touch the corneas, applying light pressure with sterile soft cotton wool or gauze, and examine the eyes for blinking or other response.	No eyelid movement should be seen.	Touching the sclera is not sufficient. Care should be taken to avoid damaging the cornea. Ancillary testing is recommended if eye trauma, anophthalmia, severe orbital edema, or prior corneal transplantation limits examination.
Reflex response to pain in the trigeminal distribution—cranial nerves V and VII Apply pain over the trigeminal distribution (e.g., pressure over the supraorbital nerve).	No facial or limb movement should be seen.	Ancillary testing is recommended in the presence of severe facial trauma and swelling that may preclude evaluation.
Oculovestibular reflex—cranial nerves III, IV, VI, and VIII Inspect the external auditory canal with an otoscope to confirm that the eardrum is visible. If the eardrum is not visible, the canal must be cleared before testing can occur. Elevate the head to 30 degrees to place the horizontal semicircular canals in the true vertical position. Irrigate with ≥30 mL of ice water using a syringe or a syringe attached to a catheter placed inside the auditory canal. Hold eyelids open and observe for eye movement for a minimum of 60 seconds. Test both sides separately.	No eye movement should occur in response to the cold water.	A ruptured eardrum does not preclude the test. Ancillary testing is recommended in the setting of severe eye trauma, anophthalmia, or a fracture of the base of the skull or petrous temporal bone that may obliterate the response. Testing for the oculocephalic reflex (rotating the head briskly horizontally to both sides) examines the same reflex pathways and is not required in addition to the oculovestibular reflex and should not be undertaken in the presence of a cervical spine injury.
Gag reflex—cranial nerves IX and X Touch the posterior pharyngeal wall, on both sides, with a tongue depressor or cotton swab. A laryngoscope or video laryngoscope may assist in obtaining a good view of the pharynx for stimulation.	No gag response should be seen.	If the patient is orally intubated, the gag reflex may be difficult to discern.
Cough/tracheal reflex—cranial nerve X Stimulate the tracheobronchial wall to the level of the carina with deep endotracheal placement of a soft suction catheter.	No cough response should be seen.	The efferent limbs for this reflex are the phrenic nerve and the nerves of the thoracic and abdominal muscles. Therefore it cannot be assessed in patients with high cervical cord injury; in this setting, ancillary testing is recommended.

TABLE 159.1 Process for the Clinical Examination in the Determination of Brain Death—cont'd

Apnea Testing

The test seeks to demonstrate a lack of spontaneous breathing in the setting of a sufficient respiratory center stimulus. Many guidelines suggest reaching a partial pressure of carbon dioxide in arterial blood ($PaCO_2$) of ⩾60 mm Hg (8 kPa).

Apnea testing should be undertaken ONLY if all the earlier reflexes are absent.

Preoxygenate (inspired oxygen concentration 100%) for >5 minutes to prevent hypoxemia during the test, and adjust the ventilator settings such that the $PaCO_2$ normalizes at 40–45 mm Hg (5.3–6 kPa). Throughout the procedure, monitor the patient's percentage blood oxygenation saturation (SpO_2).	If any respiration attempts are seen (that is, abdominal or chest excursions or activity of accessory respiratory muscles, or if there is end-tidal CO_2 evidence of a breath), the test is ceased and the patient is reconnected to the ventilator, as the criteria for brain death have not been met.	Usually $PaCO_2$ rises by ~3 mm Hg (0.4 kPa) for every minute of apnea.
Disconnect the endotracheal tube (ETT) from the ventilator, with or without the provision of oxygen. Common methods for providing oxygen include the use of a self-inflating bag with attached continuous positive airway pressure (CPAP) valve to prevent atelectasis or inserting a small cannula via the ETT to approximately the level of the carina to deliver oxygen at 4–6 L/min.		Some protocols require that a pH goal is also met, (e.g., <7.30) and/or that in the setting of prior CO_2 retention that a rise (e.g., increase of >20 mm Hg = 2.7 kPa) above a known chronic baseline is achieved.
Expose the chest and abdomen and observe continuously for any spontaneous breathing. End-tidal CO_2 monitoring can be very helpful.		If starting from normocapnia, the $PaCO_2$ is likely to be >60 mmHg (8 kPa) after 8–10 minutes.
An arterial blood gas (ABG) is taken after approximately 8–10 minutes to document the rise in $PaCO_2$ to above 60 mm Hg (8 kPa). If the patient is stable and point-of-care ABG testing is available, await the return of the result before reconnecting the ventilator in case the required change in $PaCO_2$ has not been achieved.		Patients may become hypoxic or develop hemodynamic instability. If hypoxia (SpO_2 <88%) occurs, give 1–2 mandatory breaths and continue apnea testing. Vasopressors may be adjusted to support blood pressure.
At the end of testing, return the patient to mechanical ventilation.		If the test cannot be completed due to cardiorespiratory instability, it should be ceased and an alternative approach to undertaking the test be used or, alternatively, an ancillary test may be needed. Alternative approaches to achieving the $PaCO_2$ goal while maintaining oxygenation include providing oxygen via a self-inflating bag with CPAP valve, preapnea recruitment maneuvers, and induction of hypercarbia with CO_2 or carbogen before disconnecting from the ventilator.
		Care must be taken if a tracheal catheter is used, as wedging, trauma, or a size that is large relative to the tracheal diameter may result in barotrauma. High oxygen flow rates can cause CO_2 washout with failure of the $PaCO_2$ to rise.
		If the CPAP circuit on the ventilator is used, care must be taken to identify autotriggering/autocycling, which may be misinterpreted as spontaneous breathing.

local standard because of inability to adequately examine at least one or both eyes and ears.[23]

Family presence during the clinical examination should be offered, with appropriate explanation and support, as family members may find witnessing the testing useful to their acceptance and understanding of death, especially the apnea test component. Diagrams, the use of nationally endorsed testing forms, and viewing neuroimaging and reports may also assist the family in their understanding of the patient's prognosis and the concept of brain death.

When preconditions are satisfied, then clinical examination alone is preferable for the routine determination of brain death without reliance on ancillary testing (see later).

Number of Examinations

A single clinical examination, including apnea testing, is the minimum standard for determination of brain death in adults.[24] Most jurisdictions require two examinations. If two examinations are performed, an intervening period is unnecessary because the prerequisite of irreversibility will have already been demonstrated by knowledge of the mechanism and natural history of the devastating brain injury, along with a suitable observation period before initiating testing. All that may be required is enough time to allow for physiologic stabilization between tests. Many clinicians will use this time to update the family and invite them to witness the second examination.

Spinal Reflexes

The preservation of spinal reflexes after brain death has been described for decades.[25] Spinal reflexes can be either spontaneous or provoked by noxious stimuli such as pain, passive neck movement, hypotension, and hypoxemia after terminal removal of the ventilator or during the apnea test.[26] They never involve the brainstem cranial nerves.

Prevalence is up to 50% of patients with brain death and is the result of a functioning spinal arc with loss of higher center inhibitory control.

Spinal reflexes can be simple or complex and may be upsetting when observed by family members and staff.[27] It is essential that these movements are explained and forewarned to families and staff.

The most common movements described are finger and toe jerks, the undulating toe reflex, triple flexion response, pronation-extension reflex, facial myokymia, and myoclonus.[26,28] Rarely, marked upper extremity and torso movements may occur, such as the Lazarus sign, in which there is bilateral arm flexion; shoulder adduction; and sometimes flexion of the trunk, hips, and knees.

Other physiologic signs that are compatible with brain death include sweating, blushing, tachycardia, normal blood pressure without the need for pharmacologic support, and an absence of diabetes insipidus.[29]

Observations that are incompatible with brain death include decerebrate or decorticate posturing, true extensor or flexor motor responses to painful stimuli, seizures, and limb movement elicited by stimulation of the cranial sensory nerves or facial movement elicited by stimulation of the body or limbs.

Ancillary Testing

Ancillary testing is required if the preconditions for clinical examination alone to determine brain death cannot be met. This may include the presence of confounding conditions that cannot be resolved or the inability to complete all aspects of the clinical examination, including the apnea test. Ancillary tests may also be required if there is uncertainty in the interpretation of aspects of the clinical examination, including whether movements are centrally or spinal-mediated. Other reasons for undertaking ancillary tests include a desire to determine brain death earlier than the required observation period allows, if national policies or practices require them, and, for some families, ancillary tests may assist in providing greater understanding and certainty of brain death, especially if they have not witnessed the clinical examination.[30] It is recommended that the clinical examination be completed to the fullest extent possible before undertaking an ancillary test.

Most ancillary testing is on the premise that demonstrating absence of cerebral blood flow and/or perfusion in a person with a supported somatic circulation correlates with permanent loss of brain function. An exception is EEG, which measures brain activity. The ideal test would have no false positives (incorrect diagnosis of brain death) or false negatives (incorrect ruling out of brain death). Various techniques have been described and validated, generally against clinical brain death testing. Local availability and preferences tend to guide use[6]:

1. Digital subtraction angiography (three- or four-vessel cerebral angiography)—Long regarded as the gold-standard ancillary test for this purpose, cerebral angiography in brain death demonstrates flow obstruction at the level of the carotid siphon and the foramen magnum.[31,32] Even cerebral angiography is subject to interoperator variability because of, for example, the vigorousness of contrast injection, but it is widely accepted as specific and sensitive.[33]
2. Radionuclide imaging (cerebral scintigraphy)—Radiotracer uptake should not occur in brain parenchyma in the setting of brain death. Intravenous injection of an agent such as Tc-99m labeled hexamethylpropyleneamine oxime (HMPAO), which normally crosses the blood-brain barrier and persists in brain parenchyma, together with planar or single-photon emission computed tomography (SPECT) detection is used.[34] Although there have been case reports of false-positive tests, the specificity is thought to be high.[35]
3. Computed tomography (CT) angiography/perfusion—Being relatively easily available and noninvasive, CT has obvious appeal as an ancillary modality. It was evaluated initially using a 7-point and then a more sensitive 4-point scoring system.[36,37] A Cochrane review identified only moderate sensitivity and therefore could not recommend CT angiography as a mandatory investigation.[38]
4. Transcranial Doppler (TCD)—Although portable and noninvasive, TCD is operator dependent and reliant on detection of a suitable acoustic window.[39] A systematic review and meta-analysis reported very high sensitivity and specificity when compared with clinical brain death testing.[40]
5. Magnetic resonance imaging (MRI)—Various techniques involving MRI have been evaluated in brain death (e.g., diffusion-weighted imaging [DWI], susceptibility-weighted imaging [SWI], gradient-recalled echo [GRE], magnetic resonance angiography [MRA]), but techniques suffer from uncertain specificity and the logistic impediments of transporting ventilated patients to the MRI scanner.[31]
6. EEG—In contrast to the aforementioned techniques, EEG is a test of cerebral function and not blood flow. It is a common mandatory test in algorithms for brain death determination in some jurisdictions and importantly requires clinical preconditions to be met (e.g., normothermia and absence of confounding sedative or metabolic effects).[6,41] Because of its limited utility and case reports where overreliance upon it has contributed to misdiagnosis, some countries now advise against its use.[17,23,42,43]

Repeat Testing

If clinical examination or ancillary tests demonstrate that complete and irreversible loss of brain function has not yet occurred, consideration should be given to repeating these tests after a suitable interval.

Brain Death Determination in Children and Neonates

International guidelines for the diagnosis of brain death in children and term infants are consistent with those for adults, particularly in their preference for clinical determination, with ancillary testing having a similar secondary role when clinical testing alone is not possible or reliable.[3,23,44,45] In these guidelines the observation periods, requirements for repeat testing, and other criteria are generally more conservative in the newborn and early infant period.

MANAGEMENT OF THE BRAIN-DEAD ORGAN DONOR

As discussed earlier, the diagnosis of brain death is independent of any organ donation considerations. When patients and families have agreed to donation after death, the optimal physiologic support of potential donors maximizes donation and transplant outcomes.

In 1995 Wheeldon and colleagues published the experience of a UK center of standardized donor cardiorespiratory optimization instituted by the retrieval team upon arrival at the donor hospital that increased the number of hearts and other organs recovered and transplanted.[46]

In 1999 the United Network for Organ Sharing (UNOS) in the United States introduced the Critical Pathway for the Organ Donor that recommended defined physiologic goals and a consistent and active approach to donor management. In a pilot introduction of the pathway, the numbers of organs transplanted per brain-dead donor increased by 11.3%, including a 19.5% increase in hearts transplanted.[47]

Since that time various guidelines and bundles of care have been developed to guide the physiologic management of patients with the potential to donate organs for transplantation after brain death.[23,48–54] Studies have also confirmed that being able to meet prespecified donor management goals, including in more marginal or expanded-criteria donors, results in more organs transplanted per donor, as has also been observed with the involvement of intensivists in leading donor management, particularly in optimizing lung use.[55–58]

In addition to general supportive care, specific treatment to counter the common sequelae of brain death such as hypotension, hypothermia, and diabetes insipidus is usually required. The provision of specific hormonal therapy (thyroid hormone, vasopressin, and steroids) is controversial because of a lack of high-level evidence to support its efficacy.

Pathophysiology of Brain Death

The pathophysiologic sequelae of brain death include hemodynamic changes, activation of inflammatory and coagulation pathways, and loss of autoregulatory brain functions, including the hypothalamic – pituitary axis, all of which can affect multiple organ systems.

During the development of brain death, raised ICP may lead to the classic physiologic responses first described by Cushing, with compensatory arterial hypertension and bradycardia.[59] Brainstem compression and ischemia can result in a marked sympathetic response, with tachycardia and tachyarrhythmias, hypertension, and high blood levels of catecholamine resulting in intense vasoconstriction and increased afterload—the "autonomic storm." Acute myocardial ischemia with dysfunction, electrocardiographic changes, and myocyte necrosis have been demonstrated in animals and humans.[60,61] Raised pulmonary hydrostatic pressure may cause neurogenic pulmonary edema that is accentuated by capillary endothelial damage. This is followed by loss of autonomic function and respiratory drive, leading to hypotension and apnea, and hypothalamic – pituitary dysfunction, with loss of temperature regulation and the development of diabetes insipidus.

Not all patients exhibit these classic features, and occasionally brain death can develop without any instability and is only recognized by the loss of neurologic function.

General Principles of Management

The approach to managing the potential organ donor is similar to that of other intensive care patients. The same expert treatment should be provided following the general principles of critical care management.

Awareness of the specific perturbations that may occur in brain death, in addition to consideration of the patient's underlying condition, will help with anticipating problems and the timely institution of appropriate treatment.

The physiologic goals are similar to those in any other critically ill patient, and the usual spectrum of monitoring and interventions should be employed, including the use of central venous and arterial vascular access.

Communication may be required between the intensive care team and transplant and/or surgical retrieval team regarding organ suitability and assessment or provision of specific physiologic supports and can be facilitated via the donor coordinator.

The use of coordinated care guidelines, bundles of care, and checklists increases the likelihood of medical suitability of donors and maximizes successful organ transplantation. Box 159.1 provides guidance and suggests aims for the clinical management of potential donors with brain death.

Cardiovascular Effects and Support

Cardiac arrhythmias occur commonly during the development of brain death as a result of the autonomic changes, endogenous catecholamines, and myocardial ischemia, and subsequent to brain death from hypovolemia, electrolyte abnormalities, hypothermia, and inotropes.[63]

All types of arrhythmias can be seen, including bradycardia and both supraventricular and ventricular tachyarrhythmias. Cardiac arrest has been reported to occur in 1%–25% of potential donors with brain death, and this can be reduced in frequency with careful physiologic management.[57,64,65]

Hypotension and circulatory shock develop in the majority of patients with brain death and may have multiple causes, including loss of sympathetic tone leading to vasodilatation; hypovolemia from diabetes insipidus, osmotic agents for prior treatment of raised ICP, and blood loss; cardiac dysfunction that is either acute or preexisting; and potentially hypothalamic – pituitary function.

Treatment Approach

The hypertension and tachycardia associated with the development of brain death are usually self-limited, and no treatment is required. If antihypertensives are used, short-acting agents are preferable (e.g., esmolol, nitroglycerin, sodium nitroprusside, nicardipine, labetalol), as longer-acting agents may exacerbate subsequent hypotension. It is unknown whether reducing hypertension and tachycardia protects the heart or other organs from catecholamine-mediated injury.

Arrhythmias can be minimized by maintaining normal serum electrolyte concentrations, body temperature, and blood pressure. Standard treatment (e.g., amiodarone, cardioversion) is used for atrial and ventricular arrhythmias. Bradycardia in patients with brain death is resistant to the vagolytic effects of atropine.[66] In the situation of bradycardia associated with low cardiac output, epinephrine, isoprenaline, dobutamine, dopamine, and/or pacing are recommended.

In the event of a cardiac arrest, cardiopulmonary resuscitation may result in recovery of cardiac function and successful transplantation, although some local policies require informed consent for its use from families of patients planned for donation.

Vasoactive agents are required in 80%–90% of brain-dead organ donors.[67,68] Arterial pressure goals should maintain organ perfusion based on individual patient characteristics (often MAP >70 mm Hg).

BOX 159.1 Donor Care and Physiologic Goals

General
- Monitoring: ECG, pulse oximetry, intraarterial pressure, CVP, core temperature, urine output (hourly), ABGs (4-hourly), consider cardiac function monitoring
- Routine tests: Daily or as required: CXR; ECG; full blood examination; clotting profile; urea, creatinine, electrolytes, including magnesium, calcium and phosphate; liver function tests
- Core temperature 36–38°C*
- Elevate head of bed at 30 degrees, eye care, mouth care, other routine care

Cardiovascular
- MAP 70–100 mm Hg
- Euvolemia, with CVP 4–10 mm Hg
- Adequate cardiac output and organ perfusion: urine output ~1 mL/kg/h (range 0.5–3 mL/kg/h); lactate <2 mmol/L; good capillary refill
- If hypotension: IV infusion of vasopressin (≤2.4 U/h) and/or norepinephrine or phenylephrine
- If bradycardia with low cardiac output – IV infusion of epinephrine or isoprenaline or dobutamine or dopamine and/or pacing
- If low cardiac output – IV infusion of epinephrine or dobutamine or dopamine or milrinone

Respiratory
- Regular tracheal suctioning; positioning side-to-side; maintain tracheal tube cuff inflation
- Prevent atelectasis – PEEP >5 cm H_2O; lung recruitment maneuvers; bronchoscopy as required
- Maintain ventilation and prevent lung injury – $PaCO_2$ 35–45 mm Hg; tidal volume of 6–8 mL/kg predicted body weight; plateau pressure <30 mm Hg
- Maintain oxygenation – SpO_2 92%–95% by adjusting FiO_2 and PEEP (PEEP >5 cm H_2O)

Intravenous Fluid and Metabolic Management
- Sodium 135–145 mmol/L: if sodium >145 mmol/L give additional free water (intravenous 5% glucose, or sterile water via a central venous catheter)
- Urine output ≈1 mL/kg/h (range 0.5–3 mL/kg/h)
- If polyuric >300 mL/h ± rising serum sodium, assume diabetes insipidus and give DDAVP 4 μg every 6 hours or as required and/or commence vasopressin IV infusion (≤2.4 U/h)
- Potassium 3.5–5 mmol/L; phosphate >0.7 mmol/L; magnesium >0.7 mmol/L – supplement as required
- Blood glucose level 4–14 mmol/L; if >14 mmol/L – IV infusion of insulin
- Continue enteral feeding or total parenteral nutrition
- Hb >70 g/L: consider blood transfusion if Hb <70 g/L and/or if bleeding; if bleeding, consider transfusion of clotting factors and other hemostasis strategies

Additional Hormonal Supportive Treatment†
- Give methylprednisolone 15 mg/kg IV single bolus and/or hydrocortisone 50 mg every 6 hours if requested by lung transplant team and/or if hemodynamic instability despite previous measures
- Give triiodothyronine (T_3) 4 μg IV bolus followed by 3 μg/h by IV infusion if requested by heart transplant team and/or if hemodynamic instability despite previous measures

ABGs, Arterial blood gases; *CVP,* central venous pressure; *CXR,* chest x-ray; *DDAVP,* 1-D amino-8 D arginine vasopressin desmopressin; *ECG,* electrocardiogram; *FiO_2,* fraction of inspired oxygen; *Hb,* hemoglobin; *IV,* intravenous; *MAP,* mean arterial pressure; *$PaCO_2$,* partial pressure of carbon dioxide in arterial blood; *PEEP,* positive end-expiratory pressure; *SpO_2,* percentage blood oxygen saturation.
*Some protocols recommended hypothermia (34–35°C) if the kidneys will be used for transplantation.[62]
†Hormonal supportive treatment may include steroids, thyroid hormone, vasopressin, and insulin.

This is achieved by intravenous fluid administration to target euvolemia and vasopressor agents. There is little evidence for the preferential use of either colloids or crystalloids, noting that hydroxyethyl starch should be avoided, given it can cause renal injury.[69] Vasopressin may be preferable if there is concurrent diabetes insipidus, and norepinephrine and phenylephrine are other vasopressor agents frequently used. In patients with low cardiac output, inotropic agents such as epinephrine, dobutamine, dopamine, or milrinone are recommended. A single prospective multicenter study demonstrated improved kidney graft function after transplantation when the donor received a dopamine infusion before donation, but this finding has not been repeated.[70]

Echocardiography or invasive cardiac function monitoring may be necessary in hemodynamically unstable patients or those for whom cardiac function assessment and optimization are high priorities.

If cardiopulmonary instability is refractory to these interventions, initiation of extracorporeal membrane oxygenation (ECMO) or placement of an intraarterial balloon pump can be considered, noting ECMO use is increasingly common in some jurisdictions in donation procedures such as normothermic regional perfusion.[71–73]

Diabetes Insipidus and Fluid and Electrolyte Therapy

In normal health, vasopressin, also known as *antidiuretic hormone* (ADH), is released by the posterior pituitary gland and has both vasopressor and antidiuretic effects through acting on V1 and V2 receptors, respectively. In brain death there is commonly, but not universally, a deficiency in ADH resulting in diabetes insipidus, as evidenced by brisk hypo-osmolar polyuria leading to hypovolemia, hyperosmolality with hypernatremia, and hemodynamic instability if left untreated.[74,75]

Early human studies indicate that deficient vasopressin occurs in up to 80% of brain-dead individuals.[76,77] Current outcome registries in Australia and New Zealand indicate that 77% of brain-dead organ donors develop diabetes insipidus that requires treatment with vasopressin or the synthetic vasopressin analogue desmopressin (1-D amino-8 D arginine vasopressin [DDAVP]).[68]

Treatment Approach

Treatment of diabetes insipidus is vital for donor stability. Attempts to treat with intravenous fluid alone leads to hypothermia because of the infusion of relatively cool fluids, electrolyte disturbance, and donor instability.

Diabetes insipidus is best treated early before significant hypovolemia and metabolic derangement develop. Polyuria (e.g., urine output ≥3 mL/kg/h) and/or rising serum sodium are sufficient triggers to begin treatment, as formal confirmation with paired urinary and serum osmolarity can delay treatment, resulting in donor instability.

Suitable agents include either vasopressin or DDAVP. DDAVP is highly selective for the V2 renal receptor subtypes, has no significant vasopressor activity, and may be the preferable agent to treat diabetes insipidus in the absence of hypotension. It is usually given as an intravenous bolus of between 2 and 6 μg every 6–8 hours or as required, noting it has a much longer half-life than vasopressin.

Vasopressin may be used to treat both diabetes insipidus via its action on V2 renal receptors and hypotension through its pressor effect by acting on V1 receptors on vascular smooth muscle. It must be given by intravenous infusion because of a short half-life (10–35 minutes). The usual dose range is 0.5–2.4 units per hour titrated to blood pressure and urine output. Although some guidelines suggest dose ranges of up to 4 units per hour, there is concern that doses higher than 2.4 units per hour may cause potentially deleterious vasoconstriction of renal, mesenteric, pulmonary, and coronary vasculature.[48,78]

Whether vasopressin to treat hypotension in brain death provides any advantage over other vasoactive agents in terms of efficacy in donor support and transplant outcomes is not known.

Both vasopressin and DDAVP can be administered concurrently in the potential organ donor to control diabetes insipidus and hypotension.

Hypernatremia and fluid volume loss resulting from diabetes insipidus should be corrected with salt-free fluid such as intravenous 5% glucose or with sterile water administered via a central venous catheter if there is resistant hyperglycemia.

Serum electrolytes should be monitored every 2–4 hours to guide fluid and electrolyte replacement, and electrolytes should be maintained within the normal ranges.

Endocrine Effects and Hormonal Supportive Treatment

There is less certainty about the frequency and impact of anterior pituitary gland dysfunction in brain death. Blood flow to the anterior pituitary can remain intact through perfusion from subsidiaries of the external carotid arteries, and there is uncertainty as to the occurrence and clinical relevance of reduced levels of thyroid hormone and cortisol in brain death.[79]

Observational studies in human donors with brain death tend to report a reduction in the free plasma triiodothyronine (T_3) concentration, but findings are variable with respect to changes in thyroxine (T_4) and thyroid-stimulating hormone (TSH).[76,77,80,81] These changes in thyroid hormone levels and TSH in brain death may simply constitute sick euthyroid syndrome, which is commonly seen in critically ill patients without brain injury.

Studies have also failed to identify a consistent association between circulating thyroid hormone concentrations in the brain-dead donor and the donor hemodynamic status, requirement for vasoactive drugs, or cardiac function.[80–83]

Published case series and retrospective audits of the effect of thyroid hormone in brain-dead donors tend to find a beneficial effect of thyroid hormone administration on donor hemodynamics, number of organs procured or transplanted, and/or graft survival.[84] In contrast, all randomized controlled trials have reported no benefit of thyroid hormone administration either alone or in combination with other hormonal therapies.[85–91]

Two recent systematic reviews, which included meta-analyses of placebo-controlled randomized controlled trials, concluded that thyroid hormone does not add hemodynamic benefits or result in an improved number or quality of organs procured for transplantation and cannot be recommended in the routine management of the brain-dead potential organ donor.[92,93]

Despite this, the use of thyroid hormone in brain-dead organ donors in the United States increased from 25% to 75% during 2000–2012.[94]

As with thyroid hormone, there is controversy as to the occurrence of clinically significant adrenal hypofunction in human brain death. A number of small studies in potential donors with brain death have found normal or high levels of cortisol and adrenocorticotropic hormone (ACTH), no association between serum cortisol levels and severity of hypotension, and no serial fall in serum cortisol with the development of brain death.[76,77,80]

In contrast, other small studies have found brain death is associated with low cortisol levels, along with deficient response to ACTH stimulation, as compared with patients with less severe brain injuries.[95,96] Studies of steroid administration to brain-dead patients with a poor response to synthetic ACTH have, however, been inconsistent in terms of the reported hemodynamic benefit.[96,97]

In a European multicenter observational study, steroid use in organ donors with brain death was associated with a lower dose and shorter duration of vasopressor support.[97]

Recent systematic reviews of the use of steroids in brain-dead potential donors have similarly found positive associations on donor hemodynamic and oxygenation status, organs procured, and graft function in observational studies, but neutral outcomes in the small randomized controlled trials that have occurred.[98,99]

In contrast, two large, double-blinded, placebo randomized controlled trials on steroid use (50 mg hydrocortisone every 6 hours) in critically ill patients with septic shock found steroids improved blood pressure and facilitated earlier weaning of vasopressor agents.[100,101]

Apart from hemodynamic reasons, other rationales for administering steroids to potential donors with brain death include their immunomodulatory and antiinflammatory effects.

Brain death is associated with high levels of cytokines, higher than those that occur in patients with similar types of injury though without brain death.[102] Activation of inflammatory cascades in the donor may affect organ function and likelihood of rejection episodes in the recipient.[103–105] A neutrophilic pulmonary infiltration is observed in brain death, and elevated concentrations of interleukin (IL)-8 in donor bronchoalveolar fluid correlate with early graft failure.[106,107] Higher plasma donor IL-6 concentrations are associated with fewer transplanted organs and reduced recipient survival.[108]

High-dose steroids may modulate immune function and decrease inflammation in the donor, with the potential to improve recipient graft function. High-dose methylprednisolone administration to the donor has been associated with improved donor lung oxygenation and increased organ retrieval rates, in addition to less ischemia-reperfusion injury and acute rejection in liver recipients, although no benefit on posttransplantation acute renal failure was observed in a double-blinded, placebo-controlled study when 1000 mg of methylprednisolone was administered to brain-dead kidney donors.[109–111]

Treatment Approach

The available evidence does not support the routine administration of thyroid hormone in potential organ donors with brain death. Thyroid hormone administration may provide benefit in donors who are hemodynamically unstable and/or heart donor candidates who have borderline cardiac function (e.g., <45% left ventricular ejection fraction) despite optimization of volume state with fluid therapy, vasoactive agents, and other general supportive care, including correction of electrolyte abnormalities.

It is suggested that replacement thyroid hormone improves the metabolic and hemodynamic status in brain death by reactivation of mitochondrial energy metabolism.[112]

Although the use of thyroid hormone in these circumstances is based on low-level evidence, T_3/T_4 use may be justified in that there is little indication that thyroid hormone causes harm.

Despite this uncertainty, thyroid hormone, in conjunction with other hormonal therapies, remains part of the recommended management of cardiothoracic organ donors in the UNOS Critical Pathway for the Organ Donor.[113]

T_3 may be initiated with a 4-μg intravenous bolus followed by infusion of 3 μg/h.[48,51] Intravenous T_3 may be preferable to other formulations because of its biologic potency and immediate availability to

tissues. Alternatively, T_4 may be given initially with a 20-μg intravenous bolus followed by infusion of 10 μg/h. Thyroxine requires conversion to the biologically active T_3, and so its onset of action and efficacy are less certain. Thyroxine may also be administered enterally if the intravenous formulation is not available, although impaired enteral absorption may further limit efficacy.

Physiologic stress-dose steroids (e.g., intravenous hydrocortisone 50 mg every 6 hours) may improve blood pressure and reduce vasopressor doses required. High-dose corticosteroid administration (e.g., methylprednisolone 1000 mg or 15 mg/kg intravenously) may reduce the potential deleterious effects of the inflammatory cascade that follows brain death on donor organ function and improve transplant recipient outcomes. It has been suggested, however, that low-dose as compared with high-dose steroids may have no different effect in terms of organs retrieved and transplanted.[114]

Blood for tissue typing should be collected before high-dose steroid administration, as steroids have the potential to suppress human leukocyte antigen expression.

Respiratory Effects and Support

Patients with brain death, as with other critically ill patients, are at risk of pulmonary atelectasis, aspiration, sputum retention, pneumonia, and edema from fluid overload; cardiac dysfunction; and neurogenic mechanisms.

During the development of brain death, the autonomic storm leads to systemic vasoconstriction and increased vascular resistance, which causes decreased left ventricular output and increased retrograde pulmonary venous pressure, resulting in increased hydrostatic pressure across pulmonary capillary membranes.

Deterioration of the donor's respiratory status can result in the lungs becoming unsuitable for transplantation, in addition to jeopardizing donor maintenance and donation in general.

Treatment Approach

Routine respiratory care should continue, including suctioning, positioning side-to-side and turning, and keeping the head of the bed at 30 degrees elevation, with attention to maintaining tracheal tube cuff inflation to avoid pulmonary aspiration. Techniques that reduce atelectasis and lung-protective ventilation strategies should be used such as lung recruitment maneuvers, positive end-expiratory pressure (PEEP) 5–10 cm H_2O, tidal volumes of 6–8 mL/kg of predicted body weight, plateau pressure less than 30 cm H_2O, and maintaining the fraction of inspired oxygen (FiO_2) at the lowest level to keep an oxygen saturation (SpO_2) of 92%–95%.[115–117]

Fiberoptic bronchoscopy can be considered for suctioning and clearing bronchial obstructions and may be requested by lung transplant teams. Secretions should undergo microscopy and culture and antibiotics started if there is suspicion of a pulmonary infection, although there is no role for routine antibiotic prophylaxis.

Higher rates of lung donation are associated with a minimal donor-positive fluid balance, and diuretics may be used to treat pulmonary edema.[118] Euvolemia is compatible with donation of all organs, including lung and kidneys.

As there is an association between steroid use, donor lung oxygenation, lung recovery, and transplantation, some lung retrieval teams will request methylprednisolone 15 mg/kg, but this lacks support from randomized controlled trials.[109]

Hypothermia and Temperature Management

Loss of hypothalamic thermoregulation, reduced heat production, and inability to conserve heat by vasoconstriction or generate it by shivering renders the brain-dead individual poikilothermic (body temperature varies with ambient temperature). The tendency to hypothermia is exacerbated by exposure and administration of intravenous cold fluids. Adverse effects include cardiac dysfunction, arrhythmias, platelet dysfunction, coagulopathy, and a leftward shift of the oxyhemoglobin dissociation curve, with reduced oxygen delivery to tissues.

Treatment Approach

Hypothermia is easier to prevent than reverse. Keep room temperature ≥24°C and use warming blankets, humidification and heating of inhaled gases, and warmed intravenous fluids if large volumes are required.

A recent multicenter randomized controlled trial in brain-dead donors showed a reduction in the incidence of delayed kidney graft function in recipients when mild hypothermia (34°C–35°C) in the donor was induced and maintained until retrieval surgery.[62] Concern about the potential negative impact of donor hypothermia on other organs has been raised, although a follow-up and safety analysis demonstrated no adverse effects on donor physiology or extrarenal graft survival and improved 1-year graft survival for kidneys from standard-criteria donors who received mild hypothermia.[119,120] Many published protocols, however, continue to recommend targeting normothermia, and widespread uptake of induced hypothermia for donor management may not occur until further evidence is available to support its utility.[23,54]

Other Aspects of General Care and Nutrition

Continuing enteral feeding in the donor up until the time of organ retrieval surgery may have beneficial effects on organ function in transplant recipients by restoring energy reserves, reducing cytokine generation, and protecting against ischemia and reperfusion injury.[121,122]

Hyperglycemia is common after brain death because of catecholamine surges and infusion of glucose-containing fluids.[48,67] Hyperglycemia should be treated as per standard approaches for critically ill patients and insulin be given by infusion to maintain blood glucose within the normal range. High doses may be required because of insulin resistance, in which case glucose-containing intravenous fluids should also be avoided.

Transfusion of blood and blood products is occasionally necessary. Anemia is commonly the result of intercurrent bleeding exacerbated by coagulopathy, and hemodilution the result of fluid administration and repeated blood sampling. Coagulopathy may occur secondary to tissue damage in trauma, particularly neurotrauma-induced fibrinolysis and thrombocytopenia, or it can be caused by hemodilution and is worsened by hypothermia.[123] Transfusion of blood, coagulation factors, and platelets may be required to correct severe anemia or coagulopathy, especially in the setting of active bleeding, hypotension, or shock. Procurement should be expedited if there is a worsening coagulopathy and bleeding.

KEY POINTS

- Brain death is the complete and irreversible absence of brain function characterized by loss of capacity for consciousness, unresponsive coma, brainstem areflexia, and apnea.
- Brain death may result from a devastating brain injury caused by hemorrhagic or ischemic stroke, traumatic brain injury, hypoxic-ischemic brain injury, tumor, infection, and other causes of intracranial hypertension or cerebral edema.
- The neuroprotective phase of care in the management of devastating brain injury requires mechanical ventilation to prevent cardiorespiratory arrest after the loss of central control of breathing. Therefore brain death occurs in patients receiving mechanical ventilation almost exclusively in the hospital and usually within intensive care units.
- Brain death is associated with somatic physiologic changes that include hemodynamic instability, activation of inflammatory pathways, and loss of the autoregulatory functions of the brain.
- After the diagnosis of brain death, provision of optimal supportive treatment of potential donors is important in maximizing donation opportunities, organ function, and transplant recipient outcomes.
- Donor management includes careful hemodynamic and respiratory support; maintaining normal electrolytes and euvolemia; and specific treatment to counter the common sequelae of brain death that include hypotension, hypothermia, and diabetes insipidus. The provision of specific hormonal therapies such as thyroid hormone, steroids, and vasopressin is of uncertain benefit.

References for this chapter can be found at expertconsult.com.

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Donation After Cardiac Death (Non–Heart-Beating Donation)

Stephanie Grace Yi and R. Mark Ghobrial

HISTORICAL PERSPECTIVE

The increasing gap between the number of organs available for transplantation and the number of patients listed for transplantation has become a rate-limiting step in reducing both wait times and wait list deaths in patients awaiting transplantation. Before the passage of the first US brain death law in the state of Kansas in 1970,[1] donation after cardiac death (DCD, or donation after circulatory death) was the primary mode of organ donation in the United States. Donor death was determined according to traditional cardiopulmonary criteria—that is, absence of pulse and blood pressures without cardiac activity.

Early organ procurement strategies were relatively crude and variable, which in turn prolonged warm DCD ischemia time (time from donor circulatory arrest to cold perfusion) and resulted in poor outcomes.[2] The impact of the variability of circumstances surrounding donor death, and thus the duration of ischemic time, on DCD graft outcomes did not become apparent until experiences with organs donated after brain death (DBD) increased.

The need for diagnosing brain death was a culmination of critical care physicians' growing ability to maintain physiologic organ function in patients with little or no hope of neurologic recovery after central nervous system (CNS) insults. The concept was first introduced at a CIBA Foundation meeting in England in 1965 and was subsequently endorsed with formal diagnostic criteria by Harvard Medical School in 1968.[1,3] A new debate was sparked over the precise definition and timing of death and the concept of futile care. Acceptance of this medically, philosophically, and legally novel concept of certifying death while maintaining perfusion in a potential donor to guarantee procurement with minimal warm ischemia time[4] and graft damage revolutionized transplantation. Because early experience with DBD organs showed superior outcomes, use of DCD organs declined and was subsequently abandoned.[5]

The success of DBD organs along with the refinements in medical and surgical techniques exponentially increased the number of transplants performed in the United States. The 1984 National Organ Transplant Act led to the formation of the United Network for Organ Sharing (UNOS), a nonprofit entity that provided a basis for standardizing organ procurement organizations (OPOs) throughout the United States, and the Organ Procurement and Transplantation Network (OPTN). Early national OPTN data showed that 10,794 deceased donor transplants were performed in 1988.[6] Six years later, these numbers increased by nearly 50% to 15,210 transplants. Moreover, the number of lung grafts from deceased donors increased annually from 33 to 708.[6] Intestinal transplantation also increased with the introduction of DBD donors. The first intestinal transplant was performed in 1990; by 1994, 96 patients with intestinal failure received intestinal transplants.[6] Concomitant advances in critical care reduced mortality in patients with end-stage organ disease, thereby resulting in increasing wait lists and decreased attrition. This is referred to as the growing "gap" between organ supply and transplantation demand. For example, despite the increased number of transplant centers and use of living donors in 1995, only 33% of registrants waiting for kidney transplant underwent transplantation.[6] However, the rate of transplantation decreased to 10% during 1998 to 2002.[7]

Moreover, the numbers of young and previously healthy DBD donors stagnated because of several statutory changes in areas of gun control, automobile safety (airbags, seatbelts, and lowering of legal blood alcohol limits), and helmet use. This decreased traumatic fatalities and changed the face of DBD organ donors.[8] The demographics of a typical DBD donor transitioned from a young healthy person who was rendered brain dead because of a devastating head trauma to an older person with medical problems who was rendered brain dead because of a neurovascular insult. This transformation eroded some benefit of using a DBD donor and prompted a search for other options.

Because the use of live donor organs has not kept pace with the growing deficit of organ donors, strategies such as regenerative medicine, mechanical devices, and xenotransplantation (use of grafts derived from animal donors) for treating end-organ diseases have been explored. However, these strategies are not ready to replace durable organ replacement. Further, the activity surrounding social and legislative approaches, including increased public awareness, donor registration activities, and interest in presumed consent (requiring individuals to opt out of organ donation to prevent consideration for donation at death), may have peaked because of cultural and philosophical objections. Therefore transplantation is again being performed using organs procured from DCD donors.

In the early 1990s, the Maastricht German transplant group rekindled interest in DCD organs[9] by showing equivalent long-term outcomes in recipients receiving both DCD and DBD renal transplants.[10,11] Similar findings from preliminary data have been made regarding DCD liver,[12] lung,[13,14] heart,[15] and pancreas transplants.[16] The University of Pittsburgh Medical Center (UPMC) introduced the nation's first institutional policy to permit and regulate DCD.[17] The need for such a policy arose when several patients/families were asked to participate in donation after previously electing withdrawal of life-sustaining treatment. This request fell outside the current parameters of donation policies and guidelines. The UPMC policy became the first concrete model to use cardiopulmonary criteria to determine death for organ procurement.[18] This policy highlighted a milestone in the evolution of transplantation. Since then, DCD has been adopted by many OPOs and hospitals nationwide. By December 2006 OPTN bylaws required that all OPTN members have a DCD donor protocol in effect.[18] Currently, The Joint Commission now requires that all accredited institutions develop and implement standardized DCD policies.[19]

After more than a decade of ongoing scrutiny surrounding ethical issues and outcome assessment, several key issues regarding DCD remain controversial in both the lay and medical communities. These include (1) criteria for identifying potential DCD donors, thus avoiding the financial and emotional burden of "failed" DCD; (2) optimization of DCD donor management; and (3) standardization of DCD procurement protocols to ensure a successful multidisciplinary effort with reproducible results. These issues are explored in this chapter after a brief discussion on the definition and current status of DCD.

IDENTIFICATION AND CATEGORIZATION OF POTENTIAL DONATION AFTER CARDIAC DEATH DONORS

Although seemingly straightforward, successful use of a DCD donor involves identification and classification of potential donors, appropriate diagnosis of death, and compliance with local policy of mandated wait time between pronouncement of death. The initial step in DCD organ transplantation is the recognition of potential donors with sufficient time to prepare and preserve optimal organ function before procurement. DCD is defined as organ procurement after the determination of death, which is characterized by an irreversible cessation of cardiopulmonary functions.[20] Critical care physicians and OPO staff must be familiar with diagnoses and clinical circumstances that qualify a patient as a potential DCD donor. Candidates are patients in whom withdrawal of futile life-sustaining treatment is being planned. Because optimal preservation of organ function is facilitated by coordinated perimortem care, graft quality can be compromised in situations where a patient's wishes regarding organ donation are unknown or where DCD is not offered as an option until late. Organ suitability may decline while attempts are being made to educate staff and families. Moreover, a treating physician must ensure that for patients on life support, withdrawal of life support must be independent of the decision to donate organs. At present, an OPO is responsible for coordinating surgical recovery and for preserving and transporting organs and tissues.[21] An OPO should be notified within 1 hour as soon as a patient's death is imminent from natural causes or withdrawal of life support.

The once-popular practice of managing potential DCD donors by placing vascular and/or intraperitoneal catheters to infuse cold organ preservation solution before the availability of consent for procurement[22] has now largely been abandoned. This practice stimulated contentious debate from both the medical and lay communities. Unlike several European countries, no US state adopted this presumed consent into law.

Management of DCD donors is facilitated by a classification scheme developed by the Maastricht group in 1994[23] and revised in 2000.[24] An international consensus conference was held in Paris in 2013 to clarify the Maastricht classification.[25] Maastricht categories define potential donors by circumstances under which cardiovascular death occurs. A distinction is made between donors whose cardiopulmonary failure is uncontrolled or emergent (categories 1, 2, and 4) and those whose death according to cardiopulmonary criteria occurs in a controlled manner after withdrawing futile life-sustaining support (category 3). Prior versions of the classification had a category 5, which is medically assisted cardiocirculatory death or euthanasia. This category has been mostly removed, except in Belgium and the Netherlands, where euthanasia is legal. The revised Maastricht classification is outlined in Table 160.1. Recent initiatives in the northeast United States involve training prehospital personnel to rapidly converse with preconsented victims of unsuccessful resuscitation after cardiopulmonary arrest (category 2) to determine potential DCD donors.[26] Category 3 donors constitute the majority of US and European DCD donors.[24] It is difficult to compare DCD outcomes according to Maastricht categories because few authors use this classification when reporting DCD results. Therefore, for uniformity, the remainder of this chapter focuses on category 3 donors.

TABLE 160.1 Maastricht Donation After Cardiac Death Categories

Category	Description	Condition
1	Cardiac arrest outside hospital and no resuscitation attempted	Uncontrolled
• 1A	• Out of hospital	
• 1B	• In-hospital	
2	Cardiac arrest followed by unsuccessful resuscitation either inside or outside hospital	Uncontrolled
• 2A	• Out of hospital	
• 2B	• In-hospital	
3	Cardiac arrest after planned withdrawal of life support	Controlled
4	Cardiac arrest in a brain-dead patient awaiting organ procurement	Uncontrolled Controlled

Adapted from Thuong M, Ruiz A, Evrard P, et al. (2016). New classification of donation after circulatory death donors definitions and terminology. *Transpl Int*. 2016;29(7):749–759.

Category 3 standardization is outlined in Fig. 160.1 (the UNOS Critical Pathway for DCD).[27] Typical patients may have the following characteristics: absence of or hyperactive respiratory drive, lack of adequate respiratory muscle strength, and severe hypoxemia or inadequate circulation in the absence of treatment with inotropic or vasopressor drugs. These patients are usually supported using ventilators or mechanical circulatory assistance such as ventricular-assist devices (VADs) or intraaortic balloon pumps. These patients may have also experienced severe neurologic insults but may not have met brain death criteria. Conscious patients usually develop degenerative neuromuscular diseases or end-stage cardiopulmonary diseases and are often ventilator or VAD dependent. These patients or their families may decide to discontinue life-sustaining support and request their organs to be donated.

The other category of potential DCD donors includes patients with impending cardiopulmonary death, the timing of which is either predictable based on patient-/family-requested withdrawal of care or unpredictable because of premature cardiac arrest before withdrawal. Given the lack of perfusion in DCD donors, prompt identification of death is needed to minimize organ ischemia, especially if uncontrolled cardiac arrest occurs. Organ procurement from DCD donors under uncontrolled conditions is technically feasible but is not physiologically ideal because of the inherent ischemic insult.

Various modalities have been proposed to help physicians identify death based on the absence of cardiac sounds, pulse, respiration, and response to stimuli. Confirmatory tests such as intraarterial monitoring or Doppler studies recommended by the Institute of Medicine (IOM)[28] can be used to expedite the confirmation of death; however, these tests are not widely accepted at present. A DCD work group assembled in 2006[20] indicated that electrocardiographic silence was not required for determining death but was sufficient to show the absence of circulation.

However, there is no agreement on the observation time required to rule out spontaneous unassisted cardiopulmonary resuscitation or autoresuscitation. The DCD work group[20] and the Society of Critical Care Medicine (SCCM)[29] recommend that potential donors be observed for

Patient name: _____

ID number: _____

Critical Pathway for the Organ Donor

Collaborative Practice	Phase I Referral	Phase II Declaration of Brain Death and Consent	Phase III Donor Evaluation	Phase IV Donor Management	Phase V Recovery Phase
The following professionals may be involved to enhance the donation process. *Check all that apply.* ❍ Physician ❍ Critical care RN ❍ Organ Procurement Organization (OPO) ❍ OPO coordinator (OPC) ❍ MedicalExaminer (ME)/ Coroner ❍ Respiratory ❍ Laboratory ❍ Pharmacy ❍ Radiology ❍ Anesthesiology ❍ OR/Surgery staff ❍ Clergy ❍ Social worker	❍ Notify physician regarding OPO referral ❍ Contact OPO ref: Potential donor with severe brain insult ❍ OPC on site and begins evaluation Time _____ Date _____ ❍ Ht_____ Wt _____ as documented ❍ ABO as documented _____ ❍ Notify house supervisor/ charge nurse of presence of OPC on unit	❍ Brain death documented Time _____ Date _____ ❍ Pt accepted as potential donor ❍ MD notifies family of death ❍ Plan family approach with OPC ❍ Offer support services to family (clergy, etc) ❍ OPC/Hospital staff talks to family about donation ❍ Family accepts donation ❍ OPC obtains signed consent & medical/social history Time _____ Date _____ ❍ ME/Coroner notified ❍ ME/Coroner releases body for donation ❍ ***Family/ME/Coroner denies donation—stop pathway—initiate post-mortem protocol—support family.***	❍ Obtain pre/post transfusion blood for serology testing (HIV, hepatitis, VDRL, CMV) ❍ Obtain lymph nodes and/or blood for tissue typing ❍ Notify OR & anesthesiology of pending donation ❍ Notify house supervisor of pending donation ❍ Chest & abdominal circumference ❍ Lung measurements per CXR by OPC ❍ ***Cardiology consult as requested by OPC (see reverse side)*** ❍ ***Donor organs unsuitable for transplant—stop pathway—initiate post-mortem protocol—support family.***	❍ OPC writes new orders ❍ Organ placement ❍ OPC sets tentative OR time ❍ Insert arterial line/ 2 large-bore IVs ❍ Possibly insert CVP/Pulmonary Artery Catheter ❍ See reverse side	❍ Checklist for OR ❍ Supplies given to OR ❍ Prepare patient for transport to OR ❍ IVs ❍ Pumps ❍ O_2 ❍ Ambu ❍ Peep valve ❍ Transport to OR Date _____ Time _____ ❍ OR nurse ❍ reviews consent form ❍ reviews brain death documentation ❍ checks patient's ID band
Labs/Diagnostics		❍ Review previous lab results ❍ Review previous hemodynamics	❍ Blood chemistry ❍ CBC + diff ❍ UA ❍ C & S ❍ PT, PTT ❍ ABO ❍ A Subtype ❍ Liver function tests ❍ Blood culture X 2 / 15 minutes to 1 hour apart ❍ Sputum Gram stain & C & S ❍ Type & Cross Match _____# units PRBCs ❍ CXR ❍ ABGs ❍ EKG ❍ Echo ❍ Consider cardiac cath ❍ Consider bronchoscopy	❍ Determine need for additional lab testing ❍ CXR after line placement (if done) ❍ Serum electrolytes ❍ H & H after PRBC Rx ❍ PT, PTT ❍ BUN, serum creatinine after correcting fluid deficit ❍ Notify OPC for ___ PT >14___ PTT < 28 ___ Urine output ___ < 1 mL/Kg/hr ___ > 3 mL/Kg/hr ___ Hct < 30 / Hgb >10 ___ Na >150 mEq/L	❍ Labs drawn in OR as per surgeon or OPC request ❍ Communicate with pathology: Bx liver and/ or kidneys as indicated
Respiratory	❍ Pt on ventilator ❍ Suction q 2 hr ❍ Reposition q 2 hr →	❍ Prep for apnea testing: set FiO_2 @ 100% and anticipate need to decrease rate if PCO_2 < 45 mm Hg	❍ Maximize ventilator settings to achieve SaO_2 98 - 99% ❍ PEEP = 5cm O_2 challenge for lung placement FiO_2 @ 100%, PEEP @ 5 X 10 min ❍ ABGs as ordered ❍ VS q 1° →	❍ Notify OPC for ____ BP < 90 systolic ____ HR < 70 or > 120 ____ CVP < 4 or > 11 ____ PaO_2 < 90 or ____ SaO_2 < 95%	❍ Portable O_2 @ 100% FiO_2 for transport to OR ❍ Ambu bag and PEEP valve ❍ Move to OR →
Treatments/ Ongoing Care		❍ Use warming/cooling blanket to maintain temperature at 36.5° C - 37.5 °C ❍ NG to low intermittent suction	❍ Check NG placement & output ❍ Obtain actual Ht _____ & Wt _____ if not previously obtained	→	❍ Set OR temp as directed by OPC ❍ Post-mortem care at conclusion of case
Medications			❍ Medication as requested by OPC →	❍ Fluid resuscitation—consider crystolloids, colloids, blood products ❍ DC meds except pressors & antibiotics ❍ Broad-spectrum antibiotic if not previously ordered → ❍ Vasopressor support to maintain BP > 90 mm Hg systolic ❍ Electrolyte imbalance: consider K, Ca, PO_4, Mg replacement ❍ Hyperglycemia: consider insulin drip → ❍ Oliguria: consider diuretics ❍ Diabetes insipidus: consider antidiuretics ❍ Paralytic as indicated for spinal reflexes	❍ DC antidiuretics ❍ Diuretics as needed ❍ 350 U heparin/kg or as directed by surgeon
Optimal Outcomes	The potential donor is identified & a referral is made to the OPO.	The family is offered the option of donation & their decision is supported.	The donor is evaluated & found to be a suitable candidate for donation.	Optimal organ function is maintained.	All potentially suitable, consented organs are recovered for transplant.

Shaded areas indicate Organ Procurement Coordinator (OPC) Activities.

This Critical Pathway was developed under contract with the U.S. Department of Health and Human Services, Health Resources and Services Administration, Division of Transplantation.

Fig. 160.1 UNOS donation after cardiac death critical pathway. (From United Network for Organ Sharing. Critical pathway for donation after cardiac death. 2011. https://unos.org/wp-content/uploads/unos/Critical_Pathway_DCD_Donor.pdf.)

at least 2 minutes but not more than 5 minutes to ensure the absence of spontaneous circulation. These recommendations pertain to the period between the loss of circulation and declaration of death and not between the declaration of death and organ procurement. Fugate and colleagues identified variability among DCD protocols within the United States, particularly for defining the observation of potential donors to rule out autoresuscitation.[30] Although most centers followed the 2- to 5-minute observation period, there was variability in the definition of the period starting either before or after declaration of death, thus implying a total of 10 minutes. A prospective study by Dhanani and colleagues on the timing of determination of death in DCD donors showed that the longest period of arterial blood pressure[31] resumption after declaration of death was 89 seconds.[32] Moreover, only 4 of 41 patients examined showed return of blood pressure after cessation; however, this only lasted between 1 and 172 seconds. Given the variability and limited data on the duration of observation, specific guidelines for the precise minimal duration of irreversible circulation are warranted. At present, local protocols are used to stipulate the requirements of the determination of death and duration of observation time before organ procurement.

An important part of identifying potential DCD donors includes predicting the occurrence of rapid physiologic deterioration and death in less than 30–60 minutes (depending on the organ to be procured) after withdrawing life-sustaining treatment.[20] Failure of a potential donor to progress to cardiac death within the prescribed time disqualifies the donor because of the extent of organ warm ischemia time (WIT). Factors such as age, comorbidities, and preterminal vasopressor requirement can be used as predictors; however, no strict criteria have been universally adopted.[33] Lewis and colleagues from the University of Wisconsin developed a tool that uses clinical parameters to predict the suitability of DCD candidates.[34] This resulted in the development of guidelines to predict the likelihood of circulatory death within 2 hours after withdrawing life support. The authors proposed four readily obtainable clinical criteria: (1) requirement for vasopressors to support blood pressure, (2) absence of primary brain injury, (3) history of mechanical ventilation for ≥6 days, and (4) respiratory rate of less than 20 breaths/minute (in the absence of mechanical ventilation). They noted that presence of two or more of these indicators accurately predicted death within 60 minutes after withdrawing life-supporting treatments, with a sensitivity and specificity of 81% and 78%, respectively. Munshi and colleagues observed that controlled ventilation, oxygenation, vasopressor use, Glasgow Coma Scale/Score, and brainstem reflexes consistently predicted time to death in DCD donors.[35] Other novel predictors, such as physician opinion and simultaneous withdrawal of all support, are promising and warrant additional study. Robust analysis of retrospective DCD data would enable intensivists and OPO staff to more precisely identify potential DCD donors, help minimize the financial impact on hospitals and donors that "fail to progress," and prevent unnecessary stress and disappointment for families during a psychologically vulnerable time.

Familiarity with relative and absolute contraindications for DCD, some of which overlap those associated with DBD, is important. These include the multiple-operated abdomen, active sepsis, active or recent extracranial primary malignancy, and active infections such as hepatitis B or COVID-19. With regard to virologic status, OPOs are well versed in performing rapid serologic testing to rule out latent viral infections and should be involved as early as feasible to initiate testing.

CURRENT STATUS OF DONATION AFTER CARDIAC DEATH

Volume

UNOS disseminates US transplant-related data and has reported DCD statistics since 1994.[6] Data are available on the UNOS website (www.unos.org) and in UNOS annual reports. The annual number of DCD donors increased steadily from the mid-1990s to the early 21st century (Table 160.2). In all, 42 DCD recoveries were performed in 1993, which represented <1% of the total recoveries in that year. In 2012 DCD recoveries showed a 12-fold increase of 12% of all organ procurements. The rate of DCD donations in the United States continues to increase steadily from 2012, comprising nearly 20% of all donors in 2018.[6]

Outcomes

Despite ethical controversies, the real barrier to the widespread acceptance of DCD graft use is the poor outcome observed in early DCD experiences. Suboptimal organ function characterized by primary nonfunction, delayed graft function (DGF), and/or abbreviated graft survival have traditionally threatened the success of DCD organs because of the ischemic insult associated with cardiopulmonary arrest.[5] Although these observations were valid at that time, they accumulated during early experiences with transplantation and were thus inherently confounded by era bias.

On a cellular level, DBD and DCD organs show different injury profiles. DBD is characterized by a surge in serum catecholamines because of brain death, which induces hypotension and subsequent organ hypoperfusion. Animal studies have shown that hemodynamic instability of DBD organs may be further exacerbated by inflammatory cytokines such as interleukin (IL)-1, IL-6, and IL-8 that directly affect renal grafts.[36] In vivo studies evaluating DCD kidney grafts have shown less upregulation of inflammatory markers[37]; however, these studies showed that prolonged WIT induced alternative pathways of injury, such as those related to hypoxia. Rosenberger and colleagues found that hypoxia-inducible factors were correlated with renal allograft

TABLE 160.2 Number of Donations After Cardiac Death Organs as a Percentage of Total Deceased Donor Organs Procured by Year[6]

Year	# Deceased Donors	# DCD Donors	DCD as a Percentage of Total Donors
1993	4861	42	0.86
1995	5362	64	1.20
1997	5478	78	1.43
1999	5825	87	1.49
2000	5985	104	1.74
2001	6080	169	2.77
2002	6190	156	2.52
2003	6456	268	4.15
2004	7150	319	4.15
2005	7593	556	7.32
2006	8019	538	6.71
2007	8086	793	9.80
2008	7990	728	9.11
2009	8022	803	10.01
2010	7943	831	10.46
2011	8125	956	11.77
2012	8144	993	12.19
2017	10,286	1883	18.31
2018	10,721	2130	19.87

DCD, Donations after cardiac death.

ischemia time.[38] The increased incidence of DGF with DCD renal grafts was associated with a hypoxia-specific injury. The primary lesson from the early DCD era was that the metabolically active renal cortex, biliary epithelium, pulmonary alveoli, and pancreatic islets were sensitive to ischemia, with warm ischemic injury manifesting as acute tubular necrosis, ischemic-type biliary strictures (ITBSs), pulmonary fibrosis, and impaired beta-cell function, respectively. These manifestations were postulated to result in both poor initial graft function and long-term complications.[39–41] However, contemporary outcomes for each organ have improved.

Kidneys

Recent data have shown equivalent outcomes for DCD vs. DBD grafts. Early experience with DCD kidneys showed that graft survival in recipients of controlled DCD kidney grafts is equivalent or comparable to that of DBD.[42] Long-term outcomes of DCD kidneys also had similar graft outcomes to DBD kidneys.[42,43] A recent study by Gill and colleagues observed slightly improved allograft survival from DCD kidneys compared with DBD if warm ischemia time was less than 48 minutes.[44] Similarly, Butler and colleagues did not observe a difference in likelihood of graft loss for DCD vs. DBD allografts.[45] Although DCD kidneys have comparable graft survival rates to DBD kidneys, DCD kidneys have higher rates of DGF. Donor age of >60 years (compared with donors' age of <40 years)[46] and prolonged cold ischemia time (CIT; >24 vs. <12 hours) have been cited as factors affecting DCD graft function.[47]

Pancreas

Much of the available outcome data on the transplantation of DCD pancreatic grafts are derived from cases of simultaneous pancreas-kidney (SPK) transplants. These data show that graft and patient survival rates in recipients of DCD pancreatic grafts are similar to those in recipients of DBD pancreatic grafts.[16,48–50] Transplantation of DCD pancreas-alone grafts by using the same protocols as those used for DCD SPK grafts has provided favorable results, although there was a higher odds of graft thrombosis compared with DBD organs.[16] Fortunately, these findings were not observed in the setting of heparin administration. Donor selection (i.e., age) had a higher impact on graft outcomes vs. DCD status. More experience is needed to confirm these findings.

Liver

Early studies on recipients of DCD liver grafts have provided mixed results, with both graft and patient survival rates being significantly lower compared with those in recipients of DBD liver grafts.[51] In addition, these studies reported higher recipient morbidity and mortality rates.[52,53] Recent studies have observed equivalent patient and graft outcomes[54]; however, outcomes may be influenced by recipient and donor selection.[55] DCD liver grafts are more sensitive to WIT, thus requiring experienced personnel to complete a procurement limit of 25–30 minutes after circulatory arrest (compared with 60 minutes for renal grafts).

Lungs

Rapidly increasing use of DCD lung grafts, with improved outcomes, has encouraged clinicians to consider using these previously declined grafts.[56–58] Registry data from the Internal Society for Heart and Lung Transplantation (ISHLT) showed a 30-day mortality rate of <3% and 1-year survival rate of 89% that were not statistically different compared with those observed with DBD grafts.[59] Updated ISHLT registry data demonstrated excellent long-term survival among lung transplant recipients who received a DCD organ vs. DBD.[58] Additional data from the United Kingdom Steering Group for DCD lung transplants showed equivalent 1-year survival outcomes for DCD and DBD grafts ($P = .9$).[60]

Heart

Data describing DCD cardiac transplantation are scarce. The first DCD heart transplant was performed in 1967, but this technique was abandoned largely because of organ quality and use of DBD donors. With growing wait lists, the use of DCD heart organs is currently being revisited. Farr and colleagues estimated that in the United States, almost 60% of DCD donors had hearts that met criteria for transplantation but were being discarded.[61] The UK has one of the largest experiences with DCD heart donors. Messer and colleagues described the early experience in the UK of 50 DCD heart transplants, reporting a 100% 30-day survival rate in recipients who received DCD and matched DBD organs.[62] The same group also reported comparable 1-year survival (85% vs. 88%, $P = .98$) in DCD and DBD heart transplant recipients, respectively.[63] In the United States, the first DCD adult heart recipient was performed in 2020 as part of a multicenter clinical trial.[64] Australia,[65] Spain,[66] and Belgium[67] have also published case reports describing their early experience.

Innovation in DCD

Pulsatile perfusion pumps are being widely used to improve the quality of donor organs, especially in the context of DCD. The different types of perfusion pumps include normothermic machine perfusion (NMP), normothermic ex vivo machine perfusion, and hypothermic machine perfusion. The goal of perfusion pumps is to reduce ischemic injury to the allograft before implantation. Hypothermic, or cold perfusion pumps, are used with DCD kidney grafts. Lodhi and colleagues reported a decreased risk of DGF associated with pulsatile perfusion compared with cold storage in recipients of DCD kidney grafts.[68] A meta-analysis by Bathini and colleagues on the use of cold perfusion pumps suggested an improved trend of 1-year graft survival.[69] A recent Cochrane review also observed hypothermic machine perfusion as being superior to static cold storage.[70] NMP leverages the circulation of warm, oxygenated blood to reduce kidney injury. In an early study by Valero and colleagues, NMP was observed to considerably reduce primary graft non-function (PGNF) and DGF.[71] There are emerging data that pharmacologic intervention during NMP may provide organ-directed therapy against renal ischemia-reperfusion injury.[72]

To combat the ischemic-reperfusion injury to the liver allograft, machine perfusion is being studied as a way to optimize DCD liver allografts. Schlegel and colleagues observed less graft loss in DCD livers treated with hypothermic oxygenated perfusion compared with standard cold storage.[73] Dutkowski and colleagues observed similar findings, including decreased liver enzymes, biliary complications, and 1-year graft survival.[74] Although machine perfusion continues to be investigational, more centers are enrolling in trials investigating DCD liver pumps.

One evolving strategy for maximizing DCD graft function in lung donors is ex vivo or extracorporeal lung perfusion (EVLP). There are growing data on DCD lungs.[75] EVLP allows for the assessment of the graft after resolution of edema via the biochemical markers. The lung allograft is connected to a circuit, which allows oxygenation and perfusion into the procured organ.[76] Cypel and colleagues reported similar rates of primary graft dysfunction, 30-day mortality, and 1-year survival with EVLP compared with those with control lung grafts.[77,78] Long-term outcomes from the Toronto Lung Transplant Program demonstrated no difference in chronic lung allograft dysfunction and allograft survival up to 9 years posttransplant.[79]

The use of normothermic preservation (NRP) is being studied as a means to reduce ischemic injury at the time of procurement for DCD

heart organs. There are four techniques for DCD heart procurement: direct procurement and cold storage, direct procurement and ex situ heart perfusion, NRP and ex situ machine perfusion, and NRP with cold storage. Proponents for NRP with cold storage have demonstrated that this technique allows for a functional assessment of the heart before retrieval and transplantation.[80] This allows for a less stringent time constraint for organ implantation with no significant consequences to outcome.[81]

PRINCIPLES OF DONATION AFTER CARDIAC DEATH DONOR MANAGEMENT

Because every organ from a DCD donor sustains some degree of unavoidable ischemic damage, several protective strategies to increase graft viability have been proposed. Interventions can be considered in premortem or intraoperative phases.

Premortem

During the premortem phase, early placement of large-bore arterial and venous catheters for perfusing cold preservation solution in the donor can help minimize ischemia time.[21] This is followed by administration of systemic anticoagulants such as heparin (such as 30,000 units) along with recombinant tissue plasminogen activator (50 mg) to prevent vascular thrombosis during the low flow state.[82,83] The use of vasodilators such as phentolamine can prevent agonal vasospasm induced by hypoxia and surging catecholamine levels.[84] Lastly, ischemic preconditioning via brief ischemic challenges can trigger protective mechanisms that allow compensatory tissue physiology at the time of cardiac arrest, which is suggested to be mediated by heat shock proteins.[85,86]

The use of these premortem measures is limited because they are not a part of standard end-of-life care and because some authors suggest that these measures potentially hasten death.[87] The SCCM and IOM indicate that these medications and devices can be used as long as they do not cause any significant harm to the patient[29,88] and as long as family consent is obtained wherever practical. That they are of no direct benefit to the patient is countered by the fact that they improve the likelihood that the patient's wish of organ donation will ultimately be realized.

Operative

The conduct of operative procedure is dictated by the tenets mentioned earlier. The procurement team is not physically present at the time of death, and recovery of organs is accomplished expeditiously with careful coordination of numerous personnel, equipment, and resources. To do so, the operative team prepares and drapes the patient upon arrival to the operating room (OR). The team outlines the necessary instruments and maneuvers requested by OPO staff to ensure a seamless procedure. The team is then escorted from the OR and is notified by the OPO staff if the patient is pronounced within the prescribed time frame. After withdrawal of life support and before incision, the OPO staff will complete a monitoring form that details minute-by-minute hemodynamic and oxygenation data.

Once the patient has been pronounced, the operative team returns gowned and gloved and infuses cold perfusate through a cannula or a standard terminal aortic cannula placed during the premortem phase after rapidly accessing the abdomen. Next, rapid but careful in situ cold dissection is performed because the potential for vascular injury increases without the benefit of pulsatile flow to assist the identification of aberrant anatomy. Finally, organs are packaged and implanted in the recipient as soon as possible to mitigate the added negative impact of CIT.

The two most common contingencies that the team must be prepared for are unexpected cardiac arrest while awaiting withdrawal of life support and failure to progress after withdrawal. Appropriate intravenous access, a ventilator, and a special supply cart must be available and stocked with an oxygen tank, cardiac monitor, and adequate supply of sedatives and narcotics. The patient's wishes regarding resuscitation leading to donation must be determined from the patient or family as early as possible.

Approaches to DCD in European Union Countries

DCD donors are increasingly used in Europe, making up upwards of 40% of deceased donor organs in countries where DCD is accepted.[89] In Belgium, France, Spain, and the UK, DCD organs have nearly doubled between 2008 and 2016.[90] The highest DCD activity has been reported in the UK, Spain, Russia, the Netherlands, Belgium, and France. Table 160.3 summarizes the activity of European countries with DCD programs.

DCD policies vary among the countries who use DCD donors. The "no touch" period, or time between cessation of circulation and respiration and determination of death, ranges from 5 to 30 minutes. Italy has a 20-minute "no touch" period policy, which some attribute as the reason for slow DCD program development. The overall time for retrieval also ranges from 1 to 4 hours. In the UK Potential Donor Audit, successful retrieval after 4 hours without transplant compromise was reported.[91] This resulted in a 30% increase of available DCD organs. In contrast, Australia limits the withdrawal time to 90 minutes.

Both controlled and uncontrolled DCD are used in Europe, with better outcomes in the controlled cohort. Spain, France, Italy, the UK, the Netherlands, Belgium, Switzerland, Austria, and Russia have protocols for uncontrolled DCD. As mentioned previously, Belgium and the Netherlands consider DCD after euthanasia. In controlled DCD, practices regarding antemortem and postmortem interventions also vary. Types of antemortem interventions are cannulation of vessels and heparin before withdrawal of life support. Manara and colleagues argue that use of cannulas in this setting is justified based on the donor/recipient risk-benefit profile.[91] Not all countries request donor family/representative authorization for cannulation or other antemortem intervention.

The use of NRP to reduce warm ischemic injury has invigorated the use of DCD organs in both thoracic and abdominal transplant in Europe.[92,93] This is most evident in regions where longer "no touch" times have previously discouraged DCD programs. In Italy, NRP has allowed DCD donors to increase nearly threefold over the last 2 years.[94] NRP has also been used to improve posttransplant outcomes in DCD livers, kidneys, hearts, and lungs. Spain and the UK have demonstrated improved graft survival and decreased biliary complications in the recipient.[95] The UK has the largest series in the successful use of NRP for DCD heart transplantation.[62]

DETERMINATION OF DEATH: THE EXACT SCIENTIFIC CONCEPT?

The 1980 Uniform Determination of Death Act (UDDA) established that death is determined when there is irreversible cessation of circulatory and respiratory functions.[96] Most often, death is declared based on the cessation of cardiac and pulmonary functions; however, the required asystole is perhaps the single most contentious issue in the debate surrounding DCD.[83,97] Simply, the longer you wait, the more uncertainty there is about quality of the organs, and the shorter you wait, the more uncertainty there is on whether the person is dead.[98]

As the limits of life-sustaining practices are expanded, medical professionals are encouraged to maintain focus with reference to the

TABLE 160.3 Activity of European Countries With DCD Programs From 2008 to 2016[80]

	DCD DONORS (N)		TRANSPLANTS FROM DCD DONORS (N)				
	uDCD	cDCD	Kidney	Liver	Lung	Pancreas	Heart
Austria	14	20	63	5	4	0	0
Belgium	16	633	870	440	326	37	0
Czech Republic	0	23	40	1	0	0	0
France	457	62	716	48	0	0	0
Ireland		21	42	0	3	0	0
Israel	8	0	11	0	0	0	0
Italy	29	9	45	14	4	0	0
Latvia	115	0	71	0	0	0	0
Lithuania	2	0	3	0	0	0	0
Netherlands	47	1048	1785	336	418	29	0
Norway		10	18	4	0	0	0
Poland	10	0	18	0	0	0	0
Portugal	10	0	12	0	0	0	0
Spain	997	757	2348	339	164	3	0
Switzerland	1	70	96	45	21	3	0
Russia	1280	0	2171	0	0	0	0
United Kingdom	3	4060	6630	1268	441	401	32
Total	2989	6713	14,939	2500	1381	473	32

DCD, Donation after cardiac death; *cDCD,* controlled DCD; *uDCD,* uncontrolled DCD.
Data from Lomero M, Gardiner D, Coll E, et al. Donation after circulatory death today: An updated overview of the European landscape. *Transpl Int.* 2020;33(1):76–88.

UDDA. The term *irreversible* can be interpreted as a shifting paradigm or, as per Wilner and colleagues, a concept that is subject to serial displacement by advancing clinical science. Wilner and colleagues further highlighted that the question of death is thus reformulated to explore whether the morally relevant time of death is reached when death is certain despite the administration of all possible medical interventions or whether death is assured once all ethically permissible remedies have been used.[7] Lizza argued that because of medical and technologic advances, death cannot be solely understood on the basis of biologic factors.[99] As the debate continues regarding the time at which death is irreversible, it is logical that once a principled decision is made not to correct a loss of function, the loss becomes irreversible.[100]

No investigator has documented autoresuscitation after >89 seconds of combined circulatory and respiratory arrest.[32,101] However, the standard applied by most US hospitals ranges from a 2- to 5-minute asystolic interval (pulselessness, apnea, and unresponsiveness). This broad standard is addressed by American Society of Anesthesiologists' statement that the "2 to 5 minute time interval takes into consideration that there is no literature to support auto-resuscitation of the heart following two minutes of circulatory arrest, while observing an endpoint of five minutes minimizes warm ischemic damage to perfusable organs."[102] Because of the paucity of empiric evidence, IOM continues to encourage investigators to perform additional studies on this matter.

A final logistic issue in the determination of death is the management of patients who progress very slowly to be considered for donation. This occurs in approximately 5%–10% of potential donors.[33] Most programs disqualify donors from solid organ donation if cardiac activity is noted 60 minutes after withdrawal of life support because these donors do not meet the criteria for death and their organs would have sustained excessive warm ischemic injury. Therefore contingency plans should be devised so that these patients receive appropriate end-of-life care.

Vincent and colleagues summarized this into the following: identification of no reasonable hope or survival for the patient and recognizing their organs may benefit others.[103] Thus the terminal phase should be kept at a minimum. These authors believed that an open discussion is necessary to help facilitate such action, so that these bioethical principles remain relevant for both donors and recipients.

DCD IN THE ICU SETTING

Although use of DCD organs has gained acceptance within the international transplant community,[90] it is less common in the United States compared with other countries. Kidney transplantation from DCD donors is nearly half that in the United States compared with the UK, in which 40% of donors are DCD.[89] Although the primary barriers to DCD use include concern for inferior graft quality and outcomes compared with DBD, there are additional barriers from a systems standpoint that may also affect utilization rates. This section will review some of these barriers attributed to low use of DCD organs.

As the majority of DCD donors are in the intensive care unit (ICU) setting, healthcare professionals are on the front line for identification and referral for the DCD donation process. One of the barriers to DCD acceptance in the ICU setting may be psychological distress caused by the process of DCD. In a pilot study by Zellweger and colleagues, caregivers in the ICU expressed feelings of conflict and stress during the withdrawal decision and donation process.[104] Less than half did not feel completely supported during the withdrawal process. However, 94% of respondents believed that DCD was a viable means for increasing organ donation. This study highlights the importance of psychological support for caregivers in managing the demands of DCD.

In a qualitative study by Squires and colleagues, specific barriers to DCD organ donation among frontline ICU workers in Canada included the need for DCD education, a systematic and standardized screening process for DCD donors, and communication templates for family discussions about DCD.[105] In a subanalysis, intensivists reported three additional barriers to DCD donation: public perception that DCD donation is unethical, personal religious views, and lack of legislation mandating DCD. In an early study by Vincent and colleagues, ICU nurses felt inadequately informed, which may have been associated with their unease toward DCD donors.[106] These identified barriers are useful in creating educational tools and policy regarding public acceptance of DCD.

In the United States, there is variation in DCD practices among OPOs. A survey by Choubey and colleagues showed substantial differences in DCD procurement practices across OPOs, with many centers not conforming to current societal recommendations regarding DCD.[31] This has led to a push for creating best practice guidelines and standardizing DCD protocols across OPOs.[107] The intention is to optimize outcomes in an effort to increase use of these organs.

FINAL CONSIDERATIONS

Despite the success of DCD kidney, liver, lung, and pancreatic grafts, several unmet challenges and questions remain regarding the transplantation of these grafts. These fall within the realms of medical and ethical concerns. One area of likely future research concerns the real numeric advantage of using DCD grafts. Although the number of DCD grafts used in the United States has increased, there is still a significant gap between DCD and DBD grafts[6] (Fig. 160.2). It is unclear whether the identification of DCD donors will convert would-be DBD donors to DCD donors. In addition, it is unclear whether the decrease in the number of wait-list recipients will shift the cost and burden from wait-list complications to posttransplant complications, with longer lengths of stay, increased readmissions, increased complexity of diagnostic evaluations and immunosuppressive drug regimens, and increased rate of recipient morbidity and mortality. These questions can be better answered as more prospective data are collected.

Another issue of concern is in the evaluation of pediatric donors for DCD. This is a field in which there has been resistance, given ethical concerns with DCD, although the current professional consensus is that pediatric DCD donation can be practiced in an ethical manner similar to adults.[4] It had been estimated that use of DCD organs from pediatric donors may increase organ donation by 42% if these patients were evaluated for DCD.[108] This is another growing area that may see more traction in the near future.

Lastly, public perception also plays a role in the acceptance of DCD donation. An emphasis on patients' and families' wishes is paramount for the success of any DCD program. There is public concern that the likelihood of receiving aggressive life support will be compromised by consenting for organ donation.[109] These misperceptions are particularly damaging when the overriding goal of the transplant community is to maintain and build public support of maximizing organ donation. Such misconceptions can be remedied by larger educational programs and standardization of practices across OPOs.

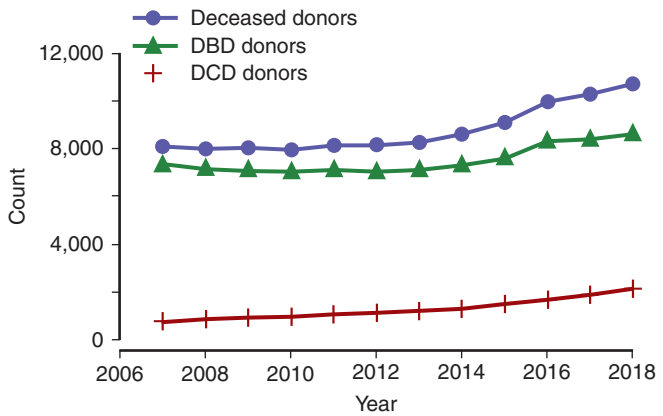

Fig. 160.2 The number of transplants in the United States performed using donation after brain death (*DBD*) and donation after cardiac death (*DCD*) grafts.[6] (From Israni AK, Zaun D, Hadley N, et al. OPTN/SRTR 2018 annual data report: Deceased organ donation. *Am J Transplant.* 2020;20[s1]:509–541.)

CONCLUSION

An Opportunity for Standardization

Appropriate management of DCD donors requires the integration of several fundamental principles for protecting the rights and interests of donors and for preventing the care of DCD organs from superseding the care of the dying patient. Debate arises in the paradox that can emerge from attempts to protect those interests while preserving the suitability of potential grafts. Hence, the role of an intensivist and/or palliative care physician (terminal care of patients and pronouncement of death) and managing OPO must be rigidly defined. The two factions must travel distinct paths to achieve their shared ultimate goal. Ozark and colleagues summarize this by stating "as a general rule two discussions—whether to forego life-sustaining therapy and whether to donate organs—must be made separately and on their own individual merit."[110] Ideally, discussion regarding the withdrawal of life-sustaining treatment should come first to prevent bias by the issue of transplantation.

The push for optimal palliative care is the hallmark of recent critical care management initiatives.[29,111,112] Dying patients who also wish to be DCD donors present a special challenge because they require care that is not only comparable to that given to all dying patients but also sensitive to the concerns described earlier. The SCCM has offered recommendations specific to DCD.[113] These guidelines are supplemented by individual transplant center reports and the UNOS Critical Pathway (see Fig. 160.1) and provide direction for intensivists caring for patients who wish to become DCD donors. It is vital that all healthcare providers involved in this process be comfortable with, and knowledgeable about, their specific role so that the patient's wishes can be respected.

Because pain relief is the single most important goal in palliative care in the final hours of life, there is a firm ethical, legal, and medical justification for using analgesics and anxiolytics in this scenario. As some patients require higher doses than others, medications should be given with the knowledge that unintended effects such as hypotension or respiratory depression may compromise organ viability. Therefore it is critical that the interest of the dying patient be represented by a completely different entity than that responsible for representing the interests of the donor. If any question arises regarding the practitioner's ability to maintain an objective position, consultation from hospitals' palliative care and ethics teams should be obtained.

In 2006 in the first criminal case against a transplant surgeon for the death of a donor, the defendant allegedly administered high doses of an analgesic and anxiolytic to a potential donor to hasten his death before organ procurement.[97] Although the surgeon was acquitted, the case highlighted the potential legal ramifications of recovery teams' involvement in the care of a dying patient. There is a consensus that "medications given to provide comfort are reasonable, even if they might hasten death," but "no medication whose purpose is to hasten

death should be given to the patient."[19] Failure to attend to potential DCD donors' comfort in contemporary practice is considered suboptimal end-of-life care and should be managed only by the physicians caring for the patient.

The need for data collection during DCD evaluation is to standardize definitions of death without variability among hospitals or OPOs. For instance, the definition of the start of WIT remains variable, with some advocating a threshold of systolic blood pressure of <80 mm Hg, a mean arterial pressure of 50 mm Hg, a systolic blood pressure of <50 mm Hg, or a decrease in arterial oxygen saturation to <80%.[114] The lack of a universal definition renders comparison of outcomes between centers and organs difficult. Although the asystolic interval to be observed remains a matter of institutional policy, it is prudent to recommend the development of standardized criteria. Highly sensitive maneuvers used to document the absence of circulation, such as intra-arterial pressure monitoring or echocardiography, may be helpful if a short asystolic interval is used.

There is debate regarding the optimal location of life-support withdrawal. Arguments for ICU withdrawal stem from proponents who prefer to provide families a normal setting to grieve, albeit briefly, at the bedside of their loved one. Others argue that effective and expedient progression to donor status allows for a more successful procurement and can only occur in the operating room. At present, there is no standard protocol, and each facility is responsible for dictating a protocol for their institution.

The widening gap between suitable donors and patients in need of transplant continues to be the only issue that keeps solid organ transplantation from achieving its complete potential in offering improved survival to patients with end-stage organ disease. Because current practices and outcomes have shifted the paradigm of binary cadaveric donor (DBD vs. DCD) to a spectrum of standard criteria to extended criteria, the ultimate impact of the estimated 22,000 DCD donors annually[115] on the actual number of organs available for transplantation will remain unclear until sufficient data are obtained under similar protocols. Although ethical questions regarding DCD persist, the process, which is increasingly practiced among transplant centers, accommodates the needs of dying patients and those of patients awaiting transplantation. Several organizations, including the SCCM,[113] American Society of Transplant Surgeons (ASTS),[83] UNOS, IOM,[88] and World Health Organization (WHO) have endorsed the concept and issued relevant guidelines. As experience grows, attitudes change, and outcomes improve, DCD may have a significant impact on the number of organs available for transplantation and thus the quality of life of patients awaiting and receiving cadaveric organs.

KEY POINTS

- Before DBD, procurement of organs from donors was referred to as non–heart-beating donation or DCD.
- DCD organs are subjected to a variable duration of WIT, which negatively affects early and late graft function.
- DCD organ procurements were reintroduced to expand the donor pool and reduce wait times and wait-list deaths.
- DCD kidney, liver, pancreas, lung, and heart grafts are increasingly used, and outcomes have now improved with experience.
- In the contemporary era of ICU care and donor shortages, DCD may be the only effective method of organ donation for terminally ill patients who do not meet DBD criteria but wish to donate organs.

References for this chapter can be found at expertconsult.com.

ANNOTATED REFERENCES

Choi E-K, Fredland C, Zachodni C, et al. Brain death revisited: The case for a national standard. *J Law Med Ethics.* 2008;824–836.
This review provides a comprehensive evaluation of the current status of brain death determination and identifies the shortcomings of the brain death determination process, including the lack of standardized definitions. The authors present viable solutions to the most troubling problems with the current status of brain death determination.

Howard RJ, Missed opportunities: The Institute of Medicine Report: Organ donation: Opportunities for action. *Am J Transplant.* 2007;7(1):14–16.
This commentary summarizes the current landscape of deceased organ donation and highlights the author's opinion that the "Institute of Medicine Report, Organ Donation: Opportunities for Action" paper misses many opportunities for organ donation. The author identifies specific verbiage in the report that does not aim to change public perception regarding the opportunities for donation, especially with DCD, and provides an argument for incentives in donation.

Kotloff RM, Blosser S, Fulda GJ, et al., Management of the potential organ donor in the ICU: Society of Critical Care Medicine/American College of Chest Physicians/Association of Organ Procurement Organizations consensus statement. *Crit Care Med.* 2015;43(6):1291–1232.
Stemming from a multidisciplinary task force, 13 subcommittees from the Society of Critical Care Medicine, the American College of Chest Physicians, and the Association of Organ Procurement Organizations provided a consensus statement regarding death determination using neurologic criteria, donation after circulatory death determination, authorization process, general contraindications to donation, hemodynamic management, endocrine dysfunction and hormone replacement therapy, pediatric donor management, cardiac donation, lung donation, liver donation, kidney donation, small bowel donation, and pancreas donation. Their recommendations are summarized in this important document, which provides critical care practitioners with essential information and practical recommendations related to management of the potential organ donor, based on the available literature and expert consensus.

Siminoff LA, Alolod GP, Wilson-Genderson EYN, et al. A comparison of request process and outcomes in donation after cardiac death and donation after brain death: Results from a national study. *Am J Transplant.* 2017;17(5):1278–1285.
This qualitative study evaluated factors associated with family consent for DCD or DBD based on OPO communication. Sociodemographic characteristics and race were statistically associated with the likelihood of DCD or DBD donation; however, distinction between the two types of donation may not be notable to families. This paper proposes communication strategies to improve the public acceptance of DCD.

Solomon M. *Maximizing Benefits, Minimizing Harms: A National Research Agenda to Assess the Impact of Non-Heart-Beating Organ Donation, Non-Heart Beating Organ-Transplantation: Practice and Protocols. By the Committee on Non-Heart-Beating Transplantation II: The Scientific and Ethical Basis for Practice and Protocols, Division of Health Care Services, Institute of Medicine.* Washington, DC: National Academy Press; 2000.
This report summarizes the discussions and insight from an important organ donation workshop organized by the Department of Health and Human Services held in Washington, DC, on May 24–25, 1999. During the workshop, hospital and organ procurement members provided recommendations for the development and implementation of non–heart-beating-donor protocols. The committee developed these recommendations as steps towards an approach to non–heart-beating-donor organ donation and procurement consistent with underlying scientific and ethical guidelines, patient and family options and choices, and public trust in organ donation.

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Conversations With Families of Critically Ill Patients

Margaret L. Isaac and J. Randall Curtis

Nearly a quarter of the deaths in the United States occur in the intensive care unit (ICU),[1] and the majority of patients who die in the ICU have had life-sustaining measures limited or withdrawn.[2,3] A decision to withhold or withdraw life support is often preceded by a family conference addressing the goals of care and treatment plans. Family conferences addressing the care of critically ill patients can be watershed events, clarifying the prognosis, defining goals of care, and providing support to family members and surrogate decision makers. Because most critically ill patients lack decisional capacity,[4] families and other surrogates are often centrally involved in medical decision making; in fact, 95% of the time, the decision to withhold or withdraw life support is made with the help of a surrogate.[5] Coping with a critically ill family member is challenging for surrogate decision makers, and many feel ill equipped to be involved in decisions on behalf of their loved ones. The care of most critically ill patients should involve explicit discussions with surrogate decision makers about goals of care and treatment plans. Skilled communication by an interdisciplinary ICU team is associated with improved outcomes for patients and family members.[6,7]

Leading an effective family conference requires specific teachable clinical skills, and our aim is to present an evidence-based approach to communication with families of critically ill patients. This chapter first provides an introduction to medical decision making, with a particular emphasis on shared decision making. We discuss a rationale for the importance of family conferences for all critically ill patients and address practical issues, including the considerations of physician reimbursement and billing. We then present an evidence-based approach for family conferences, highlighting competencies and protocols that have been developed to improve physician-family communication. Finally, we address issues of culture, language, and spirituality as they relate to the care of critically ill patients and their families.

MEDICAL DECISION MAKING

Models of Medical Decision Making

Physician-patient or physician-surrogate involvement in decision making regarding life-sustaining treatments can be conceptualized on a spectrum, with parentalism at one end, autonomous decision making at the other, and shared decision making in between. Shared decision making describes a relationship in which information is passed back and forth between physician and patient or surrogate, and both parties share opinions about treatment choices before a decision is jointly reached. There is a consensus among multiple critical care societies in Europe and North America that shared decision making should be the default model for physician-patient and physician-surrogate decisions regarding continuing, withholding, or withdrawing life support in the ICU setting.[8,9] Although most patients and family members prefer a shared decision-making approach,[10] there is considerable heterogeneity among patients and families with regard to their desired level of decision control. In the interest of patient- and family-centered care, it is imperative to individualize one's approach. One study showed that American physicians use the full spectrum of decision-making models but do not routinely assess the surrogates' desired level of involvement in medical decision making: rather than individualizing their approach to match surrogate preferences, individual physicians often have one approach that they use with all surrogates.[11]

Surrogate Decision Makers

The experience of family caregivers and surrogate decision makers is undeniably challenging. Surrogates struggle with emotional conflict and competing values, attempting to honor the wishes of their loved one, meet their own psychological needs, and promote harmony within the broader family.[12] Caregivers are often under tremendous stress and have higher rates of psychological symptoms than the general public.[13] Specifically, the prevalence of anxiety and depression symptoms in family members of critically ill patients is remarkably high,[6,14] and the symptoms of posttraumatic stress have been shown to be present in a majority of family members of critically ill patients.

In addition to the affective difficulty inherent in coping with a sick loved one, surrogate decision makers are asked to participate in complex medical decision making with which they may have very little prior experience. One study showed that 82% of family members who were asked to participate in medical decision making demonstrated symptoms of posttraumatic stress 90 days after patient discharge or death.[15] Communicating clearly about the goals of care and the withdrawal of life-sustaining interventions, in addition to exploring patients' and families' wishes, can contribute to family support and satisfaction.[16] Interprofessional family support interventions involving regular family conferences and emotional support in between meetings have been shown to improve surrogate ratings of communication quality and patient-centered care and a reduction in ICU length of stay.[17]

Though clinicians may be familiar and comfortable with the fast pace of ICUs, the tempo of medical decision making can pose a particular challenge to surrogate decision makers. One study showed decreased family satisfaction associated with a longer ICU stay, but also showed increased satisfaction when the process of withdrawing life-sustaining interventions was prolonged, suggesting family members may need time to adjust.[18] This indicates that families may benefit from time to come to terms with medical decisions and their personal feelings of loss.

Substituted Judgment and Best-Interest Standards

Substituted judgment is upheld as the highest standard for surrogate decision makers.[19,20] In the absence of an existing and specific healthcare directive, clinicians ask that surrogate decision makers imagine what the patient would want were they able to participate actively in decision making. Despite widespread endorsement of the substituted judgment standard by the medical community, ethical and practical concerns have been raised,[21] including the fact that patients frequently change their minds regarding medical decisions and preferences, making an estimation of a patient's wishes more difficult. This is especially true among patients who have not completed an advance directive.[22–24] That said, though many patients evolve and change with regard to treatment preferences, most studies evaluating preference stability have shown that a majority maintain consistency in their wishes regarding medical decisions,[25,26] particularly patients who have engaged in advance care planning and those who are seriously ill.[27]

Some authors have raised concerns about the accuracy with which surrogate decision makers can predict what choices patients would make.[21] A meta-analysis by Shalowitz and colleagues[28] found that surrogate decision makers were 68% accurate in their predictions regarding patient treatment preferences. In cases in which surrogates are inaccurate in substituted judgments, their stated preferences on behalf of the patient more closely represent their personal beliefs about end-of-life care.[29,30] A majority of seriously ill and older patients prefer to defer complex decision making to their physicians and family rather than having their advance directive strictly followed,[31] perhaps reflecting the understanding that it can be difficult to imagine what one's preferences might be given the many variables and perhaps unimaginable subjective experience of being critically ill.

Although there is significant variability in the amount of decisional leeway that patients would like their designated surrogates to have, the majority of patients prefer the implementation of a substituted judgment standard over the best-interest standard.[32] Furthermore, there is heterogeneity in the factors weighed by surrogates in medical decision making, including substituted judgment, but also factors such as shared experiences with the patient and the personal values and preferences of the surrogate decision maker.[33,34] Most of the time, clinicians do not explicitly frame the roles and responsibilities of surrogates.[35] Although this is a complex issue, substituted judgment should be a preferred standard for decision making when possible. By using phrases such as "Your role is to bring the voice of [the patient] into the room. What do you think they would say if they could be a part of this decision today?," the more abstract principles of substituted judgment can effectively frame a surrogate's responsibility.

Role of Advance Directives

The absence of an advance directive has been identified as a barrier to effective end-of-life care in the ICU setting,[36] although significant and valid concerns have been raised as to their usefulness and relevance.[37] Advance directives were not widespread in the past, with some prior studies describing rates of advance directive use between 5% and 11%.[38–40] More recent data suggest that about a third of patients in the United States have completed some type of advance directive.[41] Although advance directives have not consistently been shown to change the type of care provided to dying patients,[37,42] some studies have shown that the presence of an advance directive is associated with higher family assessment of the quality of the dying process for patients in the ICU,[43] greater use of hospice, improved communication,[44] an increased frequency of do not attempt to resuscitate (DNAR) orders, and better quality of life in the final week of life.[45] Advance directives can be helpful to surrogate decision makers, lessening the burden involved in attempting to employ accurate substituted judgment. Importantly, advance directives should be completed as part of a process of advance care planning that allows patients, their family members, and clinicians to explore the patient's values, goals, and preferences before documenting those preferences in an advance directive. Therefore although more progress needs to be made in the role advance directives play in guiding end-of-life care, there is value in advance care planning for those patients who ultimately require critical care.

FAMILY CONFERENCES IN THE ICU

Importance of Family Conferences for All Critically Ill Patients

Robust communication among clinicians (physicians, nurses, and other clinicians) and families of all critically ill patients is important, not only for families of patients who are imminently dying. Family members who felt that communication in the ICU was inadequate were at higher risk for posttraumatic stress disorder,[15] even those with loved ones who survived their ICU stay. Furthermore, families of patients who survived their ICU stay are actually more likely to be dissatisfied with their ICU care with respect to domains such as inclusion in decision making, communication, emotional support, and respect and compassion shown to family, in addition to the consideration of family needs.[46]

Practical and Logistic Considerations

Practical and logistic issues can shape the experience of surrogate decision makers in a critical care setting. Even physical space can have an important effect: a French study[47] found that family members of patients in private ICU rooms had a lower incidence of anxiety and depression symptoms compared with families of patients in multibed rooms. The same group also found that the absence of a dedicated room for family conferences was associated with increased anxiety symptoms among family members of critically ill patients.[14] Accessibility of physicians and the access to information also correlate with family satisfaction; inaccessibility has been correlated with conflicts related to prognosis,[48] suggesting that surrogate decision makers are more satisfied when clinicians are accessible, clear, and comprehensive in their communication.

Evidence-Based Approach to Communication During Family Conferences

Patients and families are consistent in defining high-quality care in the ICU: timely, clear, and compassionate communication by clinicians; clinical decision making focused on patients' values; patient care maintaining comfort and dignity; and family care with open access and proximity to patients, interdisciplinary support in the ICU, and bereavement care for families of patients who die.[49]

Family conferences in the ICU setting are challenging, both for families and clinicians, but it is important to remember that the optimal skills to facilitate these sessions are both teachable and can be rooted in evidence. Using these skills has the potential to improve

outcomes for both patients and family members. Studies suggest that planning conferences early in the ICU stay is beneficial[50]: family conferences held within the first 72 hours of ICU stay are associated with both decreased use of critical care resources among patients who die[51] and higher family assessments of the quality of death and dying.[43] Consistent communication across the medical team is also important; having a "preconference" before family meetings can ensure that families are given a consistent message.[52] As discussed earlier, having a dedicated room for family conferences is also associated with decreased anxiety among family members.[14]

It should come as no surprise that empathic communication is one of the cornerstones of leading an effective family conference. Focusing on listening to concerns of family members is particularly important. Most physicians spend a majority of time talking rather than listening when meeting with patients and families.[53] Families have been shown to have higher levels of satisfaction and lower levels of perceived conflict with clinicians who speak less and listen more.[6,53] Family satisfaction is associated with the use of empathic statements, although this is a commonly missed opportunity: one study found that one-third of physicians in the ICU missed an opportunity to use empathic statements in family meetings.[54] Table 161.1 summarizes categories and examples of empathic statements that can be used by clinicians in family conferences. The "Ask-Tell-Ask" approach advocated by Back and colleagues[55] (Table 161.2) is a helpful tool to assess baseline knowledge and evaluate the understanding of the information provided.

Assurances to families and surrogates that patients will not be abandoned before death and that efforts will be made to provide comfort and minimize suffering and statements of explicit support for medical decisions to either continue or withdraw life-sustaining interventions are associated with higher levels of family satisfaction.[56] The use of the VALUE mnemonic (value, acknowledge, listen, understand, and elicit, summarized in Table 161.3) to enhance clinician-family communication has been shown to improve mental health outcomes, including symptoms of depression, posttraumatic stress disorder, and anxiety in family members.[6] Interestingly, family meetings using this tool were somewhat longer than the usual care meetings, and the percentage of family speech was also higher. In addition, patient-centered interventions such as the Three Wishes Project (3WP), which allow patients and families to express

TABLE 161.1 Empathic Communication in Family Conferences

Category	Sample Statements
Empathy about surrogate decision making	*Withholding or Withdrawing Life Support*: "This is really hard. There's not a right answer to this situation."
	Determining Patient's Wishes: "It is very difficult to be in a position like this where you have to put your own personal feelings aside and try to advocate for what you think he would want."
	Fear of Making a Mistake: "Many families in your situation worry they will look back and think, was there something we missed or something that could've been done earlier? In her case, I do not think that would be true."
Empathy about critical illness in a loved one	*Making Sense of the Disease Process*: "I know it is very important to try and understand as best as possible what happened to see if we can make sense of this."
	Difficulty in Understanding Medical Information: "This is a lot of information to take in. Please feel free to ask any questions you might have."
	Physical Changes: "It must be really hard to see your loved one like this."
	Receiving Bad News: "It is hard to understand why something bad just can happen to anyone, and when it is someone you love and care for, that is even more difficult."
	Uncertainty: "We pretty much have to take it day by day, and I know that this uncertainty makes things even more challenging."
Empathy about confronting death in a loved one	*Helplessness*: "It must be so difficult facing this loss and feeling like there is nothing you can do to change things."
	Dying: "Letting go is so difficult, but I believe you are doing her a great service by honoring her wishes at this time."

Adapted from Selph RB, Shiang J, Engelberg R, et al. Empathy and life support decisions in intensive care units. *J Gen Intern Med.* 2008;23:1311–1317.

TABLE 161.2 "Ask, Tell, Ask" Approach to Discussing Difficult Communication Tasks

Step	Function	Sample Phrases
Ask	Ask the patient/patient surrogate to describe his or her understanding of the medical disease and prognosis.	"It would help me to know what your other doctors have told you about your father's illness."
Tell	Explain to the patient/patient surrogate, using simple, straightforward language, what you understand about the medical disease and prognosis.	"Unfortunately, it looks like your father's illness is getting worse. With a disease as serious as his, 9 out of 10 patients will die within 1 month, and 1 out of 10 will be alive at 1 month. If your father survives this illness, it is very likely he will have significant disability and will likely be unable to live independently."
Ask	Assess the patient's/patient surrogate's understanding.	"I want to make sure that I explained things clearly. Can you tell me, in your own words, what I just told you about your father's illness?"

Adapted from Back AL, Arnold AM, Baile WF, et al. Approaching difficult communication tasks in oncology. *CA Cancer J Clin.* 2005;55:164–177.

TABLE 161.3 VALUE Tool to Enhance Communication in the ICU

V	Value family statements
A	Acknowledge family emotions
L	Listen to the family
U	Understand the patient as a person
E	Elicit family questions

Adapted from Lautrette A, Darmon M, Megarbane B, et al. A communication strategy and brochure for relatives of patients dying in the ICU. *N Engl J Med.* 2007;356:469–478.

Box 161.1 Protocol for Conducting a Family Conference With Key Steps in Bold

Before the Conference

- Plan the specifics of the location and setting: a quiet, private place.
- **PRE-MEET:** Conduct a "preconference" with all interdisciplinary team members to review the conference, ensuring that team members share a similar understanding of medical details, the prognosis, the treatment options, and the goals of the discussion.

During the Conference

- **INTRODUCE**: Review names and roles of the team members and the family.
- **ASSESS:** Ask the family for their understanding of the current situation to gauge their level of understanding.
- **UPDATE:** Provide an update to the family and ask the family about the patient's values and goals.
- Discuss the prognosis frankly in a way that is meaningful to the family.
- Review the principle of substituted judgment: "What would the patient want?"
- Make a recommendation about treatment.
- **EMPATHIZE:** Provide empathy and support the family's decision.
- Acknowledge strong emotions, and use reflection to encourage patients or families to talk about these emotions.
- **PRIORITIZE**: Help the family prioritize important issues and potentially conflicting values or goals.
- **ALIGN**: Explicitly align the clinician's, patient's, and family's goals wherever possible.

Summarizing the Conference

- Summarize the discussion and plans.
- Ask what questions the family might have.
- Ensure a basic follow-up plan, and make sure the family knows how to reach you for questions.
- Document the discussion in the medical record.

Adapted from Whitaker K, Kross EK, Hough CL, et al. A procedural approach to teaching residents to conduct ICU family conferences. *J Palliat Med.* 2016;19:1106–1109 and Curtis JR, Patrick DL, Shannon SE, et al. The family conference as a focus to improve communication about end-of-life care in the ICU: Opportunities for improvement. *Crit Care Med.* 2001;29:N26–N33.

individual wishes in the ICU at the end of life (including examples such as dressing in one's own clothing and postmortem tributes), have been found to be valuable to families, staff, and providers.[57]

Box 161.1 provides a summary of an approach to conducting and teaching family conferences adapted from prior publications.[58,59] This can be a helpful guide, although it should be adapted to the individual goals and circumstances of each family conference.

Discussing Prognosis

Despite the ethical responsibility to inform patients about prognosis, many clinicians are uncomfortable doing so and identify this task as one of the most difficult parts of their job.[60] In one study,[61] clinicians did not discuss the survival prognosis in over one-third of family conferences in which the attending physician anticipated there would be a discussion of withholding or withdrawing life-sustaining interventions or discussing serious news. Because patients with a poor prognosis are more likely to decline life-sustaining treatments,[62,63] discussion of the prognosis is critically important. Interestingly, surrogates rely upon far more than just the prognostic information provided to them by physicians,[34] although most try to balance their assessment of the patient with the information provided by physicians in understanding prognosis. Surrogates also report that they understand and appreciate explanations of the uncertainty involved in prognostication,[64] although evidence suggests that the surrogates' understanding of prognostic information is low, even when they rate the quality of prognostic communication highly.[65]

Experts recommend framing prognosis numerically rather than using nonspecific terms (e.g., "1 in every 10 patients" rather than "uncommon" or "low risk"), framing prognosis both positively and negatively, and using consistent denominators when presenting rates of risk (e.g., "9 in every 10 patients with illnesses as severe as your father's will die before leaving the hospital" and "1 in every 10 patients with illnesses as severe as your father's will survive to leave the hospital").[66] In addition, family members of critically ill patients report that they prefer numeric estimates.[67] Despite these recommendations and preferences of family members, a minority of critical care physicians use numeric estimates in discussing prognosis[68] and/or verify whether or not surrogate decision makers have understood the information provided (e.g., such as using a "teach-back" method). Using an empathetic approach with statements such as "I hope" and "I worry" can also be an effective method of building trust and connection and capturing the uncertainty in estimating prognosis.[69]

Discussing Resuscitation

Most patients and their families have little personal experience with the critical care setting or with cardiopulmonary resuscitation (CPR). Knowledge of the probability of survival from CPR affects patients' choices about code status.[63] Unfortunately, many people base their assumptions on the likelihood of surviving CPR on information from the lay media, such as medical dramas on television, which dramatically overrepresent favorable resuscitation outcomes.[70,71] Consensus guidelines have highlighted specific recommendations in discussing resuscitation with patients,[72] some of which may also help guide discussions with surrogate decision makers. The authors recommend that, among other events, admission to a critical care unit should serve as a trigger for a discussion of resuscitation preferences.

Another important recommendation is that the discussion be framed to review the overall goals of care rather than merely focusing on code status. It is also important to make a distinction between life-sustaining interventions and CPR, describe cardiac arrest and care plan options (including palliative care) in detail, and offer quantitative information about the patient's likelihood of surviving to hospital discharge. Discussing longer-term survival and functional status after resuscitation, offering a code status recommendation, and focusing on trust and rapport building are also important. In summary, CPR in the critical care setting is best addressed in the context of the greater goals of care, including a candid discussion of the likelihood of CPR survival and care alternatives, such as palliative and symptom-focused care.

Billing and Reimbursement

According to the guidelines from the Center for Medicare & Medicaid Services (CMS), US physicians are permitted to bill for time spent

consulting with surrogate decision makers either in person or by telephone. Furthermore, critical care clinicians are permitted to bill for critical care time for these discussions, provided that the patient is unable to participate in giving a history and/or making treatment decisions and the discussion is necessary for determining a treatment decision. Documentation for these conversations must include:

- The medically necessary treatment decisions for which the discussion was needed
- That the patient is unable to participate in giving history and/or making treatment decisions
- The necessity of the discussion and a summary of the medical details to support this necessity[73]

Palliative care clinicians in the United States are recognized as an independent medical subspecialty by Medicare and, as such, can bill for their consultative services. Previously, prolonged service codes, frequently used in palliative care billing, required that additional time is spent "face-to-face" with the patient, meaning that time spent in meetings outside of the patient's room between clinicians and surrogate decision makers was not compensated. This changed in 2009, such that clinicians can now bill for prolonged service time spent charting, reviewing records, coordinating care with other clinicians, and importantly, meeting with surrogate decision makers outside of the patient's room.[74] Claims have been denied for palliative care specialists who are credentialed in the same specialty as the primary team physician, although these denials have been successfully appealed.[74] Of course, specifics regarding the billing for both critical care and palliative care specialists change over time, so clinicians will be well served to familiarize themselves with the most updated billing guidelines.

Role of the Interdisciplinary Team

The complexity of critical care requires the involvement of a multidisciplinary team, and interprofessional shared decision making has emerged as a standard for high-quality critical care.[75] However, conflicts between nurses and physicians are common,[76] particularly in the setting of end-of-life care, and are a source of significant work stress and burnout.[77–79] Enhanced nurse-physician communication and collaboration have been associated with higher patient satisfaction[80,81] and a lower incidence of anxiety and depression symptoms among families of critically ill patients,[14] in addition to lower rates of burnout among nurses and physicians.[77,78] Improving communication among the multiple clinicians within the ICU (i.e., physicians, nurses, respiratory therapists, social workers, and spiritual care providers) would undoubtedly improve not only workplace relationships and stress but also patient care and integrated communication with families and surrogate decision makers.[82]

Palliative care specialists are an increasingly common hospital resource. Involvement of a multidisciplinary palliative care team is associated with increased patient satisfaction and decreased rates of ICU admission after hospital discharge and significant cost savings.[83]

Role of Protocols and the Importance of Individualization

Many of the communication strategies that have shown efficacy were implemented using interventions designed with specific protocols. The tenets of patient-centered care affirm the importance of tailoring communication and interactions to specific patients and their families, rather than resorting to a scripted dialogue. However, given the many missed opportunities in the current level of communication with patients and surrogate decision makers in the critical care setting,[84] it is reasonable to look to communication approaches that have been rigorously developed and studied. Specific guidelines on communication techniques and strategies are intended as a starting point, and clinicians are encouraged to integrate these with their personal approach and authentic voice and to adapt their approach to the individual patient or family.

Culture, Language, and Spirituality

Cultural considerations are fundamental in talking with families and surrogate decision makers from diverse backgrounds. Using language interpreters and cultural mediators is critical in facilitating communication with patients and families who speak different primary languages than clinicians. Ideally, the role of an interpreter transcends mere strict literal translation. Interpreters with additional training can assume the role of a cultural mediator, helping to interpret content bidirectionally, bearing in mind that patients and families frequently participate in many cultures simultaneously, with intersectionality mediating how these cultures manifest in beliefs and actions. Although cultural competence be helpful in designing structures and systems that can best help a diverse group of patients, cultural humility—a stance of openness and curiosity about an individual patient—protects against generalizations, biases, and assumptions and promotes patient-centered care.

Even with the most skilled cultural mediators, there are challenges inherent when language discordance exists. Interpretation of family conferences is a difficult process that can include critical errors, and it is difficult to provide emotional support for families in this circumstance.[85,86] Implementing best practices (e.g., a preparatory meeting with interpreters before the clinical encounter, speaking slowly, confirming the patient's or family's understanding, and debriefing with the interpreter after the clinical encounter) can facilitate better communication and decrease the potential for misunderstandings.[87,88]

Spiritual Issues

Spiritual needs figure prominently for many critically ill patients and their families, often explicitly or tacitly shaping decision making about medical care,[89] although these considerations are rarely discussed in family conferences.[90] Increased family satisfaction has been associated with the assessment of spiritual needs.[16] Exploring underlying spiritual beliefs and values can be extremely important in supporting families and in finding common ground on medical decisions through shared decision making. In addressing spiritual concerns, clinicians should use caution in not stepping beyond one's role as a clinician or trying to resolve existential and spiritual questions[89]; rather, the focus should be on assessing potential spiritual needs and then making referrals for spiritual care providers.[91]

CONCLUSION

Conferences with families of critically ill patients are crucial and are one of the more formidable clinical challenges faced by critical care clinicians. Many approaches to medical decision making exist, and there is significant variability among patients and patient surrogates regarding their preferred role. There is a consensus that shared decision making should be the preferred approach of clinicians, although care must be taken to assess the family's desired role in medical decision making and individualize one's approach accordingly. Having a critically ill family member and functioning as a surrogate decision maker are incredibly challenging for families, but stress associated with this situation can be mitigated through integrated, thoughtful, and empathic communication by physicians and other members of the critical care team.

KEY POINTS

- The quality of family conferences can have an important impact on outcomes for patients and families.
- Shared decision making is an optimal default strategy, though some patients and families may prefer more or less decision control.
- Meeting frequently with patients and family members throughout an ICU stay is associated with higher satisfaction.
- Framing the role of surrogate decision makers, specifically related to the substituted judgment standard, is important.
- Allowing families to speak more, using empathic statements, and providing expressions of nonabandonment are associated with higher family satisfaction after family conferences.
- Using other members of the healthcare team, including translators and spiritual care providers, can help bridge gaps in understanding during and after critical illness.

References for this chapter can be found at expertconsult.com.

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Resource Allocation in the Intensive Care Unit

Gordon D. Rubenfeld

INTRODUCTION

Two truisms of economics are that the supply of goods and services is finite and that supply is never sufficient to meet all demands. The tension between supply and demand for food, water, energy, education, and other goods and services creates economies. All societies must determine how goods and services will be allocated to individuals. Although the term *rationing* connotes a specific process of allocation during circumstances of severe resource limitation (for example, rationing coupons to allocate gasoline during World War II), rationing is just a synonym—an emotionally laden synonym—for resource allocation. In this chapter the terms are used interchangeably. Although rarely recognized as such, rationing decisions occur every day in all aspects of medicine.[1] Critical care services are uniquely poised to raise difficult questions about allocation. First, this high-technology, labor-intensive area of health care is a major driver of rising healthcare costs.[2] Second, the evidence for many intensive care services, including the evidence for admission to the intensive care unit (ICU) itself, is limited. Finally, the decision not to provide intensive care services compared with, for example, the decision not to get magnetic resonance imaging (MRI) for low back pain or not to provide antibiotics for an apparently viral respiratory infection is a rationing decision with an identifiable life in the balance.

Market-based economies allocate many resources on the basis of ability to pay, but other strategies exist (Table 162.1).[1] In developed nations, some goods and services—for example, health care and education—are treated differently than luxury goods and are allocated by society using criteria other than an individual's purchasing ability. Because medical resources are finite, it is impossible to provide every effective treatment in every case where it might offer benefit and the patient desires the care. That does not mean that clinicians are aware on a daily basis of the burden of this reality. Sometimes the decisions are explicit with immediate repercussions—for example, the selection of one patient to receive a heart transplant when several might benefit from the sole available organ—or the decision to admit one patient to the last ICU bed when several patients are critically ill who would benefit from ICU admission. More frequently, the decisions are subtle and occur even when the supply of the therapy is not absolutely limited (e.g., the decisions to use cheaper antibiotics, sedative medication, imaging modalities, or nursing ratios) when more expensive options might be beneficial or, more frequently, the decision to use an ICU bed in cases of small benefit (e,g., observation of low-risk surgical patients for complications). Finally, allocation decisions can be completely implicit and almost hidden because they occur at a system level. For example, the decision to build an ambulatory care clinic instead of adding ICU beds is an allocation decision with profound implications for the delivery of critical care services that is nearly hidden to the individual clinician.

Although common and necessary, allocation decisions are stigmatized in medicine. Allocation decisions bring two major ethical principles into conflict. The principle of beneficence guides clinicians to act solely in their patient's best interests, whereas the principle of justice directs clinicians to act fairly.[2] This conflict may explain why euphemisms are frequently used to describe decisions that are essentially decisions to ration resources. For example, "triage," "optimization," "prioritization," "cost-effective," "waste," and "basic health care" all indicate some form of allocation decision.[3–5] The purpose of this chapter is to explore these decisions in their many guises as they occur in critical care and to offer some guidance to the clinician for constructing processes for allocating resources in their ICU.

ALLOCATION VERSUS EVIDENCE-BASED MEDICINE

Decisions based solely on the evidence of efficacy of medical care are *not* rationing decisions. There is no medical obligation to provide and no societal obligation to pay for care that is harmful or ineffective. In fact, clinicians use special terms to describe interventions that fall into these categories, including "futile," "not standard of care," "medically inappropriate," "wasteful," or "experimental."[3,4] For example, an intensivist who decides not to transfuse a critically ill patient with blood with a hemoglobin of 73 g/L is *not* rationing blood even though blood is an expensive and limited resource because there is evidence that this transfusion in many critically ill patients is of no benefit and may be harmful.[5] The decision not to use human growth hormone, an expensive medication, in chronically critically ill patients is not a rationing decision because this treatment has not been shown to be effective and may be harmful.[6]

Unfortunately, the assessments of benefit and harm are not as straightforward as the terms would suggest, and the line between effective, ineffective, and experimental often lies in the eyes of the individual clinician. Decision science has taught us that medical decision making is a complex process that frequently obscures the true rationale of the choice.[7] In fact, judgments allegedly based solely on objective evidence of safety and benefit often incorporate a variety of subjective values and biases.[8] These may include the value the clinician assigns to being wrong; the value assigned to trying to "rescue" a patient in imminent danger of death; the clinician's tolerance for uncertainty; the impact of the decision on the clinician's finances; biases about the patient's race, gender, functional status, or age; and the cost or availability of the resource.[9] These transitions from statements that summarize the evidence of benefit to recommendations that incorporate cost and other values are often very subtle. This is particularly problematic for many treatments in critical care where there is an absence of evidence of efficacy, no clear harm, and, for individual clinicians, strong beliefs about efficacy. For example, the authors of a recent systematic review of colloid resuscitation in critical care conclude that "there is no evidence from randomized controlled trials that resuscitation with colloids reduces the risk of death compared with crystalloids in patients with trauma, burns and following surgery."[10] This is a statement of their summary of evidence of efficacy. Like many treatments in critical

TABLE 162.1 Strategies for Allocating Resources

Principle	Definition
Autocracy	To each according to the will of one
Democracy	To each according to the will of the majority
Equality	To each according to an equal share
Lottery	To each according to an equal chance
Capitalism	To each according to their ability to buy
Personal worth	To each according to their contribution to the community
Utilitarianism	To each so that the utility of the community is maximized

care, the evidence neither supports nor completely refutes the use of colloids as resuscitation fluids in the critically ill. However, the authors conclude, "As colloids are not associated with an improvement in survival, and as they are more expensive than crystalloids, it is hard to see how their continued use in these patient types can be justified outside the context of randomized controlled trials." Although the first statement may be a fair summary of the evidence, the recommendation against using colloids in the second sentence is fundamentally a rationing or allocation assessment based on cost-effectiveness. It incorporates an implicit strategy that only recommends treatments that have demonstrated benefit related to their cost. One might conclude from the authors' review that colloid resuscitation is experimental or that its benefit is likely to be small; however, the reasoning for recommending against its use is based on the cost of the treatment. Presumably, if colloid fluids were the same price as crystalloids, the authors might reach different conclusions even though the cost does not change the evidence of efficacy.

The preceding example shows how assessments of cost can creep into evidence-based recommendations for therapy even without formally discussing allocation. Because clinicians and payers may be reluctant to admit that they are incorporating cost or availability into the rationale for a decision, they may find decisions of futility or appropriateness less ethically problematic than rationing. In fact, these judgments may implicitly contain assessments of cost by incorporating cost into the definition. Because scientific studies can never statistically *prove* a therapy is ineffective, when is there sufficient evidence to move a treatment or diagnostic device from experimental care to standard care? Does this distinction matter if the person is paying for their own care or if it is paid for by a third party? Given the statistical challenges of proving inefficacy, when is there sufficient evidence, in the absence of demonstrated harm, that a treatment is ineffective as opposed to not yet of proven efficacy? These decisions are frequently made by consensus bodies using subjective or poorly characterized criteria but usually avoiding an explicit assessment of cost. In 1989 the Oregon Health Plan attempted to extend healthcare benefits to more people by creating a prioritized list of health benefits—essentially rationing care. To develop this list, the Oregon Health Services Commission was convened.[11] It ranked treatments by their effectiveness from therapy for acute head injury with loss of consciousness (#1), anal fissure (#579), and hepatorenal syndrome (#743, near the bottom) and funded them in order based on available resources. Interestingly, although treatments were selected based on funding and the overall process was essentially a rationing plan based on cost-effectiveness, the rank list itself was not particularly correlated with formal cost-effectiveness assessment, indicating that other, potentially subjective, factors took precedence.[12]

At the bedside, clinicians also tend to subtly incorporate cost into their assessment of evidence-based recommendations. The amount of evidence required to convince clinicians to adopt treatments that are risky or expensive will always be more than treatments that are safe and cheap. For example, consider the decision to elevate the head of the bed of mechanically ventilated patients to prevent ventilator-associated pneumonia. Although the evidence supporting its effect on reducing mortality or ICU length of stay is limited, it is inexpensive and safe and has become part of routine ICU care. Conversely, kinetic beds, topical prophylactic antibiotics, and special endotracheal tubes, which are more expensive and may raise safety issues, have had considerably less uptake despite evidence supporting their use.[13]

Judgments about the evidence-based efficacy of treatments that are supposed to be independent of cost are further complicated by the motivation of the decision maker. It would be difficult for an insurance company that is assessing whether a specific therapy is experimental or standard of care to be unbiased when its decisions affect its profits.[14] Alternatively, surgeons who developed a procedure may be committed to its benefits in a way that compromises an objective evaluation. The complexity of the assessment of efficacy and costs points to the importance of making allocation decisions as objective, explicit, and public as possible.

ALLOCATION STRATEGIES

Given that an intervention is effective, clinicians will face decisions to allocate resources at the bedside. These decisions are usually separated into macro-allocation decisions (involving groups of people and usually made at a managerial or health policy level) and micro-allocation decisions (made at the bedside and involving identifiable specific cases). A hospital's decision not to hire additional ICU nurses is a macro-allocation decision. A nurse manager's decision to allocate a specific patient to share a nurse in the ICU rather than to receive 1:1 nursing is a micro-allocation decision. This chapter is primarily concerned with bedside allocation, or micro-allocation decisions, which clinicians make on a routine basis. There is an important interaction between micro- and macro-allocation decisions because macro-allocation decisions ultimately affect individuals, and macro-allocation regulations are an effective strategy for implementing allocation (Table 162.2).

There are a number of approaches to allocating resources (see Table 162.1). Although these are all feasible, they are not all equally ethical. The principles of equality, fairness, justice, and due process make some strategies less acceptable. The principle of utilitarianism directs resource allocation to maximize the "utility," or benefit, of the most people for any given amount of resources. To the extent that "utility" can be measured by measuring patient outcomes like health-related quality of life and to the extent that we can estimate the effects of medical treatments on utilities, we can theoretically calculate exactly which set of medical treatments to pay for to maximize the benefit to the population. These studies are called *cost-effectiveness analyses* and are the quantitative realization of the philosophic theory of utilitarianism. Allocating medical resources through cost-effectiveness analyses has important limitations. First, medical cost-effectiveness analyses cannot tell how much money to allocate to medical as opposed to other goods and services, just how to maximize health outcomes for any selected outlay of resources. Second, cost-effectiveness analyses may not fully account for some factors that society values. For example, cost-effectiveness analysis routinely treats all human lives as equally valuable; however, society often places a very high value on identifiable lives in imminent danger of death and may not value additional years of life in the elderly as much as years of life in the young.[15] Cost-effectiveness and other utility-based allocation

TABLE 162.2 Allocation Decisions at Different Levels

	Decision Maker	Decision	Rationale
Not an allocation decision	Physician	Not to use human growth hormone in chronically critically ill patients	Evidence of harm in critically ill patients
	President of insurance company	Not to offer routine chest computed tomography screening for lung cancer	Lack of sufficient evidence of benefit
	Healthcare minister	Not to offer basic medical coverage to all people in the country	Endorses other goals than equal access to health care: for example, the importance of choice or the value of free market
Macro-allocation decision	Physician	Not to admit routine postcoronary artery bypass patients to the intensive care unit (ICU)	Limited ICU beds used for patients with more severe illness
	President of insurance company	Not to increase reimbursement for septic shock when new, expensive drug is approved	Hopes to limit cost of care for patients to increase profitability of insurance company
	Healthcare minister	To capitate reimbursement for hospital care	By providing single fee for all care, hopes to limit costs so that increased outpatient services can be provided
Micro-allocation decision	Physician	Decision not to admit a debilitated, elderly man with urosepsis to the ICU despite a request by the patient's primary care physician	The intensivist felt the patient was moribund and that the ICU's resources could be used to better effect on other patients
	President of insurance company	Denial of claim to pay for lung transplant for 73-year-old man with pulmonary fibrosis	Treatment specifically not covered by contractual arrangement with insured patient.
	Healthcare minister	Not applicable	Not applicable

strategies fail to account for the value society places on rescuing lives in imminent peril—a not uncommon occurrence in the ICU.[16] Standard economic analyses may not value equal distribution as much as optimal distribution and, to this end, may discriminate in settings that society finds unacceptable.[17] Finally, cost-effectiveness analysis is a mathematical technique that generates comparative outcomes for populations of patients rather than an evaluation in single cases. It is worth pointing out that the term *cost-effective* is frequently misused both in informal clinical conversation and in the literature.[18] It is incorrect to speak of a treatment as being "cost-effective" without a comparator. Cost-effective does not necessarily, and actually rarely, means cost saving. Cost-effective does not necessarily mean the least expensive or the most effective of treatment options.

Cost-effectiveness analysis is a methodology that provides a ranking of treatments, which provides someone who has the authority to make decisions with the information to *compare* various strategies.[19] For example, one can compare the cost-effectiveness of captopril versus no captopril in survivors of myocardial infarction with using fluoxetine versus imipramine for major depression to decide whether to use captopril, fluoxetine, both, or neither. Cost-effectiveness analyses provide a ruler, a shared metric, usually in terms of dollars per life-year or dollars per quality-adjusted life year (QALY) that allows treatments to be compared with allocation (rationing) decisions on which treatments to provide when all effective treatments cannot be paid for. Valid cost-effectiveness ratios require an estimate of a numerator (the *cost* of one therapy compared with another) and a denominator (the *effect* of the therapy on survival or quality of life). Without evidence of effectiveness from randomized trials, estimates of cost-effectiveness are problematic and must be modeled on other data. Although we have data in critical care on strategies to reduce gastrointestinal bleeding, duration of mechanical ventilation, and ICU-acquired infections, the number of treatments that can demonstrate an improvement in QALYs is very limited.[20–22] Therefore the denominator for cost-effectiveness analyses in critical care can frequently only be expressed as dollars per event: for example, dollars per gastrointestinal bleed or ventilator-associated pneumonia prevented.[23] These ratios, sometimes referred to as *cost-benefit analysis,* cannot be used to compare a treatment to prevent gastrointestinal bleeding with a treatment to prevent catheter-related infections or with a treatment to improve weaning because they are all expressed with different denominators. Cost-effectiveness analyses with non-QALY denominators can be helpful in bedside rationing decisions when the intervention is known to be safe and equally or more effective and *reduces cost.* For example, special beds in the ICU have been shown both to prevent decubitus ulcers and to reduce the overall costs of care even when the cost of the bed is factored in. Therefore the cost-effectiveness ratio, expressed in dollars per decubitus ulcer prevented, is a negative number.[24]

ILLUSORY COST SAVINGS

If cost-effectiveness analyses are difficult in critical care because of a paucity of data for the denominator, the numerator—cost—is also challenging to calculate.[25] Since the earliest days of intensive care, technologic, workforce, and organizational innovations have been proposed as opportunities to reduce the exorbitant cost of critical care. In 1972 an optimistic author wrote, "[The] more promising approaches to cost reduction are all in an early stage of development now. Both deprofessionalization of the ICU by wider use of allied health personnel, and the automation of therapeutic functions are just beginning to be applied."[26] Despite implementation of both of these measures, there is little evidence that cost increases in hospital or ICU-based care have been curbed by technologic innovation. In fact, the opposite has occurred. This is not surprising because technologic innovation in other areas of health care, although often associated with better outcomes, is rarely a source of cost savings.

Cost analyses are problematic in medical care, and critical readers must be able to identify cost savings that are real and that will appear in their budgets as opposed to savings in indirect costs that will be

accrued elsewhere.[27] There are several common, but problematic, arguments about cost reduction in critical care: (1) that reduced ICU length of stay will reduce the cost of care in the ICU, (2) that reduced test ordering will reduce the cost of care in the ICU, and (3) that fewer admissions of futile-care patients will save money. It is important to recognize that not all calculated cost savings will be realized at the ICU or hospital level.

ICU costs are frequently inferred from length of stay. For example, in a cost-effectiveness analysis of antibiotic-coated catheters, the authors assigned a cost of $9738 to a catheter-related bloodstream infection.[28] Epidemiologic studies show that patients with catheter-related infections spend more time in the hospital, even after controlling for severity of illness.[29] The cost of a catheter-related infection is, in part, derived by simply multiplying the estimated number of extra days patients with such infections spend in the hospital by the cost (based on hospital charges) of a day in the ICU or ward. In fact, we do not really know whether using antibiotic catheters shortens ICU length of stay because the randomized trials demonstrating that antibiotic-coated catheters prevent infection were not sufficiently powered or did not show a reduction in mortality or length of stay.[22] Even if the antibiotic-coated catheters reduce length of stay, money "saved" by reducing length of stay is a different kind of money than money spent in buying the catheters. By reducing length of stay, the ICU will be able to care for more patients, but they will be sicker and more expensive patients.

Identifying treatments for specific conditions in the ICU that reduce overall costs, even if they have no effect on QALYs, is extremely useful to the intensivist allocating resources. Implementing economically dominant strategies is an easy allocation decision, as they do not worsen patient outcomes and reduce costs. However, predicting the actual effect of any decision on actual costs in an ICU or hospital is complex because each hospital performs cost-accounting and budgeting in idiosyncratic ways. The effect of different payor mixes, contracts for nursing and respiratory therapist labor, allocation of indirect costs, and whether the ICU budget is fixed or grows with the number of patients served all influence whether allocation decisions accrue savings that can be appreciated at the ICU level. For example, the drug acquisition costs of once-daily medications are frequently higher than medications given more frequently. However, labor costs are associated with administering medication more frequently that may offset the costs of the once-daily medication. Unfortunately, unless there is a sufficient workload reduction from changing to once-daily medication to actually firing a nurse, there will be little realized savings. This is because labor costs are not infinitely scalable. If there is 15% less work to do, you may not be able to hire 15% less nursing hours. Patients who need 1:1 nursing care will continue to need this level of care regardless of whether the nurses are administering once-daily medication or not. It may be that changing medication routines improves care by more efficient use of nursing time, but this may not be reflected in a cost reduction. A reasonable question for ICU managers who are considering a cost-saving intervention is whether it will reduce the amount of staff that need to be hired or whether it can reduce acquisition costs for equipment or medication. If it will not, then cost savings is not likely to be realized in the ICU.

The cost estimate used in many cost-effectiveness analyses assumes that every day in the ICU costs the same. This is certainly true for what the hospital charges, from which these ICU costs were derived. However, this is not true in reality. The first few days in the hospital and ICU are far more expensive than the last days.[30] Patients are more likely to require active interventions and closer nursing care in the early days in the ICU. Clearly, interventions that reduce ICU length of stay cannot reduce early days in the ICU and simply eliminate later lower-cost days. This is rarely accounted for in the cost analyses. This was validated at the national level as US healthcare costs peaked during a period when hospital inpatient days declined by 40%.[31] Therefore cost analyses may overestimate cost savings likely to be realized by reducing length of stay when this leads to a reduction in marginal low-cost days, and these days are merely shifted to other areas with similar or greater costs.

Reducing test ordering in the ICU has been offered as a technique for cost reduction. This, too, is a perfectly reasonable option to be offered on clinical grounds. Overtesting yields increased false positives, which may lead to clinical complications in search of diseases that never existed. However, the actual cost reduction that will be seen at the ICU level by reducing test ordering is likely to be overestimated in a simple charge-based analysis of test ordering. The actual marginal cost of performing the 101st arterial blood gas once you have already purchased the analyzer and paid for the technician time to perform 100 arterial blood gases is minimal. If reductions in test ordering are of sufficient magnitude to staff the laboratory with fewer people or to forego purchasing new equipment, then significant cost reductions can be realized. In fact, depending on how indirect costs in the hospital are allocated, it is possible that a reduction in test ordering will place the clinical laboratory under considerable budgetary constraints. Fewer tests may reduce the amount of money that the laboratory director receives to cover staff costs, which may not decrease in the same proportion as test ordering. Therefore clinicians should be wary of bedside testing device claims of reduced testing costs. There may or may not be valid clinical reasons to have bedside laboratory testing; reducing overall hospital costs is unlikely to be one of them.

Patients may be admitted to the ICU even when they have a negligible chance of survival. It seems reasonable to assume that if these patients receive care outside the ICU that the resources that would have been expended without benefit in the ICU would be saved. On its face, this appears to be the sort of painless cost saving that intensivists should look for. Unfortunately, a careful analysis of the potential savings from limiting care at the end of life shows that it is a relatively small amount of overall healthcare spending; that implementing these strategies may worsen overall health outcomes by affecting care that nonterminal patients receive; and that care would have to be withheld from young patients, some of whom would have had prolonged survival, to achieve any savings.[32]

STRATEGIES FOR BEDSIDE ALLOCATION OF RESOURCES IN THE ICU

Ultimately, allocation decisions will occur at the bedside in the ICU. A number of studies demonstrate that under settings of restricted access to ICU beds, physicians allocate these beds on the basis of severity of illness. In these situations the average severity of illness in the ICU increases as it does on the hospital ward.[33] The empiric research on ICU bed rationing is limited and complex because some authors do not distinguish between allocation made for efficacy (futility) from those made because of lack of beds or cost-effectiveness.[34] In fact, most clinicians in the United States do not perceive that they do any rationing at all and, if anything, feel that too much intensive care is provided to patients.[35] When they occur, rationing decisions may not always be driven by bed availability and prognosis and are also guided by arbitrary factors including age, gender, reimbursement, and physician power in the institution.[36] One of the few studies to actually document rationing through "revealed preferences" (actual behavior as opposed to stated rationale) looked at goals-of-care conversations with patients who had a sudden

decompensation on the ward. The more ICU beds were available, the less likely physicians were to have goals-of-care discussions to avoid ICU admission and the more likely they were to admit to the ICU.[37] However this study failed to find an association with mortality, suggesting that within the limits of the study, the physicians' rationing of ICU beds when limited had no negative effect. This study also suggests that similar rationing could occur safely when ICU beds were not limited but physicians did not behave that way. It is important that clinicians plan in advance of these difficult decisions so that their deliberations are explicit, open, and guided by principles rather than ad hoc case-by-case decisions.

SPECIAL SCENARIOS

Pandemic and Disaster Triage

The pandemics of SARS (2002), H1N1 (2009), Western African Ebola (2014), and COVID-19 (2019) and disasters like Hurricanes Katrina and Sandy (2005, 2012) and the Tohoku earthquake (2011) have focused policy makers on the demands these can place on the public health system in general and on critical care systems in particular. In developed countries, it is rare for critical care providers to have to choose between patients, both of whom could benefit from critical care. Although investments in preparedness are ongoing in many developed countries that include stockpiling of medication and ventilators, the likelihood that clinicians will have to ration lifesaving ICU resources during a disaster is real. There have been several responses to this inevitable clinical challenge: ethical, empiric, and legal.

Bioethicists have long struggled with the "lifeboat" scenario where only one person can be saved out of many who could be saved. In fact, the "ethics committee" was born out of the need to allocate dialysis and organ transplants.[38] There has been rapid growth of publications and online resources devoted to pandemic planning and ethical triage.[39] The issues are complex and extend beyond resource allocation—for example, whether healthcare professionals have a duty to provide treatment during an outbreak that poses risks to themselves and families or how care for severely ill patients not affected by the disaster should proceed. Conceptually, the allocation solutions are no different from the ones outlined at the beginning of this chapter; however, the absolute scarcity of resources, youth of the afflicted, and medical risk to providers make the decisions significantly more pressing. The issues relate to whether one should include factors other than prognosis in deciding on allocation: for example, social value, service value during the crisis, and age.[40,41] The principles are far from resolved, and perhaps the most valuable contribution of these deliberations is their focus on the need for transparent processes to be developed in advance of the crisis. Whether or not any of these rules can be enforced under the incredible pressures of life and death decisions at the bedside, where some of the critically ill patients may very well be colleagues who are ill after an infection acquired during the care of other patients, is completely untested.

Empiric solutions to disaster triage that rely on objective estimates of prognosis to guide end-of-life decisions are not new.[42] Unfortunately, previous attempts to ration intensive care based on computerized prognostication in any formal fashion has met with public disapproval.[43] Because of their inherent uncertainty, the literature on objective probability estimates in critical care generally criticizes their use as tools to make individual decisions about withdrawing life-sustaining treatments. Nevertheless, objective prognostic tools have been proposed for pandemic triage. They are clinically intuitive, relying on inclusion criteria (respiratory failure requiring mechanical ventilation or hypotension requiring vasopressors) and exclusion criteria (severe chronic comorbidities, age >85, metastatic cancer). Then patients are assigned a triage category based on the Sequential Organ Failure Assessment (SOFA) score and its trajectory.[44] Applying these criteria requires training and external adjudication in some cases.[45] Not surprisingly, patients excluded from the ICU and those who had life-sustaining treatment withdrawn under the hypothetical implementation of these triage criteria had significant survival rates, emphasizing that these triage rules will result in deaths that otherwise could have been avoided.[45]

Primarily as a result of Hurricane Katrina and subsequent lawsuits, there has been an interest in developing a legal framework about institutional and personal liability during disasters. If a clinician makes a triage decision to withdraw life support from one patient and provide it to another, can she be sued or prosecuted? The legal framework for resolving these issues derives from Good Samaritan statutes that protect civilian volunteers from legal liability related to their activities. Three laws passed in Louisiana after Katrina protect physicians and nurses from civil liability in the absence of gross negligence or willful misconduct and require a review panel before criminal indictment for activities that occur during a declared disaster.[46]

Global Critical Care

Getting accurate data on the burdens of global critical illness is almost impossible because many countries have insufficient resources to have ICUs or track these illnesses. Estimates of the rates of critical illness globally based on epidemiology in developed countries, which may be gross underestimates of what would be seen in developing countries, are astounding.[47] There are even more limited data on the availability of critical care services globally. However, viewed on a global level, it certainly appears that health care, and particularly critical care, is allocated based primarily on the wealth of the country.[48]

CONCLUSION

Allocation of resources in medicine is an unavoidable process. Clinicians do have control over whether these decisions are implicit or explicit, are made after open discourse or with no discussion, and whether the decisions are informed by evidence or not. Clinicians in the ICU may, in fact, face fewer implicit allocation decisions than their colleagues in other areas because of the imminent risk of death in the ICU and society's value for protecting those lives. In fact, there is relatively little empiric evidence of how often intensive care services are rationed. The effect of different interventions on actual costs will vary depending on local factors, including reimbursement and indirect cost allocation. Allocating ICU beds is the most challenging allocation decision most intensivists will face. The best time to handle these decisions is before they occur. Public, explicit triage and discharge criteria that are developed in collaboration with ICU users (emergency department, surgery, oncology) well in advance of the actual decisions are essential for fair and efficient use of intensive care resources. It is important that when cost-saving decisions are considered that the entire healthcare system be evaluated. Formal economic evaluation is crucial, as some treatments in the ICU, despite their expense, are likely to be more cost-effective than diagnostic and therapeutic regimens routinely offered.

THE FUTURE

Predictions about rationing of healthcare services are particularly challenging. In addition to making predictions about the future of critical care and critical illness, one must make predictions about the funding and delivery of healthcare services, international migration,

and disasters. My crystal ball makes several assumptions. The ICU of the near future will look very familiar to the intensivist of today. Patients will have more noninvasive monitoring, their complex information will be better organized, they will be more likely to receive noninvasive ventilation, and they will be managed with less sedation and more mobilization; but there will be no magic bullets for sepsis, genomics and personalized medicine will not make it to the routine care of critically ill patients, and patients will still require intensive and expensive nursing care. The aging population at risk for sepsis and respiratory failure will drive demand for critical care services. Successes in other fields—notably cardiovascular medicine, transplant medicine, and oncology—will turn rapidly fatal diseases into slowly fatal diseases marked by multiple visits to the ICU, some of which will be successful. Finally, the changes in healthcare funding will be incremental. At some point, and it may be quite soon for the United States, the costs of providing limitless and frequently wasteful health care to some and inadequate health care to others will become politically untenable. Although advocates for healthcare reform in the United States argue that shifting to a single-payer model will solve these problems painlessly, these benefits will be one-time savings in overhead costs. Countries with single payers like Canada and the United Kingdom are facing medical inflation curves that are similar to the United States. It is likely that only a crisis will drive explicit discussions about allocation of expensive, marginally effective life-sustaining treatments.

KEY POINTS

- Allocation of resources is synonymous with rationing and is an inevitable part of medical practice.
- Clinicians often use a variety of euphemisms, including triage, optimization, prioritization, and cost-effective care, to obscure what are essentially allocation decisions.
- Clinical decisions that are based solely on the evidence of risk, benefit, or patient utilities are not rationing decisions because they do not incorporate cost or availability.
- Clinicians may implicitly incorporate cost or availability into their judgments of the evidence of risk or benefit in an attempt to avoid an explicit decision incorporating cost.
- Allocation can occur at the macro level, where decisions affect populations of patients, or at the micro level, where decisions affect individually identifiable patients.
- Cost-effectiveness analysis is a quantitative methodology that applies a utilitarian approach to allocating resources to maximize the benefit to a population for any specified cost.
- Cost is difficult to measure in complex endeavors like medical care.
- Claims to reduce cost by reducing the length of stay, ordering tests, or admitting patients who will likely die should be examined critically.

References for this chapter can be found at expertconsult.com.

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Basic Ethical Principles in Critical Care

Nicholas S. Ward, Nicholas J. Nassikas, Thomas A. Bledsoe, and Mitchell M. Levy

BACKGROUND

Since the inception of the practice of medicine, there have been ethical challenges for doctors and other health care professionals. Many of the challenges, such as who has the authority to make key decisions (autonomy vs. paternalism) and what the boundaries of life are at the beginning and the end, have existed for a long time. However, the ever-changing landscape of modern technology has presented new and unforeseen questions surrounding when new technologies should be applied and when they exceed ethical boundaries—technologies such as life support and genetic manipulation. Finally, changes in society and its values have led to new ethical challenges. Ethics exist as a perceived set of rules that are formed and judged by the culture in which they exist. Different cultures can have very different ethical systems. In many countries, not only are there very diverse cultures but these cultures continue to change and evolve. The net result of these forces is that modern ethics can change as well. Things once thought unethical may become ethical or vice versa.

The practice of medicine in intensive care units (ICUs) has been the source of many ethical challenges. These are often driven by conflicts surrounding death, a common occurrence in ICUs. Our ability to keep human beings alive has increased steadily, and thus rules and beliefs surrounding when not to continue life support have been tested on a regular basis. Once firmly fixed concepts, such as death or "brain death," are now coming under increasing attack. In other areas, the concept of patient autonomy has been used to request life-prolonging therapies once thought "futile." Finally, ICU physicians are increasingly finding themselves caring for patients who are unable to express their wishes and must rely on some kind of surrogate decision maker, which can add further ethical challenges.

GOALS OF CARE AND MEDICAL DECISION MAKING

Surrogate Decision Making

Modern medicine has embraced the concept of shared decision making between patients and their physicians based on the principles of autonomy honoring the patient's wishes, beneficence (trying to help), and nonmaleficence (not doing harm).[1,2] This approach, as noted, is often more complicated in the ICU. Whether decisions are made to continue with aggressive and likely quite burdensome care or to withdraw such care,[3] there will often be some tension within the care team or between the care team and members of the patient's family (who may be conflicted themselves).[4] In the ICU, as in other medical situations, this model of shared decision making affirms that patients have an ethical (and in many places a legal) right to determine the goals of their medical care. Choosing which health-related goals to pursue for a patient who has temporarily or permanently lost decision-making capacity is an imperfect science, but an individual patient's wishes regarding care may have been made known in advance of a serious medical illness to the physician or to a specific preferred surrogate decision maker or to family or friends. The process by which patients, with or without the assistance and participation of their physicians, family members, or other close personal relations, plan for future medical care is called *advance care planning*.[5] In general, the results of these deliberations are known as *advance directives*; defined broadly, they may be verbal or written and may be quite specific or very general. In this process, the patient may designate a preferred decision maker or health care proxy, may lay out general goals and values related to illness and medical treatment, and may determine what kind of care he or she would want in the settings of some anticipated situations. Subsequently, the advance directive helps direct medical care in the case of the patient's incapacity and comes into play only if the patient is unable to make his or her current wishes known.[6] For example, a patient who awakens after a surgical procedure and is deemed to have decision-making *capacity* (see later) is asked outright about his or her wishes, and the advance directive is no longer necessary.

Advance directives have ethical authority in whatever form (including verbal), as long as the directive was promulgated within the requirements of valid informed decision making (see later) as a tool for formally bringing the patient's values into consideration at a time when the patient is not capable of supplying them himself or herself. As noted, this method of approximating the patient's goals and values in times of serious illness is not perfect, and the reliability of a specific advance directive as "authentic representations of autonomous patient choices" is often suspect.[7] Advance directives specific enough to guide the day-to-day clinical decision making in the ICU are rare; more commonly, the ICU physician is left to work with a surrogate to understand the priorities of the patient and then to make shared decisions for the patient. Even in situations in which the physician "knows what the patient would want," the prudent clinician will seek counsel from individuals who know the patient well to mitigate the risk of paternalism. Who then may and should act as surrogate? How should that surrogate make decisions for the ill patient?

In some cultures, physicians often turn to the "next of kin" for surrogate decision making. However, the legal status of surrogates varies from country to country, and in many jurisdictions this individual has no de facto legal or even ethical grounds for assuming this role. (However, in some cultures, religion, and legal traditions, serious decisions about life-sustaining care are not made by individuals, but rightfully by the religious authority or clan leadership.) In a culture that favors individual autonomy, the best surrogate decision maker is the one chosen in advance by the patient.[8] Often this individual comes from the patient's valued community; usually, this individual is a member of the patient's family or close social circle. In those jurisdictions in which such a hierarchy has been determined by law, a typical sequence might

be (1) spouse, (2) eldest child, (3) next child, (4) parent, (5) sibling, and (6) close friend. Once a surrogate decision maker has been named, it may be helpful for the patient to clarify the role of the surrogate, from simply "tell the doctors what I want" to "use your judgment to make the best decision about my care." Interestingly, when asked whether they would prefer that their advance directives be followed no matter what or that their care be discussed with their chosen surrogate, a majority of patients would cede authority to the surrogate along the lines of "use your judgment."[9]

Even in situations where the appropriate decision maker is not the patient, it is helpful to have documented that the patient agrees with this approach. Similarly, some statement of the values to be used when deciding about medical treatment can be helpful.

Documentation of advance directives allows patients to make their values regarding and wishes for future care known, either formally or informally. As noted, these directives may also designate a specific surrogate decision maker who then has ethical and often legal standing to make medical decisions for the patient. In the absence of advance directives, the legally appointed surrogate or, in the absence of such a surrogate, those who know the patient well make decisions for the patient using substituted judgment based on his or her knowledge of the patient's health-related values. When no information is available about a patient's wishes or values, the decision makers should apply a "reasonable-person" or "best-interest" standard. In such cases, consultation with an ethics committee may be helpful.

Advance Directives

As noted, advance directives are formal or informal instructions to health care providers, family members, or others involved in a patient's care regarding treatment that may be required while the patient is unable to participate in medical decision making. The earliest form of advance directive was the "living will." Classically, the living will is restricted in terms of both scope and applicability. Living wills are usually reserved for patients with terminal illnesses and are typically restricted to statements about forgoing medical treatments that would "only prolong my dying"; they typically make explicit statements about the acceptability of discontinuing intravenous fluids and artificial nutrition if death is imminent and there is no significant hope for recovery. They usually do not provide instructions in the case of nonterminal illness and typically do not name a surrogate. A more generally useful legal document is the one that gives statutory authority to an individual to make medical decisions for a patient in the case of incapacity. This document is sometimes referred to as a *durable power of attorney for health care*. Similar to a durable power of attorney that provides legal decision-making authority for financial and other matters in the case of incapacity, this document provides legal standing to a named surrogate with regard to health care decisions. These documents typically provide an opportunity for an individual to give general information about health care preferences in a variety of situations. Some also provide an opportunity for the person to make a statement about the quality of life and the kind of life that would and would not be worth living. Preferences for organ donation, wishes for spiritual care, and even funeral arrangements are sometimes included.

Additionally, a number of advisory documents have been developed, including "values histories" and the medical directive developed by Linda and Ezekiel Emanuel.[10] These documents may present a series of increasingly dire scenarios and ask about overall preferences ("do everything possible to prolong life," "continue aggressive care but reevaluate often," "keep me comfortable, but do not provide care that prolongs my life"), or they may ask more general questions about what makes the person's life "worth living." It is hoped that this information will be helpful to a surrogate who must decide whether to continue supportive care in the case of irreversible injury or damage or even to continue disease-oriented care in the case of critical illness and impaired decision-making capacity.

For a variety of reasons, advance directives have not achieved wide popularity. When they exist, they are often not specific enough to provide meaningful guidance.[11] Even when a detailed directive exists, questions often remain about whether the individual was adequately informed and, in some cases, whether the individual had decisional capacity at the time. For example, a patient's advance directive says that she would never want to be on life support, but when she is asked about mechanical ventilation in the case of reversible respiratory failure from pneumonia, she says of course she would want that. Thus following a legally executed advance directive without verifying what was meant by the patient and whether the written wishes apply to the current illness can be quite problematic. It could in fact result in a preventable death in a patient who, with proper education, would wish to be treated.

A more limited form of advance directive, known as a *code status,* is frequently sought on admission to the hospital. A code status is an advance directive that is specifically limited to a patient's (or surrogate's) preferences regarding cardiopulmonary resuscitation (CPR) and other measures in the event of a cardiopulmonary arrest. In many hospitals and other health care institutions, as a matter of policy, any patient who suffers a cardiac arrest is treated with interventions designed to attempt to reverse the life-threatening derangement, including CPR, electrical defibrillation, and intubation and mechanical ventilatory support. Because a patient who suffers a cardiopulmonary arrest will die in a very short time without interventions, the discussion about code status is as much about how a patient wishes to die as it is about whether he or she wishes to live. Tomlinson and Brody distinguished three distinct rationales for a do-not-resuscitate (DNR) status[12]: (1) CPR has such a low likelihood of producing the desired outcome that it is effectively "futile," (2) there would be an unacceptable quality of life after CPR, and (3) there is already an unacceptable quality of life and cardiopulmonary arrest would be a welcome deliverance. Although often conflated with wishes for treatment of a variety of current or future medical conditions, a decision about CPR may not give much useful information about a patient's preferences regarding other aspects of his or her illness. A patient may choose aggressive disease-oriented measures well into a severe illness but still choose to forgo resuscitation in the event of an arrest. This approach may be voiced in a statement such as, "I want to fight this thing with all I have, but when it is my time, I want to go quickly without suffering." Such a statement would be an opportunity to address resuscitation status in addition to addressing overall goals of care (see later).

Many ICU patients who are actively receiving intensive disease-oriented care have a DNR code status. Such a directive may save surrogates and family members from the emotionally difficult task of removing life-supporting care. A patient's acceptance of DNR status may signify acceptance of the limits of medical science; refusal of DNR status in the setting of progressive irreversible illness may be an indication that the patient has an incomplete and perhaps unrealistic understanding of the illness. Further discussion addressing knowledge deficits or unspoken fears may increase the likelihood that the patient's true wishes will be followed.

A number of common errors may occur when discussing the code status. The first is failure to convey accurate information about the likelihood of success after an attempt at resuscitation. Many patients have an unrealistic impression of the utility of this intervention.[13] Another type of error is failure to address postresuscitation issues, when caregivers mistakenly assume that "do everything in the case of a cardiopulmonary arrest" also means the patient wishes the care team

to continue to "do everything" afterward. Patients who undergo CPR will most likely be incapacitated for at least a period after the resuscitation, even in the best scenarios. A third type of error is to not take the opportunity to identify a preferred surrogate decision maker, given the significant risk of temporary or even permanent brain injury after the attempt at resuscitation.

Any discussion of advance directives should attempt to answer at least three questions: (1) In the event of a cardiac arrest, do you want the health care team to attempt resuscitation? (2) If you become incapacitated, who do you want to make decisions for you? (3) If you were left significantly impaired after an attempt at resuscitation, under what circumstances would you want us to discontinue life-sustaining care? Additionally, preferences for resuscitation are best understood in the context of an individual's values, beliefs, relationships, and culture.[7]

Many problematic end-of-life issues can be traced to a focus on interventions ("Would you wish to be intubated?") without an adequate exploration of values ("What do you value about your life? What are the things that make your life worth living?"). It is also a mistake to think about advance directives as an issue limited to end-of-life situations. Advance directives are really just part of informed consent for any treatment, and discussion of advance directives is an important aspect of good medical care.

Informed Decision Making (Informed Consent)

In the United States, individuals are free to develop their own conceptions of happiness or a good life. By extension, choices about medical tests or treatment are made by patients in ways that maximize the likelihood of that good being achieved. This is called *patient autonomy,* and some would call it one of the core principles that define the relationship between a doctor and a patient. Respecting autonomy requires respect for the values and wishes of the individual. Additionally, the exercise of autonomy requires adequate information, the power of reason, and freedom of choice. Shared decision making happens when an autonomous individual has a conversation with the physician that incorporates the patient's values (autonomy) and the values of the physician.

Brock discussed the basic requirements for informed consent and identified three critical elements: the person giving consent must be competent, informed, and able to make a decision free from coercion.[13] *Competence* has several critical elements.[14] First, the decision maker must be capable of understanding relevant information, which involves both memory and mental processing. Second, it requires the ability to attend to and retain information, the ability to manipulate information, and the ability to foresee consequences. The third element is the ability to formulate and communicate choice. Some standards of competency strengthen this requirement by demanding the ability to communicate a *stable* choice (in this case, ambivalence may be a sign of incompetence).

To adequately participate in medical decision making, patients must have enough information to weigh the risks and benefits of various medical interventions. In the past, the standard for being informed was the standard practice of other physicians in the community.[15] Subsequently, *informed* came to mean what a "reasonable person would want to know." Because the main point of informed consent is to respect the rights and values of individuals, it is most appropriate to address this issue in terms of what a particular patient needs to know.[16] In general, patients need to know about the illness and its natural history to make informed decisions about medical care. They need information about the effectiveness of treatment, the risks of treatment, and the likelihood of success with treatment. This information must be presented in a way that is understandable to the patient, at an appropriate educational level, and is in the patient's language. Whether enough information has been transmitted can be assessed at the most basic level by simply asking a patient whether he or she has any questions. Brock writes of "informed understanding" and notes that this "permits an informed exercise in self-determination and promotes a decision most in accord with the patient's well-being."[13] In addition, this approach values autonomy.

The decision must also be voluntary—that is, free of coercion. The decision maker must have the freedom to accept or refuse the intervention or test being proposed. Consent given as a result of undue coercion is generally not valid.

Informed consent in the ICU raises some special issues. First, as mentioned earlier, the decision maker is often a surrogate rather than the patient. The surrogate decision maker should have access to all relevant information the patient would need to make informed decisions; however, the surrogate should not routinely be given confidential information *simply because the patient is no longer competent*. An example may be helpful in illustrating this point. An HIV-positive patient in the ICU has designated a family member as his surrogate; however, the family is unaware of his HIV status. The ICU physician believes a central line is indicated for continued care and seeks informed consent from the family member. In this case, it may be possible to obtain true informed consent for the procedure without divulging the patient's HIV status. Alternatively, a decision about a test or treatment specifically related to the patient's HIV status may require that this information be divulged to the surrogate for him or her to make an informed decision.

The adequacy of a properly designated surrogate is usually assumed but should be questioned in two situations. The first is when the surrogate acts in contrast to the patient's known wishes. Anyone who knows that the surrogate's directions conflict with the patient's expressed wishes has an obligation to work with the surrogate to come to a treatment decision more in keeping with the patient's wishes or to seek outside assistance from the hospital ethics committee or the hospital's legal department. The second situation occurs when there is doubt about the surrogate's competence, specifically his or her ability to retain and process information. Again, the ethics committee or the risk management department can be of help in this situation. An important study by Schneiderman and colleagues[17] demonstrated the value of ethics consultation for ICU patients in whom a conflict arose regarding a value-based treatment decision. In that randomized controlled trial, patients receiving an ethics consultation had shorter ICU and hospital stays and a decrease in the use of "nonbeneficial treatments." This study led to a call in the literature for more frequent use of ethics consultations in the ICU.[18–20]

FUTILITY

It is often said that "it is futile to define futility," and this has never been truer than in the current era of medical care. Many diseases that were once thought to be untreatable are becoming treatable, and diseases with high mortality rates are seeing a decline. It is now common for ICUs to have patients who would have been considered too old or too sick to warrant critical care decades ago. As more of these patients go on to survive the ICU, the boundaries of medical futility get pushed back even further.

There are many definitions put forth for the term *medically futile,* but most prove inadequate for practical use. The term has been generally used to describe either a patient who simply could not be kept alive (i.e., refractory shock) or a patient in whom death was inevitable in the near future (i.e., advanced cancer). The term *terminally ill* probably better describes the second situation. Nevertheless, these concepts have often been invoked as a justification for limiting lifesaving

interventions or denying admission to the ICU. However, this has become problematic. With modern medical interventions such as extracorporeal membrane oxygenation and others that can support vital organ functions, there are fewer times when physicians cannot keep a patient alive. Additionally, as patients with advanced illnesses are increasingly treated in ICUs with the goal of only a few more weeks or days of life, it becomes clear that one person's definition of *terminally ill* may not be the same for another.

In 2015 several key professional societies (American Thoracic Society, American Association of Critical Care Nurses, American College of Chest Physicians, European Society for Intensive Care Medicine, and Society of Critical Care Medicine) jointly produced and published a statement addressing conflicts of this nature. Notably, the authors chose to avoid using the word *futility* whenever possible, given its subjective nature, and instead use the wording *requests for inappropriate care* to describe situations in which patients or family request care that the physicians feel is of no benefit based on poor prognosis. The statement made several recommendations for physicians addressing such requests.

First, institutions should try to prevent intractable treatment conflicts through proactive communication and early involvement of expert consultants. The term *potentially inappropriate* should be used, rather than *futile,* to describe treatments that have some chance of accomplishing the effect sought by the patient but clinicians believe that competing ethical considerations justify not providing them. If there is disagreement, clinicians should explain and advocate for the treatment plan they believe is appropriate. Conflicts regarding potentially inappropriate treatments that remain intractable despite intensive communication and negotiation should be managed by a fair process of conflict resolution; this process should include hospital review, attempts to find a willing provider at another institution, and opportunity for external review of decisions. Finally, when time pressures make it infeasible to complete all steps of the conflict resolution process and clinicians have a high degree of certainty that the requested treatment is outside accepted practice, they should seek procedural oversight to the extent allowed by the clinical situation and need not provide the requested treatment.

The group further recommended that the use of the term *futile* should be restricted to the rare situations in which surrogates request interventions that simply cannot accomplish their intended physiologic goal. Clinicians should not provide futile interventions. The medical profession should lead public engagement efforts and advocate for policies and legislation about when life-prolonging technologies should not be used.[21]

Controversies Emerging From New Technology and Cultural Change

Advances in medicine and cultural changes have introduced new ethical challenges. Technologies such as extracorporeal membrane oxygenation (ECMO) and continuous venovenous hemofiltration (CVVH) can keep patients who would otherwise have died alive longer, forcing physicians to consider limited resources—distributive justice—and balance an obligation to respect the patient's wishes—autonomy—with concerns by some providers that the care may only be inflicting harm—nonmaleficence. Postmortem gamete retrieval (PMGR) now helps people create life under circumstances that otherwise would have been impossible, while introducing ethical questions pertaining to informed consent, surrogate decision making, and conflicts of interest. At the same time, the rules and beliefs surrounding these new technologies are being tested on a regular basis.

In addition to the challenges posed by new technologies, the increasing interest in complementary and alternative medicine (CAM) presents ethical issues. Given the incredible variety of therapies sought by patients that exist outside traditional medicine, assessing the potential efficacy and harm of the therapies can be difficult. On the one hand, a patient's decision to pursue an alternative medicine such as acupuncture falls within the realm of autonomy, yet on the other hand, if the CAM is used at the exclusion of an effective therapy, a physician's tacit approval may test the principle of nonmaleficence. Today, medical pluralism, or the use of CAM practices in conjunction with conventional medical practices, is widely encouraged, and thus these ethical challenges are unlikely to disappear.

In summary, ethics in critical care are founded on the same four primary directives common to all disciplines of medicine. Critical care decision making presents special challenges because these decisions often involve the life or death of patients who are unable to participate in the decision-making process. Although the balance between physician and patient responsibility for decision making may vary across cultures, the primary directive for physicians to act in the best interest of their patients is universal.

KEY POINTS

- Ethics in medical care is based on four fundamental principles: beneficence, nonmaleficence, autonomy, and justice.
- In the United States, competent patients have the right to make their own decisions about health care.
- The process of making known one's wishes regarding future care is called *advance care planning.*
- In the absence of an advance directive, a surrogate decision maker attempts to make medical decisions for a patient using substituted judgment. When no specific information is available about a patient, decision makers apply a "reasonable-person" standard and sometimes resort to a "best-interest" standard.
- Discussions about advance directives should be rooted in the patient's values and goals for medical care and the appropriateness of specific interventions.
- Shared decision making is a process that combines patient autonomy and physician judgment.
- New technologies are introducing ethical challenges for physicians and patients.

References for this chapter can be found at expertconsult.com.

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Building Teamwork to Improve Outcomes

Daleen Aragon Penoyer, Carinda Feild, and Joseph Abdellatif Ibrahim

The intensive care unit (ICU) is a complex environment with multiple professionals practicing together to provide patient care. Although technology and care options for critically ill patients have advanced, resulting in improved patient outcomes, they add to the complexity of care and knowledge needed by critical care providers. Nontechnical skills, such as teamwork and communication, are also essential for effective, efficient, and safe care provided by a multitude of professionals in a variety of roles. This chapter addresses the importance of teamwork in critical care, components of effective teamwork, the impact of teamwork on outcomes, strategies to build effective teamwork, and barriers to teamwork in critical care.

THE IMPORTANCE OF TEAMWORK IN CRITICAL CARE

Patients admitted to the ICU have a high acuity, are older, and require complex and costly care by interdisciplinary critical caregivers. The caregivers' charge is to carry out evidence-based protocols and guidelines of care while meeting the individual needs of the patient and family. This takes place in a fast-paced environment with constant change and states of readiness. Care requires considerable coordination across caregivers working in concert, executing their contribution to the care of patients in this complex environment. With the increased need for ICU beds, efficient use of resources and throughput of patients across the healthcare system are of high priority. The emphasis on using current best evidence to guide practice, advances in critical care research, and knowledge makes keeping up with best practices difficult. With the challenge of providing quality care in the complex ICU environment, teamwork is essential for efficient care in the ICU.[1–3]

Healthcare regulatory agencies, commissions, and professional organizations also value team collaboration to achieve quality outcomes. The Society of Critical Care Medicine (SCCM) focuses on delivering the right care at the right time with an integrated team of dedicated experts. In 2015 the American College of Critical Care Medicine updated the 2001 guideline on processes of care and ICU structure,[4] reaffirming recommendations for intensivist-led, high-performing multidisciplinary teams as a key part of delivering effective care. Further, an expert panel conducted a systematic review on shared decision making in the ICU and recommended that clinicians consider using a interprofessional decision-making process whereby information is exchanged, there is deliberation among the team, and treatment decisions are made jointly.[5] In a concise definitive review, Donovan and colleagues[3] (2018) found robust literature to support an interprofessional approach as part of achieving high quality of care in the ICU. They illustrated the patient and family surrounded by a host of interprofessional care team members, integrating care through an intersection of unique expertise with valued contributions toward a common goal.

The importance of teamwork and collaborative practice extends to health professional education. The Association of American Medical Colleges (AAMC), along with five other health professional programs, created the Interprofessional Education Collaborative (IPEC) to advance interprofessional education. The IPEC revised their expert report in 2016,[6] outlining core competencies related to teamwork across interprofessional teams. Currently, a multitude of health professions include interprofessional teamwork in their accreditation standards and competencies. These include but are not limited to nursing, pharmacy, respiratory therapy, nutritional support, physical and occupational therapy, and social work.[7] Goldman and colleagues[2] (2017) found interprofessional competencies are important for affecting competencies in skills and beliefs, but that organizational, environmental, and resource factors greatly affect the ability of team members to enact these competencies in the real-world setting.

Leaders are gaining an appreciation for how organizational structures and processes affect patient outcomes and the importance of highly functional teams. The best systems are those that allow teams to function at the highest level to reduce costs and improve patient outcomes. Successful hospitals are those that attract, train, and retain expert team members in an environment where they experience meaningful work and thrive within effective teams. Top hospitals build environments with top-notch teamwork, are intolerant of poor performance, and are supportive of team members who vocalize concerns.

COMPONENTS OF EFFECTIVE TEAMWORK

Broadly, *teamwork* is defined as two or more people working dynamically together to accomplish a common goal. Important components include communication, competence, trust, cooperation, coordination, respect, interdependence, accountability, conflict resolution, and shared decision making.[8,9] Although the term *teamwork* is widely used to describe interventions across teams and is valued by caregivers,[10,11] results from some qualitative and ethnographic studies indicate that in their work together, critical caregivers are performing activities that are more indicative of interprofessional communication interactions such as collaboration, coordination, and networking,[12] rather than what are considered "idealized"

definitions of teamwork, as defined by a shared team identity, interdependence, integration, and shared responsibility.[13,14]

Historically, healthcare professionals have practiced as individuals, demonstrating autonomy in their respective field of practice supported by its own body of research. ICU patients require complex and multifaceted interventions by an interdisciplinary team of experts. This process requires moving away from isolated practice toward collaborative practice with other healthcare providers. Ongoing interaction among the interdisciplinary team focused on patient-centric goals fosters greater collaboration and communication and can optimize patient care and outcomes. Through the exchange of ideas and expertise, practitioners become familiar with the nature and scope of one another's practice and are able to assess individual competence. This can build trust and promote the understanding of the unique contributions of team members and their interdependence for providing care. Focusing on the common goal to provide the best possible care for patients is key to minimizing team conflict.[8,15–17]

Over time, trust and open communication promote respect. Team members begin to appreciate each other's skills, knowledge, and judgment. In collaborative practice, responsibility is shared, so that goal setting and decision making occur jointly.

Being a good team player is key to a team's success. Given the ethical obligation to provide the best care for patients, every team member has the responsibility to make an optimal contribution during team communications or rounds, speaking up and providing relevant input, and listening actively to others' input while maintaining an open mind. Mutual support among the team (encouraging expression of ideas and positive professional communication) is important to build confidence in and perceived value of the team. These actions can lead to collective intellectual capital by the team and potentiate clinical effectiveness.

Team leadership is also critical to performance. Good leaders generate two-way trust, respect, and communication. They have vision, self-confidence, enthusiasm, tolerance, and a commitment to excellence. They are organized and prepared, fulfill commitments, inspire shared missions, grow new leaders, model behaviors, challenge processes, tolerate ambiguity, and remain calm. Leaders who think out loud help novices develop their teamwork skills and competence. Leaders set the tone for the function of the group and must demonstrate respect for the collective contribution of its members. Team members must ask for help when needed and express concerns without retribution in an environment that is psychologically safe. To have high-quality ICU teamwork, each team member should possess some leadership characteristics, as team leadership often changes, depending on the issue at hand.

IMPACT OF TEAMWORK ON OUTCOMES

Despite the support for teamwork and the development of an interdisciplinary team model for the care of critically ill patients, research on the relationship to outcomes is limited.[4,11,18] ICU patients are highly susceptible to medical errors. Severity of illness, intervention complexity and number, invasive devices, and ICU length of stay (LOS) put critically ill patients at a higher risk for adverse events and errors. One comprehensive review of critical incidents in intensive care showed an increased incidence of adverse events when there was a deficit in nontechnical skills, including elements of teamwork.[19]

Ineffective communication and poor teamwork have been identified as significant contributors to patient errors and critical incidents in the ICU.[8,9] Improved communication may reduce adverse events and errors.[20,21]

A systematic review and meta-analysis demonstrated improvements in outcomes with pharmacist participation on the ICU team. Interventions by pharmacists during ICU team rounds were associated with reduced odds of mortality, lessened LOS, and reduction in preventable/nonpreventable adverse drug events.[22] Another initiative was aimed at improving early mobility in ICU patients through active engagement of the multidisciplinary team. Multidisciplinary team engagement significantly improved rates of mobilization within the first 24 hours of ICU admission.[23] A pediatric study on the effect of team training for resuscitation demonstrated that training increased the chance of survival after in-hospital cardiopulmonary arrest.[11]

Whereas some studies have shown improvement of team performance outcomes associated with improved teamwork, research on patient outcomes are less often seen.[11] Intensivist-led multidisciplinary teams have been espoused as an ideal model for critical care. However, insufficient numbers of trained intensivists exist to meet current or future demands, and a limited number of ICUs have implemented intensivist staffing.[18] Furthermore, outcome studies on intensivist-led care demonstrate mixed findings.[4,18] One large patient cohort study compared the mortality outcomes from hospitals with daily multidisciplinary team rounds with and without intensivist models.[18] Hospitals with high intensivist staffing and multidisciplinary team care had the greatest reduction in odds ratio of death. Interestingly, hospitals with multidisciplinary care but low physician staffing also had significant odds reduction in mortality, reinforcing the idea that patients benefit from care by a multidisciplinary team. Mortality has been significantly reduced in patients with acute lung injury cared for by multidisciplinary teams led by full-time critical care physicians.[24] A literature review summarized that the team model for ICU care delivery was associated with reduced mortality, ICU and hospital LOS, and cost of care.[25]

One hospital in Illinois implemented evidence-based bundles of care and a multidisciplinary daily goals rounding tool, resulting in decreased ICU LOS, improved protocol compliance, reduced ventilator-acquired pneumonia (VAP), bloodstream infections, falls, and pressure ulcers in surgical ICU patients.[26] Multidisciplinary teams developed to respond to shock in nontrauma patients resulted in decreased time to treatment, intensivist arrival, and admission to the ICU.[27] This led to a significant reduction in mortality and improved patient outcomes.

Teamwork and Team Outcomes

Engaging in interprofessional teamwork has an overall impact on the team itself. In a narrative review of the effects on team training in critical care, Low and colleagues[11] summarized several outcomes. Overall, interdisciplinary team members were positive and satisfied with the programs and found them useful for clinical practice. Most often, team members acquired new skills and abilities to manage difficult clinical situations, frequently augmented by simulation. When using team tools such as checklists, they had improved behavioral outcomes, including role clarity, improved communication, and conflict resolution. Overall, although the clinical skills and behaviors were enhanced, other aspects, such as sustainability of learning or comparison of training programs, were less studied.

Hellyar and colleagues[28] implemented a case study investigation process in the ICU that included interprofessional peer review as a means of improving teamwork and optimizing patient outcomes from learnings achieved. This strategy demonstrated significant increases in the percentage of team members who felt free to speak up on issues that could potentially affect patient care, more open communication between nurses and physicians, and perceived improvement of teamwork across the interprofessional team. Additionally, there was a reduction in caregiver burnout and an accompanying reduction in central line– and catheter-related urinary tract infections.

When teamwork increases the efficiency of care, an increased sense of accomplishment can occur.[29,30] Research has shown that nurses preferred communicating with attending physicians over first-year residents and valued shared understanding and open, accurate communication, citing this as a predictor of nurse job satisfaction.[31] When a higher level of nurse-physician communication was reported, medication errors were reduced,[32] and when the timeliness of communication improved, the prevalence of pressure ulcers decreased through timely reporting of relevant information.[33] This further reinforces the notion that good communication and teamwork may translate into better overall care.

STRATEGIES TO ESTABLISH BETTER TEAMWORK

Because teamwork is so important for practice in the ICU, it is vital that steps be taken to implement team structures and processes that can help build teamwork in critical care. Models to develop strong teamwork have come from industries with high risk for errors, including aviation, the military, and nuclear power. In these industries, effective teamwork is an important mechanism used to maintain safety, reduce errors, and increase efficiencies.[34,35] Team members use specific processes for communication, leadership, coordination, and decision making to achieve positive team performance outcomes.

Although health care is different from these industries, lessons can be learned to improve teamwork in critical care.[34] Applicable strategies include standardizing work processes and using checklists to ensure patients are consistently receiving care based upon the best current scientific evidence and to improve teamwork skills, collaborative engagement, and communication. All interdisciplinary team members should be able to speak up when they identify potential patient safety hazards, and mechanisms should be developed to openly identify areas of high risk for errors and harm. A blame-free culture encourages team members to recognize, report, and thus minimize errors and learn from mistakes. Much like in an assembly line, when one team member recognizes the potential for harm, it must be pointed out and managed expeditiously.

Reader and colleagues[35] consolidated the research literature on the relationship between teamwork and patient outcomes in critical care. They emphasized that effective teamwork is crucial to provide optimal patient care in the ICU and good leadership is vital for team interaction and coordination. Four key performance competencies are needed to build effective teams in the ICU: (1) communication, (2) coordination, (3) leadership, and (4) decision making.

Another strategy to engage ICU interdisciplinary teams is involvement in quality improvement initiatives.[4] Participation in quality efforts is known to improve patient safety, reduce mortality, and decrease costs and LOS, among others. Adoption of evidence-based guidelines is also associated with coordinated care by the interdisciplinary team and improved outcomes.[4]

Barriers to Team Performance

Implementing teamwork strategies within health care has its challenges. Barriers to implementing a critical care team model can include local customs, hospital patterns, and reluctance to change despite proven benefit.[25] Hierarchic and status differences can present a barrier to team function and the ability of team members to openly contribute to the plan of care if they are not convinced that their input is valued.[8,36]

Several factors may influence the ability of teams to function at the highest level. Although the intensivist-led model for high-performing interprofessional teams is recommended,[4] there remain insufficient numbers of qualified physicians trained in critical care to meet demands. Costa and colleagues[37] found that having daytime high-intensity physician staffing did not show a significant impact on mortality, and other studies show mixed results with regard to intensity of intensivist staffing. Sufficient evidence, however, concludes that an intensivist-led highly functional team improves ICU care and may improve outcomes. The benefit of high-intensity 24/7 intensivist staffing remains unclear. Increasing reliance on team function for protocolized and systematic care and engagement of advanced practice professionals in the ICU may reduce the continuous need for supervised care by an intensivist-led team.[9,37] Other recently identified barriers are at the organizational level, where the environment is not conducive to practicing learned team competencies. Insufficient space for interaction, time, and resources to carry out team-related activities may reduce the ability to make optimal impacts from teamwork interventions and training. Organizational priorities on patient throughput and LOS, staffing concerns, and efficient workflow influence the overall environment where teamwork takes place and the ability to enact effective teamwork and collaboration across the team.[2,12,14] Even when intensivists are engaged with the interprofessional team, organizational characteristics and environment can affect the degree of effective teamwork and communication. Ensuring that the intensivist or other team leader can overcome barriers to effective communication is important to foster an environment of open communication and psychological safety.[9]

Educational Programs Used to Develop Teamwork in the ICU

Many practitioners in the ICU have not been trained in teamwork activities and are unfamiliar with the nontechnical skills required to perform well on a team.[19] Individual team members' knowledge, skill, and personality characteristics influence their effectiveness on teams. Because teamwork competency is being promoted as an essential practice needed by healthcare providers, interprofessional team training and experiential learning are needed, particularly in high-risk units like ICUs. Dirks[38] summarized key components in a comprehensive teamwork training program for the interprofessional team. This program emphasized strategies and structures to support teams and major components on teamwork behaviors and communication skills.

Programs to improve patient safety and collaboration in the ICU have been developed using a crew resource management (CRM) approach.[11,39] One group identified five key components needed for hospital CRM training: communication, task management, situational awareness, decision making, and leadership.[40] Program content included interpersonal communication; conflict resolution; nonthreatening critique of team performance; and methods to improve system processes for care, such as checklists, handoff improvements, and debriefing after errors.

Simulation-based learning is another mechanism for training the team to function under specific circumstances and is widely used in medical professional education.[41] Team learning in scenario-based simulation exercises allows professionals to learn their roles and practice safely under circumstances outside of stressful clinical settings.

Examples of using simulation for team training include managing septic shock using high-fidelity mannequins and scenario-based videos,[42] resuscitation and management of acute respiratory failure, airway management, myocardial ischemia, trauma, and shock.[43] Simulation-based learning can be used to improve handoff communication and reduce errors in relaying critical information across teams,[44] build teamwork competencies, and CRM. In one study, a critical event simulation was used for an interprofessional team in a surgical-trauma-burn ICU, which resulted in significant improvement in retention of teamwork skills and knowledge. Using simulation for team training is

an effective strategy for emphasizing roles and responsibilities across the interprofessional team.[41]

Multiprofessional Support for Teamwork in Critical Care

Key professional organizations support teamwork enhancements to drive improvements in practice. SCCM promotes an intensivist-led model for care by a team of multidisciplinary experts with supportive guidelines for characteristics of multidisciplinary teamwork (sccm.org).

The American Association of Critical Care Nurses actively supports teamwork within their healthy work environment initiative. Their website has tools to evaluate and promote teamwork (aacn.org). The Institute for Healthcare Improvement promotes quality improvement with teamwork as a key component in their initiatives, and their website (ihi.org) also has many useful team-building tools. The Agency for Healthcare Research and Quality has a comprehensive, evidence-based program to improve communication and teamwork skills among healthcare professionals called TeamSTEPPS. Information on this comprehensive program is housed on their website (teamstepps.ahrq.gov).

EXAMPLES OF INITIATIVES REQUIRING AN INTERPROFESSIONAL APPROACH IN CRITICAL CARE

Adoption and Implementation of Evidence-Based Care Guidelines and Protocols

Many opportunities exist for collaboration and teamwork in developing and executing patient care initiatives. Examples where interdisciplinary team members intersect for care include sedation awaking with agitation/delirium management, ventilator management and the use spontaneous breathing trials, palliative care, sepsis and other emergent care, and early mobility.[3]

Collaborative Practice Teams

Collaborative practice teams (CPTs) are groups of interdisciplinary team members assembled for a particular patient population to address issues related to clinical practice and outcomes. They design initiatives to drive evidence-based practice and improve quality of care. Critical care CPT composition depends on the patient population and disciplines involved in the care of those patients and should capture expertise from multiple disciplines (e.g., physicians, nurses, respiratory therapists, physical therapists, pharmacists, nutritionists, social workers, clergy, administrators, risk managers, infection control, and quality and safety personnel). Examples of CPT initiatives are disease-specific protocols, care "bundles," order sets, and quality programs. Some teams are formed to manage urgent clinical conditions, such as medical emergency response teams who respond to calls on clinical deterioration, sepsis,[42] stroke, and shock.[27]

Daily Interdisciplinary Team Rounds

Daily ICU rounds provide a forum for the individual interprofessional team members, with their respective roles, to exchange information and make decisions about the patient care plan.[3,9] Daily rounds also provide opportunities to augment new clinical initiatives. O'Brien and colleagues[45] redesigned multidisciplinary rounds using a structured approach and Lean-inspired methods. After soliciting barriers and insufficiencies from team members, the team implemented a tool kit to standardize key elements for discussion during rounds. Results showed improved communication and participation of nurses in rounds and reduced communication errors. Communication regarding the plan of care by the team can be facilitated by using a daily goals checklist during rounds. Checklists and protocols for care facilitate team functioning and provide a structure and guidelines for team actions and streamlining care.[9] Team accountability for assignments and goals established during rounds occurs during reviews for completion at day's end. This approach has demonstrated improved team and patient outcomes.[26,46,47]

CONCLUSION

As we struggle to increase patient safety, prevent harm, decrease chaos, and improve outcomes, mechanisms to integrate complex behavior into functional teamwork have become increasingly important. Harmonious and efficient integration of personnel and their respective expertise in the complex critical care environment is key to the delivery of high-quality intensive care. Ideally, care will be coordinated and delivered by a team with a high degree of mutual respect, who values and listens to all contributions, resulting in care that is optimized, efficient, and timely.

KEY POINTS

- An emphasis on collaborative teamwork to improve outcomes and reduce costs has increased as the care of the critically ill has become more complex and resources more limited.
- Key skills required for teamwork include communication, competence, trust, cooperation, coordination, respect, interdependence, accountability, conflict resolution, and shared decision making.
- Barriers to ICU teamwork include increasing patient acuity, rapidly evolving evidence-based practice, lack of teamwork competencies and training, insufficient physician-led multidisciplinary teams, and the stressful nature of intensive care practice.
- With the increased focus on teamwork, several models of teamwork in the critical care environment and increased resources have become available.
- Research shows that improved processes in teamwork and communication can lead to improved patient outcomes and healthcare team satisfaction.
- The interdisciplinary team has an opportunity to partner together through adoption and implementation of evidence-based care guidelines and protocols, CPTs, and daily rounding teams to drive quality improvements in the care of the critically ill.

References for this chapter can be found at expertconsult.com.

ANNOTATED REFERENCES

Alexanian JA, Kitto S, Rak KJ, et al. Beyond the team: Understanding interprofessional work in two North American ICUs. *Crit Care Med.* 2015;43:1880–1886.

The authors of this paper conducted an ethnographic, qualitative study to evaluate ways that healthcare professionals work together in the ICU setting. They used direct observations and interviews of members of the multidisciplinary team. They found that although the term "teamwork" is used often to describe the interactions in the ICU, the type of work that they observed was more like interprofessional work, such as collaboration, coordination, and networking, as compared with teamwork behaviors, which include shared team identity, clarity, interdependence, integration, and shared responsibility.

American Association of Critical Care Nurses. AACN's Healthy Work Environments Initiative. Available at http://www.aacn.org/wd/hwe/content/hwehome.pcms?pid=1&&menu=.

The AACN has established an initiative to promote healthier work environments that allow teamwork to flourish. The website includes descriptions of ingredients for success in creating healthy environments, tools for assessing teams, and links to many other helpful resources.

Donovan AL, Aldrich JM, Gross AK, et al. Interprofessional care and teamwork in the ICU. *Crit Care Med.* 2018;46:980–990.
This concise definitive review was conducted to determine the importance of interprofessional care in the current intensive care unit setting. They defined interprofessional care as the care that a team of multiple healthcare professionals with overlapping expertise provide in partnership with other members of the healthcare team towards a common goal. They emphasize that all disciplines play an important role to meet the complex needs of patients. They advocate for inclusion of patients and families as partners in their care. In summary, they found a robust body of evidence to support the inclusion of the interprofessional team as a care model in the ICU.

Institute for Healthcare Improvement (IHI). http://www.ihi.org/ihi.
The IHI has been very successful in teaching teams to use a rapid-cycle change process to improve care delivery and patient outcomes. The website includes information on process improvement, tools for implementing change and evaluating progress, and guidance for addressing specific patient and system problems.

Michalsen A, Long AC, Ganz FD, et al. Interprofessional shared decision-making in the ICU: A systematic review and recommendations from an expert panel. *Crit Care Med.* 2019;47:1258–1266.
This systematic review of four papers evaluating the effect of interprofessional decision making on quality of care was done and recommendations for action were made. Interprofessional shared decision making should be a collaborative process regarding decisions for patient care. Clinicians should engage in interprofessional decision making to foster balanced treatment decisions. Clinicians and hospitals should develop a climate conducive to shared decision making. Clinicians involved in decision making should have a structured approach for interdisciplinary collaboration. The authors concluded that further studies are needed to determine the impact of interprofessional shared decision making in the ICU.

Weled BJ, Adzhigirey LA, Hodgman TM, et al. Critical care delivery: The importance of process of care and ICU structure to improved outcomes: An update from the American College of Critical Care Medicine task force on models of care. *Crit Care Med.* 2015;43:1520–1525.
This article outlines a revision in a previous guideline from 2001 on practice models of care in the ICU. After the task force review, four key recommendations were made: (1) an intensivist-led, high-performing, multidisciplinary team dedicated to the ICU is an integral part of effective care delivery; (2) process improvement is the backbone of achieving high-quality outcomes of care; (3) standardized protocols, bundles of care, and order sets are useful to measure processes and outcomes and are recommended for use; and (4) support by institutions for a comprehensive quality improvement program, including tele-ICU programs, should be implemented.

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Severity of Illness Indices and Outcome Prediction

David Harrison, Paloma Ferrando-Vivas, and James Doidge

Predicting outcome is a time-honored duty of physicians, dating back at least to the time of Hippocrates.[1] The need for a quantitative approach to outcome prediction, however, is more recent. Although a patient or family members will still want to hear a prognosis, there is increasing pressure to measure and publicly report medical care outcomes and assess the value of care.[2,3] deliver comparative information website (www.leapfroggroup.org).[4] enacts penalties and provides incentives for providers based on quality.[5] Public reporting of intensive care unit (ICU) performance, in the form of risk-adjusted mortality rates, is now mandated in some European countries[6] and Veterans Administration (VA) hospitals in the United States[7] and used in many ICUs in the United States.[8] Thus clinicians need to understand the science behind these systems[9] and how risk adjustment models may properly be applied. Risk adjustment systems allow performance (process of care) to be evaluated independent of the presenting condition (baseline risk).

Prognostication based on clinical observation is affected by heuristic bias, inaccurate estimation of the relative contribution of multiple factors, false beliefs, and human limitations such as fatigue.[10] Outcome prediction models, on the other hand, will consistently replicate an estimate when considering relevant data. This presupposes that the model has been well developed and includes the most important predictive variables. Over time, we have learned that accepting patients in transfer,[11] sociodemographic factors,[12] and the point at which an outcome is assessed[13] can lead to misinterpretation of supposedly objective measures. This chapter discusses what can (and should) be measured, how benchmarking models are created and assessed, how they are applied in clinical practice, how this information may be used, and the pitfalls and confounders associated with their use.

WHAT SHOULD BE MEASURED

What is perceived as "quality" depends not only on individual subjective experience but also on integrating multiple perceptions and understanding the limitations of any one observation. Table 165.1 lists over 80 potential metrics categorized into process measures (what is done) or outcomes (what is achieved) in three categories: quality, efficiency, and patient/family experience. Process measures are important insofar as they provide guidance to interpreting outcomes that are out of range. A high urinary catheter utilization rate will affect the rate of catheter-associated urinary tract infections. Fig. 165.1 displays a "radar" plot where every variable has been normalized, such that 1.0 indicates performance at benchmark and the red-shaded areas indicate concern. In this hypothetical example, the neuro ICU appears to have issues with prolonged hospital length of stay (LOS), possibly related to hospital-acquired conditions. The medical ICU appears to excel at research, publication, and education, while having some issues with patient experience and wait times. Some metrics, such as mortality rate and LOS, will be determined primarily by a patient's underlying physiology and health status. Thus rates are normalized using the ratio of observed to expected events and creating standardized rates.

Designation as an ICU, 24-hour availability of consultants, an adverse event reporting system, routine multidisciplinary rounds, a standardized handover process, rate of catheter-related bloodstream infections, unplanned extubation rates, ICU readmission rate, and reporting and analysis of the standardized mortality rate (SMR) have been considered key indicators.[14] The SMR is one of the most frequently used adjusted outcomes measured worldwide.[6]

Mortality is a commonly chosen ICU and hospital outcome because it is unambiguous and readily available from a variety of data sources. Mortality, although clearly important, does not necessarily reflect quality of care or other important issues such as patient/family satisfaction, return to work, quality of life, or even cost, as early death results in a lower cost than prolonged hospitalization.[15] There is a poor correlation between hospital rankings based on death and those based on other complications.[16] A retrospective cohort study from 138 US ICUs contributing to Project IMPACT from 2001 to 2008 found that none of the 10 common performance indicators (e.g., mortality, readmission, LOS, bundle compliance) consistently correlated with the other 9.[17] There is also little standardization on how mortality should be defined—traditional ICU or hospital rates are subject to discharge bias,[13] but time-based outcomes (30-day, 1-year mortality rates) require intensive manual processes. Regionalized health information organizations or health information exchanges could make data collection easier but are not yet widely available.[18]

Other potential outcomes of interest include morbidity, organ failure, complications, ICU or hospital LOS, ICU or hospital readmission, and health-related quality of life after hospital discharge.[19] With electronic medical records (EMRs) and good coding, comorbidities may be identified by International Classification of Disease (ICD-9) and ICD-10 codes,[20] but administrative records may not reflect all relevant events.[21] ICU LOS is difficult to use as a proxy for quality of care because the frequency of distribution is usually skewed by long-stay outliers.[22] In addition, early death shortens the LOS, resulting in competing risk effects. It is difficult to develop accurate models for ICU LOS at admission,[23] and discrimination is usually inferior to that of mortality models based on the same database. A variety of regression methods have been applied to LOS prediction, with somewhat disappointing results.[24] More success has been achieved by combining variables from ICU day 1 and day 5; variables with the most impact include mechanical ventilation, the PaO_2:FiO_2 (arterial oxygen partial pressure/fraction of inspired oxygen) ratio, physiologic components, and day 5 sedation.[25]

TABLE 165.1 Possible Metrics for Evaluating ICU Performance

Process Measures	Quality Metrics	Efficiency	Experience	Optional (Local)
Daily wakeup/screen for weaning readiness	ICU SMR	ICU LOS	Patient satisfaction	Trainee performance
Glucose control	Hospital SMR	Hospital LOS	Family satisfaction	Publications
Lung protective ventilation (Vt/IBW)	1-year SMR	ICU occupancy (95% CI)	Delirium rate	Funded research
Semirecumbent position (HOB at 30)	Sentinel events	Bed turnover rate	Tracheostomy rate	Local research
Stress ulcer prophylaxis	CNS events (CVA)	ED to ICU transfer time	% transfer to SNF	Regional transfers in
Mobilization of patients	Cardiac events (MI)	ICU to SD/floor time	Rehabilitation days	Workload (TISS)
Communication (daily goal transfer)	Respiratory events	Readmission to ICU	1-year QOL/PICS	Organ donation rate
Antibiotic stewardship	Renal events (AKI)	Hospital readmission	Noise levels in ICU	Autopsy rate
Medicine reconciliation	GI events (GIB)	Cost/discharge	EOL care and DNR rate	
Handwashing	EMR (no cut/paste)	Cost/day	N:P staffing ratio	
DVT prophylaxis	DVT and HIT rates	Transfusion rates	MD:patient ratio	
Central line use and insertion	CLABSI rate	Ratio acute/LTAC days	Provider engagement	
Foley use and early removal	CAUTI rate	Palliative care referrals	Collaborative practice	
Ventilator and NIV utilization rates	VAP rate	Ventilator days	Procedure complications	
Assessing sedation RASS/CAMICU				

AKI, Acute kidney injury; *CAMICU,* confusion assessment method–intensive care unit; *CAUTI,* catheter-associated urinary tract infection; *CLABSI,* central line–associated bloodstream infection; *CVA,* cerebrovascular event; *DVT,* deep venous thrombosis; *ED,* emergency department; *EMR,* electronic medical record; *GIB,* gastrointestinal bleeding; *HIT,* heparin-associated thrombocytopenia; *ICU,* intensive care unit; *LOS,* length of stay; *MI,* myocardial infarction; *N:P,* nurse to patient; *RASS,* Richmond Agitation-Sedation Scale; *SMR,* standardized mortality ratio; *SNF,* skilled nursing facility; *TISS,* Therapeutic Intervention Severity Score; *VAP,* ventilator-associated pneumonia.

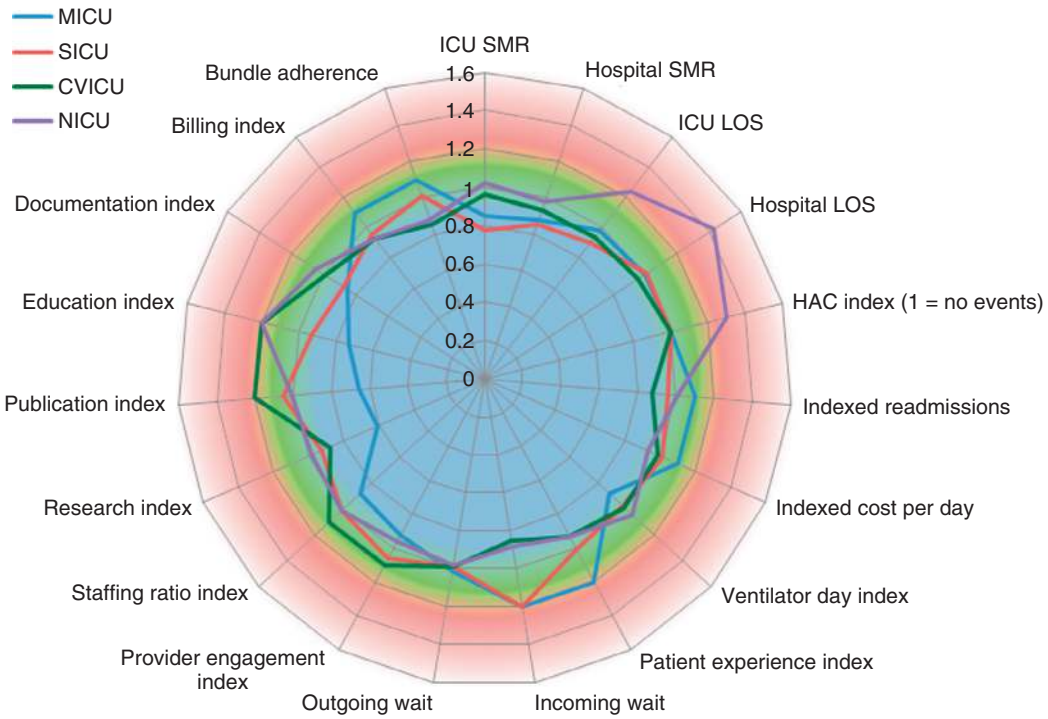

Fig. 165.1 Radar display of three hypothetical intensive care units, demonstrating a balanced scorecard approach to outcome assessment. Domains include metrics for quality of care (standardized mortality and hospital-acquired conditions); efficiency (standardized length of stay, readmissions, costs); subjective experience (family satisfaction, provider engagement, quality of life, wait times); and unit-specific measures such as publications, education, and quality of documentation. *CVICU,* Cardiovascular intensive care unit; *HAC,* hospital-acquired conditions; *ICU,* intensive care unit; *ICU SMR,* intensive care unit standardized mortality ratio; *LOS,* length of stay; *MICU,* medical intensive care unit; *NICU,* neuro intensive care unit; *SICU,* surgical intensive care unit.

Patients readmitted to ICUs have increased hospital mortality and LOS. However, readmission rates are difficult to interpret without careful case-mix adjustment.[26] Readmission rates are affected by triage decisions when ICU beds are constrained, but one study suggests that readmissions are only slightly higher with bed constraints, and, in any case, do not appear to affect short-term patient outcomes.[27] In a retrospective study of 263,082 first-admission patients in 105 US hospitals, the median unit readmission rate was 5.9% (interquartile range [IQR], 5.1%–7.0%). Hospitals with high readmission rates, however, did not have higher standardized mortality rates or LOS after case-mix adjustment.[28]

Patient satisfaction is an outcome highly valued by purchasers of health care, but it is subjective and requires substantial effort to quantify successfully.[29] Evaluation of ICU performance requires a combination of indicators, but risk adjustment has mostly been developed for short-term mortality outcomes, with only a few studies risk-adjusting for other indicators.

DATABASES AND DEFINITIONS

The quality of a risk stratification system largely depends on the quality of the underlying database. Retrospective studies using existing data are quicker and less expensive but may be compromised by missing data, imprecise definitions, interobserver variability,[30] and changes in medical practice over time. Data derived from discharge summaries or insurance claims do not always capture the presence of comorbid disease[31] if the number of reportable events is truncated. Such coding bias is most apparent in severely ill patients.[22] A variety of methods can assess the quality of the database, such as reabstraction of a sample of charts by personnel blinded to the initial results. Kappa analysis is a method for quantifying the rate of discrepancies between measurements (values) of the same variable in different databases (i.e., original and reabstracted). A kappa value of 0 represents random agreement and of +1.0 represents perfect agreement, but this statistic must be interpreted in light of the prevalence of the factor being abstracted.[32]

MODEL DEVELOPMENT

Once data integrity is ensured, there are several possible approaches to relate outcome to the presenting condition.[9] The empiric approach is to use a large database and subject the data to a series of statistical manipulations (Box 165.1). Typically, death, one or more specific morbidities, and resource consumption (LOS) are chosen as outcomes (dependent variables). Factors (independent variables) thought to affect outcome are then evaluated against a specific outcome using univariate tests to establish the magnitude and significance of any relationship.[9]

WHAT INDEPENDENT VARIABLES AFFECT OUTCOME?

ICU-specific systems typically adjust for patient physiology, age, and chronic health condition. They may also assess admitting diagnosis, location before ICU admission or transfer status, cardiopulmonary resuscitation (CPR) before admission, surgical status, and mechanical ventilation use. An ideal approach would use only variables that characterize a patient's initial condition, can be statistically and medically related to outcome, are easy to collect, and are independent of treatment decisions. There is also benefit to serial assessment of the condition, as the influence of independent variables may vary throughout the hospitalization.[33] The Glasgow Coma Scale[34] (GCS) is frequently used as a component of ICU severity scores but can be difficult to calculate correctly in sedated patients. The Full Outline of UnResponsiveness score,[35] which includes information on brainstem reflexes and respiration, may be an alternative as a mortality predictor.

BOX 165.1 Steps in Developing a Severity-of-Illness Model

- Precisely define outcome(s) of interest.
- Identify and define candidate predictor variables (data analysis, expert opinion).
- Collect data, and ensure its accuracy (reabstraction, kappa analysis).
- Examine continuous variables, and transform or dichotomize as necessary.
- Perform univariate analysis (chi-square, Fisher's exact, Student's t-test) against outcome(s).
- Perform multivariate analysis (logistic regression, neural nets, Bayesian, others).
- Examine and adjust for interactions among variables.
- Develop a score or equation that relates independent variables to outcome.
- Test calibration of model (goodness of fit, typically Hosmer-Lemeshow method).
- Test discrimination of model (ROC area C-statistic, sensitivity, and specificity).
- Validate model with independent data, split sample, or jackknife techniques.
- Obtain external validation in new settings, and customize as needed.
- Publish in peer-reviewed journal.

ROC, Receiver-operating characteristic.

Measured variables such as "cardiac index" or "hematocrit" are preferred over "use of inotropes" or "transfusion given" because the criteria for intervention may vary. Widely used models rely on common measured physiologic variables (heart rate, blood pressure, and neurologic status) and laboratory values (serum creatinine level and white blood cell count). Models may consider age and chronic health status and include interaction terms when variables are not independent. Items chosen for inclusion in a scoring system should be readily available and relevant to involved clinicians. Specialized scoring systems become necessary for specific patient populations (pediatric, burn, trauma, cardiac surgery) whose underlying physiology or treatment course differs from that of the general adult ICU population. For example, left ventricular ejection fraction and reoperative status are important predictors of outcome in the cardiac surgical population but are neither routinely measured nor directly relevant to other population groups.[36]

If the independent variable is dichotomous (yes/no, male/female), a two-by-two table can be constructed to examine the odds ratio and a chi-square test performed to assess significance (Table 165.2). If multiple variables are being considered, the level of significance is generally set smaller than $P = .05$, using a multiple comparison correction.[37]

TABLE 165.2 Two-by-Two Contingency Table Examining Relationship of MOF After Open Heart Surgery (Outcome) to a History of CHF (Predictor) in 3830 Patients*

Predictor Variable: History of CHF	OUTCOME VARIABLE: MOF	
	Yes	No
Yes	121	846
No	166	2697

*The odds ratio is defined by cross-multiplication (121 × 2697) ÷ (846 × 166). The odds ratio of 2.3 indicates patients with CHF are 2.3 times as likely to develop postoperative organ system failure as those without prior CHF. This univariate relationship can then be tested by chi-square for statistical significance.

CHF, Congestive heart failure; *MOF,* multiple organ failure.

Data from Higgins TL, Estafanous FG, Loop FD, et al. ICU admission score for predicting morbidity and mortality risk after coronary artery bypass grafting. *Ann Thorac Surg.* 1997;64:1050–108.

If the independent variable under consideration is continuous (e.g., age), a Student's t-test is an appropriate choice for statistical comparison. With continuous variables, consideration must be given to whether the relationship of the variable to outcome is linear, exponential, or segmented across its range. Fig. 165.2 shows the relationship of ICU admission serum bicarbonate to mortality outcome in cardiac surgical patients[38]; data points have been averaged with adjacent values to produce a smoothed graph.[39] Serum bicarbonate values higher than 22 mmol/L at ICU admission imply a relatively constant risk. Below this value, the risk of death rises sharply. Analysis of this locally weighted smoothing scatterplot graph suggests two ways for dealing with the impact of serum bicarbonate on mortality. One would be to make admission bicarbonate a dichotomous variable (i.e., >22 mmol/L or <22 mmol/L). The other would be to transform the data via a logarithmic equation to make the relationship more linear. Cubic splines analysis[40] can be helpful when the relationship between independent and dependent variables is not linear or cannot be described by a simple transformation.

Univariate analysis assesses the forecasting ability of variables without regard to possible correlations or interactions between them. Linear discriminant and logistic regression techniques can evaluate and correct for overlapping influences on outcome. For example, both a history of heart failure and depressed left ventricular ejection fraction predict poor outcome in patients presenting for cardiac surgery.[41] As might be expected, there is considerable overlap between the population with systolic heart failure and those with low ejection fraction. The multivariate analysis in this specific instance eliminates history of heart failure as a variable and retains only measured ejection fraction in the final equation to avoid double-counting of this general risk.

Because linear discriminant techniques require certain assumptions about data, logistic techniques are more commonly used.[9] Multiple logistic regression produces an equation with a constant, a beta coefficient and standard error, and an odds ratio that represents each term's effect on outcome. Table 165.3 displays the results of the logistic regression used in the Mortality Probability Model III ICU admission model (MPM_0 III).[42] There are 17 variable terms, and a constant term, each with a beta value that, when multiplied by the presence or absence of a factor, becomes part of the calculation of mortality probability using a logistic regression equation. The odds ratios reflect the relative risk of mortality if a factor is present.

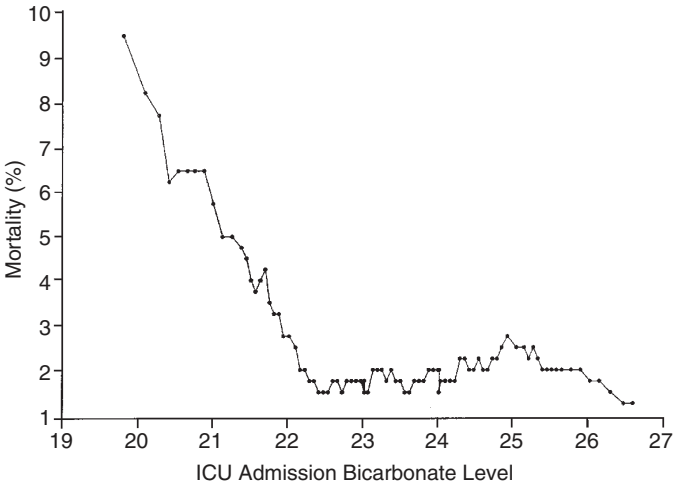

Fig. 165.2 A locally weighted smoothing scatterplot (LOWESS) analysis of the relationship between intensive care unit (*ICU*) admission bicarbonate level (*x*-axis) and mortality (*y*-axis). Individual patient data are grouped and averaged with surrounding data to produce a smooth plot. In this instance, the mortality rate appears to be stable with admission serum bicarbonate levels of 22 mmol/L and above but rises rapidly with lower values. Admission bicarbonate level of less than 21 mmol/L was given prognostic weight in the model that used these data. (Data from Higgins TL, Estafanous FG, Loop FD, et al. ICU admission score for predicting morbidity and mortality risk after coronary artery bypass grafting. *Ann Thorac Surg.* 1997;64:1050–1058.)

TABLE 165.3 Variables in the MPM_0 III Logistic Regression Model

Variable	Odds Ratios (95% Confidence Intervals)	Coefficients (Robust Standard Errors)
Constant	NA	−5.36283 (0.103)
Physiology		
Coma/deep stupor (GCS 3 or 4)	7.77* (5.921, 10.201)	2.050514 (0.139)
Heart rate ≥150 bpm	1.54 (1.357, 1.753)	0.433188 (0.065)
Systolic BP ≤90 mm Hg	4.27* (3.393, 5.367)	1.451005 (0.117)
Chronic Diagnoses		
Chronic renal insufficiency	1.71 (1.580, 1.862)	0.5395209 (0.042)
Cirrhosis	7.93* (4.820, 13.048)	2.070695 (0.254)
Metastatic neoplasm	24.65* (15.970, 38.056)	3.204902 (0.222)
Acute Diagnoses		
Acute renal failure	2.32 (2.137, 2.516)	0.8412274 (0.042)
Cardiac dysrhythmia	2.28* (1.537, 3.368)	0.8219612 (0.200)
Cerebrovascular incident	1.51 (1.366, 1.665)	0.4107686 (0.051)
GI bleed	0.85 (0.763, 0.942)	−0.165253 (0.054)
Intracranial mass effect	6.39* (4.612, 8.864)	1.855276 (0.166)
Other		
Age (per year)	1.04* (1.037, 1.041)	0.0385582 (0.001)
CPR before admission	4.47* (2.990, 6.681)	1.497258 (0.205)
Mechanical ventilation within 1 hour of admission	2.27* (2.154, 2.401)	0.821648 (0.028)
Medical or unscheduled surgical admit	2.48 (2.269, 2.719)	0.9097936 (0.046)
Zero factors (no factors other than age from previous list)	0.65 (0.551, 0.777)	−0.4243604 (0.088)
Full code	0.45 (0.416, 0.489)	−0.7969783 (0.041)
Interaction Terms		
Age × Coma/deep stupor	0.99 (0.988, 0.997)	−0.0075284 (0.002)
Age × Systolic BP ≤90	0.99 (0.988, 0.995)	−0.0085197 (0.002)
Age × Cirrhosis	0.98 (0.970, 0.986)	−0.0224333 (0.004)
Age × Metastatic neoplasm	0.97 (0.961, 0.974)	−0.0330237 (0.003)
Age × Cardiac dysrhythmia	0.99 (0.985, 0.995)	−0.0101286 (0.003)
Age × Intracranial mass effect	0.98 (0.978, 0.988)	−0.0169215 (0.003)
Age × CPR before admission	0.99 (0.983, 0.995)	−0.011214 (0.003)

BP, Blood pressure; *bpm,* beats per minute; *CPR,* cardiopulmonary resuscitation within 24 hours preceding admission; *GCS,* Glasgow Coma Scale; *GI,* gastrointestinal; ×, interaction between each pair of variables listed.

Odds ratios for variables with an asterisk (*) are also affected by the associated interaction terms.

Reprinted with permission from Higgins TL, Teres D, Copes WS, et al. Assessing contemporary intensive care unit outcome: an updated mortality probability admission model (MPM_0-III). Crit Care Med 2007;35:827–835.

The challenge in building a model is to include sufficient terms to deliver reliable prediction while keeping the model from being cumbersome to use or too closely fitted to its unique development population. Generally accepted practice is to limit the number of terms in the logistic regression model to 10% of the number of patients having the outcome of interest to avoid "overfitting" the model to the developmental data set. It is important to identify interaction among variables that may be additive, subtractive (canceling), or synergistic and thus require additional terms in the final model. In the earlier example, seven interaction items were added to reflect important observations in elderly patients,[43] where the very old without significant comorbidity frequently have better outcomes than unhealthy younger individuals.

The patient's diagnosis is an important determinant of outcome,[44] but conflicting philosophies exist on how disease status should be addressed by a severity adjustment model. One approach is to define principal diagnostic categories and add a weighted term to the logistic regression equation for each illness.[45] This acknowledges the different impact of physiologic derangement by diagnosis. For example, patients with diabetic ketoacidosis have markedly altered physiology but a low expected mortality; a patient with an expanding abdominal aneurysm, conversely, may show little physiologic abnormality and yet be at high risk for death. Too many diagnostic categories, however, may result in too few patients in each category to allow statistical analysis for a typical ICU, and such systems are difficult to use without sophisticated (and often proprietary) software.

The other approach is to ignore disease status and assume that factors such as age, chronic illness, and altered physiology will suffice to explain outcome in large groups of patients. This method reduces manual data collection and avoids issues with inaccurate labeling of illness in patients with multiple problems and the need for lengthy lists of coefficients but could result in a model that is less accurate[46] and somewhat dependent on having an "average" case mix.[47] Regardless of the specific approach, age and comorbidities (metastatic or hematologic cancer, immunosuppression, and cirrhosis) are given weight in nearly all ICU models to help account for the patient's physiologic reserve or ability to recover from acute illness. Yet many influential variables (e.g., frailty[48] in elders, mental illness,[49] paraplegia) increase the risk of poor outcome but are seldom incorporated into models. For example, acutely intoxicated patients tend to have low in-hospital mortality but striking rates of long-term mortality, particularly when street drugs are the intoxicating agent.[50] Do-not-resuscitate (DNR) orders are a strong confounder in mortality evaluations[51] but have only been included as a scoring variable in more recent models.[42]

VALIDATION AND TESTING MODEL PERFORMANCE

Models may be validated on an independent data set or by using the development set with methods such as jackknife or bootstrap validation.[52] Two criteria are essential in assessing model performance: calibration and discrimination. *Calibration* refers to how well the model tracks outcomes across its relevant range. A model may be very good at predicting good outcomes in healthy patients and poor outcomes in very sick patients yet unable to distinguish outcomes for patients in the middle range. The Hosmer-Lemeshow goodness-of-fit test[53] assesses calibration by stratifying the data into categories (usually deciles) of risk. The number of patients with an observed outcome is compared with the number of predicted outcomes at each risk level. If the observed and expected outcomes are very close at each level across the range of the model, the sum of chi-squares will be low, indicating good calibration. The *P* value for the Hosmer-Lemeshow goodness-of-fit *increases* with better calibration and should be nonsignificant (i.e., >.05). Special precautions apply when using the Hosmer-Lemeshow tests with very large databases,[54] where massive numbers can produce significance without clinical importance.

The second measurement of model performance is *discrimination,* or how well the model predicts the correct outcome. A classification table (Table 165.4) displays four possible outcomes that define sensitivity and specificity of a model with a binary (died/survived) prediction and outcome. Sensitivity (the true-positive rate) and specificity (the true-negative rate, or 1 minus false-positive rate) are measures of discrimination but will vary according to the decision point chosen to distinguish among outcomes when a model produces a continuous range of possibilities. The sensitivity and specificity of a model when using 50% as the decision point will differ from that using 95% as the decision point. The classification table can be recalculated for a range of outcomes by choosing various decision points: for example, 10%, 25%, 50%, 75%, and 95% mortality risk. At each decision point, the true-positive rate (proportion of observed deaths predicted correctly), the false-negative rate (proportion of survivors incorrectly predicted to die), and overall correct classification rate can be presented. The C-statistic, or area under a receiver-operating characteristic (ROC) curve, is a convenient way to summarize sensitivity and specificity at all possible decision points. A graph of the true-positive proportion (sensitivity) against the false-positive proportion (1 minus specificity) across the range of the model produces the ROC curve (Fig. 165.3).

TABLE 165.4 Classification Table

	ACTUAL OUTCOME	
Predicted Outcome	**Died**	**Survived**
Died	a	c
Survived	b	d

True-positive ratio = a/(a + b) (sensitivity)
False-positive ratio = c/(c + d)
True-negative ratio = d/(c + d) (specificity)
False-negative ratio = b/(a + b)
Accuracy (total correct prediction) = (a + d)/a + b + c + d
Adapted from Ruttiman UE. Severity of illness indices: Development and evaluation. In Shoemaker WC, ed. *Textbook of Critical Care Medicine,* 2nd ed. Philadelphia, PA: Saunders; 1989.

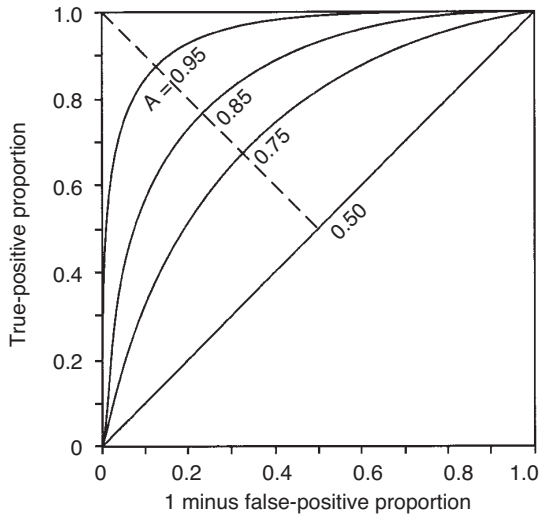

Fig. 165.3 Relative operating characteristic (ROC) curves. A coin toss gives an ROC of 0.5. In models that discriminate outcome, an increasing area under the curve, also called the *C-statistic,* is enclosed. (From Swets JA. Measuring the accuracy of diagnostic systems. *Science.* 1988;240:1285–1294.)

A model with equal probability of producing the correct or incorrect result (e.g., flipping a coin) will produce a straight line at a 45-degree angle that encompasses half of the area (0.5) under the curve. Models with better discrimination will incorporate increasingly more area under the curve to a theoretical maximum of 1.0. An area under the ROC curve (auROC) higher than 0.70 is acceptable, with higher than 0.80 considered excellent, and higher than 0.90 outstanding.[8] Most ICU models have ROC areas of 0.8–0.9 in their development set, although the ROC area usually decreases when models are applied prospectively to new data sets. The ROC analysis is valid only if the model has first been shown to be well calibrated.

A model may discriminate and calibrate well on its development data set yet fail when applied to a new population.[55] Discrepancies in performance can also relate to differences in surveillance strategies and definitions[55] and can occur when a population is skewed by an unusual number of patients having certain risk factors, as could be seen in a specialized ICU.[47] Large numbers of low-risk ICU admissions will result in poor predictive accuracy for the entire ICU population.[56] The use of sampling techniques (i.e., choosing to collect data randomly on 50% of patients rather than all patients) also appears to bias results.[57] Models deteriorate over time[58] owing to changes in populations and medical practice. These explanations should be considered before concluding that quality of care is different between the original and later applications of a model.

STANDARDIZED MORTALITY RATIO

Application of a severity of illness scoring system involves comparison of observed outcomes with those predicted by the model. The SMR is defined as observed mortality divided by expected mortality and is generally expressed as a mean value ±95% confidence intervals (CIs), which will depend on the number of patients in the sample. SMR values of 1.0 (± the CI) indicate that the mortality rate, adjusted for presenting illness, is at the expected level. SMR values significantly lower than 1.0 indicate performance better than expected. Small differences in scores, as could be caused by consistent errors in scoring elements, timing of data collection, or sampling rate, cause important changes in the SMR.[58,59] Different models applied to the same data set may produce discordant results, with the same hospital being identified as performing better than expected by one model and worse than expected by another.[46]

MODELS BASED ON PHYSIOLOGIC DERANGEMENT

Three widely used general-purpose ICU outcome systems are based on changes in patient physiology: the Acute Physiology and Chronic Health Evaluation (APACHE II,[60] APACHE III,[61] APACHE IV[44]), the Mortality Probability Models (MPM_0-II,[62] MPM_{24}-II,[33] MPM_0-III),[42] and the Simplified Acute Physiology Score (SAPS II,[63] SAPS III[64,65]). MPM_0-II and SAPS II were developed from the same data set and initially shared variables. All models have been regularly updated and are in at least their third generation. Although variables and weighting differ, all are based on the premise that as critical illness increases, patients will exhibit greater deviation from physiologic normal for a variety of common parameters such as heart rate, blood pressure, neurologic status, and laboratory values. Risk is also assigned for advanced age and chronic illness. Variables from these models have also been incorporated into the US VA hospital system model[66] (based on APACHE) and the California Outcomes Study[67] (similar to MPM_0-II and -III), in addition to models customized for international populations.

Acute Physiology and Chronic Health Evaluation

APACHE II was developed from data on 5815 adult medical and surgical ICU patients at 13 hospitals between 1979 and 1982; patients undergoing coronary artery bypass grafting, coronary care, or burn treatment were not part of the initial analysis. Severity of illness was assessed with 12 routine physiologic measurements plus the patient's age and previous health status.[61] Scoring was based on the most abnormal measurements during the first 24 hours in the ICU, with a maximum score of 71 points. The physiology score was then combined with coefficients to adjust the score for 29 nonoperative and 16 postoperative diagnostic categories, producing a mortality estimate.

APACHE II does not control for admission source or pre-ICU management, which could restore a patient's altered physiology and lead to a lower score and thus underestimate a patient's true risk.[68] Mortality estimates are most accurate for patients admitted directly from the emergency department and less so for interhospital and intrahospital transfers. Failure to consider the location before ICU admission could thus lead to erroneous conclusions about the quality of medical care.[69] Although the developers now consider APACHE II to have significant limitations based on its age, it is still in widespread use.

APACHE III, published in 1991, addressed limitations of APACHE II, including the impact of treatment time and location before ICU admission.[62] The number of separate disease categories was increased from 45 to 78. APACHE III was developed on a representative database of 17,440 patients at 40 hospitals, including 14 tertiary facilities that volunteered for the study and 26 randomly chosen hospitals in the United States. APACHE III went through several partial updates between 1991 and 2003.[45] Compared with APACHE II, the ranges of physiologic "normal" are narrower; deviations from normal are asymmetrically weighted to be more clinically relevant. Interactions between variables were considered, and five new variables (blood urea nitrogen, urine output, serum albumin, bilirubin, and glucose) were added, whereas the APACHE II variables serum potassium and bicarbonate were dropped. Information was also collected on 34 chronic health conditions, of which seven (AIDS, hepatic failure, lymphoma, solid tumor with metastasis, leukemia/multiple myeloma, immunocompromised state, and cirrhosis) were significant in predicting outcome. Customized models were developed for patient populations (e.g., cardiac surgery)[70] excluded from APACHE II. Overall correct classification for APACHE III was much improved over the prior model, and for the first time sequential scoring was introduced to update the daily risk estimate. APACHE III scores were also correlated with predictions for ICU LOS, need for interventions, and nursing workload.

APACHE IV was published in 2006[44] with refinements to address the impact of sedation on GCS, expand the number of diagnostic groups, and add or rescale predictive variables (Table 165.5). APACHE IV, based on a sample of 110,558 patients in the United States, has excellent discrimination (ROC area = 0.88) and impressive calibration (Hosmer-Lemeshow C-statistic 16.8, $P = .08$). Outcome assessment using the revised model differed substantially from prior versions. A hospital using APACHE III software in 2006, for example (calibrated to 1988–1989 results), might have congratulated themselves on a superb SMR of 0.799, whereas using APACHE IV would have revealed their SMR to be not different from the average at 0.997.

APACHE IV relies on physiologic abnormalities to account for 66% of the model's explanatory power. ICU admission diagnosis (using 116 categories) accounts for about 17%, with the remainder accounted for by age, chronic illness, location before admission, and interaction terms. There are limitations to the use of APACHE IV. First, the increased complexity of the model makes it impossible to use without dedicated software. The data entry burden, however, can be mitigated

TABLE 165.5 Variables Used in Acute Physiology and Chronic Health Evaluation IV

Variable	Coefficient	Odds Ratio
Emergency surgery	0.2491	1.28
Unable to access GCS	0.7858	2.19
Ventilated on ICU day 1	0.2718	1.31
Thrombolytic therapy for acute myocardial infarction	−0.5799	0.56
Rescaled GCS (15-GCS)	0.0391	1.04
15-GCS = 0		1.00
15-GCS = 1, 2, 3		1.04–1.12
15-GCS = 4, 5, 6		1.17–1.26
15-GCS = 7, 8, 9		1.31–1.42
15-GCS = 10, 11, 12		1.48–1.60
PaO_2/FiO_2 ratio	−0.00040	1.00
≤200		1.00–0.92
201–300		0.92–0.89
301–400		0.89–0.85
401–500		0.85–0.82
501–600		0.82–0.79
Chronic health items		
AIDS	0.9581	2.61
Cirrhosis	0.8147	2.26
Hepatic failure	1.0374	2.82
Immunosuppressed	0.4356	1.55
Lymphoma	0.7435	2.10
Myeloma	0.9693	2.64
Metastatic cancer	1.0864	2.96
Admission source		
Floor	0.0171	1.02
Other hospital	0.0221	1.02
Operating/recovery room	−0.5838	0.56

AIDS, Acquired immunodeficiency syndrome; *GCS,* Glasgow Coma Scale; *ICU,* intensive care unit; *PaO_2/FiO_2,* arterial oxygen partial pressure/fraction of inspired oxygen.

Adapted with permission from Zimmerman JE, Kramer AA, McNair DS, et al. Acute Physiology and Chronic Health Evaluation (APACHE) IV: Hospital mortality assessment for today's critically ill patients. *Crit Care Med.* 2006;34:1297–1310.

by porting data into APACHE from a hospital's clinical information system. Second, APACHE IV was developed and validated in ICUs in the United States, and international differences in ICU resources, triage policies, models of care, and bed availability affect benchmarking performance in a new environment.[71] The authors also stress that "prediction for an individual contains variance" and that "a prediction is only an approximate indicator of an individual's probability of mortality."[44] As an example, they mention that the 95% CIs around a predicted mortality of 5% would typically be 3.9%–6.5% and that the absolute ranges of CIs widen as the predicted rate increases. APACHE IV has been recalibrated to APACHE IVa, and APACHE V is currently under development.

Mortality Probability Models

The original MPM was developed on 755 patients at a single hospital using multiple logistic regression to assign weights to variables predicting hospital mortality.[72] The MPM-II models were developed on an international sample of 12,610 patients and then validated on a subsequent sample of 6514.[33] A subscript (0, 24, 48, 72) designates time of the evaluation in approximate hours post admission. MPM-II, as with APACHE II, excluded pediatric, burn, coronary, and cardiac surgical patients and estimated hospital mortality risk based partly on physiologic derangement, using a smaller number of variables. However, MPM puts more weight on chronic illness, comorbidities, and age and less on acute physiologic derangement compared with APACHE. MPM models can use data obtained at ICU admission (MPM_0) and also at the end of the first 24-hour period (MPM_{24}), with the latter covering a time interval more comparable to APACHE. Whereas APACHE generates a score and then, with additional information, converts that score into a probability estimate of survival, MPM directly calculates a probability of survival from the available data. Because this involves a logistic regression equation, it is difficult to accomplish at bedside without a computer or programmable calculator.

The MPM_{24} variables account for differences in patients who remain in the ICU for 24 hours or longer versus those who die early or recover rapidly. This line of reasoning has been further extended to create 48- and 72-hour models,[73] although these have not yet been updated from MPM-II to MPM-III. Additional variables in MPM_{24}, MPM_{48}, and MPM_{72} but not MPM_0 are prothrombin time, urine output, creatinine, arterial oxygenation, continuing coma or deep stupor, confirmed infection, mechanical ventilation, or intravenous vasoactive drug therapy. Probability of death increases at 48 and 72 hours even if the MPM variables and coefficients are unchanged, implying that mortality risk is increasing in patients whose clinical profile remains unchanged over time.[74] The most important difference between MPM and APACHE is that the MPM_0 produces a probability estimate that is available at ICU presentation and is independent of ICU treatment. MPM also does not require specifying a diagnosis, which can be an advantage in complex ICU patients but may also make it more susceptible to error with changes in case mix[47] and generates, on average, a lower auROC.

MPM_0-II became the mortality benchmarking component for the Society of Critical Care Medicine's (SCCM) Project IMPACT database launched in 1996. By 2002 it was apparent that mortality predictions based on mid-1980s results were outdated, and average SMRs in Project IMPACT hospitals had drifted to 0.85.[74] MPM_0-III was developed from a population of 124,855 patients in 135 ICUs at 98 Project IMPACT hospitals. Hospital mortality in this population was 13.8% versus 20.8% in the MPM_0-II cohort.[42] All of the 15 variables from MPM_0 -II remained associated with mortality, but the relative impact had changed. For example, gastrointestinal bleeding was no longer a serious risk factor, presumably because of advances in resuscitation, endoscopic procedures, treatment of *Helicobacter pylori,* and availability of proton pump inhibitors since the original study. Additionally, two new variables were added: "full code" resuscitation status at ICU admission and "zero factor" or absence of all MPM_0-II risk factors except age. Seven age interaction terms were added to reflect the declining marginal contribution of acute and chronic medical conditions to mortality risk in the elderly.[43] MPM_0-III calibrated well (Hosmer-Lemeshow goodness-of-fit 11.62; $P = .31$) with an auROC of 0.823, similar to that of MPM_0-II. Although the ROC area is lower than with APACHE, MPM users do not need to specify a diagnosis, which may be difficult in a complex patient with multiple problems. The simplicity of data collection and ability to generate a prognosis soon after arrival (rather than at 24 hours) are advantages.

Limitations of the MPM_0-III include lower discrimination and use of a self-selected population of Project IMPACT participants in North America. Although in theory, extreme case-mix differences might affect MPM performance, in practice, SMRs obtained using MPM_0-III versus specially constructed subgroup models were nearly identical in the 135 ICUs studied, suggesting specialized subgroup models are not usually necessary.[75] MPM_0-III has been prospectively validated on an additional 55,459 patients at 103 adult ICUs in North America and calibrates well with more contemporary Project IMPACT hospitals (78 units participating in both studies plus 25 new participants).[76] The Project IMPACT database was also used to update the resource utilization "Rapoport Teres" graph that plots severity-adjusted mortality versus severity-adjusted LOS[77] (Fig. 165.4).

The California Intensive Care Outcomes Projects (CALICO) was developed to produce public reports comparing outcomes for patients treated in California ICUs as part of the larger California Hospital Outcomes Project mandated by the state of California.[68] After evaluating risk models available in the early 2000s, the California Healthcare Foundation and the National Quality Forum endorsed a modified and recalibrated version of the MPM_0-II model termed "ICU Outcomes Model," or $ICOM_{mort}$,[78] which has an auROC of 0.84 in prospective validation. The model includes 28 additional interaction terms and differs in patient exclusions from MPM-II and MPM-III. An additional model ($ICOM_{LOS}$) considers LOS. The CALICO project yielded several important findings, most notably that substantial (twofold) variation exists in mortality rates among hospitals, even after risk adjustment.[68] Beginning in 2007, California required every ICU in the state to report severity-adjusted mortality rates. A recent study of 936,063 patients comparing the California experience with that of Arizona, Nevada, and Texas (which did not have public reporting requirements) concluded that while outcomes in California had improved, mortality rates also decreased in the control states.[79]

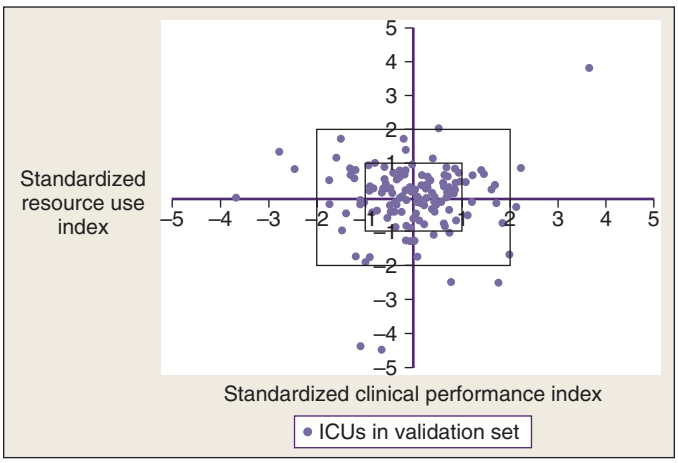

Fig. 165.4 Project IMPACT consolidates the display of mortality probability model (MPM) severity-adjusted mortality data (*x*-axis) with standardized resource use (weighted hospital days, *y*-axis). Hospitals within the 1 and 2 standard deviation boxes (most observations) are performing as expected. One hospital in the upper-right corner has superior performance in both dimensions. Four hospitals have longer-than-expected length of stay (negative numbers on standardized resource use), while being within range for mortality. Three hospitals have worse-than-expected adjusted mortality, whereas two have better-than-expected mortality; all are still within expected resource use. *ICUs,* Intensive care units. (From Nathanson BH, Higgins TL, Teres D, et al. A revised method to assess ICU clinical performance and resource utilization. *Crit Care Med.* 2007;35:1853–1862.)

Simplified Acute Physiology Score

SAPS II[64] was developed on 13,152 patients at 137 adult medical or surgical ICUs in Europe and North America, sharing the MPM-II data set. Like MPM and APACHEII, SAPS excluded burn patients, patients younger than 18 years, coronary care patients, and cardiac surgery patients. The outcome measure for SAPS II was vital status at hospital discharge. Seventeen variables were used in the SAPS II model: 12 physiologic variables; age; type of admission; and the presence of AIDS, metastatic cancer, or hematologic malignancy.

Not surprisingly, the SAPS II model also drifted out of calibration over time.[65] SAPS III, a multicenter, multinational study, collected data on 19,577 patients from 307 ICUs during the fall of 2002. When applied to this cohort, SAPS II underestimated hospital mortality, and although it discriminated well (ROC area, 0.83), calibration was poor, and model performance differed by geographic region. The final SAPS III model (Box 165.2), created based on 16,784 patients using logistic regression methods, contains 20 variables and has good discrimination (ROC area 0.848) and calibration (Hosmer-Lemeshow C-statistic = 14.29; $P = .16$).[66] Customized models were generated for seven worldwide regions to address geographic variation in population outcomes.

Intensive Care National Audit and Research Center Model

As noted earlier, risk adjustment models require validation and recalibration if they are to be applied in a new geographic setting.[55,80] The Intensive Care National Audit and Research Center (ICNARC) collected data on 216,626 critical care admissions in 163 adult general critical care units in England, Wales, and Northern Ireland from December 1996 to August 2003.[81] Logistic regression techniques were used to create the ICNARC model (Box 165.3), which includes 12 physiologic variables, age, source of admission, diagnostic category, and CPR status. This model has an ROC area of 0.863 and a Hosmer-Lemeshow C-statistic of 64.2. This study also evaluated performance

BOX 165.2 Variables Used in Simplified Acute Physiology Score III

- Age (in years)
- Comorbidities: cancer, cancer therapy (scored separately), chronic heart failure (NYHA IV), hematologic cancer, cirrhosis, AIDS
- Length of stay before intensive care unit (ICU) admission, days
- Intrahospital location before ICU admission
- Use of major therapeutic options before ICU admission (e.g., vasopressors)
- ICU admission: planned or unplanned
- Reason for ICU admission
- Surgical status at ICU admission: emergency, elective, or none
- Anatomic site of surgery
- Acute infection at ICU admission
- Lowest estimated Glasgow Coma Scale score (points)
- Total bilirubin (highest)
- Body temperature (highest)
- Creatinine (highest)
- Heart rate (highest)
- Leukocytes (highest)
- Hydrogen ion concentration (lowest pH)
- Platelet count (lowest)
- Systolic blood pressure (lowest)
- Oxygenation (P/F ratio)

AIDS, acquired immunodeficiency syndrome; *ICU,* intensive care unit; *NYHA,* New York Heart Association. *P/F,* arterial oxygen partial pressure/fraction of inspired oxygen (PaO_2/FiO_2).

BOX 165.3 Elements in ICNARC Score

- Highest heart rate
- Lowest systolic BP
- Highest temperature
- Lowest respiratory rate
- Mechanical ventilation (yes/no)
- Lowest PaO_2/associated FiO_2 (P/F ratio)
- Lowest pH
- Highest serum urea
- Highest serum creatinine
- Highest serum sodium
- Urine output (24 hours)
- Lowest WBC
- Paralyzed/sedated (yes/no)
- Lowest Glasgow Coma Scale score
- Age (years)
- Source of admission
- Diagnostic category
- CPR (yes/no)

BP, Blood pressure; *CPR,* cardiopulmonary resuscitation; *PaO_2/FiO_2,* arterial oxygen partial pressure/fraction of inspired oxygen; *WBC,* white blood cell count.
Adapted with permission from Harrison DA, Gareth JP, Carpenter JR, et al. A new risk prediction model for critical care: The Intensive Care National Audit & Research Centre (ICNARC) model. *Crit Care Med.* 2007;35:1091–1098.

of APACHE II, APACHE III, SAPS II, and MPM-II on the same population. The ICNARC outperformed all other models in terms of discrimination (ROC area), but SAPS II had better calibration and MPM-II had the best accuracy of average prediction, although these differences were all relatively minor. ICNARC, having no exclusions, may be applied to all critical care admissions regardless of diagnosis, and it calibrates well in the United Kingdom. ICNARC has recently been externally validated in 23,269 patients in 24 Scottish critical care units, with good discrimination (0.848) and calibration.[82]

Veterans Affairs Intensive Care Unit Risk Adjustment Model

Arguably, the VA population in the United States could represent a specialized population, owing to being predominantly male (>97%). In 1996–1997, the VA developed a customized, automated ICU risk adjustment tool[67] based on APACHE variables; this model has been validated, updated, and recalibrated.[83] Risk predictors include age, mutually exclusive ICD-9 diagnosis/procedure groups, comorbid disease groups, admission source, and 11 laboratory values measured during the 24 hours surrounding ICU admission. Revisions to the model refit the predictor coefficients and expanded the number of diagnostic categories from 38 to 84. The model has an impressive ROC area (0.874–0.877) in two data cohorts and calibrates well by Hosmer-Lemeshow statistics. SMRs derived from the VA ICU model correlate well ($r^2 = 0.74$) with those of the National Surgical Quality Improvement Performance (NSQIP) tool developed for surgical postoperative assessment. The VA model, however, has not yet been tested internationally or outside of the VA population.

Specialized Models

MPM, SAPS, and early versions of APACHE excluded patients younger than age 18, burn patients, and coronary care and cardiac surgical patients. Murphy-Filkins and colleagues[47] reported that performance of severity of illness models deteriorates when critical population values are reached for individual scoring variables, as might be seen in a highly specialized ICU. For example, 20% of the patients in the MPM-II database were aged 75 or older. When this percentage of elderly patients was experimentally increased to 42%, the model became unstable. Similar changes were seen if the proportion of patients with cardiac dysrhythmias, cerebrovascular disease, intracranial mass effects, coma, CPR before ICU admission, emergency admission, or gastrointestinal bleeding differed substantially from baseline values. Thus severity of illness scoring systems should be used with caution when units become highly specialized to care for subsets of patients.

To address this issue, specific models have been developed for pediatric,[84] trauma,[85] and cardiac surgical populations.[41,86–88] ICU admission physiologic values in the cardiopulmonary bypass population are determined by routine hypothermia, hemodilution, and deliberate control of hemodynamics by the operating room team. Important variables for predicting outcome after cardiac surgery are ventricular function, coronary anatomy, and heart valve pathology and reoperation status.[36] The Cooperative CABG Database Project, analyzing 172,000 patients, identified seven core variables (urgency of operation, age, prior heart surgery, gender, ejection fraction, percent stenosis of the left main coronary artery, and number of major coronary arteries with >70% stenosis) to be predictive of mortality.[89] The independent variables predicting morbidity do not perfectly overlap those predicting mortality or LOS, suggesting that different scores may be required to best predict various outcomes. Currently, the two most widely used preoperative cardiac surgical models are the Society for Thoracic Surgeons model[90] in the United States and the EuroSCORE-II[91] in Europe; both have been updated from their original iterations.

The preoperative cardiac surgical models are useful for evaluating the results of an entire hospitalization but do not specifically address the ICU component of care. Operating room events can neutralize or amplify preoperative risk, depending on such events as reopening the chest, hemodynamic management in an emergency patient, and the degree of myocardial protection. In 5000 patients undergoing CABG, eight risk factors available at ICU admission appeared to predict hospital mortality, and an additional five factors also predict morbidity.[38] APACHE has also been successfully modified for use in cardiac surgical patients.[71]

Patients receiving prolonged mechanical ventilation (MV) are resource-intensive, and although their mortality can be accurately estimated, they have a disproportionate effect on ICU and hospital LOS, which is magnified with high hospital MV volume.[92] The ProVent model, measured on day 21 of MV, predicts overall 1-year mortality (48%) with acceptable discrimination and calibration[93] by assigning points for four categorical variables: age, platelet count, vasopressors, and hemodialysis.

SEQUENTIAL ORGAN FAILURE ASSESSMENT SCORE

The Sequential Organ Failure Assessment (SOFA) score was developed to quantify organ dysfunction of the respiratory, cardiovascular, hepatic, coagulation, renal, and neurologic systems. One to four points are assigned based on the degree of physiologic derangement; high scores imply poor outcome. A maximum SOFA higher than 15 is associated with more than 90% mortality.[94] SOFA is intended to be used sequentially, in part to address the issue that a first-day severity score has limited ability in predicting outcome when patients have a longer ICU experience with attendant events or complications. Although developed to assess organ failure rather than prognosis, SOFA (and similar scores, such as the Logistic Organ Dysfunction System [LODS][95] and the Multiple Organ Dysfunction Score [MODS])[96] correlates with mortality. The change in score during the first 96 hours can help with prognosis: regardless of the initial score, an increasing score is associated with more than 50% mortality.[97]

Most risk-adjustment models provide initial estimates for both ICU and hospital mortality, with the potential for updating predictions during the ICU stay. Although subjective, the Sabadell score allows ICU clinicians to categorize patients at ICU discharge into good prognosis (0 points), poor long-term prognosis (>6 months) with unlimited ICU readmission (1 point), poor short-term prognosis (<6 months) with debatable ICU readmission (2 points), and death expected during hospitalization (3 points). Age and the Sabadell score correlate with ward mortality after ICU discharge with good calibration (auROC, 0.88) and discrimination.[98] Patients with high predicted ward mortality would likely benefit from palliative care consultation. Conversely, less than 2% of patients with good prognosis die on the ward after ICU discharge.

ADMINISTRATIVE MODELS

Initial versions of the most popular models were developed by research teams using data largely collected manually using trained abstractors.[45] There has been interest in automating this process,[99] and with the widespread availability of electronic health records, real-time calculations have become routine. Although extracting relevant clinical variables can still be an informatics challenge, successful models based on administrative data have been developed for predicting in-hospital mortality for community-acquired pneumonia[100] and sepsis.[101] With automated data collection, these models can extend beyond just ICU admissions to encompass all hospitalized patients. The next iteration of APACHE will reportedly address outcomes across venues and allow automated outcome predictions for all hospitalized patients. The Multiparameter Intelligent Monitoring in Intensive Care II (MIMIC-II) database promises to promote research in epidemiology and clinical decision-rule creation by establishing a public-access, deidentified database.[102] Caution is raised by a large Dutch study, however, where SMRs calculated using administrative data were unfavorable to those calculated using modified SAPS II clinical data, especially in institutions with a more severely ill population.[103]

COMPARISONS AMONG MODELS

A number of papers have compared relative performance of the three most widely used ICU systems.[104–106] Using data from 11,300 patients in 35 hospitals participating in the CALICO Project, APACHE IV, MPM_0-III, and SAPS II all showed adequate discrimination and calibration, with APACHE IV delivering the best predictive accuracy, albeit with longer data collection time.[107] Substantial variation occurred in ICU risk-adjusted mortality rates between ICUs, regardless of the model used.

Performance of three models based on 24-hour data (APACHE II, APACHE III-J, and SAPS II) was compared with that of three models based on admission data (MPM-II, SAPS III, and SAPS III-A using Australian coefficients) for 1741 patients in an urban university-affiliated teaching hospital in Australia.[108] SAPS II and SAPS III-A fulfilled predetermined calibration and discrimination criteria, APACHE II failed both criteria, and the remaining models discriminated well but overpredicted mortality risk. There did not appear to be an advantage in using 24-hour data versus data available at admission. The improved results with SAPS III-A versus SAPS III again underscores the benefit of customizing models with local coefficients. A Brazilian study found APACHE IV, MPM_0-III, and SAPS III to have good discrimination (auROC 0.883, 0.840, and 0.855, respectively) but uniformly poor calibration, leading to overestimates of in-hospital mortality.[109] Calibration was particularly problematic with SAPS III, but APACHE IV and MPM_0-III also performed poorly at higher predicted mortality rates.

More recently, MPM_0-III, the $ICOM_{mort}$ modification of MPM (also known as the National Quality Forum or NQF model), and APACHE IVa were compared based on a database of 174,001 ICU admissions from 2008 to 2012 at 38 US hospitals.[110] Only 109,926 patients (63%) met inclusion criteria for all three models. APACHE IVa offered the best discrimination and calibration and excluded fewer patients than the other models. APACHE IVa overpredicted mortality by 1.5%, MPM_0-III overpredicted by 3.1%, and the ICOM-NQF model underpredicted by 1.2%. Calibration was best for APACHE IVa, which has implications for benchmarking using SMR when case mix varies among hospitals; this will be discussed later.

Table 165.6 summarizes the results of nine studies in which two or more of the risk-adjustment models were applied to a specific regional population. There is no consistent pattern to accuracy (discrimination), with examples of observed mortality higher than predicted, lower than predicted, as predicted, or predicted differently by different systems. There is also no consistent leader in calibration; it tends to be poor in many studies. Ratios of observed-to-expected mortality rates are influenced by case mix and by quality of care.[111]

TABLE 165.6 Regional Application of Severity Scoring Models

Study	Country	Systems	Findings
Arabi et al.[112]	Saudi Arabia	APACHE II	Predicted mortality similar to that observed for all systems (SMR 1.0–1.09)
	n = 969	$MPM\text{-}II_0$ and $\text{-}II_{24}$	Calibration best with $MPM\text{-}II_{24}$
		SAPS II	Discrimination best with $MPM\text{-}II_0$ followed by $MPM\text{-}II_{24}$, APACHE II, and SAPS; all ROC >0.79
Capuzzo et al.[113]	Italy	APACHE II	ROC area >0.8 both models
	Single center	SAPS II	Mortality in high-risk patients overpredicted by SAPS II and underpredicted by APACHE II
	n = 1721		
Katsaragakis et al.[114]	Greece	APACHE II	Good discrimination but poor calibration with both models
	Single center	SAPS II	Better performance with APACHE II
	n = 661		
Livingston et al.[80]	Scotland	APACHE II	Discrimination adequate (ROC areas 0.74–0.795)
	22 centers	APACHE III	
	n = 10,393	UK APACHE II	Observed mortality significantly different from that predicted by all systems
		$MPM\text{-}II_0$	APACHE II had best calibration followed by $MPM\text{-}II_{24}$ and SAPS II
		$MPM\text{-}II_{24}$	

TABLE 165.6 Regional Application of Severity Scoring Models—cont'd

Study	Country	Systems	Findings
Markgraf et al.[71]	Germany	APACHE II	Observed mortality higher than predicted by any model
	Single center	APACHE III	Worst discrepancy with trauma, respiratory, neurologic, and renal disease
	n = 2661–2795	SAPS II	Best calibration with APACHE II
			ROC area >0.8 all models
Moreno et al.[115]	Europe	MPM-II_0	Discrimination adequate (ROC 0.822 for SAPS II, 0.785 for MPM_0)
	89 centers	SAPS II	Both models overestimated risk of death
	n = 16,060		Large variations across subgroups of patients
Nouira et al.[116]	Tunisia	APACHE II	Observed mortality higher than predicted except with MPM_0
	3 centers	MPM-II_0 and II_{24}	Good discrimination, poor calibration for all models
	n = 1325	SAPS II	
Tan et al.[117]	China (Hong Kong)	APACHE II	Discrimination good (ROC area 0.87–0.88) but calibration poor
	Single center	SAPS II	Both models overpredict mortality
	n = 1064		
Metnitz et al.[118]	Austria	SAPS III	Original SAPS III overestimated mortality even with Central and Western Europe equation
	22 ICUs		Calibration improved with customization
	n = 2060		
Poole et al.[119]	Italy	SAPS III	Discrimination good
	147 ICUs		Calibration poor—general and South Europe
	n = 28,357		Mediterranean equations overestimated hospital mortality (SMR 0.73)

ICU, Intensive care unit; *ROC,* receiver-operating characteristic; *SMR,* standardized mortality ratio.

UTILITY OF SEVERITY OF ILLNESS INDICES

There are four major applications for severity of illness scoring systems:
1. Assessing ICU performance for quality improvement
2. Predicting and planning resource use and staffing
3. Comparing or stratifying populations in clinical research
4. As one factor to consider in guiding individual patient care

Risk-adjusted outcomes data will be shared with a variety of "customers," each of whom will have a different focus. In broad terms, clinicians and quality leaders will use data to drive improved care and efficiency, whereas patients, governments, and funders will be more interested in comparing performance among institutions.[15]

Quality Improvement and Benchmarking

Meaningful evaluation of ICU performance must consider both severity of illness of the patient population and characteristics of the institution. *Benchmarking* refers to the process of comparing an individual unit's performance against established case mix–adjusted standards with similar ICUs or with the units' own data over time. Benchmarking need not be for morbidity and mortality outcomes alone; severity adjustment also helps explain variations in cost and ICU LOS.[120] Outlier LOS status is only partially predicted by severity of illness, and factors such as long ward stays before ICU admission and absence of an intensivist-directed multidisciplinary care team increase LOS.[121]

The mortality rate and LOS for patients transferred to a referral hospital is higher than that of nontransferred patients,[122] and this referral bias[123] has implications in profiling hospital quality. Medical patients transferred from another hospital have higher acute physiology scores, but even after adjustment for case mix and severity of illness, experience longer hospital and ICU stays and have more than twice the risk of hospital mortality compared with directly admitted patients.[11] These authors suggest that a referral hospital with a 25% transfer-in rate would suffer a penalty when undergoing profiling. Conversely, transferring patients to a tertiary care center has beneficial effects to the exporting hospital, because death is attributed to the receiving hospital.[124] Transfer of mechanically ventilated patients from ICU long-term acute care (LTAC) facilities also significantly affects reported mortality and LOS.[125] Intrahospital transfers to a higher level of care after admission are also associated with excess mortality and LOS.[126] As noted earlier, discharge practices affect risk-adjusted rates, with a greater impact on large hospitals and when in-hospital, rather than 30-day mortality rates, are considered.[13]

Factors unrelated to quality of medical care or patient severity of illness thus affect public reporting of SMR results. Does the benchmarking tool play a role? SMR was calculated for 47 ICUs at 36 US hospitals using APACHE IVa and the ICOM-NQF models. Overall SMR was 0.89 using APACHE IVa and 1.07 using the NQF model. Disturbingly, the two models agreed on the significance and direction of the SMR only 45% of the time (Fig. 165.5). Units caring for more severely ill patients and with a higher percentage of patients receiving MV had the highest discordance.[127] SMR and SMR rank position of ICUs also depend on whether the endpoint is in-hospital mortality or mortality at 1, 3, or 6 months after ICU admission.[128] In an age of outcome-driven reimbursements, these discrepancies are financially important and also ethically troubling.[129] Public disclosure and rank-ordering ICUs on the basis of SMR or other metrics is thus highly problematic. Identifying hospitals with higher-than-expected mortality has no effect on market share[130] and, reportedly, does not improve process-of-care indicators.[131] Benchmarking relative performance among ICUs should likely be replaced by comparing improvement in performance over time. Furthermore, discrepancies between observed and expected outcomes should primarily be a marker to prompt more careful review.[132]

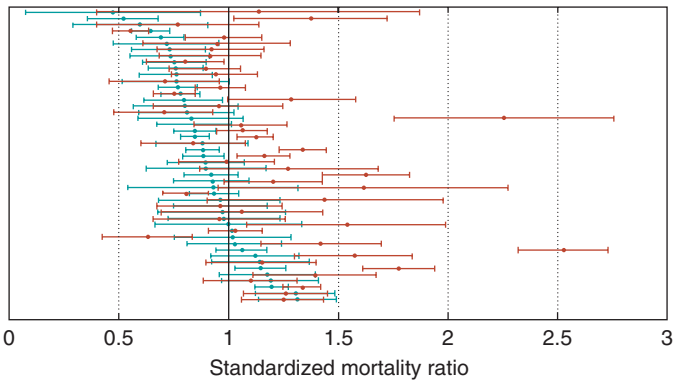

Fig. 165.5 Standardized mortality ratio (mean and 99% confidence interval) for 47 intensive care units (ICUs) evaluated using APACHE IVa *(blue)* and the ICOM-NQF *(red)* models. Over half of the performance assessments are discordant. (From Kramer AA, Higgins TL, Zimmerman JE. Comparing observed and predicted mortality among ICUs using different prognostic systems: Why do performance assessments differ? *Crit Care Med.* 2015;43:261–269.)

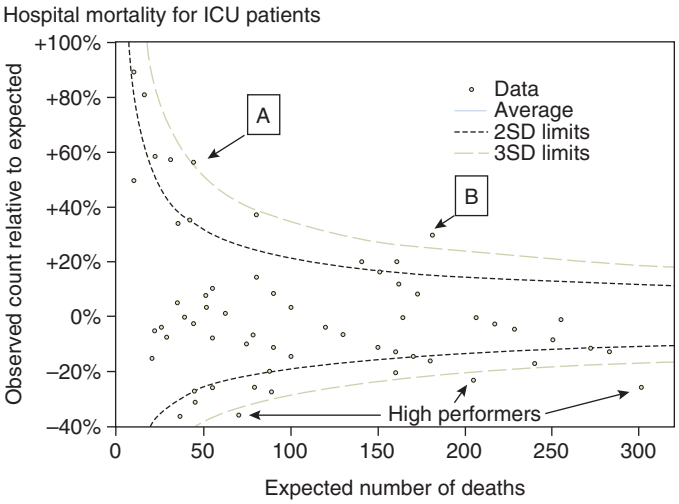

Fig. 165.6 Example of a funnel plot, using hypothetical data. The ratio of observed to expected deaths is plotted on the *y*-axis, with number of deaths on the *x*-axis. Two- and three-standard deviation (*2SD and 3SD*) limits are plotted, which helps identify two hospitals (A and B) as significant outliers ($P < .001$). Three hospitals ("high performers") have significantly fewer deaths than expected. Note that the observed count relative to expected (similar to the standardized mortality ratio [SMR]) is +50% (SMR 1.5) for the lowest-volume hospital, which is still within the 95% confidence intervals. Hospital B has a lower SMR at 1.35 (+35%) but, because of volume, can be identified as a significant outlier. *ICU,* Intensive care unit. A template for generating funnel plots like this can be downloaded from http://www.apho.org.uk/resource/item.aspx?RID=47242.

Case volume is an important consideration for evaluation and reporting. SMR should not be presented as a single number, but rather as a range that encompasses the 95% Cis based on sample size. Units with a low mortality rate require larger numbers of patients; this is well illustrated in a study by Dimick and colleagues examining the problems with small sample size when evaluating surgical mortality.[133]

Risk-adjusted mortality rates can be displayed over time—usually quarterly in smaller units and monthly in larger facilities. Standard statistical quality control charts and cumulative sums (CUSUM, a sequential technique) can be used to detect changes requiring investigation.[134] Exponentially weighted moving average control charts are said to signal the fastest compared with other types of risk-adjusted control charts.[135] For comparisons among institutions, funnel plots (Fig. 165.6) are preferable to league tables, as they incorporate volume-based control limits that reduce the risk of spurious interpretation inherent in a ranked list.[136] Other investigators have argued that funnel plots have difficulty identifying outliers with small volumes, while identifying divergence of statistical, but not clinical, importance when the numbers are large.[137]

Predicting and Planning Resource Use

The Therapeutic Intervention Scoring System (TISS) was developed as a method for quantifying patient care and severity of illness.[138] TISS was supplanted as a prognostic tool by the newer scoring systems once it was realized that application of technology depended on local availability and local practice. TISS is now used primarily to quantify nursing workload and costs.[139] The Rapoport-Teres graph (see Fig. 165.4) displays MPM risk-adjusted mortality on the *x*-axis and resource use (LOS) on the *y*-axis.[78] Similar displays are possible using other risk adjustment systems.

Use of Severity Indices In Clinical Research

Existing databases permitting severity adjustment make possible hypothesis-generating observations and conclusions about therapeutic choices in situations where randomized, prospective evaluations might not be permitted or funded. For prospective studies, severity scoring indices can be used to risk-stratify the population before randomization, thereby reducing the number of patients recruited and the cost of clinical trials. Clinical studies have also used scoring systems as part of inclusion criteria and to show that control and study groups have similar disease burdens.[140] Cytokine profiles correlate with APACHE and MPM scores in septic individuals[141]; however, severity scores were not designed for this purpose, and calibration has not been assessed in the clinical trial population. There is the danger that inclusion of age and chronic health points may exclude younger, previously healthy patients from trial entry.[142]

Uses of Severity Adjustment for Individual Predictions

The short answer is that risk-adjustment models are designed for evaluating groups and not for determining care of individuals. The problems with using scoring systems for individual patient care decisions arise from attempts to apply a probability estimate, which may range from 0 to 1, to an individual for whom the result will be 0 *or* 1. No model is accurate enough to predict that a given patient will certainly survive or invariably die, so scoring systems alone cannot dictate decisions to direct or withhold therapy. Sequential risk estimates, an approach explored by APACHE,[143] MPM,[33] and SOFA,[144] improve prognosis by incorporating data reflecting patient response to therapy over time. Objective predictions of the need for next-day life support are used by APACHE III and IV to guide triage and discharge decisions.[145] Increases in organ dysfunction scores after admission generally carry a poor prognosis,[146] although others have reported limited ability of the SOFA and MODS tools to discriminate outcome.[147] A meta-analysis of 46 studies suggests that 3%–7% of patients discharged from the ICU will die before hospital discharge[148]; ICU readmissions in this same population were 4%–6%.

Use of scoring systems to individualize therapy has not been well studied. Recombinant human activated protein C (rhAPC), now off

the market, considered an APACHE II score higher than 25 as a criterion for drug administration based on post hoc subgroup analysis of the PROWESS trial.[149] However, issues with this approach include wide variability in severity score between ICU admission and time of drug administration,[150] the confounding effect of DNR orders,[51] and bias against younger, previously healthy patients.[143] Further, an efficient emergency department may well stabilize the patients and lower the APACHE II score before arrival in the ICU.[151]

Objectively calculated severity scores are not necessarily more accurate than physician or nurse intuition when dealing with individual patients.[152,153] Accurate prognosis may be most difficult for patients with the highest risk of death. A multicenter study addressing the issue of medical futility found that divergent judgments on patient prognosis by doctors and nurses increased with higher SAPS II scores and longer ICU stays.[154] ICU physicians discriminate between survivors and nonsurvivors more accurately than SAPS II, MPM-I, or APACHE II.[153]

APACHE, SAPS, and MPM scores are *specific,* having more than 90% ability to predict survival, but are relatively *insensitive* in predicting death. Such information should not be taken as a rationale to rely on clinical judgment alone and forgo the use of formal scoring. The existing severity indices, despite their flaws, provide useful, objective information that can supplement clinical judgment for prognosis and triage, bearing in mind that patient autonomy and medical ethics also influence these decisions. Surrogates of critically ill patients generally appreciate reliable prognostic information but cope with unfavorable news in a variety of ways, including seeking information from other sources and avoiding or disbelieving prognostic information.[155]

PITFALLS IN THE APPLICATION OF SEVERITY OF ILLNESS INDICES

The use (and abuse) of databases for profiling ICUs and/or individual physicians is growing, despite flaws in administrative databases and problems identified with the application of statistical models[21] and physician profiling.[156] Assuming a properly developed model is applied, potential pitfalls in application fall into four major categories: data collection and entry errors,[157] misapplication of the model,[11,47,58] use of mortality as the sole criterion of outcome, and failure to account for sample size and chance variability[56,108,120] when reporting results (Box 165.4).

Errors in the EMR tend to propagate and become immortalized in the absence of a data collector who might note and correct artifacts and out-of-range values.[8] Upgrading hardware or software can lead to obscure errors. Determination of the diagnosis is prone to bias,[158] but using a system that is blind to diagnosis will be inaccurate if case mix is markedly skewed.[47] Less obvious is the fact that many models start the "clock" with ICU admission, the timing of which is not standardized[159] and frequently influenced by local conditions such as ICU bed availability.[160] ICUs also do not function in isolation in the process of care,[152] and the growing trend toward aggressive use of step-down facilities and offsite chronic ventilation and rehabilitation units raises the question of whether hospital mortality is valid when patients may be transferred to other facilities alive but are still technology dependent.[13,161] The issue of lead-time bias (pre-ICU stabilization) requires consideration; assessment is further complicated for patients with multiple ICU admissions,[161] whose second ICU admission during a single hospitalization is frequently excluded from subsequent analysis.[26] It is, for example, unclear which ICU stay should be counted for a patient who has a period of ICU observation after an uneventful vascular procedure and then develops complications requiring ICU readmission on the fifth postoperative day. It is increasingly necessary to evaluate the performance of an ICU *system,* which includes pre-ICU, ICU, and post-ICU care. Models now in development will address outcomes across the entire arc of care.

BOX 165.4 Potential Pitfalls in the Application and Reporting of Severity-Adjusted Outcome

Data Collection and Entry
- Inclusion of ineligible patients
- Missing variables and data management errors
- Substitution of available for properly timed data
- Transcription and data entry errors
- Improper communication between hospital clinical and risk adjustment applications
- Wrong diagnosis selected
- Administrative data reflective of clinical situation
- Deliberate "gaming" of the system—upcoding of comorbidities

Models
- Case-mix differences (critical threshold exceeded)
- Application to subsets of development population
- Changes in influence of variable with improving medical care
- Small clinical changes become large risk increments when continuous data are categorized.
- Lead-time bias

Outcomes
- Insufficient range of outcomes reported
- Use of proxy outcomes that inadequately reflect true status
- Patient lost to follow-up
- Chance variability masquerading as true difference
- Relationships of scores to resource use and costs reflect observed practice, not ideal

Reporting
- Confidence intervals not reported
- Inadequate sample size
- Physician of record misidentified
- Computational errors
- Misapplication of group data to individuals
- Misinterpretation of statistical significance as clinical significance

RECENT DEVELOPMENTS

The collection of large national databases has become established in several jurisdictions such as the United Kingdom, Finland, Australia, and New Zealand.[162] They have led to the accumulation of large bodies of illness severity scoring data exceeding >1 million patients, which has enabled the development of local recalibration of predicted mortality risk. For example, in the UK, the Intensive Care National Audit and Research Centre (ICNSARC) has developed a locally relevant prediction model ($ICNARC_{H\text{-}2018}$), which is calibrated to the UK critical care patient.[163] Similarly, the Australian and New Zealand Intensive Care Society (ANZICS) Centre for Outcome Research and Evaluation (CORE) has developed a risk prediction model for mortality calibrated to the local population (the ANZ Risk of Death model: ANZROD).[164] In each population such model outperforms generic US-developed models in accurately predicting outcomes. It is likely that such models will become more common as other national bodies create and maintain locally relevant ICU databases.

In the opposite direction, in the field of sepsis and of relevance to ICU clinicians, rapid assessment of severity with minimal information

has become relevant on a global scale outside of high-income countries and, in high-income countries, in the setting of emergency departments. In this regard, there has been much interest in the usefulness of a simple assessment of severity in patients with suspected infection called *qSOFA* (quick Sequential Organ Failure Score), which relies on the rapid assessment of patients with suspected infection by observing their respiratory rate, mental state, and blood pressure.[165] Such assessment allows the identification of patients with a higher illness severity and a high risk of requiring prolonged ICU stay and/or mortality and is being promoted as clinically useful.[166]

Finally, the increasing availability of EMR data, which is now routinely collected in many hospitals, can expand the data sources, their granularity, and their breadth and may allow a further evolution in prediction in the next decade in addition to providing electronic real-time information as the patient's condition changes.[167] More work in this field of dynamic digital illness severity scoring is expected in the next decade.

PEDIATRIC ILLNESS SEVERITY SCORES

Illness severity scoring systems developed for adults do not apply to children because the diagnoses are different, comorbidities are different, and normal physiologic values (e.g., heart rate, blood pressure, respiratory rate) are different and change according to age. Over the last 30 years several pediatric illness severity scoring systems have been applied children to specific populations and to a general severity of illness scoring system. Among such generic scoring systems are the Pediatric Index of Mortality (PIM),[168] the Pediatric Logistic Organ Dysfunction (PELOD) score,[169] and the Pediatric Risk of Mortality (PRISM).[170] Such systems carry similarities with the adult systems in terms of the principles applied, the use of physiology, the generation of predictive equations, and the probability of death. The SMR is also calculated and used to benchmark performance. However, pediatric illness severity scores have unique challenges because the databases used for their generation tend to be smaller in size and because mortality is a rare event. For example, the PRISM update of 2015 involved 10,078 admissions with a mortality rate of only 2.7%.[168] Despite such challenges, it achieved good model fit and validation and an auROC curve of between 0.88 and 0.9. Thus this new version (PRISM IV) provides a useful structure for an updated illness severity assessment in children, and the algorithm is now in the public domain for other users to take advantage of such improvements in prediction. However, the low mortality in pediatric ICUs of high-income countries has raised concern about the clinical validity of focusing on mortality as the outcome of interest and concern about the value of such information to low-income countries, where mortality is up to 10-fold higher. Given these observations, it is likely that high-income pediatric ICUs will focus on predicting functional outcomes rather than mortality, whereas low- or middle-outcome countries will need to develop locally relevant models.

CONCLUSION

APACHE, MPM, and SAPS are highly developed, prospectively validated tools useful for comparison of ICU performance in the care of groups of patients. Specialized models are available for burn, trauma, sepsis, cardiac surgery, and pediatric patients. When used as intended, these models allow stratification of patients for performance assessment, utilization management, clinical research, and dissemination of outcome results. Important implementation considerations include careful data collection, appropriate matching of the model and the population under study, and use of proper sample sizes and CIs in reporting results.

None of the models can perfectly predict the outcome for an individual patient.[169] However, this limitation is true of almost any test used in medicine and need not preclude the use of prognostic estimates for clinical decision support. Physicians must be alert to the limitations of severity-adjustment models in performance-based assessment because case-mix differences, inadequate sample sizes, or systemic errors in data collection can generate erroneous conclusions about the quality of care. In the end, what is measured is less important than what is done with the measurement. The encouraging news is that despite an increase in severity of illness between 1988 and 2012, risk-adjusted hospital mortality for patients admitted to ICUs has decreased significantly, an observation that would have been impossible without the benefit of severity of illness scoring systems.[170]

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KEY POINTS

- Stratification of outcome based on risk factors is necessary when comparing outcomes obtained by different institutions, intensive care teams, and treatment strategies.
- Although mortality is readily defined and easily captured, it is insufficient as the sole measure of clinical outcome and does not capture other important endpoints such as complications, quality of life, or costs.
- Administrative data are plentiful but are typically less reliable than carefully collected clinical information. The quality of administrative databases can be improved by including laboratory information.
- Most outcome stratification models are developed empirically by performing univariate analysis of independent variables against a chosen outcome and are then refined using multivariate techniques.
- Model performance is assessed by measuring discrimination (typically by ROC-curve area) and calibration (typically by goodness-of-fit procedures).
- The SMR is created by dividing observed by expected mortality rates. Values less than 1.0, if statistically significant, suggest performance better than expected. SMR rankings can be problematic because of chance variation.
- The APACHE II through APACHE IV, the MPMs, and the SAPS are well-developed, prospectively validated models useful in adult general critical care units. The ICNARC and VA ICU models are also available. Customized models are useful in highly specialized ICUs or when evaluating population subsets such as pediatric, trauma, or cardiac surgery patients.
- Outcome predictions are intended for groups, not individuals. Mortality probability estimates range from 0 to 1.0, but an individual patient will either live or die. Mortality predictions also vary depending on when the data were geographically and temporally collected; results at ICU or hospital discharge do not necessarily correlate with 30-, 60- or 365-day results. Use of scoring systems to direct therapeutic choices has not been adequately studied, and risk-adjustment systems should never be the sole criteria for directing or withholding therapy in an individual patient.

References for this chapter can be found at expertconsult.com.

ANNOTATED REFERENCES

Harrison DA, Gareth JP, Carpenter JR, et al. A new risk prediction model for critical care: The Intensive Care National Audit & Research Centre (ICNARC) model. *Crit Care Med.* 2007;35:1091–1098.

The ICNARC model uses patient physiology in addition to age, diagnostic category, source of admission, and the use of CPR before admission. In a population of 216,626 patients from England, Wales, and Northern Ireland between 1995 and 2003, this model discriminated better (ROC area 0.86) than APACHE II, APACHE III, SAPS II, or MPM-II. This study offers further evidence that geographic variation occurs and that misleading SMR results may occur when models developed in one environment are applied to a new population.

Higgins TL, Teres D, Copes WS, et al. Assessing contemporary intensive care unit outcome: An updated mortality probability admission model (MPM_0-III). *Crit Care Med.* 2007;35:827–835.
MPM-III was developed on 124,855 patients admitted to 135 ICUs at 98 hospitals in the United States (94), Canada (3), and Brazil (1) between 2001 and 2004. It corrects the drift in calibration since MPM-II and adds terms for "full code" resuscitation status at admission and for the absence of any MPM-II risk factor except age to account for better-than-expected outcomes in otherwise healthy elderly patients. Discrimination by ROC is 0.82, and the model calibrates well. Subsequent publications have prospectively validated the model, examined patient subgroups, and updated the "Rapoport-Teres" resource utilization graph used by MPM and Project IMPACT.

Kramer AA, Higgins TL, Zimmerman JE. Comparing observed and predicted mortality among ICUs using different prognostic systems: Why do performance assessments differ? *Crit Care Med.* 2015;43:261–269.
Two widely used contemporary models (APACHE IVa and the National Quality Forum–endorsed ICOM modification of MPM) were evaluated in a common data set of 89,353 consecutive unselected ICU admissions from 2008 to 2013. SMR was assessed and compared for each of the 47 ICUs. Surprisingly, the two models agreed on the significance and direction of the SMR only 45% of the time. Differences were most pronounced in units with a high percentage of mechanically ventilated and/or severely ill patients. Four hospitals were assessed as having inferior performance using the NQF model but superior performance using APACHE. In addition, two more hospitals would have been stigmatized by NQF results while being acceptable using APACHE. This study highlights the risk inherent in stigmatizing hospitals when performance depends on the benchmarking system used.

Metnitz PG, Moreno RP, Almeida E, et al. SAPS 3—From evaluation of the patient to evaluation of the intensive care unit. Part 1: Objectives, methods and cohort description. *Intensive Care Med.* 2005;31:1336–1344.

Moreno RP, Metnitz PG, Almeida E, et al. SAPS 3—From evaluation of the patient to evaluation of the intensive care unit. Part 2: Development of a prognostic model for hospital mortality at ICU admission. *Intensive Care Med.* 2005;31:1345–1355.
The SAPS 3 study used an international population of 19,577 patients in 307 ICUs. Regional variation in outcomes occur, and SAPS 3 has customized admission equations for Australasia, Central/South America, Central/Western Europe, Eastern Europe, North Europe, Mediterranean countries, and North America. ROC area is 0.85 with satisfactory calibration.

Nathanson BH, Higgins TL. An introduction to statistical methods used in binary outcomes modeling. *Semin Cardiothorac Vasc Anesth.* 2008;12:153–166.
This report is for those who enjoy getting "under the hood" of risk-adjustment models.

Render ML, Deddens J, Freyberg R, et al. Veterans Affairs intensive care unit risk adjustment model: Validation, updating, recalibration. *Crit Care Med.* 2008;36:1031–1042.
In total, 36,420 consecutive ICU admissions in 1999–2000 and a second cohort of 81,964 cases in 2002–2004 were used to update the VA-ICU model. ROC areas were good. The VA-ICU population is overwhelmingly male (97.2%) and somewhat older. ROC area was 0.89, comparable to APACHE IV in this population, and better than MPM_{24}-II (ROC 0.84), SAPS III (ROC 0.86), or the SOFA score (ROC 0.81).

Seferian ED, Bekele A, Ognjen G, et al. Comparison of community and referral intensive care unit patients in a tertiary medical center: Evidence for referral bias in the critically ill. *Crit Care Med.* 2008;36:2779–2786.
Patients referred to the Mayo Clinic medical ICU between 1996 and 2004 were more severely ill, had higher mortality and longer length of stay, and were more likely to receive an active ICU intervention compared with local patients. When adjusted for severity of illness, mortality was as expected. Unadjusted differences were not seen in the surgical ICU, although hospital mortality rate was lower in referral surgical patients. Referral bias likely occurs because of differences in prior care or the transfer process that are not captured by risk adjustment. This bias has potential impact on clinical trials.

Sinuff T, Adhikari NKJ, Cook DJ, et al. Mortality predictions in the intensive care unit: Comparing physicians with scoring systems. *Crit Care Med.* 2006;34:878–885.
This analysis of observational studies (one using SAPS II, two using MPM-II, six using APACHE II, and three computer models) found that ICU physicians and objective models have moderate accuracy in the first 24 hours of ICU stay but that physicians better discriminate between survivors and nonsurvivors (physician ROC area 0.85 + 0.03 versus 0.63 + 0.06 for scoring systems). The conclusion that neither physicians nor scoring systems are sufficiently accurate to determine end-of-life decisions in the first 24 hours of ICU care is well supported by the data.

Timmers TK, Verhofstad MHJ, Moons KGM, et al. Intensive care performance: How should we monitor performance in the future? *World J Crit Care Med.* 2014;3:74–79.
Mortality is a limited outcome; health-related quality of life is another important benchmark to be followed after ICU or hospital discharge. Items that we do not routinely measure at present (both clinical and nonclinical) should be quantified and addressed by future systems.

Vincent JL, Opal SM, Marshall JC. Ten reasons why we should NOT use severity scores as entry criteria for clinical trials or in our treatment decisions. *Crit Care Med.* 2010;38:283–287.
Whereas the seemingly objective nature of scores make it tempting to apply their predictions to individuals, it is important to remember that these tools were designed for evaluating large groups of patients, not for individual prognosis or decision making. The authors point out that interobserver variability in score calculation, age bias, and issues with the starting time of critical care call into question the use of these scores for patient enrollment into clinical trials.

Zimmerman JE, Kramer AA. A history of outcome prediction in the ICU. *Curr Opin Crit Care.* 2014;20:550–556.
A firsthand account of how APACHE evolved between 1979 and the present. Key points about model complexity, advances in computer technology, government support, and risk adjustment in the public realm are considered.

Zimmerman JE, Kramer AA, McNair DS, et al. Acute Physiology and Chronic Health Evaluation (APACHE) IV: Hospital mortality assessment for today's critically ill patients. *Crit Care Med.* 2006;34:1297–1310.
APACHE was the first widely used prognostic scoring system and has been periodically updated over the past 30 years. The latest iteration was developed on 110,558 patients in 2002–2003. APACHE IV has very good discrimination (ROC area 0.88) and calibration and corrects the systematic overestimation of mortality that developed since publication of APACHE III.

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Long-Term Outcomes of Critical Illness

Florian B. Mayr and Sachin Yende

Despite a continuous increase in the incidence of critical illness syndromes such as sepsis and acute respiratory distress syndrome (ARDS), improvements in supportive care have resulted in improved survival over the past few decades.[1–4] For example, sepsis is estimated to affect between 30 and 50 million people each year worldwide.[5,6] Global sepsis mortality has declined from 30% in 1990 to 20% in 2017,[5] resulting in an increasing number of sepsis survivors with variable prognosis.[7,8] Half of patients recover, one-third die during the following year, and one-sixth have severe persistent impairments.[7] Impairments include development of an average of one to two new functional limitations; a threefold increase in prevalence of moderate to severe cognitive impairment; and a high prevalence of mental health problems, including anxiety, depression, or posttraumatic stress disorder, for which survivors will seek care from many types of clinicians (Table 166.1).[8–11] Current guidelines provide no recommendations on management for these complex patients after discharge, and there is a desperate need for improvement. According to an international survey of 1731 critical illness survivors, the majority reported dissatisfaction with or complete lack of support services after hospital discharge.[12]

Patients who survive their initial acute illness but consequently experience persistent organ failures necessitating prolonged intensive care meet the definition of chronic critical illness (CCI).[13,14] This illness is characterized by high hospitalization costs, frequent post–acute care use, and poor long-term survival. For example, a third of sepsis survivors are readmitted within 90 days, and rehospitalization after sepsis accounts for 12.2% of all US hospital readmissions and 14.5% of readmission costs.[15] The clinical and financial burden of CCI is expected to increase in the coming years because of both an aging population and improvement in short-term survival. In a population-based sample of five US states, we found that the prevalence of CCI based on a consensus definition has been increasing over time, with associated in-hospital costs exceeding $25 billion per year.[16] These findings underscore the importance of CCI to the field of critical care, particularly for healthcare policy and planning. Spending on CCI is likely to rise further as the population ages, because the prevalence of CCI increases dramatically with age.[16] The most common initial diagnoses that lead to CCI are acute respiratory failure requiring mechanical ventilation and sepsis. Hospital-acquired infections may contribute to mortality among hospitalized patients and to the burden of CCI.[17]

With this shift in critical illness epidemiology, traditional outcomes such as short-term mortality need to be complemented by patient-centered outcomes that capture long-term health-related quality of life (HRQoL), physical and mental functioning, time spent at home, hospital readmissions, and morbidity and mortality (Fig. 166.1).

In this chapter, we review recent advances in our understanding of long-term outcomes after critical illness. Most literature focuses on long-term outcomes after ARDS and sepsis. We describe the epidemiology, risk factors, clinical manifestations, management, and outcomes for each domain of post–intensive care syndrome (PICS).

COGNITIVE IMPAIRMENTS AFTER CRITICAL ILLNESS

Critical illness frequently results in new cognitive impairment, including deficits in memory, attention, and concentration. The reported incidence has been highly variable depending on study population and trial size, ranging from 4% to 62%.[18] Cognitive impairment after intensive care unit (ICU) admission is also taxing to patients and their families and carries an enormous societal cost estimated at $18 billion per year.[19]

Risk factors for long-term cognitive impairment, particularly preventable ones, are not well understood. A complicating factor is the uncertainty of whether critical illness and/or its treatment is the cause of the observed neurocognitive impairments or if it worsens preexisting subclinical disease. A prospective cohort study in elderly adults who had no known cognitive dysfunction at baseline showed that acute care or ICU hospitalization resulted in a greater cognitive decline and incident dementia compared with individuals who did not require hospitalization.[20] Similarly, Pandharipande and colleagues reported new severe cognitive deficits affecting memory, attention, processing speed, and executive function in a broad population of 328 ICU survivors that were detectable at 3 and 12 months after critical illness.[21] The etiology of cognitive impairments after critical illness is likely multifactorial and results from various factors that interact dynamically with preexisting and acute illness variables to produce adverse outcomes. Acute illness severity alone does not explain the cognitive impairments experienced by ICU survivors. Although current data do not suggest a clear association between age, acute illness severity scores, cumulative doses of analgesia and sedation, hypoxia, hypotension, hyperglycemia, and inflammation with adverse neurologic sequelae, the duration and severity of acute delirium have emerged as the strongest predictors of adverse cognitive outcomes in several recent studies.

In the study by Pandharipande and colleagues, longer duration of delirium was independently associated with worse cognitive performance at 3 and 12 months in tests of global cognition and executive function.[21] Similar findings were reported in a small prospective study of 77 patients with ARDS who had in-person cognitive testing 3 and 12 months after ICU discharge. The duration of delirium was an independent risk factor for cognitive decline at both time points even after adjusting for preexisting cognitive impairment, age, severity of illness, level of education, severity of sepsis, and cumulative exposure to sedatives.[20] Interventions to prevent or shorten delirium in critically ill patients are therefore much needed and center around promoting and improving the quality of sleep.[22] Ziprasidone and haloperidol, two drugs commonly used to treat ICU delirium, neither increased the number of days alive without coma or delirium nor reduced 90-day

TABLE 166.1 Common Sequelae in Survivors of Critical Illness

Neurocognition	Behavioral	Neuromuscular	Immune System	Caregiver & Family
Cognitive dysfunction	Depression	Polymyopathy	Immunosuppression	Caregiver burden/burnout
Attention deficits	Anxiety	Polyneuropathy	Inflammation	PTSD
Impaired executive function	Posttraumatic stress disorder (PTSD)	Chronic pain	Recurrent infection	Anxiety
Chronic fatigue	Insomnia		Exacerbation of chronic disease	Depression

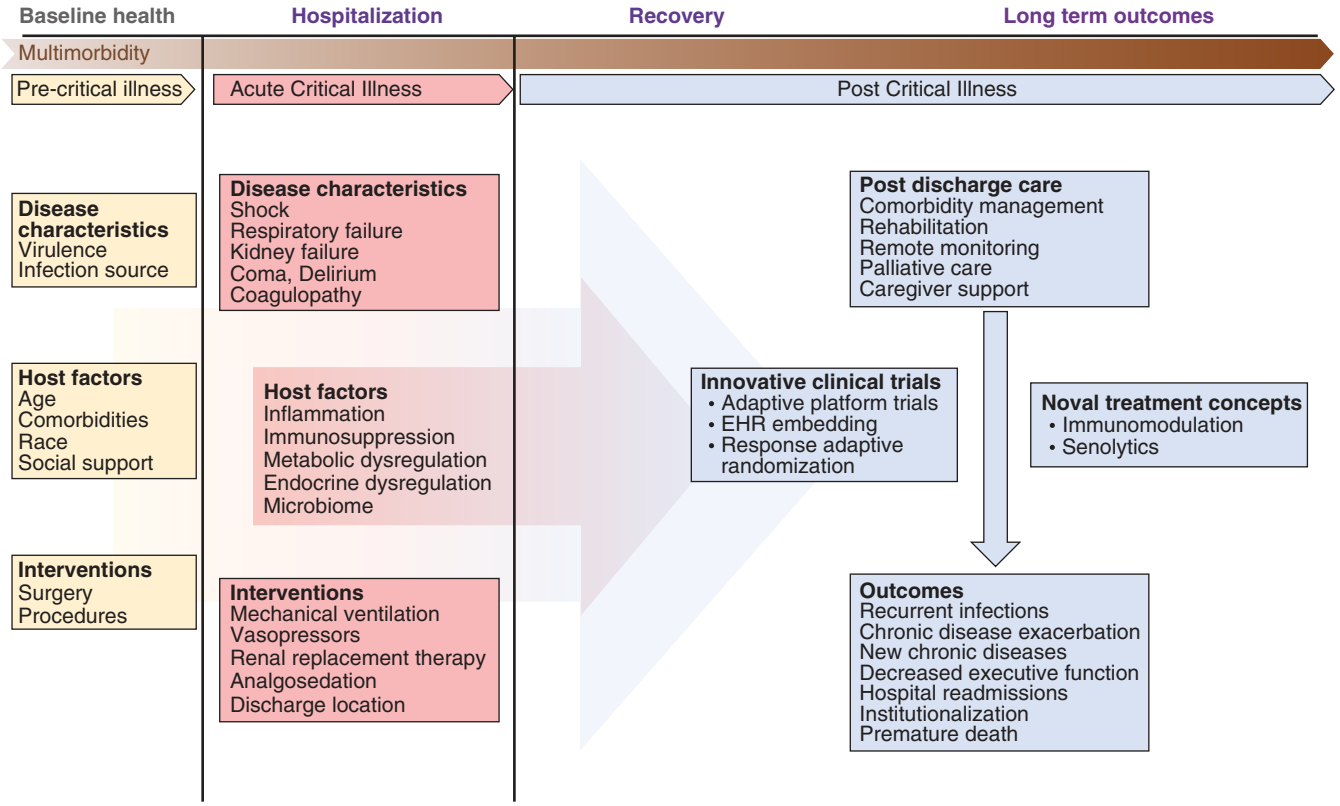

Fig. 166.1 Conceptual Model of Factors Contributing to Long-Term Outcomes After Critical Illness.
EHR, Electronic health record.

mortality, time to freedom from mechanical ventilation, and time to ICU or hospital discharge in a large multicenter placebo-controlled trial.[23] Nocturnal administration of low-dose dexmedetomidine (average dose 0.36 μg/kg/h) was recently reported to prevent delirium, reduce days spent with coma, and have an opiate-sparing effect in a randomized placebo-controlled trial in critically ill adults.[24] Interestingly, dexmedetomidine did not improve patient-reported sleep quality. An earlier systematic review also suggested potential for dexmedetomidine and quetiapine to prevent ICU delirium, but neither drug influenced long-term outcomes.[25]

Early identification of cognitive impairment should in theory expedite appropriate evaluations and treatment. Evaluation for cognitive dysfunction in the critical care setting must be brief, easy to administer, and widely applicable. Currently available tests such as the modified mini-mental state examination (MMSE) and Montreal Cognitive Assessment (MoCA), however, cannot be used to predict long-term cognitive dysfunction.[26,27] Evolving research suggests that patients who experience critical illness–induced delirium and persistent cognitive dysfunction may have a variety of abnormal findings on neuroimaging, including brain atrophy; leukoencephalopathy; and neuronal loss in the insula, frontal lobes, and thalamus.[28] In addition, a multicenter prospective cohort study in 321 critically ill patients showed generalized slowing on routine clinical electroencephalography (EEG) correlated with delirium severity, length of hospitalization, functional outcomes, and mortality and may be a promising biomarker to identify patients at high risk for adverse outcomes early during hospitalization.[29]

Integrated approaches specifically geared toward the management of mechanically ventilated patients have proven useful, with the most widely applied being the ABCDEF bundle.[30] Initially focusing on daily sedation interruption and spontaneous breathing trials, this bundle also emphasizes the importance of delirium management, delirium prevention, early mobility, and family engagement.[30] Despite never being formally tested in clinical trials, clinical practice suggests that the ABCDEF bundle is safe and may improve delirium outcomes in real-world settings.[31,32] These findings were confirmed in a recent prospective multicenter cohort of over 15,000 adults from the ICU Liberation Collaborative, in which use of the ABCDEF bundle was

associated with a reduced incidence of delirium along with improvements in other patient-centered outcomes.[33]

PSYCHIATRIC SEQUELAE OF CRITICAL ILLNESS

Psychiatric disorders, including depression, anxiety, and posttraumatic stress disorder (PTSD), are common among critical illness survivors. For instance, in a recent systematic review, Rabiee and colleagues reported that approximately 30% of ICU survivors had clinically significant depression.[34] Early post-ICU depressive symptoms were a strong risk factor for subsequent depressive symptoms, and post-ICU depressive symptoms were associated with substantially lower HRQoL. Patients exposed to mechanical ventilation and longer ICU lengths of stay are at higher risk for developing a new diagnosis of "mental illness" compared with noncritically ill hospitalized patients. Further study is necessary to better understand patient predisposition, illness, and treatment-specific determinants of affective morbidity and appropriate tools for diagnosis and monitoring. Another important and understudied area is the frequency of suicide after critical illness, particularly given the increasing prevalence with age and burden of chronic illness.[35–37]

Several studies have examined the relationship between critical illness and the development of PTSD. Schelling and colleagues were the first to introduce the concept of PTSD resulting from critical illness and traumatic experiences in the ICU.[38,39] Among their cohort of 80 long-term ARDS survivors, almost one-third reported impaired memory, nightmares, anxiety, and sleeping difficulties after ICU discharge, with a PTSD prevalence rate of 28%. A recent meta-analysis of prevalence, risk factors, and prevention/treatment strategies for PTSD symptoms in critical illness survivors reported clinically important PTSD symptoms in approximately one-fifth of critical illness survivors at 1-year follow-up.[40] Patients with underlying psychiatric comorbidities, benzodiazepine use, or early memories of frightening ICU experiences had the highest prevalence of PTSD. A randomized controlled trial in 35 French ICUs studied the use of an ICU diary filled by caregivers and family members on PTSD symptoms, anxiety, and depression in patients and family members at 3 months after ICU discharge. In this study, the overall prevalence of significant PTSD symptoms was 29.9% among ICU survivors and was not reduced by an ICU diary.[41] Equally disappointing, a nurse-led complex psychological intervention that was initiated in the ICU did not reduce the prevalence of self-reported PTSD symptoms at 6 months.[42]

CRITICAL ILLNESS–ASSOCIATED NEUROMUSCULAR DYSFUNCTION

ICU-acquired weakness is common in patients with ARDS and other complex critical illness. Regardless of disease process, muscles and nerves are injured, resulting in prolonged mechanical ventilation and poor functional outcomes. Previous research has highlighted the concept of a continuum of weakness that begins with muscle injury documented within hours of mechanical ventilation that may persist with incomplete recovery for years after ICU discharge.[43] Muscle weakness and impaired function constitute an important morbidity of severe critical illness.[44] In a recent prospective cohort study that used daily point-of-care ultrasound to measure diaphragm thickness in mechanically ventilated patients, almost 50% of patients had a 10% reduction in diaphragm thickness by ICU day 4. Diaphragm atrophy was associated with prolonged mechanical ventilation and ICU length of stay. Interestingly, development of increased diaphragm thickness as a marker of excessive inspiratory effort was also associated with prolonged mechanical ventilation.[45]

Critical Illness Polyneuropathy

Critical illness polyneuropathy (CIP) primarily manifests itself as a mixed sensorimotor neuropathy. CIP is quite common in patients with systemic inflammatory response syndrome and sepsis, with an occurrence of 70%–100% of patients with a longer ICU stay.[46] It affects limb and respiratory muscles, whereas facial muscles are usually spared.[46] Limb involvement is symmetric and most prominent in the proximal muscle groups of the lower extremities. Detection of the true incidence of CIP is complicated by lack of consensus on surveillance, timing, and nature and limitations of testing because of patient sedation or poor cooperation, formal definition, and diagnostic criteria.[47] Weakness may initially be absent or difficult to detect clinically in these patients, but subsequent electromyography testing will demonstrate abnormalities showing an initial primary axonal degeneration of the motor neurons, followed by the sensory neural fibers, and this coincides with acute and chronic changes of denervation noted on muscle biopsies in affected patients.[48]

In sepsis, the pathogenesis of CIP is linked to a perturbation in the microcirculation, with resultant axonal injury and degeneration. There is also evidence for a disruption of nerve action potential, which may be reversible over the course of the disease.[49] Other risk factors associated with the development of CIP include hyperglycemia, and tight glycemic control has been shown to reduce the incidence of CIP in critically ill patients.[50] The exact pathophysiologic link between glucose control and neuroprotection remains unclear but may involve preservation of mitochondrial functioning, calcium homeostasis, or modulation of nitric oxide production.[51–53] In contrast to earlier associations between neuromuscular dysfunction and use of neuromuscular blockers, subsequent research has not been able to corroborate this previous association.[54,55] Data on the association between glucocorticoid use and weakness remain controversial; however, a national multicenter prospective trial in acute lung injury survivors reported a significant association between mean daily corticosteroid dose with impairments in physical outcomes after 1 year.[56]

Critical Illness Myopathy

The reported incidence of critical illness myopathy (CIM) varies between 48% and 96% in prospective studies that have included muscle biopsy as part of their diagnostic evaluation.[47] Pathologically, CIM is characterized by a diffuse, nonnecrotizing myopathy associated with fatty degeneration of muscle fibers, fiber atrophy, and fibrosis.[43] This has been described in patients with sepsis and in those treated with corticosteroids and neuromuscular blockers. Patients clinically appear weak and paretic and are difficult to wean from the ventilator. They may be indistinguishable from patients with CIP. Muscle biopsy allows differentiation among these lesions.[43,47]

The pathophysiology of CIM entails catabolism, inflammation, and derangement of membrane excitability. Protein catabolism and an increase in urinary nitrogen loss are observed in CIM.[57] Muscle biopsies in affected patients show low glutamine, protein, and DNA levels. There is evidence for the upregulation of the calpain, caspase-3, and ubiquitin proteolytic pathways in concert with an increase in apoptosis,[57–59] but mitochondrial dysfunction and oxidative stress likely do not play a significant role.[60]

Early Mobility and Rehabilitation

The results of studies examining the effects of early mobilization and physical rehabilitation in ICU patients do not suggest any improvement in short- and long-term outcomes. Most recently, a single-center randomized controlled study in 312 mechanically ventilated

adults that evaluated early in-bed cycling and electrical stimulation of the quadriceps muscles in addition to standard early rehabilitation did not result in greater muscle strength at ICU discharge, more ventilator-free days, better walking capability, or better HRQoL at 6 months.[61] The heterogeneity of critically ill populations, inability to risk-stratify patients because of the lack of detailed understanding of underlying pathophysiology, and resulting lack of standardization are potential explanations for the negative results to date.[62]

CRITICAL ILLNESS–ASSOCIATED MORBIDITY AND PERSISTENT IMMUNE DYSFUNCTION

Critical illness survivors face a substantially elevated mortality after discharge from the hospital, a problem best documented for sepsis.[63,64] In addition, most severe sepsis survivors are either diagnosed with a new health condition or have worsening of existing health conditions, such as cardiac disease (including heart failure), chronic kidney disease, and chronic pulmonary disease, among others.[7]

More recent work suggests that patients with CCI experience concurrent immunosuppression and inflammation that are associated with persistent protein catabolism. Despite early enteral nutrition, there is a tremendous loss of lean body mass with proportional functional decline and poor wound healing. An estimated 30%–50% of patients with CCI progress into PICS.[65] Clinically, patients with PICS have recurrent nosocomial infections and poor wound healing and are often discharged to long-term acute care facilities where they experience recurrent infections, hospital readmissions, failure to rehabilitate, and an indolent death.

Acute sepsis is characterized by concurrent inflammation and immunosuppression, which persists in two-thirds of survivors and has been associated with an increased risk of hospital readmission and cardiovascular death, including atrial fibrillation, myocardial infarction, stroke, need for coronary revascularization, diabetes, and new-onset seizures.[66–70] Indeed, severe sepsis is a complex disease process with a plethora of potential mechanisms to explain how different aspects of sepsis and the short-term care of patients with sepsis may drive late sequelae. Some of these pathways may be more relevant to sepsis (i.e., immunosuppression), whereas others may be shared with other acute illnesses (i.e., inflammation). The recognition of persistent immunosuppression in many sepsis survivors has resulted in exciting and novel therapeutic approaches.[71–73] Several early clinical trials have demonstrated the safety and efficacy of immunomodulatory drugs such as interleukin-7 and immune checkpoint inhibitors in reversing biomarkers of immunodeficiency.[74–76] Whether these immunomodulatory drugs modify clinical disease trajectories and improve clinical outcomes is uncertain and an area of active research.

QUALITY OF LIFE

Each of the outcomes described earlier may adversely affect the quality of life after critical illness.[77] Approximately a third of sepsis survivors have significant impairments in various domains of quality of life 6 months after hospital discharge.[77] The impairments in cognition and physical function described earlier may persist, leading to problems in mobility and performing activities of daily living and lasting disability. Furthermore, although many sepsis survivors return home, approximately one-third require additional help at home or are in a skilled nursing facility, acute care hospital, or rehabilitation facility.[7]

CAREGIVER AND FAMILY BURDEN IN CRITICAL ILLNESS

Caregiver outcomes and their interaction with ICU survivors have gained importance in understanding the effect of critical illness on the family unit.[78] There is a considerable body of work evaluating these interactions in other medical conditions, such as stroke or cancer.[79,80] These data show that caregivers who are challenged in their caregiving contribute to poor outcomes and threaten home care for survivors. Studies indicate that most ICU survivors who received long-term mechanical ventilation required the assistance of a family caregiver 1 year after their critical illness.[81] Providing such care may result in PTSD, emotional distress, depression, anxiety, and reduced HRQoL.[22,82,83] In addition, caregivers experience significant burden because of a patient's physical and psychological dysfunction and lifestyle disruption associated with the challenges of managing complex care at home.

MODELS OF AFTERCARE FOR CRITICAL ILLNESS SURVIVORS

Most ICU survivors are discharged home and return to their primary care physicians and subspecialists for aftercare. Alternative care models such as ICU survivor clinics are rapidly expanding, where integrated care is provided at a single location focused on treating sequelae of critical illness.[84–86] Most of these programs are associated with large academic medical centers, and wide variation in staffing exists. Some clinics are led by a single discipline; others embrace a multidisciplinary team approach, including health and social services to address the frequent socioeconomic problems that patients and their caregivers experience during recovery from critical illness. However, clinic-based care may not be accessible to debilitated patients or those with poor social support. Innovative aftercare delivery models are currently being explored to address these barriers, including the use of mobile ICU recovery programs and of telemedicine services.[87,88] In addition, the importance of peer support has been recognized through which survivors and their families can facilitate their own recovery and improve their quality of life by relating to others with shared experiences. Several different models of peer support are currently being developed and piloted to help patients and families recover and grow in the postcritical care setting.[89]

PALLIATIVE CARE FOR CRITICAL ILLNESS SURVIVORS

One-third of older adult ICU survivors are discharged to post–acute care facilities, nearly half are rehospitalized, and 25%–65% die within the following year.[7] Baldwin and colleagues demonstrated in their single-center analysis that 90% of elderly ICU survivors that were discharged to a post–acute care facility had at least one potential palliative care need, but less than 3% of patients had received a palliative care consultation during their hospitalization. Since then, larger multicenter studies have confirmed that palliative care services are underused in both medical and surgical patients who are seriously ill and at high risk of poor long-term outcomes.[90–93] Palliative care focuses on providing relief from pain and stress to patients with serious illness and is often provided simultaneously with curative or life-sustaining treatments.[94] Palliative care also seeks to align treatment plans with patients' goals and therefore may facilitate transitions to hospice in older ICU survivors who often have high end-of-life healthcare resource use. Indeed, recent studies have demonstrated

that palliative care can have a meaningful effect on patients' quality of life and end-of-life care, reduce end-of-life use of acute care resources, and prolong survival.[91,95,96]

FUTURE DIRECTIONS

The findings that a large proportion of patients who survive critical illness have poor long-term outcomes, which may be attributed to a combination of CCI and preexisting poor baseline health, have implications for endpoints of future clinical trials. Traditionally, primary endpoints included only mortality. However, a comprehensive evaluation of new therapies should include assessment of long-term morbidity and mortality. Because such an assessment is time-consuming and often cost-prohibitive, particularly given decreasing federal funding for clinical trials,[97] short-term surrogate endpoints as proxies for long-term patient-centered outcomes are increasingly important in the early evaluation of novel therapeutic interventions.[98] With increasing insight into the pathophysiology of CCI,[65,66,99] future studies that combine big data, artificial intelligence, and wearable health technology to augment medical decision making,[100,101] in addition to refined approaches to clinical trial design,[102,103] are necessary to maximize chances of identifying successful novel interventions for distinct subgroups of critical illness survivors.

CONCLUSION

With the growth of intensive care and concurrent improvements in supportive care, patients are more likely to survive their initial episode of critical illness. Critical illness survivors subsequently face a wide array of problems, including developing functional deficits, neuromuscular and neuropsychological morbidity, and worsening of existing chronic diseases or development of new chronic diseases, which often result in permanent functional impairment. This results in ongoing high healthcare use, frequent hospitalizations, and substantial strain on families and caregivers. Despite exciting advances in the last few years, future research is needed to better understand the pathophysiology of CCI, to develop innovative ways to engage with patients and their caregivers to optimize the delivery of post-ICU care, and to improve patient selection and clinical trial design in a way that maximizes our chances of identifying interventions that will improve patient-centered outcomes.

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KEY POINTS

- Despite a continuous increase in the incidence of critical illness syndromes such as sepsis and ARDS, improvements in supportive care have resulted in improved survival over the past few decades. Current guidelines provide few recommendations on how to manage these complex patients after hospital discharge.
- CCI is associated with in-hospital costs of >$25 billion per year, which underscores its importance to the field of critical care, particularly for healthcare policy and planning.
- Most ICU survivors are discharged home and return to their primary care physicians and subspecialists for aftercare. Innovative aftercare delivery models are currently being explored to reduce barriers to high-quality post-discharge care, including the use of mobile ICU recovery programs and telemedicine services.
- The recognition of persistent immunosuppression in many critical illness survivors has resulted in exciting and novel therapeutic approaches. Several early clinical trials have demonstrated safety and efficacy of immunomodulatory drugs such as interleukin-7 and immune checkpoint inhibitors on reversing biomarkers of immunodeficiency.
- Future studies that combine big data, artificial intelligence, and wearable health technology to augment medical decision making, in addition to refined approaches to clinical trial design, are necessary to maximize chances of identifying successful novel interventions for distinct subgroups of critical illness survivors.

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This retrospective cohort study identified a high burden of unmet palliative care needs among elderly ICU survivors, suggesting that the hospital postcritical acute care period should be targeted for improving access to palliative care services.

Pandharipande P, Girard T, Jackson J, et al. Long-term cognitive impairment after critical illness. *N Engl J Med*. 369:1306–1316.
This seminal cohort study studied the association between delirium and post-discharge cognitive function in patients with respiratory failure and shock and demonstrated that a longer duration of delirium was associated with worse global cognition and executive function at 3 and 12 months.

Prescott HC, Angus DC. Enhancing recovery from sepsis: A review. *JAMA*. 2018;319:62–75.
This review article provides an excellent review of the epidemiology, pathophysiology, clinical sequelae, and management strategies for patients discharged after hospitalization for sepsis.

Yende S, Kellum JA, Talisa VB, et al. Long-term host immune response trajectories among hospitalized patients with sepsis. *JAMA Netw Open*. 2019;2:e198686.
This prospective cohort study demonstrated a high prevalence of persistent inflammation and immunosuppression in sepsis survivors for up to 1 year after hospital discharge. Studies like these provide a compelling rationale to study novel immunomodulatory treatments in subgroups of critical illness survivors.

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Early Ambulation in the ICU

Erika L. Brinson, Angela K.M. Lipshutz, and Michael A. Gropper

Bedrest has historically been prescribed as an adjunct to the treatment of acute illness and to rehabilitation after surgery. Even as physicians and researchers began to realize the "evil sequelae of complete bed rest"[1] in both medical and surgical patients, this therapy remained commonplace in the intensive care unit (ICU). Indeed, healthcare providers in the ICU have traditionally focused their attention on normalizing the physiologic derangements that threaten their patients' survival. However, therapeutic advances and improvements in the management of critically ill patients have improved the outcomes in this patient population.[2–4] As survival from critical illness has improved, the long-term complications and associated therapies have become more apparent. A large proportion of these patients experience long-term cognitive, psychological, and physical disability, with less than half of critical illness survivors returning to their prior functional status 1 year after discharge.[5–8] Early mobilization and ambulation of critically ill patients are feasible, safe, and cost-effective interventions that improve physical, functional, and neuropsychiatric outcomes.[9–18]

THE PHYSIOLOGY OF BEDREST

Bedrest has, at one time or another, been promoted as therapy for almost all ailments. Hippocrates suggested that all pain could be relieved by bedrest.[19] However, as early as the 1940s, it was recommended that "the physician . . . always consider complete bed rest as a highly unphysiological and hazardous form of therapy."[1] Nonetheless, it was not until recently that the medical community began to acknowledge the ill effects of complete inactivity and immobility during critical illness.

Inactivity and immobility have profound effects on skeletal muscle. Disuse leads to reduced protein synthesis, accelerated proteolysis, and increased apoptosis, ultimately resulting in a catabolic state, atrophy, and physical weakness.[20,21] In a study of young, healthy volunteers, 28 days of bedrest resulted in a 0.4 ± 0.1 kg loss of lean leg mass and a 22.9 ± 3.5% reduction in leg extension strength.[22] When healthy volunteers were subjected to 28 days of bedrest and hydrocortisone to achieve plasma cortisol levels mimicking trauma or critical illness, leg extension strength decreased even further (28.4 ± 4.4%, $P = .012$), and the loss of lean leg mass was increased threefold compared with bedrest alone (1.4 ± 0.1 kg, $P = .004$).[23] Therefore it is apparent that both immobility and the systemic effects of critical illness contribute to the development of weakness in ICU patients.

ICU-ACQUIRED WEAKNESS

Neuromuscular weakness is a common complication of critical illness. Approximately half of ICU patients with sepsis, multiorgan failure, or prolonged mechanical ventilation have electrophysiologic evidence of neuromuscular dysfunction.[24] In patients with both sepsis and multiorgan failure, the incidence can approach 100%.[25] Electrophysiologic (EP) testing can detect weakness as early as 18–24 hours into the onset of critical illness.[25,26] Clinical evidence of weakness is present in a smaller, but significant, portion of ICU patients. The duration of bedrest is associated with worsening muscle weakness. Muscle strength has been estimated to decrease by 3%–11% with each additional day.[27,28] Many ICU survivors continue to have significantly impaired physical function and decreased quality of life for years after their hospitalization.[8,27]

One of the many causes of generalized weakness in the critically ill population is intensive care unit–acquired weakness (ICUAW), a clinical syndrome of acquired neuromuscular dysfunction with no identifiable causative factors other than critical illness and its treatment.[29] ICUAW is an umbrella term for different pathophysiologic entities, including muscle atrophy, critical illness polyneuropathy (CIP), critical illness myopathy (CIM), or a combination of polyneuropathy and myopathy called *critical illness neuromyopathy* (CINM).[28,30] The pathophysiology of ICUAW is complex and not well-understood; it includes the sequelae of bedrest and the effects of critical illness–induced cytokine production such as impaired microcirculation, metabolic derangements, increased protein catabolism, and changes in nerve and muscle membrane excitability.[31]

Diagnosis

The lack of a gold-standard diagnostic test has made it difficult to study ICUAW. Diagnosis of the pathophysiologic entities of CIP, CIM, and CINM requires advanced and/or invasive testing; EP evidence of axonal polyneuropathy confirms the diagnosis of CIP, whereas either EP and/or histologic findings of myopathy are used to diagnose CIM.[32] The Medical Research Council (MRC) muscle strength score is one of the most commonly used clinical evaluations of ICUAW.[29] It involves grading the strength of different muscle groups in each extremity on a scale from 0 to 5. The MRC sumscore, initially developed to assess muscle strength in patients with Guillain-Barré syndrome, involves testing strength in six different muscle groups bilaterally and adding these 12 scores together.[33] The result can range from 0 (paralysis) to 60 (normal strength), and the diagnosis of ICUAW requires a score less than 48. The MRC sumscore is nonspecific for ICUAW; therefore other causes of weakness in critical illness must be excluded. In addition, the MRC sumscore has many limitations in the critically ill, most notably the need for an awake, cooperative patient who is able to maximally contract all extremities.[29]

Routinely performing EP studies and muscle biopsies on all at-risk patients presents an obvious challenge, and using manual strength testing requires active participation. Developing a single diagnostic test that could be used even on comatose patients would facilitate

uniformity in study design and help determine the incidence, risk factors, and outcomes of ICUAW. Limited nerve conduction studies (NCS) and quantitative neuromuscular ultrasound have both been evaluated, and limited NCS in particular shows promise as a sole diagnostic tool. Peripheral muscle ultrasound may be able to detect muscle weakness and assist with early diagnosis, but further studies are needed to help standardize this technique.[34] Because of the current lack of an effective therapeutic option, making the early diagnosis of ICUAW does not affect outcomes, and as such, routine use of EP studies or quantitative muscle ultrasound in the ICU has not become standard practice.[30]

Risk Factors

A number of risk factors have been implicated in the development of ICUAW. Some of the earliest and most frequently identified factors are related to severity of illness and include the systemic inflammatory response syndrome, sepsis, and multiorgan failure.[28,30,35–42] The relationship between ICUAW and other factors, such as age, gender, corticosteroids, hyperglycemia, aminoglycosides, or neuromuscular blocking agents, is inconsistent.[4,24,27,28,42–45] Few, if any, studies have examined whether prehospital factors such as frailty or poor functional status are associated with developing ICUAW.[30] The presence of multiorgan failure as one of the most consistently associated risks lends support to the hypothesis that ICUAW may be another manifestation of multiple organ dysfunction syndrome (MODS).[28,30,37–40]

Implications

ICUAW increases the duration of mechanical ventilation, ICU and hospital lengths of stay (LOSs), healthcare–related costs, and mortality.[24,46–48] In addition, ICUAW is associated with significant long-term sequelae. As treatment of critical illness has improved, many more patients are surviving their acute illness but continue to suffer serious long-term effects, a phenomenon called *post–intensive care syndrome* (PICS).[49] PICS includes new or worsened impairments in many areas that affect quality of life, including physical, mental, and social health.[50] ICUAW is an important contributor to PICS.[49] Patients with respiratory failure requiring mechanical ventilation who were living independently before ICU admission rarely return to this level of functioning at 6-month follow-up.[51] Survivors of acute respiratory distress syndrome report poor functional status at 1 year after discharge despite normalization of their pulmonary function tests. Only 49% of such previously employed patients are able to return to work within 1 year of their critical illness as a result of muscle loss, weakness, and fatigue.[7] Five years after ICU discharge, 100% of survivors reported subjective weakness and decreased exercise capacity compared with their status before ICU admission.[8] Similarly, survivors of severe sepsis with no functional limitations before ICU admission developed significant limitations in their ability to perform activities of daily living and continued to develop functional limitations at a more rapid rate after hospital discharge.[5]

Prevention

Despite the serious long-term consequences of ICUAW, there have been few investigations aimed at prevention.[31,52] Because longer duration of bedrest is associated with increased severity and duration of ICUAW, early mobilization and ambulation have been suggested as possible interventions to prevent the weakness and functional decline associated with critical illness.[27,31] Studies assessing the amount of physical activity performed by patients in the ICU using actigraphy have demonstrated that patients are "profoundly inactive," suggesting there is significant room for improvement.[53] Decreasing the level of sedation may be one step to help facilitate this goal.[40] Minimizing sedation as much as possible offers a host of benefits,[54] including improving a patient's ability to participate in rehabilitation.

Neuromuscular electrical stimulation (NMES), whole-body vibration, and passive tilting have also been investigated as preventive measures that could be used with even heavily sedated or comatose patients, but the results thus far have been variable, and there are not enough data to recommend widespread use.[55–61] Passive movement in particular does not appear to produce the intensity needed to constitute an effective early rehabilitation intervention.[62]

In addition to mobilization and other attempts at neuromuscular stimulation, a small number of randomized controlled trials (RCTs) have evaluated interventions aimed at reducing or avoiding other possible risk factors of ICUAW.[40] Two older studies showed that intensive insulin therapy (IIT) may reduce ICUAW,[44,63] but because IIT is associated with increased risk of severe hypoglycemia and death, this approach is not recommended.[64] Corticosteroids have also been trialed, but have not been shown to reduce (and may even increase) the risk of ICUAW.[65] Attempts at improving nutritional support have also been unsuccessful in decreasing muscle wasting.[66]

EARLY MOBILIZATION AND AMBULATION IN THE ICU

Safety and Feasibility

Multiple studies have confirmed the safety and feasibility of physical therapy in the medical ICU population. Morris and colleagues performed a prospective cohort study of 330 patients in a university-based medical ICU and showed that an ICU mobility team was able to initiate an early mobilization protocol within 48 hours of mechanical ventilation, without observing any adverse events or accruing increased cost.[67] Similarly, in a study by Pohlman and colleagues, patients were successfully mobilized as early as 1 day after the initiation of mechanical ventilation.[9] Physical therapy was successfully provided on 90% of medical ICU days during mechanical ventilation, despite a potential barrier to mobilization (e.g., acute lung injury, administration of vasoactive medications, delirium, renal replacement therapy, or obesity) being present at 89% of the sessions. Minor adverse events, such as oxygen desaturation, increased heart rate, agitation, or ventilator dyssynchrony, occurred in 16% of sessions, but required cessation in only 4%. No unplanned extubations occurred. A prospective observational study of 1110 medical ICU patients, in which 5267 physical therapy sessions were conducted on 4580 patient days, revealed a physiologic abnormality or potential safety event in only 0.6% of sessions.[12] Only four (0.1%) of these occurrences required additional treatment or increased cost, and LOS was not increased.

A recent systematic review of safety data from 48 studies of early mobilization showed an incidence of 2.6% for potential patient safety events and that events requiring intervention were even more rare (0.6%).[68] The authors point out that adverse events are quite common in the ICU, even in the absence of mobilization. A quality improvement study by de Jong and colleagues found an adverse event frequency of more than 37% during routine morning turning of patients in a medical-surgical ICU.[69]

Furthermore, ICU rehabilitation programs aimed at reducing the time from ICU admission to active physical therapy are both feasible and sustainable in the long term. One RCT demonstrated that the introduction of a structured program led to earlier mobilization in sicker patients, who then achieved higher levels of mobility by time of discharge from the ICU.[70] Another RCT evaluated the effect of a rehabilitation program in a medical ICU and showed a sustained decrease in time to mobilization over a 5-year period.[71]

Some centers may not have the necessary staff or equipment to routinely ambulate patients who are mechanically ventilated. In these settings, or as an adjunct to other techniques, methods of early mobilization that can be performed in bed, such as cycle ergometry, are feasible.[58,72,73]

Fewer studies have evaluated the safety and feasibility of early mobilization and ambulation in surgical ICU patients, where issues such as wound healing, fractures, weight-bearing limitations, and incisional pain must be considered. A review of the evidence for early mobilization in critically ill trauma patients concluded that there is a lack of evidence in this population, but outlined injury-specific guidelines.[74] In a retrospective study of early mobilization in a trauma and burn ICU, Clark and colleagues reported no adverse events with physical therapy.[75] A prospective observational study of early mobilization in a surgical ICU showed that early mobilization can occur safely as early as ICU day 1,[76] and more recently, a multicenter RCT of 200 surgical ICU patients reported no serious adverse events with early mobilization.[77] Another small study showed intensive early rehabilitation was safe and feasible after liver transplantation.[78]

Early mobilization also appears to be safe in the neuro intensive care unit (neuro-ICU) populations.[79] The implementation of a comprehensive mobility initiative in a neuro-ICU resulted in a 300% increase in mobility among patients, with no significant adverse events, such as falls or inadvertent line disconnections.[80] Patients with a Glasgow Coma Scale of 8 or less can safely undergo early mobilization without incurring additional harm and are more likely to achieve functional independence at hospital discharge.[81] Patients with external ventricular drains (EVDs) can also safely be mobilized.[82,83] Case reports suggest that even patients with left ventricular assist devices[84] and those on extracorporeal membrane oxygenation (ECMO)[85–88] can safely participate in physical therapy programs. At our institution we routinely ambulate patients on ECMO and other extracorporeal life support systems.

One commonly cited barrier to early mobilization and ambulation is the femoral catheter. However these, too, need not be a barrier to safe physical rehabilitation. In a cohort of 239 patients with femoral venous, arterial, and hemodialysis catheters, 101 patients received physical therapy interventions for a total of 253 sessions over 210 ICU days.[89] The highest daily activity level was standing or walking, which occurred on 23% of days, and no adverse events were reported. However, only six patients had femoral hemodialysis catheters, and none of these patients achieved a level of standing or walking. Another cohort of 77 patients with 92 femoral catheters underwent a total of 210 physical therapy sessions with 630 mobility activities and similarly encountered no adverse events.[90] However, ambulation accounted for less than 10% of mobility activities, and it is unclear if any patients with hemodialysis catheters stood or walked. A more recent study of patients on continuous renal replacement therapy included only 4 physical therapy sessions with a femoral hemodialysis catheter in place; although there were no significant complications during these sessions, the authors concluded that the data are insufficient to draw conclusions regarding safety.[91] Based on these studies, femoral catheters need not be viewed as prohibiting mobilization, but caution must be taken with femoral hemodialysis catheters until there is more convincing evidence of safety. At our institution, we cautiously mobilize even patients with femoral venoarterial ECMO cannulae, with great care taken to minimize movement of the leg at the hip joint (Fig. 167.1).

Fig. 167.1 Patient Awaiting Lung Transplant Mobilizing While on Femoral Venoarterial extracorporeal membrane oxygenation (ECMO).

Outcomes

Observational studies have shown that early mobilization and ambulation are associated with decreased ICU and hospital LOS,[67,92–94] in addition to decreased incidence of delirium,[93] without an increase in cost.[18,67] Early mobilization and ambulation can even lead to cost savings.[16,17,94] In the trauma and burn population, early mobilization and ambulation have been associated with decreased airway, pulmonary, and vascular complications, including ventilator-associated pneumonia (VAP) and deep vein thrombosis.[75] In the neurosurgical ICU, increased mobility resulted in decreased restraint use, reduced infections (including VAP), and decreased ICU and hospital LOS.[80] For patients recovering from cardiac surgery, early mobilization can help prevent postoperative complications, improve functional capacity, and reduce hospital LOS.[95] Patients also report some less tangible benefits of rehabilitation, such as helping them to adapt to their new situation and regain a sense of autonomy after critical illness.[96]

Results of RCTs examining the outcomes of early mobilization in the ICU have been mixed. Two of the first RCTs to specifically look at early mobilization in the ICU showed significant benefits for critically ill patients. Burtin and colleagues randomized 90 medical and surgical ICU patients on ICU day 5 to bedside ergometry with standard treatment, including respiratory physiotherapy and active motor sessions of the upper and lower limbs, compared with standard treatment alone.[97] At hospital discharge, a 6-minute walking distance and the subjective feeling of well-being were significantly higher in the treatment group. Schweickert and colleagues randomized 104 medical ICU patients who had been mechanically ventilated for less than 72 hours to either daily sedation interruption plus early exercise/mobilization or daily sedation interruption plus therapy as ordered by the primary medical team.[13] Patients in the intervention group had less delirium, more ventilator-free days, and a faster return to independent functional status at the time of hospital discharge.

Over the past decade, numerous additional RCTs have examined the risks and benefits of early mobilization in the ICU,[58,59,70,72,73,77,78,98–110] but the results have been variable because of significant heterogeneity. But compared with standard therapy, early mobilization has been consistently shown to increase the number of patients who can stand,

increase ventilator-free days, decrease the incidence of ICUAW, increase walking distance at hospital discharge, and increase the likelihood of discharge to home from the hospital.[111] Additional RCTs of early mobilization, such as the TEAM trial,[112] are ongoing, as are investigations of early in-bed cycle ergometry, either alone or combined with amino acid supplementation,[72,113,114] and bedside treadmill training.[115]

One reason that recent studies may not have shown consistent benefit is the increasing prevalence of early mobilization in the ICU as part of standard care, particularly in units that have dedicated physical therapists[116]—the same ICUs are those most likely to take part in these studies. In some recent RCTs both the intervention and control groups had similar access to rehabilitation with only small differences in timing or frequency. For example, in one pilot study the intervention group received a specific physical therapy protocol within 48 hours of admission for sepsis, but 42% of patients in the standard care group also received physical therapy within 48 hours.[103,117] A Cochrane review of very early mobilization after stroke that failed to show a benefit found that the median delay to beginning mobilization was 18.5 hours in the intervention group, but was only 33.3 hours in the control group.[118] The design of these studies could make it difficult to detect significant differences in patients receiving early mobilization.

The Society of Critical Care Medicine, European Society of Intensive Care Medicine, American College of Chest Physicians, and American Thoracic Society have endorsed ICU liberation guidelines that include minimizing sedation and beginning physical therapy early in a patient's stay.[119–122] The ideal timing of early mobilization is still unclear, but recent reviews suggest initiation within 48–72 hours of admission to the ICU.[123,124] Rehabilitation should only begin once the patient has stable cardiovascular, respiratory, and neurologic status, but mechanical ventilation or infusion of vasoactive medications should not preclude mobilization. Caution must be exercised during each session. Major indicators for stopping include development of new clinical instability (cardiovascular, respiratory, neurologic, etc.), accidental device removal or malfunction, fall, or patient distress.[121] The most beneficial frequency and duration of rehabilitation sessions are currently unknown and require further study.[125]

EARLY MOBILIZATION PROGRAMS IN THE ICU

Implementation and Monitoring

Implementation of an early mobilization and ambulation program is an iterative process that requires a structured approach, transdisciplinary team, collaborative environment, and support from administration and senior management.[124] The use of a vetted framework, such as the Plan-Do-Study-Act (PDSA) model, the Six Sigma model,[126] or the four-step model for large-scale knowledge translation suggested by Pronovost and colleagues[127] increases the likelihood of success and sustainability of an intervention.

Planning and Engaging Phase

The first stage begins with summarizing and publicizing the evidence of early mobilization, including its safety, feasibility, sustainability, and effectiveness. Next, an interdisciplinary team, including physicians, nurses, physical therapists, respiratory therapists, senior executives, and other stakeholders, should be created. Social influence appears to be important for implementing and sustaining change, so identifying "champions" and having the support of local opinion leaders can be useful.[128,129] Once created, the team works with the frontline staff to navigate the early mobilization process and ensure a supportive and collaborative culture within the unit. Culture is of utmost importance, as "unnecessary immobilization" is a perception (sometimes justified) that may occur in ICUs where early mobilization is not ingrained in the culture.[130] The team should then create a protocol for early mobilization, explicitly defining inclusion and exclusion criteria, with the goal of capturing as many patients as possible and avoiding unnecessary exclusions. Implementing a formal protocol has been shown to decrease the time to first initiating mobilization and increase the number of rehabilitation sessions.[131]

Of course, clinicians should consider each patient's baseline, current clinical status, and clinical trajectory within the context of the prespecified criteria. Fig. 167.2 provides a sample algorithm for the delivery of physical therapy in critically ill patients.[93] Note that the type of physical activity performed depends on the status of the individual patient. Various methods of physical activity have been used successfully in the ICU, including traditional activities such as sitting on the edge of the bed, standing, sitting in a chair, and ambulating. However, other activities, such as cycle ergometry[58,72,73,97] and even video games,[132] are also safe and feasible. Careful consideration should be given to certain populations (e.g., trauma patients, neurosurgical patients, patients with open abdominal wounds)[133] and may require consultation with specialty services to delineate the appropriate activity level for these patients.[74] Additionally, the team should consider whether early mobilization will be implemented on its own or as part of a larger bundle of care processes such as the awakening and breathing, coordination, delirium monitoring and management, and early exercise and mobility (ABCDE) bundle[11,133] or the ABCDEF bundle, which also includes family engagement.[134,135]

Once a preliminary protocol has been identified, a sample patient can be used to assess workflow and potential barriers. Potential barriers should be discussed with all stakeholders, as perceived barriers may differ among disciplines. Table 167.1 describes a number of potential barriers to early mobilization and ambulation in addition to associated solutions.[93,136] Note that these barriers include not only patient-related variables (e.g., the presence of lines, tubes, and drains) but also the organizational, cultural, and environmental barriers. The latter include the lack of appropriate equipment (e.g., portable monitors and ventilators) and default bedrest orders. Cost is also a common concern, particularly among hospital administrators, despite evidence that early mobilization can be implemented with no additional cost and may indeed prove cost-saving.[16,17,94] Perceived barriers tend to decrease as providers gain more experience with early mobilization.[137,138]

The planning and engaging phase also includes the development of a measurement plan and specification metrics used to evaluate the program. These can be either process or outcome measures. Process measures include the percentage of patients being referred to physical therapy, the number of physical therapy sessions occurring per ICU day, and the time from ICU admission to ambulation. Possible outcome measures include the highest activity level achieved, incidence or duration of delirium, functional status at time of ICU discharge, ICU or hospital LOS, cost, patient and family satisfaction, hospital discharge destination, and mortality. The metrics chosen should be easily measured and reproducible. Ideally, data should be collected both before and after implementation of the program to ensure that a pre/post analysis can be performed. Adverse events should also be defined and recorded to ensure that the program is safe for patients, family, and staff.

Executing Phase

Pilot testing of the program in a subset of ICU beds may be prudent to help identify issues and optimize the protocol before dissemination to all critically ill patients. Unit-based marketing campaigns advertising and supporting the initiative should precede the initial rollout to

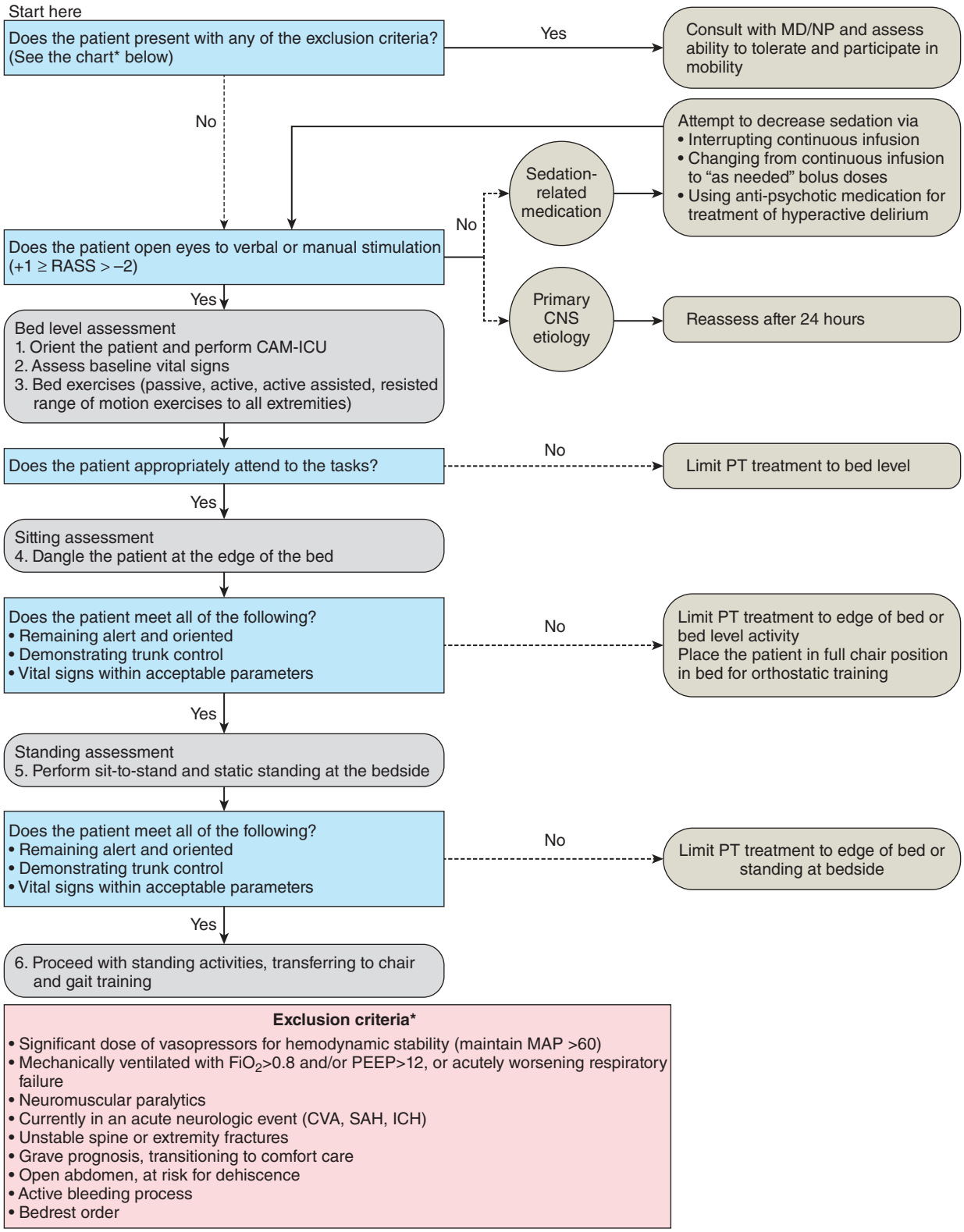

Fig. 167.2 Sample daily mobility assessment and treatment algorithm.[93] Vital sign parameters are on a case-by-case basis. *CAM-ICU,* Confusion Assessment Model for the Intensive Care Unit; *CNS,* central nervous system; *CVA,* cerebrovascular accident; *FiO_2,* fraction of inspired oxygen; *ICH,* intracerebral hemorrhage; *MAP,* mean arterial pressure (mm Hg); *PEEP,* positive end-expiratory pressure (cm H_2O); *PT,* physical therapy; *RASS,* Richmond Agitation-Sedation Scale; *SAH,* subarachnoid hemorrhage. (From Engel HJ, Needham DM, Morris PE, et al. ICU early mobilization: From recommendation to implementation at three medical centers. *Crit Care Med.* 2013;41[9 Suppl 1]:S69–80.)

TABLE 167.1 Potential Barriers to Early Mobilization and Suggested Solutions

Barrier	Solution
Endotracheal tubes, central venous catheters, other lines and drains	Secure device
	Train staff in best practices
Hemodynamic derangements	Educate staff on evidence of safety
	Provide specific exclusion guidelines
Sedation	Integrate daily sedation holiday into PT/OT protocol
	Encourage sedative administration on an as-needed basis instead of continuous infusion
	Use validated sedation scoring system to evaluate sedative needs
Delirium	Normalize sleep-wake cycle
	Expose patient to sunlight during daytime hours
	Redirect and reorient patient frequently
	Minimize benzodiazepines and narcotics
	Monitor for delirium with validated scoring system
Inappropriate equipment	Purchase necessary equipment (portable monitors, portable ventilators)
	Consider options for bedside or in-room PT/OT if equipment purchase is not feasible
Insufficient staffing	Hire additional personnel
	Reorganize staff (example: shifting one nurse from night to day shift because PT/OT is more likely to occur during the day)
	Train and use nursing students and PT students taking an ICU elective
	Implement technologic solutions to maximize staff efficiency
Lack of physician referrals for physical therapy	Streamline physical therapy orders
	Use computerized order entry
	Make default activity order "ad lib"
	Perform joint PT/nursing/ICU team rounds to identify patients appropriate for mobilization
	Implement automatic referral for PT
Fear of intervention/cultural roadblock	Create ongoing dialogue to address stakeholder concerns
	Educate staff on safety and benefits of intervention
	Incorporate early mobilization into ICU culture
Lack of leadership	Recruit transdisciplinary team
	Identify PT champion
	Include senior management/hospital administrators

ICU, Intensive care unit; *OT,* occupational therapy; *PT,* physical therapy.

alert providers and remind staff of the benefits of physical therapy in the ICU. Members of the interdisciplinary team should be readily available to encourage and support frontline providers, answer questions, and quell anxieties associated with ambulating critically ill patients. Additionally, team members should continuously request feedback on the implementation process and the algorithm in use. They should also attempt to identify barriers not previously recognized, with the goal of rapidly making changes to address concerns and improve the program. Early achievements should be applauded and celebrated, acknowledging staff, patients, and families for their efforts. Once providers and staff are comfortable with early mobilization, consideration should be given to involving family in these efforts. Family engagement increases patient- and family-centered care, provides a sense of personhood to patients, gives meaning to the intervention, and has been shown to increase compliance with early mobilization protocols.[139]

Evaluating and Improving Phase

The evaluation phase continues indefinitely. Evaluation can be both qualitative (e.g., in the form of informal interviews, focus groups, and surveys) or quantitative. The quantitative assessment is composed of the metrics previously defined in the planning phase. One feasible and reliable way to evaluate the success of an early mobilization and ambulation program is to use an ICU mobility scale. Hodgson and colleagues developed and validated an 11-point mobility scale.[140] This scale (Table 167.2) describes the highest level of activity achieved by a patient on a given day, ranging from a score of 0, which indicates no activity (patient lying in bed), to 10, which indicates being able to walk independently without an assistance device. In a study of 100 medical, surgical, and trauma ICU patients, the scale was a feasible tool with high interrater reliability among nurses and physical therapists of various levels. Other important metrics include the incidence of delirium, ICU and hospital LOS, hospital discharge destination (i.e., home versus rehabilitation facility or skilled nursing facility), and incidence of adverse events. Ongoing improvement should take place in response to issues, staff concerns, or poorly performing metrics. Metrics that improve initially and then show a decrement indicate a problem with sustainability and should trigger an in-depth review of the program and re-engagement of frontline staff.

TABLE 167.2 ICU Mobility Scale

	Classification	Definition
0	Nothing (lying in bed)	Passively rolled or passively exercised by staff but not actively moving.
1	Sitting in bed, exercises in bed	Any activity in bed, including rolling, bridging, active exercises, cycle ergometry, and active assisted exercises; not moving out of bed or over the edge of bed.
2	Passively moved to chair (no standing)	Hoist, passive lift, or slide transfer to the chair, with no standing or sitting on the edge of the bed.
3	Sitting on edge of bed	May be assisted by staff, but involves actively sitting on the side of the bed with some trunk control.
4	Standing	Weight bearing through the feet in the standing position, with or without assistance. This may include use of a standing lifter device or tilt table.
5	Transferring bed to chair	Able to step or shuffle through standing to the chair. This involves actively transferring weight from one leg to another to move to the chair. If the patient has been stood with the assistance of a medical device, they must step to the chair (not included if the patient is wheeled in a standing lifter device).
6	Marching on spot (at bedside)	Able to walk on the spot by lifting alternate feet (must be able to step at least four times, twice on each foot), with or without assistance.
7	Walking with assistance of two or more people	Walking away from the bed/chair by at least 5 m (5 yards) assisted by two or more people.
8	Walking with assistance of one person	Walking away from the bed/chair by at least 5 m (5 yards) assisted by one person.
9	Walking independently with a gait aid	Walking away from the bed/chair by at least 5 m (5 yards) assisted by a gait aid, but no assistance from another person. In a wheelchair-bound person, this activity level includes wheeling chair independently 5 m (5 yards) away from the bed/chair.
10	Walking independently without a gait aid	Walking away from the bed/chair by at least 5 m (5 yards) without a gait aid or assistance from another person.

From Hodgson C, Needham D, Haines K, et al. Feasibility and inter-rater reliability of the ICU Mobility Scale. *Heart Lung*. 2014;43(1):19–24.

CONCLUSION

ICUAW is a common complication of critical illness and adversely affects the long-term function of ICU survivors. Although current understanding of the most effective means of preventing and treating ICUAW is limited, early mobilization and ambulation appears to be an important component. When performed with care, early mobilization of critically ill patients is safe, feasible, and cost-effective with very few contraindications. Taking a structured approach to implementing an early mobilization and ambulation program increases the likelihood of success and sustainability.

KEY POINTS

- A large proportion of survivors of critical illnesses experience long-term cognitive, psychological, and physical disability, with less than half of survivors returning to prior functional status and/or work by 1 year after ICU discharge.
- Prolonged periods of inactivity and immobility lead to reduced protein synthesis, accelerated proteolysis, and increased apoptosis. This ultimately results in a catabolic state, atrophy, and clinical weakness.
- Early mobilization and ambulation have been suggested as possible interventions to prevent weakness and functional decline associated with critical illness.
- Early mobilization is safe, feasible, and sustainable in various ICU populations.
- Mobilization is beneficial, decreasing the incidence and duration of delirium, reducing ICU and hospital LOS, improving functional status, and increasing the likelihood of being discharged home from the acute care hospital.
- Early mobilization therapy should be considered in all critically ill patients.

References for this chapter can be found at expertconsult.com.

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Mass Critical Care

Ariel L. Shiloh and David C. Lewandowski

Natural and man-made disasters have always been a part of life and are occurring with increasing frequency. They create varied degrees of chaos owing to mismatch of resources and needs, and they place a huge burden on healthcare systems. Restoring an affected society to its present status requires extraordinary efforts and incurs substantial costs. Thousands of people are injured physically and emotionally as the result of such events, and their effects continue long after worldwide attention has disappeared.

The devastating events of September 11, 2001, in the United States, subsequent acts of bioterrorism, and emerging infectious disease pandemics have brought new challenges to the field of disaster management and multidisciplinary hazard mitigation. Even though war- and terrorism-related disasters have gathered much attention, natural disasters have occurred with increasing frequency over the past decades. This has been attributed to the growth of human population in geographically disaster-prone areas, rapid industrialization, and increasing exposure to toxic and hazardous materials (HazMat).[1–3]

Analyses of the response of different healthcare systems to major disasters in the past have demonstrated the need for a more clearly identified planning process to attend to the response to multihazard events.[4] This provides a basic understanding of common disaster scenarios and highlights the role of intensivists in the medical response to disasters. It is important for practicing critical care clinicians to keep in mind that their role is first and foremost as a first receiver rather than a first responder; well-trained intensivists may be of much greater value remaining in the hospital setting rather than quickly mobilizing to the field, where their lack of situational preparedness may make them more of a hindrance than an asset.[5]

BACKGROUND

Major disasters occur regularly and cause widespread human death and suffering.. In the last decade, over 2.6 billion people have been affected by disasters and emergencies, with an annualized mortality of 90,000 people.[6] Even though the numbers of geophysical disasters such as earthquakes and volcanic eruptions have remained fairly constant, recent years have seen the highest number of weather-related disasters.[6] As populations grow and occupy spaces that are vulnerable to different hazards, disasters will increase in severity and impact. Events since the September 2001 terrorist attacks have brought attention to the effects of man-made disasters on the healthcare system and the need to anticipate and plan for such low-probability yet catastrophic events. Although there is basic similarity in the response to them, each type of disaster presents responders with unique demands. After any disaster, healthcare systems are tasked with preventing excessive deaths, mitigating suffering, and dealing with an often overwhelming inadequacy of resources. Over the past few years, disaster medicine has grown into a unique specialty to deal with planning and preparing for such cataclysmic events. It shares a common ideal with public health: "greatest good for the greatest number."[3]

A fundamental part of designing a medical response to disasters is to coordinate with healthcare personnel across the hospital system so that they overcome natural differences associated with each group and maximize efficient use of scarce resources. Because the sickest of all viable patients will require intensive care, critical care physicians can play an invaluable part in coordination efforts. In addition to their usual role of being caregivers for patients in the intensive care unit (ICU), intensivists will be expected to help in triage decisions, transport critically ill patients, and treat the multitude of injured in a rational order. They can also help by providing essential medical care at the actual disaster site via mobile ICU teams. It is thus important for critical care physicians to be familiar with the basics of disaster management, acquire organizational and leadership skills, practice delivery of unconventional critical care, and be familiar with different disaster-related medical syndromes.

TERMINOLOGY

Physicians and healthcare personnel should be familiar with the basic nomenclature and terminology in disaster medicine. Clear, common, and concise definitions are important to effective communication and evoking appropriate responses in disaster situations. Uniform use of terminology across healthcare systems provides a basis for analyzing and constructing an effective disaster plan and response by all responders.[7] Controversies surrounding the definitions of *disasters, hazards,* and *casualties* are included in the discussions that follow.

The word *disaster* connotes a subjective assessment that has various meanings to different people and has an inherent bias, depending on the person using it. For example, a local, state, or federal "disaster declaration" implies commitment of financial and other resources. Similarly, a disaster in one community is not necessarily the same in another. Currently, there is no uniformly accepted definition for the word *disaster*.[7] De Boer and colleagues recognize the lack of a meaningful definition for the word and instead propose the term *medical severity index*.[8] This term, however, has not gained sufficient acceptance for routine use. Different modifiers can lead to different definitions of the term *disaster*. They include the type of disaster; geographic area involved; timing; onset of the event; size of the community affected; baseline resources available; and physical, psychosocial, and economic injuries caused by the event. However, from a healthcare standpoint, the most important variable that defines a disaster is its functional impact on the healthcare facility.[7] Despite various attempts to clear this confusion, the issue remains unresolved.[7,9,10] What follows

are the commonly used definitions in disaster medicine from a healthcare perspective:

Hazard. An event with the potential to cause catastrophic damage. It may be a "naturally" occurring phenomena, such as volcano eruptions, or "man-made," such as nuclear power plant accidents.[11]

Emergency. A natural or man-made event that significantly disrupts the environment of care (e.g., damage to an organization's buildings caused by severe winds, storms, or earthquakes), resulting in disrupted care and treatment (e.g., loss of utilities, such as power, water, or telephones, because of floods, civil disturbances, accidents, or emergencies within the organization or in its community); or resulting in sudden, significantly changed, or increased demand for the organization's services (e.g., bioterrorist attack, building collapse, or plane crash in the organization's community).

Disaster. A hazardous event causing physical, psychological, social, economic, or even political effects on a scale such that the stricken community needs extraordinary efforts to cope with it and often outside help or international aid.[9,10] Medical disasters form a subset of this category, in which physical and/or psychosocial injuries exceed the medical response capabilities of the community affected.

Casualty. Any person suffering from physical and/or psychological damage by outside violence leading to death, injuries, or material losses. Again, the word has no standard definition and is sometimes used to imply injury, death, or both. It may also bear financial implications, because federal reimbursement may be approved only for people classified as casualties.[7,9,10]

Potential injury-creating event (PICE) system. A new system developed to overcome the differences in disaster nomenclature. It uses the functional impact on the healthcare facility as the only determining factor to define an "emergency" or "disaster." It uses four modifiers to communicate the impact caused by the situation on the healthcare facility.[7]

Multicasualty incident. A hazardous event that, regardless of its size, is containable by local emergency medical services (EMS). From an operational standpoint, an event becomes a multicasualty incident when its impact exceeds the day-to-day response routine to the EMS. Adjustments within the local response system are required to cope with this demand without the need to request outside help (level 1 response).[12]

Mass-casualty incident. A hazardous event that overwhelms local response capability. It is likely to impose a sustained demand for health services rather than a short, intense peak typical of many smaller-scale disasters. This may require a level 2 response (neighboring and regional resources are activated) or a level 3 response (state, interstate, and federal resources are activated in the rescue and recovery process).[13]

Hazard vulnerability analysis (HVA). The identification of potential emergencies and the direct and indirect effects these emergencies may have on the organization's operations and the demand for its services.[14]

CLASSIFICATION OF DISASTERS

Natural disasters arise from the forces of nature and include earthquakes, volcanic eruptions, hurricanes, floods, fire, and tornadoes. In addition, infectious disasters can be classified as epidemic or pandemic. Man-made disasters are the result of identifiable human causes and may be further classified as complex emergencies (e.g., terrorist attacks) and technologic disasters (e.g., industrial accidents).[15] Other classifications include those based on onset (acute vs. insidious disasters), predictability, duration, and frequency. From a public health perspective, disasters must be defined by their effect on people and the healthcare system. The concept of functional impact to the healthcare system is paramount.[15,16]

The PICE system attempts to create uniformity to address the wide spectrum of situations.[7] The two major aims of this system are to communicate both the operational consequences to a hospital or community and the type and amount of outside assistance needed. Four modifiers for an event are chosen from a standardized group of prefixes, and a stage is assigned (Table 168.1). *Column A* (first prefix) describes the potential for additional casualties. For example, a finite number of people injured in an airplane crash is a "static event," whereas an ongoing fire is a "dynamic" event. *Column B* (second prefix) describes whether local resources are sufficient ("controlled") or overwhelmed. If they are overwhelmed, the two modifiers "disruptive" and "paralytic" indicate whether they must be simply augmented or totally reconstituted. Paralytic PICEs are the most daunting of all situations, and they can be either destructive or nondestructive (Table 168.2). *Column C* describes the extent of geographic involvement. The *PICE stage* refers to the likelihood that outside medical help is required (Table 168.3). This PICE model provides important concepts for disaster planners, researchers, and responders. Using this system, disasters can be described both prospectively and retrospectively. PICE is a valuable tool for use in planning and disaster mitigation, but the system warrants validation on a wider scale. It may also require further refinement to delineate the type of aid needed by an affected community.[7] Regardless of the type of classification used to categorize disasters, certain unique features are associated with each kind of disaster. It is important to understand the common effects of different natural and man-made disasters to predict their impact and plan effectively. Some common disaster situations are reviewed next.

TABLE 168.1 PICE Nomenclature

A	B	C
Static	Controlled	Local
Dynamic	Disruptive	Regional
	Paralytic	National
	International	

PICE, Potential injury-creating events.
Data from Koenig KL, Dinerman N, Kuehl AE. Disaster nomenclature—a functional impact approach: The PICE system. *Acad Emerg Med.* 1996;3:723–727.

TABLE 168.2 Paralytic PICE

Destructive	Nondestructive
Bomb explosion	Snowstorm
Earthquake	Employee strike
Tornado	Power failure
Civil unrest	Water supply cutoff
HazMat spill	
Fire	
Building collapse	

HazMat, Hazardous materials; *PICE,* potential injury-creating events.
Data from Koenig KL, Dinerman N, Kuehl AE. Disaster nomenclature—a functional impact approach: The PICE system. *Acad Emerg Med.* 1996;3:723–727.

TABLE 168.3 PICE System Staging With Examples

Stage	Projected Need for Outside Help	Status of Outside Help
0	Little to none	Inactive
I	Small	Alert
II	Moderate	Standby
III	Great	Dispatch
EXAMPLES OF PICE STAGING		
1. Multiple-vehicle crash in a big city	Static, controlled, local PICE, stage 0	
2. Multiple-vehicle crash in a small town	Static, disruptive, local PICE, stage I	
3. Los Angeles civil disturbance	Dynamic, disruptive, regional PICE, stage II	
4. SARS outbreak in China	Dynamic, disruptive, national PICE, stage III	

PICE, Potential injury-creating events; *SARS,* severe acute respiratory syndrome.

From Koenig KL, Dinerman N, Kuehl AE. Disaster nomenclature—a functional impact approach: The PICE system. *Acad Emerg Med.* 1996;3:723–727.

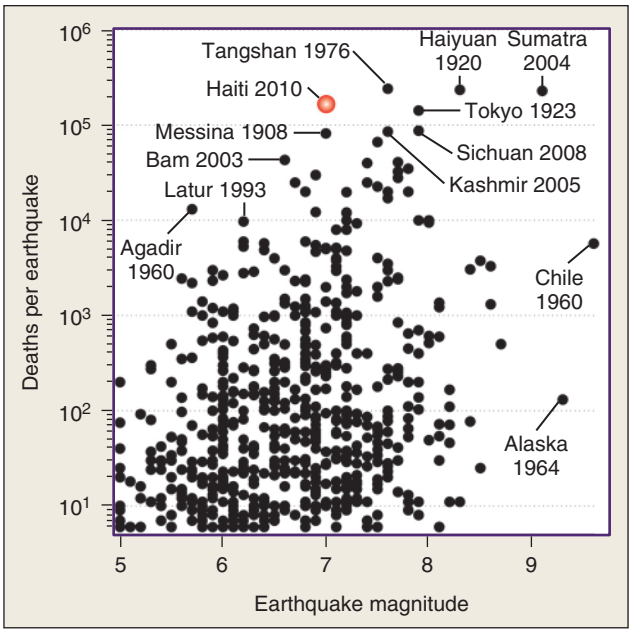

Fig. 168.1 Deaths from earthquakes since 1900. The toll of the Haiti quake is more than twice that of any previous magnitude 7.0 event and fourth worst since 1900. (From Hough SE, Bilham R. *After the Earth Quakes: Elastic Rebound on an Urban Planet.* New York, NY: Oxford University Press; 2006; and Bilham R. The seismic future of cities. *Bull Earthq Eng.* 2009;7:839–887.)

NATURAL DISASTERS

Earthquakes

Earthquakes are a model of a disaster that results in significant mortality,[17] as can be seen in Fig. 168.1. A homogeneous population well trained in both basic trauma and life support and the architectural design of the housing and public facilities of the stricken area are the two major determinants of outcomes for earthquake victims. The massive earthquakes in recent years in Turkey, Taiwan, Sumatra, Kashmir, Sichuan, and Haiti have shown us that a sound engineering design for earthquake resistance in civil structures such as schools and hospitals has a major impact on outcomes. In addition, urban earthquakes generate massive fiscal impact on the world in terms of reconstruction grants provided by wealthier countries for devastated urban areas. Moderately destructive earthquakes in the developing world usually cost up to $10 billion in reconstruction; the needs of developing countries with urban earthquakes may cost an order of magnitude more.

Despite extensive experience and published literature dealing with medical response to earthquakes, the earthquake in Haiti shows that we are frequently doomed to relearn the lessons forgotten.

The Haiti earthquake occurred on January 12, 2010, and was of magnitude 7.0 on the Richter scale, resulting in some 230,000 mortalities and 1.5 million homeless. Let us consider first the military medicine response delivered, especially in the face of continuous exposure of the military medicine establishment to mass-casualty management in the wars in the Middle East.

Responders from the very experienced Israel Defense Forces (IDF) were air-deployed within 48 hours of the Haiti earthquake. This team has had extensive experience over the years with international response and consists of 230 people. The team unpacked and built their portable hospital within 8 hours, and during 10 days of operation treated more than 1100 patients in a facility designed to provide 60 inpatient beds, including 4 intensive care beds and one operating room.[18] Most of the first wave of casualties presented with crushed limbs with open infected wounds, and the later arrivals presented with sepsis and poor chance of outcome. Despite the repeated experience from prior earthquakes showing that victims of crush syndrome and acute renal failure require emergency dialysis to prevent death, this facility relied on other international teams for dialysis. Their major dilemmas were practical implementation of the triage algorithm by military personnel to a civilian population. The simple priorities were urgency, resources available, and probability of saving life. Patients with brain injury, paraplegia caused by spine injuries, or a low Glasgow Coma Scale score were immediately transferred to other facilities, because no neurosurgical capabilities were available. A triage panel of three senior physicians relieved individual physicians of personal accountability. Half of the intensive care capability was always dedicated to postoperative care, with the remaining two beds used for prolonged intensive care; only patients who were expected to stabilize within 24 hours were placed in these beds. The very early discharge policy permitted this facility to treat more than 100 patients per day.

Second, let us consider the response of the US military, which had a considerable portfolio on providing disaster relief in catastrophic events such as the Indonesian tsunami that devastated Sumatra. The US Naval Ship (USNS) *Comfort,* one of the hospital ships of the Military Sealift Command, was deployed as part of the mission termed *Operation Unified Response*. It started accepting casualties within 7 days of the earthquake. The ship is a 1000-bed facility that includes 75 ICU beds, blood bank, hemodialysis, pathology, physical therapy, morgue, and radiology with computed tomography and ultrasonography capability. It is staffed with 1000 active-duty US medical personnel, including three physician intensivists, and it was allocated to stay up to 6 months.[19,20] The first wave of casualties were critically ill trauma patients airlifted from field hospitals by US helicopters. Within 72 hours, the *Comfort* admitted 254 patients, and the census rapidly increased to 430, more than a third of them pediatric cases. A team of six internists provided 24/7 coverage. Dozens of patients underwent mechanical ventilation simultaneously; the open-bay design did not allow for isolation, and the nurse-to-patient ratio

was about 7:1. A large volume of hemodialysis was provided to patients with crush syndrome, leading to rapid depletion of dialyzers and dual-lumen dialysis catheters. The discharges exceeded admissions in about 2 weeks, and after a total of 629 admissions, the ship completed its mission. Although the standard of care exceeded community expectations, the US Navy personnel followed naval protocol and standards.

Third, let us consider the relearning of the lessons of civil-military collaboration in disaster response.[21] A volunteer medical team with civilian personnel under the auspices of the international medical corps flew to the Dominican Republic and reached the Hôpital de l'Université d'Etat d'Haïti in Port-au-Prince after a long bus ride on January 17, 2010. There were more than 800 injured in the partially destroyed facility, with the primary diagnoses being crush injuries, compartment syndrome, infected fractures, and hemorrhagic shock. One physician and one nurse were covering up to 80 critically ill patients in the wards. An aftershock of 5.9 magnitude resulted in an exodus of casualties and higher rates of heat stroke in dehydrated hypovolemic patients exposed to tropical temperatures. Destruction of the prison system released 4000 criminals into the community, and no security was available until the arrival of a US airborne infantry regiment. With the arrival of the USNS *Comfort* on January 20, evacuation of the most critically ill patients started, but a triage list developed rapidly, with ship facilities accepting preferentially complicated injuries, obstetric patients, and maxillofacial injuries. Patients with pelvic fractures, closed head injuries, complete spinal cord lesions, and mechanical ventilation cases were of too high acuity for the USNS *Comfort*. Family structures became fragmented, as separation of children from parents occurred. Yet the collaboration of civilian and military medical personnel was considered a success.

Next, let us consider the experiences of academic centers delivering care to victims of the Haitian earthquake onsite.[22] The Miller School of Medicine of the University of Miami and Project Medishare had the advantage of long experience of collaboration with Haiti and close geographic proximity, and they were able to provide emergency relief within 20 hours. Within 8 days, they were able to establish a field hospital at the city airport, and by January 21, 140 patients were transferred into the upgrade facility. The well-organized command center with satellite links for telephone and Internet access was available. A joint adult-pediatric triage team accompanied by Creole-speaking medical staff of Haitian origin was used. Multiple surgeries were performed under local peripheral nerve blocks, with guillotine amputations being frequent. The highest-acuity patients were transferred to the IDF field hospital or the USNS *Comfort*. The command center eventually provided psychiatrists to manage the posttraumatic stress syndrome and a buddy system for the follow-up support.

Finally, one must consider the critical care response from New York City. Although many small teams and a large volume of supplies were dispatched, an organized response was delivered under the leadership of Dr. Ernest Benjamin, division chief of critical care in surgery at Mt. Sinai Hospital. Dr. Benjamin arrived in Port-au-Prince 3 days after the initial event, and after rapid assessment of needs and resources, organized the deployment of the 27-member critical care team to his home country, which arrived on January 20. The team remained onsite for 2 weeks and was responsible for postanesthesia and postoperative care delivery, with Dr. Benjamin being deputized as the director of critical care and recovery at the national hospital. The home institution effectively secured anonymous donations of private jets able to transport the team personnel and some 3000 pounds of medical supplies per flight. The team delivered intensive care with minimal technology but with kindness and dignity toward the suffering population. This was a truly integrated response with both language and cultural sensitivities and capabilities, which are very important in catastrophic situations that will take decades for the local population to recover from.[23]

Experience in managing catastrophic international disasters continues to accumulate with unfortunate regularity. The preceding discussion suggests that combinations of dialysis, orthopedic surgery, pediatric trauma, security, transportation, posttraumatic stress treatment, and cultural and language sensitivities are crucial in earthquakes. Disasters produce well-defined syndromes with well-defined mortalities. It is the recovery phase that continues to require persistence and improvement. One of the most experienced managers and thought leaders in disaster management, Dr. Eric Noji, enumerated the most important factors in public health after disasters: environmental health, epidemic management, immunization, controlling the spread of human immunodeficiency virus/acquired immunodeficiency syndrome, management of dead bodies, nutrition, maternal and child health, medical services, and thorough public health surveillance. It is a common error to deliver a few weeks of heroic quality care and then abandon the population to the ravages of destroyed infrastructure, including public health organization.[24]

Volcanic Eruptions

A volcano is a hill or a mountain built around a vent that connects with reservoirs of molten rock below the earth's surface.[25] Different types of eruptive events occur, including pyroclastic explosions, hot ash releases, lava flows, gas emissions, and glowing avalanches (gas and ash releases). Lava flows tend not to result in high casualties because they are easily avoidable. The "composite" type of volcano is associated with a more violent eruption from within the chimney. These eruptions are associated with air shock waves, rock projectiles (some with high thermal energy), release of noxious gases, pyroclastic flows, and mud flows (lahars). Pyroclastic flows and lahars are often fast moving and are the main cause of damage and deaths from volcanoes, as evidenced by the small eruption of the Nevado del Ruiz in Colombia that killed more than 23,000 people.[26] The release of ash and its subsequent rapid buildup on building structures can be substantial, causing them to collapse within hours. Ash is also responsible for the clogging of filters and machinery, causing electrical storms and fires, and interfering with communications. Ash is a main cause for respiratory-related syndromes and conjunctival and corneal injury. A variety of toxic gases (e.g., carbon dioxide, hydrogen sulfide, sulfur dioxide, hydrogen chloride, hydrogen fluoride, and carbon monoxide [CO]) are released during eruptions, causing bronchospasm, pulmonary edema, hypoxemia, cellular asphyxiation, topical irritation of skin and other mucosal surfaces, and death.[27] Damage to health infrastructures and water systems can be severe. Problems related to communication (ashes cause serious interference) and transportation (poor visibility and slippery roads) are likely. On the basis of the initial assessment, various needs can be anticipated. Reducing the risk for vulnerable groups of being exposed to ash, raising awareness of the risk associated with ash (health and mechanical risk), and maintaining food security conditions over the long term (lava, ash, and acid rain cause damage to crops and livestock) can help limit suffering.[28]

Hurricanes, Cyclones, and Typhoons

The large rotating weather systems that form seasonally over tropical oceans are variously named, depending on their geographic region of origin.[29–31] They consist of a calm inner portion called the *eye,* surrounded by a wall of rain and high-velocity winds. On the basis of central pressure, wind speed, storm surge, and potential destruction, their severity is graded on a scale of 1–5 (Saffir-Simpson scale).[30] They are among the most destructive natural phenomena. Cyclones during 1970 and 1991 in Bangladesh claimed 300,000 and 100,000 lives,

respectively, because of flooding.[32] The most devastating hurricane ever to hit the United States occurred in 1900 at Galveston, Texas. It claimed an estimated 8000–12,000 lives.[33] The greatest damage to life and property is not from the wind but from secondary events such as storm surges, flooding, landslides, and tornadoes. Ninety percent of all hurricane-related deaths occur from storm surge–related drowning.[1] The most common injury patterns include lacerations (during the cleanup phase), followed by blunt trauma and puncture wounds. Late morbidity can be the result of postdisaster cleanup accidents (e.g., electrocution), dehydration, wound infection, and outbreaks of communicable diseases.[31,34] Data from Hurricane Katrina confirmed data from previous meteorologic events. The leading mechanisms of injuries are fall, lacerations, and piercing injuries, with cleanup being the primary activity at the time of injury.[35] Resources may have to be provided for an extended period after the initial inciting event, and significant resources may have to be provided for patients with chronic medical illnesses.[34,36]

Floods

There are three major types of floods: flash floods (caused by heavy rain and dam failures), coastal floods, and river floods. Together, they are the most common types of disasters and account for at least half of all disaster-related deaths.[37,38] The primary cause of death is drowning, followed by hypothermia and injury caused by floating debris.[39,40] The impact on the health infrastructures and lifeline systems can be massive and may result in food shortages. Interruption of basic public services (e.g., sanitation, drinking water, and electricity) may result in outbreaks of communicable diseases.[38,40] Another concern is the increase in both vector-borne diseases (e.g., malaria and St. Louis encephalitis) and displacement of wildlife (e.g., poisonous snakes and rodents).[39,40]

Landslides

Landslides are more widespread than any other geologic event. They are defined as downslope transport of soil and rock resulting from natural phenomena or man-made actions. Landslides can also occur secondary to heavy storms, volcanic eruptions, and earthquakes. Landslides cause high mortality and few injuries. Trauma and suffocation by entrapment are common. Pending an assessment, needs can be anticipated, such as search and rescue, mass-casualty management, and emergency shelter for the homeless.[41,42]

Pandemic 2009 H1N1 Influenza A Virus

Pandemic H1N1 2009 is a new strain of influenza A virus that was first identified in Mexico and the United States on March 18 and April 15, 2009, respectively. It originated from the quadruple reassortment swine influenza (H1N1) virus closely related to the North American and Eurasian swine lineage. However, this new virus circulated only in humans, with no evidence of transmission between humans and animals.

Within weeks, the virus quickly spread worldwide through human-to-human transmission. On April 26, 2009, the Strategic National Stockpile of the Centers for Disease Control and Prevention (CDC) began releasing 25% of the supplies in the stockpile for the treatment and protection from influenza.[43] On June 11, 2009, the World Health Organization (WHO) declared the 2009 H1N1 influenza a global pandemic, generating the first influenza pandemic of the 21st century, with more than 70 countries reporting cases of H1N1 infection. By June 19, 2009, all 50 states in the United States, the District of Columbia, Puerto Rico, and the US Virgin Islands had reported cases of 2009 H1N1 infection. More strikingly, the CDC Emerging Infections Program estimated the number of hospitalizations and deaths in people aged 64 years and younger. The virus was most likely to strike children, young adults, and those with underlying pulmonary and cardiac disease. Pregnant women in their second and third trimester were also at high risk. Patients requiring intensive care had a remarkable prevalence of obesity.[43]

Influenza vaccines are most effective not only to prevent but also to mitigate the severity of illness. The pandemic H1N1 influenza vaccine was promptly developed by the WHO and national authorities. A national influenza vaccination campaign was launched in the United States in October 2009, and the first H1N1 vaccine was made available at that time. Despite the rapid response of the authorities, developing countries in the Southern Hemisphere experienced delays and shortages of the vaccines. Thus research and developmental work have been encouraging for developing a "universal" influenza vaccine that could provide efficacious cross-reactive immunity and induce broad protection against different variants and subtypes of the influenza virus.[44]

Data show that about 8% of H1N1 patients were hospitalized (23 per 100,000 population); 6.5%–25% of these required being in the ICU (28.7 per million inhabitants) for a median of 7–12 days, with a peak bed occupancy of 6.3–10.6 per million inhabitants; 65%–97% of ICU patients required mechanical ventilation, with a median ventilator duration in survivors of 7–15 days; 5%–22% required renal replacement therapy; and the 28-day ICU mortality was 14%–40%.[45–51] Critical care capacity is a key element of hospital surge capacity planning.[10] The proportion of ICU beds occupied by patients with H1N1 varied. In Australia and New Zealand, it peaked at 19%,[7] whereas in Mexico, many patients required mechanical ventilation outside the ICUs.[6] To match the surge capacity with increasing ICU demands during a pandemic is a difficult task, because uncertainty exists for many of these parameters. The disease brought a surge of not only critically ill patients but also patients who required prolonged mechanical ventilation and ICU management. Hospitals should maximize the number of ICU beds by expanding ICUs and other areas with appropriate beds and monitors. Elective procedures should be minimized when resources are limited, and critical care capacity should be augmented.

Safe practices and safe respiratory equipment are needed to minimize aerosol generation when caring for patients with influenza. These measures include handwashing and wearing gloves and gowns; using N95 respirators, which reduce the transmission of epidemic respiratory viruses; staff training in personal protective equipment (PPE); minimizing the use of bag-mask ventilation and disconnection of the ventilator circuit; and avoiding the use of heated humidifiers on ventilators, Venturi masks, and nebulized medications.[52]

When the number of critically ill patients far exceeds a hospital's traditional critical care capacity, modified standards of critical care to provide limited but high-yield critical care interventions should be the goal to accommodate far more patients. Triage criteria should be objective, transparent, and ethical and applied justifiably and publicly disclosed. The ICU triage protocols for pandemics should only be triggered when ICU resources across a broad geographic area are or will be overwhelmed despite all reasonable efforts to extend resources or obtain additional resources.[53] The Sequential Organ Failure Assessment score, though not validated, has been proposed to determine qualification for ICU admission during mass critical care.

The major characteristics of 2009 H1N1 influenza A infection were the rapidly progressive lower respiratory tract disease leading to acute respiratory distress syndrome (ARDS) with refractory hypoxemia. A substantial number of H1N1 ICU patients required advanced ventilatory support (ranging from 1.7% to 11.9%) and rescue therapies, including high levels of inspired oxygen and positive end-expiratory pressure (PEEP), inverse ratio ventilation, airway pressure release

ventilation, neuromuscular blockade, inhaled nitric oxide, high-frequency oscillatory ventilation, extracorporeal membrane oxygenation (ECMO), volumetric diffusive respiration, and prone-positioning ventilation.[46,49,51,54] ECMO was successful in managing refractory hypoxemia in these patients in two studies. The median durations of therapy and survival rates to ICU discharge were 10 days and 15 days—71% and 67%, respectively.[55,56]

As of March 13, 2010, the CDC estimates of 2009 H1N1 influenza cases, hospitalizations, and deaths in the United States since April 2009 were 60 million cases, 270,000 hospitalizations, and 12,270 H1N1-related deaths, respectively.[57] The virus did not mutate during the pandemic to a more lethal form. Widespread resistance to oseltamivir did not develop. The WHO declared an end to the H1N1 pandemic on August 10, 2010. The H1N1 virus is expected to take on the behavior of a seasonal influenza virus and to circulate for some years.

Ebola Outbreak (2014–2016)

In late 2013, Ebola virus disease (EVD) became an international disaster of crisis proportion in West Africa, primarily in the countries of Liberia, Sierra Leone, and Guinea. This became the largest outbreak of EVD in history, greater than all previous epidemics combined, with a total number of 28,616 suspected cases and 11,310 deaths, all in the aforementioned countries; additionally, there were 36 suspected cases and 15 deaths outside of those countries.[58–61] This point cannot be overemphasized: although the mortality of confirmed cases has been documented to be as high as 68% in the affected nations of West Africa, if patients are quickly recognized and given appropriate aggressive supportive care, the case fatality ratio drops dramatically. There are, to date, no specific approved pharmacotherapeutic interventions available to cure EVD; however, the VSV-EBOV Ebola vaccine has been shown to be safe and highly effective and was fast-tracked to use by the epidemic.[62] The dramatically decreased case fatality ratio noted in developed nations is related to strict enforcement of isolation, hygiene, and use of supportive care.

With regard to the scope of the issue, the CDC predicted that the number of confirmed EVD cases would double approximately every 20 days, with estimated cases ranging as high as 1.4 million. From a mass-casualty perspective, it rapidly became clear that the aforementioned nations of West Africa did not have an adequate governmental infrastructure to create Ebola treatment units, nor were they able to strictly implement the necessary public health infrastructure of hygiene and isolation. At that point, important nongovernment organizations (NGOs) such as Médecins Sans Frontières, Red Cross, WHO, and worldwide military support intervened to create the lacking infrastructure.[63,64]

From the initial outbreak to December 2015 the WHO, with its partners, achieved unprecedented progress in combating the disease. From an environment of minimal diagnostic tools and scant medical personnel emerged 24 rapid diagnostic laboratories, a phase III trial of the VSV-EBOV vaccine, and a global network of thousands of healthcare professionals ready for rapid deployment in the Foreign Medical Teams (FMTs) Registry. These efforts were achieved through a three-phase approach. Phase 1 (August–December 2014) was of a rapid scale-up of the response. This consisted of increasing the number of treatment centers, rapidly hiring and training teams in safe dignified burials, empowering social mobilization, and launching the UN Mission for Ebola Emergency Response (UNMEER). Phase 2 (January–July 2015) emphasized increasing capacities for case finding, contact tracing, and community engagement. Phase 3 (August 2015–2016) focused on interrupting all chains of transmission. This was achieved by rapidly identifying all cases, contacts, and deaths; establishing safe facilities; developing multidisciplinary response teams; incentivizing local communities to comply with public health goals and local response; supporting survivors; and ending human-to-human transmission of the virus in the affected populations and countries.[65]

When patients with EVD first started appearing in the United States, it required some fundamental reevaluation of the role of the CDC in such events. Normally the agency is tasked with providing information and guidance to both healthcare facilities and state and local health departments, but given the rapid, complex, and international nature of this particular epidemic, the routine approach of having state health departments manage these situations with oversight by the CDC was not particularly effective. The president created the role of "Ebola Response Coordinator" to help provide a coordinated federal oversight for the US approach to this disease. In addition, the CDC created Ebola "SWAT teams" that were sent in real time to appropriate locations to ensure appropriate resource allocation to hospitals, and, if necessary, transfer patients with suspected EVD to properly equipped regional centers. For example, in New York State, the governor mandated that eight medical centers (five in New York City alone) were to be designated centers for patients with suspected EVD and that all hospitals needed to develop strategic plans for initial management of patients with suspected EVD.[66]

The CDC's response to the Ebola virus epidemic was the largest in the agency's history, in an area of the world with little operational experience. The CDC developed relationships with health ministries of local West African governments, US governmental agencies, and NGOs and developed a Global Rapid Response Team in June 2015.[67]

Interestingly, despite the extremely low number of actual patients who were diagnosed with EVD in the United States, a challenging problem was media management; an initial lack of clear federal leadership rapidly led to confusion, fear, and misinformation being spread throughout the country. As an example, the PPE recommendations from the CDC were not aligned with the recommendations from the WHO. This left hospital officials confused about the best manner in which to protect their employees. Eventually, the recommended approach became more aggressive, and there was agreement between the CDC and WHO regarding PPE.[61,68–73]

In conclusion, major important lessons were learned during the outbreak of EVD, many of which have clear-cut implications for future epidemics. First, it became clear that for many developing nations, the existing governmental infrastructure is inadequate to provide appropriate containment, public health infrastructure, and treatment facilities; early aggressive intervention by a combination of NGOs and militaries is required to quell the spread. Second, the standard existing paradigm of local and state health agencies providing adequate resources, information, and guidance to health facilities may not be adequate; a rapid top-down federalized approach may be required. Clearly, more resources must be allocated to our federal and international health agencies to prepare for such possible events in the future.

OTHER NATURAL DISASTERS

Tornadoes occur most commonly in the North American Midwest. Over 4115 deaths and 70,000 injuries have been ascribed to them during the years 1950–1994. They cause widespread destruction of community infrastructure. Injuries most commonly seen are complex contaminated soft tissue injury (50%), fractures (30%), head injury (10%), and blunt trauma to the chest and abdomen (10%).[74,75] Firestorms, wildfires, tsunamis, winter storms, and heat waves are other natural phenomena capable of creating mass injuries from thermal burns, airway injury, smoke inhalation, heat-related disorders, and hypothermia.[76–79]

MAN-MADE DISASTERS

Transportation Disasters

Transportation accidents can produce injuries and death similar to those seen in major natural disasters. Some of the largest civilian disasters in North America have been related to the transportation of HazMat.[80] Motor vehicle accidents, railway accidents, airplane crashes, and shipwrecks are some of the common transportation accidents. They cause a wide range of injuries, including multiple trauma, fractures, burns, chemical injuries, hypothermia, dehydration, asphyxiation, and CO inhalation. The hazard risk to a healthcare facility increases with its proximity to a chemical plant or highway, and such factors should be considered in the emergency preparedness plan of a hospital.[81]

Weapons of Mass Destruction

Weapons of mass destruction (WMDs) are those nuclear, biological, chemical, incendiary, or conventional explosive agents that pose a potential threat to health, safety, food supply, property, or the environment. Since the terrorist attacks in September 2001 and intentional release of anthrax spores in the United States, there is growing concern around the world about the possible threat of chemical, biological, or nuclear weapons being used against a civilian population. The incidence of use of WMD to cause death and injury is rare. However, biological and chemical weapons are relatively accessible, and WMDs are thought to be available to most foreign states and terrorist groups. In response to a WMD incident, healthcare personnel will be called on to manage unprecedented numbers of casualties in an environment of panic, fear, and paranoia that accompanies terrorism. Because most attacks occur without warning, the local healthcare system will be the first and most critical interface for detection, notification, rapid diagnosis, and treatment. The best defense in reducing casualties will therefore rest on the ability of medical and public health personnel to recognize symptoms and provide rapid clinical and epidemiologic diagnosis of an event. This requires that healthcare providers be well informed of potential biological, chemical, and nuclear agents. They must have a heightened index of suspicion and be able to identify unusual disease patterns to determine whether WMDs are the etiologic agents of illness. Physicians will need to practice appropriate surveillance and reporting and develop knowledge of mass decontamination; use of proper PPE; and safety protocols related to a biological, chemical, or radiologic event.[82–84] Salient characteristics and brief management strategies of different WMD are discussed here.

Biological Weapons

Biological weapons can be either pathogens (disease-causing organisms such as viruses or bacteria) or toxins (poisons of biological origin). Compared with other WMDs, biological weapons are characterized by ease of accessibility and dissemination, difficulty in detection because of their slow onset of action, and their ability to cause widespread panic through the fear of contagion. They can be spread through various means, including aerial bombs, aerosol sprays, explosives, and food or water contamination. Multiple factors, including particle size of the agent, stability of the agent, wind speed, wind direction, and atmospheric conditions, can alter the effectiveness of a delivery system. The CDC has classified biological weapons into three categories (Table 168.4) based on the ease of dissemination; ability to cause high mortality, public panic, and social disruption; and requirement for special action for public health preparedness.[85] Category A agents are of particular concern because they can cause widespread disease through their ease of transmission, result in high mortality rates, cause panic and social disruption, and require special attention during public health preparedness. General features that should alert healthcare providers to the possibility of a bioterrorism-related outbreak include[86] the following:

1. A rapidly increasing disease incidence (e.g., within hours or days) in a normally healthy population
2. An epidemic curve that rises and falls during a short period
3. An unusual increase in the number of people seeking care, especially with fever or respiratory and gastrointestinal complaints
4. An endemic disease rapidly emerging at an uncharacteristic time or in an unusual pattern
5. Lower attack rates among people who had been indoors, especially in areas with filtered air or closed ventilation systems, versus people who had been outdoors
6. Clusters of patients arriving from a single locale and large numbers of rapidly fatal cases
7. Any patient presenting with a disease that is relatively uncommon and has bioterrorism potential (e.g., pulmonary anthrax, tularemia, or plague)

The main steps involved in managing a bioterrorist attack are containment, notification, confirmation, and directed antibiotic treatment and prophylaxis. In the event of a suspected bioterrorist attack, the CDC has issued protocols for early notification of local and state public health department agencies.[87] The Association for Professionals in Infection Control and Epidemiology in cooperation with the CDC devised the "Bioterrorism Readiness Plan," with a template for healthcare facilities to serve as a reference document to facilitate preparation of bioterrorism readiness plans for healthcare facilities. This tool guides infection-control professionals and healthcare epidemiologists in the development of practical and realistic response plans for their institutions in the event of a bioterrorism attack.[88] The reader is referred to other documents for a review of

TABLE 168.4 Triage Classification

Groups	Color	Symbol	Type of Injury
Priority I (emergent)	Red	R	CRITICAL: likely to survive if simple* care given within minutes
Priority II (catastrophic)	Blue	B	CATASTROPHIC: unlikely to survive and/or extensive or complicated care needed within minutes
Priority III (urgent)	Yellow	Y	URGENT: likely to survive if simple† care given within hours
Priority IV (nonurgent)	Green	G	MINOR: likely to survive even if care delayed hours to days
Priority V (none)	Black	X	Dead

*Simple: Care that does not require unusual equipment or excessive use of time or personnel.
†Assigned THIRD priority (after YELLOWS) when there are so many casualties that if resources are used in vain to try to save BLUE cases, the YELLOWS will needlessly die.
From Auf Der Heide E. Disaster Response: Principles of Preparation and Coordination. St. Louis, MO: Mosby; 1989.

BOX 168.1 Additional Disaster Information Resources

General Disaster Resources and Websites

1. Centers for Disease Control and Prevention. Emergency preparedness and response. Available at https://emergency.cdc.gov/
2. World Health Organization. Natural disaster profiles. Available at http://www.who.int/health-topics
3. Federal Emergency Management Agency. Disaster management. Available at http://www.fema.gov/ or http://www.ready.gov

Resources for Radiation Accidents

1. Centers for Disease Control and Prevention. Radiation emergencies. Available at https://emergency.cdc.gov/radiation/

Resources for Bioterrorism

1. Centers for Disease Control and Prevention website for bioterrorism. Available at http://emergency.cdc.gov/bioterrorism

bioterrorism and critical care,[89,90] in addition to other resources and websites (Box 168.1).

Chemical Weapons

Chemical incidents are accidental or intentional events that threaten to or do expose responders and members of the public to a chemical hazard. Agents that have been commonly used as chemical weapons are also used in industrial processes. Most industrial incidents occur at an interface between transport, storage, processing, use, or disposal of hazardous chemicals, where these systems are more vulnerable to failure, error, or manipulation. The catastrophic effect of these agents has been used several times in the past for military purposes, and with the proliferation of these weapons, civilian populations are now faced with a significant threat.[91] Typically, chemical warfare agents are classified into the following categories[92]:

Nerve agents (e.g., tabun, sarin, VX, and soman) are organophosphates that inhibit an enzyme, anticholinesterase, resulting in the overstimulation of both muscarinic and nicotinic receptors. Muscarinic symptoms include lacrimation, bronchorrhea, bronchospasm, miosis, salivation, rhinorrhea, vomiting, and diarrhea. Nicotinic receptor stimulation produces muscle fasciculations, flaccid paralysis, tachycardia, and hypertension. They can also produce central nervous system effects (i.e., seizures and coma). Death is usually from respiratory failure. They are extremely toxic and have a rapid effect. Sarin presents as a vapor threat, and the onset of symptoms is within seconds, with a peak effect in 5 minutes. Exposed victims who are asymptomatic after 1 hour are unlikely to be contaminated. VX represents a liquid exposure, with as little as a drop being lethal. The onset to action and death is less than 30 minutes. The cardinal rule in decontaminating patients is to remove and dispose of all articles of clothing. Therapy is directed toward the predominating symptoms. Atropine is used for the relief of muscarinic symptoms, pralidoxime chloride (2-PAM) is used for nicotinic effects, and benzodiazepines are used for the central nervous system manifestations. Most of the care is supportive and includes mechanical ventilation for respiratory failure and treatment of arrhythmias.[93]

Vesicants (e.g., mustard gas and lewisite) cause wounds on the skin and mucosal surfaces. They are capable of causing second-degree burns of the skin within 4–8 hours. Airway injury and edema can be severe and are dose dependent. Of concern to the ICU physician is the need for correcting fluid losses and maintaining the airway.

Pulmonary agents (e.g., chlorine gas and phosgene gas) mainly affect the respiratory system, inducing inflammation of the airway and the lung and leading to ARDS and death. Treatment is mainly supportive.

Cyanides bind to cytochromes in the mitochondria and inhibit cellular oxygen use. In smaller doses they cause tachypnea, headache, dizziness, anxiety, and vomiting. With higher doses, seizures, respiratory arrest, and cardiac arrest occur. They are highly toxic, and sufficient levels can cause death within 5 minutes of inhalation. They are most commonly inhaled but can also be absorbed through the skin. Care is primarily supportive with supplemental oxygen. Specific therapy is with amyl nitrates, sodium nitrite, and sodium thiosulfate.

Unlike biological weapons, disease secondary to release of chemical agents is likely to be more obvious, rapid in onset, and homogeneous. However, they pose serious problems for emergency care providers because of their potential to cause a large number of casualties rapidly and their potential for secondary contamination. Any emergency medical or public health response to a major incident involving a chemical warfare agent will require coordination among local, state, and federal organizations. First responders should be aware of access to specialized local and federal response teams, basic triage, demarcation of the contaminated area, use of handheld devices for agent detection and identification, use of PPE, and knowledge of appropriate medical treatment and antidotes.

Nuclear Weapons and Radiation Accidents

A variety of terrorist applications of radiation exist that could produce varying degrees of damage to public infrastructure and operations, human casualties and illnesses, and most important, fear.

Radiation devices include radionuclides from the healthcare industries (e.g., brachytherapy and radiation oncology sources). The consequences of the exposure are dose and source dependent.

Radionuclide dispersal devices are also known as *dirty bombs*. These have limited nuclear yield but can contaminate a wide area.

Improvised nuclear devices are made of uranium or plutonium constructed by a nongovernmental source and limited by the critical mass of nuclear material. They yield less destructive power than a conventional nuclear warhead but are still capable of contamination effects.

Tactical and strategic nuclear weapons are those that are created by governments and vary in yields from 0.5 kiloton to greater than 1 megaton. Their destructive capacities are enormous, and they contaminate a vast perimeter of space depending on the yield.

Approximately 50% of the energy released from a nuclear bomb is from the blast and shock waves, giving a majority of the survivors blast-related injuries and creating extensive infrastructure damage. About 35% of the energy released is thermal radiation (in orders of tens of millions of degrees), giving rise to high-degree skin burns. Depending on the size of the device and the altitude of detonation, an electromagnetic pulse is generated with the explosion. This is capable of disrupting all electrical equipment within 20 kilometers to several hundreds of kilometers.[94] The radiation-related energy released gives rise to external contamination, systemic irradiation, and internal contamination-related illness. Immediate ionizing radiation consists of gamma, beta, neutron, and a small amount of alpha radiation. Residual radiation occurs in the forms of induced radiation and fallout. Induced radiation occurs because of neutron-induced gamma activity of the immediate soil, silicon, manganese, aluminum, zinc, copper, and sodium. The half-lives of the various substances are a few minutes to 15 hours. *Fallout* is the fusion of various radionuclides generated in the fission reaction with condensation, producing a snowflake-like debris

that falls to earth. Fallout is a potential form of delayed radiation exposure and can cause internal contamination.[94]

Surviving hospitals and staff near an impact area should serve as a triage center and transport victims to unaffected centers elsewhere through the notification of the National Disaster Medical System Hospital Activation System.[95] Other agencies that have to be notified include the Federal Bureau of Investigation, Nuclear Regulatory Commission, Department of Energy, and Department of Defense. Large-scale decontamination should be managed outside the hospital area as far as is possible, but plans for indoor decontamination should also be in place. A radiation emergency area (both in and out of the hospital) should be designated, with checkpoints nearing the cold zone. Management plans for the safe disposal of human waste and bodies should be in place so as not to increase the exposure risk. Triage of patients should be done on the basis of doing the greatest good for the greatest number. On the basis of predictive models, isolated irradiation, burns, and blast-related injuries would constitute 40% of injuries. Combined injuries would account for the rest. Attending to trauma victims should take precedence over all other medical issues, because a given patient is not likely to succumb immediately from radiation injury.

Patient care should begin with the use of universal precautions and PPE.[94] Dosimetry readings of the area may help during triage, defining those with systemic irradiation injury (possibly received >450 rad exposure). In determining patient viability, three parameters are of the most use: time of onset of vomiting, decrease in the absolute lymphocyte count over a 24-hour period, and presence of conventional trauma burns.[96] Victims who are not viable or who have lethal doses of radiation exposure are likely to benefit from supportive/palliative care.

Hazardous Materials Disasters

HazMat are substances potentially toxic to the environment or living organisms. Full-scale disasters from HazMat are relatively rare, but isolated incidents are among the most common in the community and are not limited to chemicals but can include various biological and radiologic materials. Knowledge of the types of industries present in the community would be helpful in developing a potential plan to deal with likely HazMat situations. Management of a HazMat situation requires attention to several key points: identification of the offending agent, appropriate PPE of responders, prompt containment of the agent, demarcating areas for decontamination (including removal and disposal of clothes and waste from the decontamination), and resuscitation of victims. Injuries secondary to release of HazMat can present as chemical burns, inhalational injury, and a variety of systemic injuries.[97,98]

Armed Conflict

Armed conflict continues to be the most preventable and most destructive of man-made disasters in terms of human physical and emotional suffering, economic loss, and environmental destruction. Specific healthcare issues during these conflicts that are relevant to the intensivist include trauma from blast injuries, projectiles, and crush-related injuries; communicable diseases caused by the breakdown of public infrastructure and mass displacement of populations; and burns and radiation-related injury.

MEDICAL DISASTER SYNDROMES

Disaster situations present with many unique medical syndromes that require specific therapy. Treatment of these entities is often difficult because of a large volume of patients, lack of qualified medical personnel onsite, and inadequate supplies and equipment. It is important to emphasize that initial recognition of the medical syndromes and appropriate intervention are critical to minimizing morbidity and mortality. Appropriate triage, knowledge of field management of each syndrome, flexibility to adapt to each situation, ability to ignore natural differences among different specialties, and recognition of limits of medical care that can be provided in overwhelming situations are key to a good disaster medical response. In the following paragraphs, we discuss commonly encountered medical syndromes in a disaster situation.

Blast Injuries

Bombs contain an array of compounds such as nitroglycerin, trinitrotoluene, and others that are encased in a metal or plastic case. Decomposition of the solid or liquid compound into gas leads to massive dissipation of energy and pressure that creates a blast wave (shock wave). This destructive effect can be increased by the presence of nuts, nails, and bolts in the casing. Water transmits blast waves more efficiently than air, with the greatest impact being on structures that are the deepest.[99] There are four types of blast injuries:

1. *Primary blast injury* is caused solely by the blast wave and almost always affects air-filled structures such as the lung, ear, and gastrointestinal tract. The presence of tympanic membrane rupture may indicate exposure to a high-pressure wave and is thought to correlate with more severe organ injury.
2. *Secondary blast injury* is caused by the rapid acceleration of small fragments caused by the blast injury.
3. *Tertiary blast injury* is a feature of high-energy explosions. They result from the collision of the flying victim against a hard surface.
4. *Miscellaneous blast-related injuries* encompass all other injuries caused by explosions. They include flash burns, inhalation injuries, and blunt trauma.

The most common injuries associated with fatality in blast incidents include subarachnoid hemorrhage (66%), fracture of the skull (51%), lung contusion (47%), tympanic membrane rupture (45%), and liver laceration (34%). Unfortunately, the extent of the blast injury cannot be assessed during the course of rapid triage examinations. In the absence of overt trauma, a focused physical examination should include examination for ruptured tympanic membrane, hypopharyngeal contusions, hemoptysis, and auscultation for wheezing. The presence of a ruptured tympanic membrane is almost always an indicator that the patient has been exposed to a blast wave powerful enough to cause serious damage. The thorax is frequently involved in a blast injury, manifesting with wheezing, hemoptysis, pneumothorax, hemothorax, and air embolism. Patients may have myocardial contusion as well. The presentation of serious pulmonary injury may be delayed. Pulmonary barotrauma is the most common fatal primary blast injury. Patients with nonpenetrating lung injury will likely have hypoxia requiring support ranging from oxygen therapy to mechanical ventilation. This may result from pulmonary contusion, systemic air embolism, and disseminated intravascular coagulation. Acute gas embolism, a form of pulmonary barotrauma, is also associated with blast injuries. Air emboli most commonly occlude blood vessels in the brain or spinal cord, resulting in neurologic symptoms that must be differentiated from the direct effects of trauma. Patients thought to have gas embolism require decompression treatment. Administering 100% oxygen by tight-fitting face mask and left lateral recumbent position may help. Definitive treatment is with the use of hyperbaric oxygen. Patients with blast injury of the lung are likely to present with abdominal injuries that are usually more delayed. These include delayed bowel perforation and liver lacerations. The former may warrant exploratory laparotomy.[100–103]

Blast victims receiving general anesthesia have an increased mortality rate; other forms of local and spinal anesthesia are preferred, and general

anesthesia should be deferred if possible for 24–48 hours. Intensivists should be aware of the increased need for resuscitation equipment, ventilators, and movement in and out of the operating room during such situations.

All patients with significant burns, suspected air embolism, radiation or white phosphorus contamination, abdominal signs of contusion/hematoma, or clinical evidence of pulmonary contusion or pneumothorax should be admitted to the hospital. Patients with tympanic membrane rupture and suspected pneumothorax should get some form of chest imaging, and a significant observation period may be warranted. Other investigations must be judiciously ordered, keeping in mind the limited availability of resources in a mass-casualty incident. Screening urinalysis for presence of hematuria, tests for CO poisoning (explosion in a closed space or associated with fire) and cyanide toxicity (because of combustion of plastics), and assessment of acid-base status may be indicated. Using abdominal computed tomography to rule out intestinal hematomas should be dictated by clinical signs and symptoms. Pregnant patients with blast injuries warrant special consideration, and appropriate consultation is necessary to rule out blast injury to the fetus.[101] Supplemental oxygen, maintaining spontaneous respiration, and low PEEP (if mechanical ventilation is required) are guiding principles. Routine corticosteroids and antibiotics are not warranted.

Exposure to white phosphorus explosives (e.g., in hand grenades) deserves special mention. Using a Wood's light in a darkened resuscitation suite or operating room may help identify white phosphorus light particles in the wound. White phosphorus injury can cause lung injury through irritation, in addition to severe hypokalemia and hyperphosphatemia with cardiac arrhythmias and death. External burns should be lavaged with 1% copper sulfate solution. This forms a blue-black cupric phosphide coating and prevents combustion so that the particles can be safely removed.[104]

Crush Injury Syndrome

Crush injury syndrome refers to systemic manifestations of extensive muscle damage caused by entrapment of victims under collapsed buildings or debris. Reported incidence depends on the type of disaster, ranging from 2% to 40%. Metabolic alterations from the release of muscle constituents into the circulation include myoglobinemia leading to acute renal failure, hyperkalemia, hyperphosphatemia, and disseminated intravascular coagulation. Muscle damage that occurs is caused by not only direct crush injury but also by vascular injury and insufficiency leading to altered compartment pressures and reperfusion injury. Inelastic fascial sheaths encase skeletal muscles in the forearm and lower leg and are particularly vulnerable to dramatic increases in compartment pressures, resulting in compartment syndrome. An intracompartmental pressure greater than 40 mm Hg lasting longer than 8 hours defines this syndrome. Pressures as high as 240 mm Hg can be seen with crush injuries. Compartment syndromes are seen with limb fractures, use of military antishock trousers, pneumatic splints, vascular injuries, and crush injuries. The affected limb may present with severe pain associated with passive stretch or extension, flaccid paralysis, and sensory loss. Capillary refill and peripheral pulses are usually present unless the compartmental pressure equals the diastolic pressure. Diagnosis requires a high degree of clinical suspicion and entails prompt bedside measurement of compartmental pressures. A simple and easy method that can be performed in the hospital or field hospital is using an 18-gauge needle attached to a mercury manometer. In an ICU, pressure transducers used to measure central venous pressures can be attached to the 18-gauge needle to obtain the same information.[105]

Resuscitation of patients with crush injury (any victim crushed or immobilized for more than 4 hours) should begin in the field. After adequate intravenous access is achieved, isotonic fluid replacement with normal saline (rate of 1–1.5 L/h) should begin even before extrication of the crushed limb. If fluid therapy is delayed, the incidence of renal failure increases to 50%; delays of 12 hours are associated with a 100% incidence. Occurrence of renal failure is associated with a mortality rate of 20%–40%. Urinary alkalinization with sodium bicarbonate and mannitol or acetazolamide administration is used to maintain urine pH above 7.5. Although this is widely used, there are no prospective randomized controlled trials to support it. Dialysis may be indicated if aggressive fluid resuscitation fails, and this may create a huge demand for dialysis machines in disaster situations. Peritoneal dialysis if the abdomen is intact and continuous arteriovenous hemofiltration may be other useful options. However, the latter option is complicated by hemorrhage problems related to the use of heparin and immobilization. Life-threatening infections are common and may be increased in the presence of a fasciotomy. In unsalvageable limbs, it may be advisable to perform on-field amputations to avoid the systemic effects of crush injury syndrome. For this purpose, ketamine is the anesthetic and analgesic of choice because of its safety profile in the field.[105]

Particulate Health Problems

Many disasters result in the release of copious particulate matter, causing a wide spectrum of respiratory illnesses, including cough, wheezing, smoke inhalation injury, reactive airways disease, and ARDS. Volcanic eruptions with associated pyroclastic flows and ash fall are some of the most devastating producers of particulate matter. Mortality arises from suffocation by ash in the upper airways, ARDS, and inhalation burns. The massive building collapse and fires associated with the 2001 World Trade Center terrorist attack caused significant pulmonary complaints among rescue personnel.[106]

Smoke inhalation injury resulting from exposure to noxious products of combustion in fires may account for as many as 75% of fire-related deaths in the United States. The three primary mechanisms that lead to injury in smoke inhalation are thermal damage, asphyxiation, and pulmonary irritation. Combustion uses oxygen in the airways and causes a decrease in fraction of inspired oxygen, leading to hypoxemia. Increased CO levels decrease the oxygen-carrying capacity of the blood and cause myocardial depression. Combustion of plastics, polyurethane, wool, silk, nylon, rubber, and paper products can lead to the production of cyanide gas, resulting in anaerobic metabolism and decreased oxygen consumption. Rarely, we may also find methemoglobinemia, which reduces oxygen-carrying capacity.[107] Mortality rate with smoke inhalation alone is about 10% but increases to about 77% in the presence of major burns or respiratory failure. Early deaths are mostly caused by airway compromise or metabolic poisoning. Laboratory work-up should include co-oximetry; CO, methemoglobin, and cyanide levels (if there is discordance in measured saturation and pulse oximetry readings); blood lactate levels (a level >10 mmol/L that is refractory to restoration of adequate ventilation, oxygenation, and perfusion is considered a surrogate marker of cyanide toxicity) on blood gases; and a calculated alveolar-arterial pressure gradient. Initial blood gas measurements and chest radiograph may be normal. Carboxyhemoglobin level obtained in the emergency department does not correlate with tissue hypoxia or long-term neurologic sequelae; ideally, a carboxyhemoglobin level at the scene would be most valuable.

Serial bronchoscopy is indicated in the first 18–24 hours to assess airway edema and sloughing. Early bronchoscopy can be of diagnostic and therapeutic value, particularly when lobar atelectasis is present. High-flow humidified oxygen is critical to reverse or prevent hypoxemia. About 50% of patients with an inhalation injury require tracheal intubation, and this increases in patients who have burn injuries. The need for intubation is determined by the need to maintain airway

patency and pulmonary toilet and to provide positive-pressure ventilation. Positive-pressure ventilation with PEEP increases short-term survival and is associated with decreased tracheobronchial cast formation. Cyanide toxicity (levels >0.1 mg/L) should be promptly treated using a cyanide antidote kit. Recommendations for the use of hyperbaric oxygen in the setting of CO poisoning include CO levels greater than 25%–30%, neurologic compromise; metabolic acidosis; or electrocardiographic evidence of myocardial ischemia, infarction, or dysrhythmias. Hyperbaric oxygen has been used in cyanide toxicity but has not been proven effective. The role of corticosteroids is controversial, and they can be detrimental if given in the presence of cutaneous burns. Empirically administered antibiotics are also in dispute. Common pitfalls in the initial management of smoke inhalation are using initial PaO_2 to predict adequacy of oxygenation, placing small-diameter nasotracheal tubes, intubating without applying PEEP, and restricting fluids for concomitant inhalation and burn injury.[107,108] General measures that could be employed in a field setting include simple airway protection by clearing any particulate matter in the airway, supplemental oxygen, and nebulizer treatment if available. Patients with preexisting asthma and emphysema should be observed for exacerbations.

Acute Radiation Syndrome

Ionizing radiation can be either charged or uncharged particles (photons). Beta particles are capable of penetrating a few centimeters of tissue. Gamma rays and x-rays are capable of penetrating through tissue and concrete. Gamma, x-ray, and beta radiations are considered low linear energy transfer radiation. Alpha particles have no penetrating power past the keratinized layer of skin, but they take on clinical significance if they are internalized by ingestion or inhalation. Neutron emission (e.g., from nuclear reactors, nuclear devices, and industrial moisture detectors) is a highly potent radiation that penetrates deep and creates denser ionization trails. Alpha and neutron emissions are considered high linear energy transfer radiation and have more biological effects than low linear energy transfer radiation by a factor of up to 20. When the process of ionization occurs in living tissue, it denatures cellular DNA. This leads to impaired mitosis and subsequent organ failure. Large doses of radiation are considered to cause more biological destruction than fractionated doses. Systemic radiation illness and lethality from it can result from as little as 450 rad. Precise measurements of the amount of radiation after a nuclear accident will be delayed. Hospital gamma cameras are an invaluable resource for helping determine the exposure in an individual. Higher systemic doses are suggested by shorter onset of prodromal symptoms such as nausea, vomiting, and diarrhea. Serial absolute lymphocyte counts will screen those patients who have psychogenic vomiting. Acute radiation syndrome has four distinct phases[83,94,96]:

1. *Prodromal phase*, characterized by nausea, vomiting, and diarrhea. Other symptoms of eye burning, abdominal pain, and fever can also occur with higher doses. This phase may last from 0 to 2 days, depending on the dose received.
2. *Latent phase,* in which the patient will have a period of relative well-being because of subsidence of the inflammation. However, ultimately the damaged cells will not be able to repair or regenerate. This may last for 2–3 weeks.
3. *Manifest phase,* in which the cellular deficits of various organs affected will become apparent. Mature cells of the skin slough off, revealing an atrophic dermis. Endothelial cells are not replaced, leading to vascular permeability. Mucosal linings slough, causing mucositis and diarrhea. Hematopoietic progenitor cells fail to produce cell lines, leading to anemia, thrombocytopenia, and neutropenia. Fibrosis of organ beds develops. This may last for up to 3 weeks.
4. *Recovery phase/death,* in which some stem cells may proliferate and lead to slow recovery, or there will be symptoms of progressive organ failure leading to death.

For radiation syndrome to occur, radiation must be of the penetrating type in a sufficiently large dose (>0.7 Gy), must be external, and must occur within a short time. The disease complex has three syndromes: bone marrow, gastrointestinal, and cardiovascular/central nervous system. Serial absolute lymphocyte counts should be measured immediately on suspicion of exposure (every 3 hours), because lymphocytes are among the most radiosensitive cells and reach nadir within 2 days, platelets reach nadir in 15–30 days, and neutrophils at about 30 days. Patients are immunocompromised and susceptible to infections, including septic shock. Gastrointestinal syndrome leads to mucosal sloughing, decreased nutrient absorption, and translocation of bacteria and endotoxin. Veno-occlusive disease may also develop if the dose is large enough. Cardiovascular and central nervous system disease develops with doses greater than 5000 rad, and death can occur in as little as 3 days from myocarditis, capillary leak, pulmonary edema, and brain edema. Pneumonitis and subsequent fibrosis can lead to respiratory failure and the need for ventilator support. Treatment of acute radiation syndrome (ARS) is supportive. If internal contamination is thought to have occurred, enhancement of excretion and specific antidote therapy are warranted. For inhalational contamination, bronchoalveolar lavage may be necessary, and for ingestion, gastric lavage and purgative management are warranted. Plutonium and transuranic elements can be treated with chelating agents such as calcium or zinc diethylenetriamine pentaacetic acid. Radiocesium can be treated with Prussian blue, which helps enhance excretion in feces. Radioiodine exposure can be treated with potassium iodide. Uranium excretion can be enhanced by the alkalinization of urine and with potassium supplementation.

Psychological Trauma

The psychological component in a traumatic event is often overlooked, with the major focus usually being on physical health issues. Studies evaluating the emotional impact from disasters indicate that a majority of victims, first responders, and mortuary volunteers will suffer some form of psychological trauma. Intensivists should be aware that behavioral changes may be the result not only of the catastrophic insult but also organic causes such as head injury, inability to take predisaster psychiatric medications, and toxin or chemical exposure. Groups at risk, such as children, adolescents, and victims who have been exposed to traumatic stressors of bereavement, witnessing death, and situations evoking guilt, fear, or anger, should receive prompt psychiatric and posttraumatic counseling. Interventions, such as debriefing, eye movement desensitization and reprocessing, and critical incident stress management, may help minimize emotional suffering and morbidity.[109]

Other Syndromes

Burns, blunt trauma, intraabdominal injury, head injuries, penetrating trauma, and hypothermia are some of the other disaster syndromes encountered in the field. Specific discussion of these entities is beyond the scope of this chapter; please see other reviews.[5]

DISASTER PREPAREDNESS

For intensivists to be able to deal with a disaster, it is paramount that they be a part of the disaster-planning effort. Disaster planning includes development of action programs to minimize loss of life and damage during a disaster, provide the greatest good for the greatest number of people, train healthcare personnel and civilians, coordinate

response efforts, maintain adequate supplies of equipment and personnel, and rehabilitate the community after the disaster. Knowledge of potential disasters to which the community is prone should be an integral part of the planning process. Having an understanding of what the resources and capabilities are of the community, hospital, and its ICU on a continual basis and provision for modular expandability are vital for any successful emergency response. The mere existence of a disaster plan does not ensure that the hospital system is actually prepared.[110] The following paragraphs elucidate some of the common issues and misconceptions related to disasters and common principles useful in designing a disaster plan. Subsequently, a pragmatic view is presented of the role of the ICU physician in a disaster situation.

Common Issues and Misconceptions in Disaster Planning

Typically, the hospital nearest to the disaster site will receive the bulk of the casualties. It is thus important to conduct a careful survey of a disaster plan's jurisdiction to identify potential sites (i.e., industries, nuclear reactors, and highways) and likely types of hazardous events that could occur in the area. Hospitals in the nearby area receive few disaster victims, and an average have at least 20% of their beds vacant. Disaster plans would thus need to include transfer agreements between hospitals and nearby ICUs to meet bed shortages by activating the National Disaster Medical System Hospital Activation System.[95,110,111]

Very few casualties actually require hospital admission. A study of 29 mass-casualty incidents found that less than 10% of casualties required overnight admission under usual criteria (even though more were admitted because they were involved in the disaster rather than because of severity of their condition). Large numbers of casualties with minor conditions will appear at the nearest hospitals, often on foot or in private vehicles, police cars, buses, taxis, and other nonambulance forms of transport. Field triage stations are often bypassed, and this in turn causes enormous strain on the emergency department services.[112]

Most of the logistical problems faced in disaster situations are not caused by shortages of medical resources, but rather from failure to coordinate their distribution.[110] Inexperienced volunteers may not be familiar with the triage system or principles of personal safety, and massive numbers of volunteers can present serious administrative challenges. This results in disorganization and inefficiency.[97] Technical hazard sheets designed by the WHO for most disasters also suggest that medical personnel, blood donors, and blood products should not be sent empirically to a disaster site.[113]

Principles in Disaster Planning

Existing Preparedness Requirements

In developing disaster plans, hospitals must take into account the broad national and local requirements imposed by various governmental agencies. Common agencies involved in this process include the Centers for Medicare & Medicaid Services (CMS) and The Joint Commission (TJC). The CMS's conditions for emergency preparedness and services establish minimum requirements for hospitals that participate in Medicare or Medicaid programs. Similarly, TJC standards apply to a full range of hospitals and are focused on four areas: (1) emergency preparedness management plan (Standard EC 4.1), (2) security management plan (Standard EC 2.1), (3) HazMat and waste management plan (Standard EC 3.1), and (4) emergency preparedness drills (Standard EC 4.2). Readers are referred to the TJC website for the most up-to-date standards.[114]

Hazard Vulnerability Analysis

This is the first step of any disaster plan, with the main aim of identifying potential hazardous events and situations that can occur in or around the healthcare facility. This process of evaluating and predicting hazard risk is not restricted to geographic events but extends to institution-specific variables such as utility failures, local threats of gang-related activity, and presence of a local high-risk industry such as a chemical or nuclear power plant. TJC requires a formal documented HVA that is integrated with the emergency management plan, setting priorities among potential emergencies and also defining the hospital's role in the local community-wide emergency plan.[114]

Incident Command System

The Incident Command System (ICS) is designed to provide the basic architecture of an emergency management response. Major barriers to medical response arise from the lack of coordination among various public and healthcare agencies and from the lack of operational integration of various medical specialties. The ICS incorporates all these agencies and ensures a cooperative and effective response to a crisis. The concept of ICS resulted from the analysis of the devastating wildfires in Southern California in 1970 and has since been modified and successfully adapted to different disaster situations related to healthcare facilities.[100–102] The ICS specifies a common terminology and a command structure with five functional sections:

1. *Command:* Unified command staff responsible for overall management of the incident.
2. *Operations:* Performs the actual response work under the directives of the command center.
3. *Planning:* Gathers relevant information and develops response strategies as the situation progresses.
4. *Logistics:* Responsible for facility-wide supplies, equipment, personnel, and services. It also provides for basic services to personnel of the command center.
5. *Finance:* Authorizes expenditures, maintains records, and provides documentation of the incident.

A designated person will have the authority to declare an emergency. All personnel involved in the command system should be aware of the exact predetermined location of the command center. The plan should also provide protocols that will guide notification and the sequence of mobilization of these personnel in a disaster situation. The command system must also have independent telephone lines to ensure uninterrupted communication with the external world in a disaster situation. Once initiated, the ICS has a built-in chain of command that is responsible for triage of patients and allocation of personnel and resources.[115]

Triage

Appropriate triage is a vital function during an emergency management response. This is a dynamic process that is not necessarily confined to the disaster site or the emergency department, but rather is carried through several levels of the medical response pathway of a disaster response. Modern triage is based on the likelihood of survival in relation to the resources available at the time of the decision.[116] Problems often encountered in the triage process include the following[117]:

1. Lack of medical direction at the scene. Making triage decisions in a chaotic situation requires skill and experience and can often initially seem confusing and unmanageable. Lessons from the first Persian Gulf War showed that on-field triage was correct only 70% of the time. It is necessary to entrust experienced physicians with this job and to have simple and clear guidelines for the decision-making process. In addition to emergency physicians and trauma surgeons, critical care physicians bring with them the expertise to deal with complex and time-bound situations and are thus well suited to head a triage team.

2. Lack of interorganizational planning. Dynamic management of the triage process requires interorganizational coordination and flow of information. Up-to-date assessment of medical resources and personnel should be communicated from the command center to the triage site, and similar communication should occur from the scene to the command center. This will allow for rational and appropriate triage based on the availability of resources.
3. Transport of victims from the site by nonambulance vehicles to nearby hospitals.
4. There is no universally accepted form of triage. A recommended system uses a color-coded system to sort out disaster victims.[116]

Major Utilities, Supplies, and Equipment

Disaster plans and drills should factor in the possibility of internal and external power outages and related disruptions (ventilator and monitoring device failures, communication failures including breakdown of cellular phones, and elevator failures) and water and gas supply shortages. The plan should have an up-to-date inventory of all supplies and capabilities of the facility. The numbers of ventilators in use and their absolute capacity, inventory of various ICU supplies, and vendor lists should be readily available if there is sudden demand for supplies. The disaster plan should allow for at least 2 days' worth of supplies. Regular drills will help identify various bottlenecks and provide knowledge of the absolute capacity of devices, equipment, and services in a disaster situation. Plans to evacuate critically ill patients to nearby hospitals in the event of failure of backup systems should be addressed. Since the anthrax attacks and the resulting strain on antibiotic supplies in 2001, more attention has been paid to the national repository of lifesaving pharmaceuticals and medical supplies called the *National Pharmaceutical Stockpile Program*. This response is a component of the CDC's larger Bioterrorism Preparedness and Response Initiative and is composed of a stockpile of pharmaceuticals, vaccines, medical supplies, and equipment to augment local and state resources in a disaster situation. After a federal decision to deploy, a "push package" will arrive by ground or air in 12 hours or less at any location in the United States. A CDC team accompanying the push package will then define shipments in the second phase.[118]

Security and Casualty Reception

Security is a major concern during natural or man-made disasters. Desire to seek immediate medical evaluation, panic, and curiosity are factors that place the healthcare facility and its personnel under enormous strain. Internal and external traffic control, protection of personnel involved in the response effort, and strict enforcement of staging and triage areas are key security-related issues. Law enforcement plays a more critical role during terrorist attacks or bioterrorism, and failure to maintain order will lead to rapid overwhelming of the facility's resources and a disorganized medical response. Because most victims will arrive at the hospital by foot or by personal vehicles, provision must be made for a predetermined staging area with adequate mass decontamination facilities and respiratory protective equipment.[114,119]

ISSUES UNIQUE TO THE INTENSIVE CARE UNIT

The responsibility of caring for the most serious salvageable casualties in natural and man-made disasters will ultimately involve the critical care physician. As opposed to the overwhelming shortage of resources, lack of coordination among various agencies and specialties has been often cited as the main contributing factor to an ineffective emergency medical response. This response therefore requires the cooperation of not just physicians but also among prehospital medical personnel, nurses, and ancillary services such as radiology and laboratory services.[53]

Possible roles for the intensivist as part of a disaster management planning team include the following:

1. Clear role definition and understanding of the overall organization of the emergency response plan
2. Knowledge of the usual limit, surge capacity, and absolute limit of ICU resources
3. Construction of appropriate staffing models

CRITICAL CARE IN UNCONVENTIONAL SITUATIONS

Mobile ICU Teams

There have been numerous examples in the medical literature describing extended critical care through mobile ICU teams. Using mobile ICU teams has not been restricted to disaster settings but has also been used throughout the world during peacetime. Various factors that have to be considered in forming ICU teams are discussed next.

Personnel

On the basis of the anticipated needs of the disaster, appropriate specialists and ancillary personnel are chosen. Given the complexity and inherent unpredictability of staffing for disaster management, a flexible and adaptable approach must be taken to staffing such events.[120]

Training

Adequate predeparture training is essential for a coordinated and effective response. In addition, interaction and onsite training ensure effective functioning of a foreign medical unit and allow for the smooth transition of care to local physicians when the foreign team departs.[96]

Casualty Assessment

Studies from the past and also the experience of the IDF in providing care to earthquake victims in Turkey showed that the effectiveness of mobile ICU teams was limited by time. It may take 3 days to mobilize such an effort, and crucial time is lost before delivery of care. Efforts must thus be made to epidemiologically assess the efficacy of such teams. They should include review of the overall effort and adequacy of the ICU teams, outcome of victims, operational costs, and analysis of the structure and process of the ICU in the field.[120]

CRITICAL CARE TRANSPORT

Common principles involved in the safe transport of patients include the following[120]:

1. Rapid assessment of the severity of injuries, recognition of the need for transport, and anticipation of problems during transport
2. Safe movement of patients in and out of vehicles, continuous monitoring of vital signs, and recognition and treatment of problems encountered during transport
3. Documentation of the events during transport and provision of a detailed report to the admitting personnel

Types of Transport

Ground Transport

Ground ambulances have the advantage of rapid deployment, high mobility, and lower cost. However, patients and equipment are subject to significant deceleration and vibration forces. Equipment may vary depending on the size of the ambulance and usually includes blood pressure and electrocardiograph monitors, pulse oximeters, ventilators, and in some cases, modern support devices such as intraaortic balloon pumps.

Air Transport

It is beyond the scope of this chapter to provide a full detailed discussion of fixed-wing or rotary aeromedical transport, but it may be necessary during certain disasters to extricate victims via air.[120]

CONCLUSION

Understanding the characteristics of different disasters, developing an interdisciplinary approach to hazard mitigation, and knowledge of related clinical syndromes are key to an effective medical disaster response. To ensure an integrated and effective response to future disasters, it is necessary for critical care physicians to understand the fundamental principles in disaster medicine and participate in the disaster-planning process.

KEY POINTS

- Disaster medicine is a unique specialty that has evolved over the past few years. It shares a common ideal with public health: "greatest good for the greatest number." Critical care medicine forms an indispensable part of this science because intensive care physicians not only care for the sickest of the salvageable patients in any hospital but also bring with them their clinical expertise in triage, resuscitation, and help in providing care outside the domains of the unit through mobile ICU teams.
- Clear, common, and concise definitions are important in effective communication and evoking appropriate responses to disaster situations. The concept of functional impact of a disaster on the healthcare system is paramount while classifying disasters.
- It is important to understand the common effects of different natural and man-made disasters to predict their impact on the healthcare system. Even though man-made disasters such as terrorist attacks have gained attention, the numbers of geophysical disasters such as earthquakes, floods, and hurricanes have remained fairly constant and place the greatest burden on the healthcare system.
- Disaster situations produce many unique medical syndromes that require specific therapy. Knowledge and immediate recognition of different medical syndromes with appropriate interventions is critical to minimizing morbidity and mortality.
- Disaster planning includes developing action programs to minimize loss of life and damage during a disaster, training healthcare personnel and civilians, coordinating response efforts, maintaining adequate supplies of equipment and personnel, and rehabilitating the community after the disaster. Knowledge of potential man-made and natural disasters to which the community is prone should be an integral part of the planning process. Common principles involved in the creation of an emergency response plan should be followed and applied from an ICU perspective.
- With their natural role of caring for critically ill patients, intensivists bring with them unique abilities that can be applied to a disaster situation: a multidisciplinary approach to patient care, management skills, procedural expertise, and flexible attitudes.
- Intensivists can also provide care outside the domains of the ICU through mobile ICU teams and transport of critically ill patients. Various factors have to be considered in forming such teams and in the safe transport of patients.

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Telemedicine in Intensive Care

Alejandro J. Lopez-Magallon, Joan Sánchez-de-Toledo, and Ricardo A. Muñoz

Worldwide, there is a need for novel strategies to alleviate the lack of specialized medical care, including critical care medicine. Societal changes in demographics, epidemiology, and culture, in addition to significant technologic advances, have positioned telemedicine as a useful tool to narrow the gap between available and needed medical care. Thus far, it has proved to be a disruptive technology, potentially altering traditional paradigms in the critical care environment, particularly in medical education, team organization, medical licensing, quality improvement, disaster response, and research. A recent report estimated that 13% of non–federal-funded hospital adult intensive care unit (ICU) beds were supported by some form of ICU telemedicine program.[1] Despite its relative novelty and rapidly changing technology and legislation, additional information has accumulated in the last few years suggesting potential features that can be leveraged to achieve an ideal model of tele-ICU care. Here we present our perspective for the current state-of-the-art and practical considerations on these matters (Fig. 169.1).

DEFINITION

Telemedicine can be described as the use of electronic information and telecommunications technologies to support and promote long-distance clinical health care, patient and professional health-related education, public health, and health administration. Technologies include videoconferencing, the Internet, store-and-forward imaging, streaming media, and terrestrial and wireless communications.[2]

Potentially related benefits may include improved access and enhanced efficacy, quality, and efficiency in the delivery of healthcare services, in addition to equality in distributing scarce resources and the reduction of costs.

Although we can track the use of telecommunications with this purpose to the first half of the 20th century in Australia[3] and decades later with the National Aeronautics and Space Administration (NASA)[4] and the space race,[4] it was not until the past 2 decades when critical technologic developments allowed for an explosive increase in its use as an alternative for overcrowded traditional models of care.

Traditionally, telemedicine modalities can be classified into store-and-forward, real-time, or remote monitoring. In store-and-forward, medical information is sent electronically to a remote physician for assessment offline, without direct simultaneous interaction between a remote medical team and a telemedicine physician. In the real-time mode, a direct video interaction exists between a telemedicine physician (or a physician extender) and a remote patient, physician, or medical team. Finally, remote monitoring implies the monitoring of a patient from a distance using different technologies depending on the physiologic system to be followed.[5]

TELEMEDICINE IN INTENSIVE CARE

The implementation of a new tele-ICU program should focus on each one of the following aspects:

1. Telemedicine-related laws and regulations at state and national levels
2. Technologic platform
3. Staffing
4. Model of care

Telemedicine-Related Laws and Regulations

There are basic elements that any telemedicine program should consider to comply with national and state laws, in addition to technical regulations pertaining to the particularities of the telemedicine interaction (Box 169.1). The American Telemedicine Association has published core guidelines for baseline technical requirements and telemedicine operations and guidelines for tele-ICU operations in particular.[5] Policies that foster telemedicine use are being promoted in most states (state parity laws) and should be consulted to adjust the tele-ICU program model accordingly, given that they will affect reimbursement and credentialing.[6] In broad terms, signed patient consent must be obtained and patient confidentiality should be preserved at all times regardless of the model of care used in any tele-ICU program. A practitioner licensed in the state where the medical care is being delivered is mandatory during the teleconsultation, and by-proxy credentialing issues should be addressed between connecting hospitals. The Interstate Medical Licensure Compact is an agreement between 29 states, the District of Columbia, and the territory of Guam, offering an expedited way for licensure in those states participating in the compact.[7] Moreover, documentation of the telemedicine consult should be in the patient's medical record.

Finally, the unique setting of virtual telepresence results in distinct communication needs that are different from the regular onsite, traditional team interactions and "telemedicine etiquette" (Box 169.2). They should be kept in mind during telemedicine consultations to be efficient in the art of "the systematic finding and delivery of bad news to the remote team."

Technologic Platform

Robust information technology (IT) department support is needed to ensure seamless and safe communication between the tele-ICU team and remote ICUs.

The cost-efficiency of a tele-ICU technologic platform reached a critical point a few years ago, when data transmission migrated from costly dedicated optical cable networks to wireless encrypted communication via the Internet.[8]

The technologic infrastructure should conform with the IT policies of the enterprise. Devices must have up-to-date security software, and systems must comply with all current and applicable state and federal

Fig. 169.1 Telemedicine suite. Wall screens, from *left to right panels*: Panoramic room cameras, ICU summary snapshot, room video cameras, and AI sniffing algorithm. Remote monitoring screens not shown. Telemedicine stations for access to remote EMR. *AI,* Artificial intelligence; *EMR,* electronic medical record; *ICU,* intensive care unit.

BOX 169.1 Telemedicine-Related Laws and Regulations

- National telemedicine laws
- State parity laws US
- Patient confidentiality/consent (Health Insurance Portability and Accountability Act)
- By-proxy credentialing

BOX 169.2 Telemedicine Etiquette

- Identify yourself and the remote team
- Ensure patient confidentiality
- Respect the remote team's work
  - Listen to the remote team first
  - Connect in time
  - Keep teleconsultations as brief as possible
- Comply with telemedicine laws and regulations
- Objectively evaluate the patient
- Provide advice based on the best available evidence

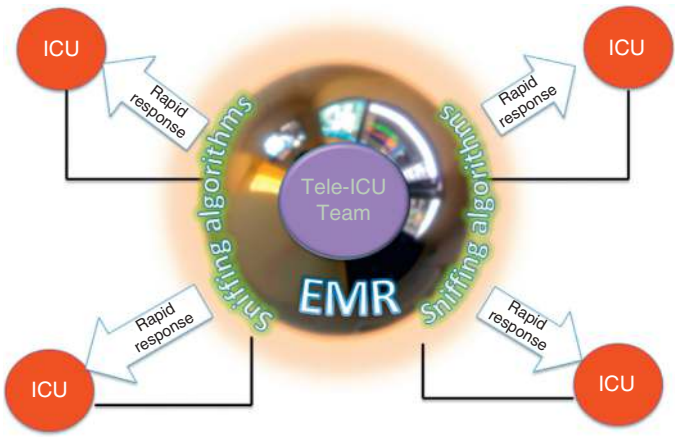

Fig. 169.2 Diagram of a state-of-the-art tele-ICU. An electronic database with physiologic data and other medical information is updated in real time in the EMR. A tele-ICU team works on surveillance of patient information assisted by remote monitoring, EMR, and sniffer algorithms. Once a dangerous trend is detected, the patient is reviewed with the remote team and a response is elicited. *EMR,* Electronic medical record; *ICU,* intensive care unit.

laws and regulations governing the use of medical devices and medical information: Food and Drug Administration (FDA), Health Insurance Portability and Privacy Act (HIPAA), Health Information Technology for Economic and Clinical Health (HITECH), and Waste Electrical and Electronic Equipment (WEEE).[5] Depending on the scope of the particular tele-ICU program, minimal hardware could include a simple telemedicine cart on both ends, escalating to a fully autonomous robotic telepresence with access to remote electronic medical records (EMRs), medical imaging, and monitoring systems supplemented with automated rapid response algorithms[9,10] (Fig. 169.2).

Staffing

Given the significant disparity between available and needed qualified specialists to meet current safety standards, the Leapfrog group has endorsed telemedicine as an appropriate alternative to reach these goals.[11] It would be wise then to redesign the workflow of the existent and future ICU staffing considering the telemedicine time. In those tele-ICU programs with staff dedicated mainly to telemedicine, a minimum amount of time of direct clinical practice must be ensured to maintain proficiency.

Reimbursement for telemedicine care remains a significant challenge. In a national survey, 55% of respondents reported not billing for telemedicine services.[12] A number of tele-ICU ventures have jumpstarted their programs with the assistance of grants. A common arrangement is also a contractual arrangement between connecting hospitals.

Model of Care

Clinical models for tele-ICU can be classified in the following manner:

- Continuous care model: Continuous care is monitoring of the patient without interruption for a defined period (e.g., on an 8-, 12-, or 24-hour basis).
- Scheduled care model: Scheduled care occurs with a periodic consultation on a predetermined schedule (e.g., during patient rounds).
- Responsive (reactive) care model: In this model virtual visits are prompted by an alert and are unscheduled (e.g., telephone call, page, monitor alarm).[5]

Tele-ICU in Adult Patients

Different models of care have been adapted for telemedicine in the critical care environment.[13] These models can range from physician-to-physician consultation with limited[14] tele-ICU team involvement to fully autonomous telemedicine team intervention without the need of the presence of a physician in the remote place. Consequently, reports in the intensive care settings have shown conflicting findings related to any effect from a telemedicine system in patient outcomes.[15]

The reason for these discrepancies is not completely understood, and the quality of reported data has been suboptimal. In a systematic literature review and meta-analysis, Young and colleagues investigated more than 721 critical care and telemedicine articles and 2683 critical care or telemedicine abstracts, including 13 studies with more than 41,000 patients in their final analysis. The tele-ICU coverage was associated with a significant reduction in ICU mortality and length of ICU stay but not with in-hospital mortality or length of hospital stay. There was a significant degree of heterogeneity in the studies included in their analysis and a striking degree of variation in how tele-ICU coverage was defined, the hospitals where it was evaluated, and the impact that tele-ICU coverage had on patient outcomes.[16]

Kahn has proposed a conceptual model to describe potential factors influencing program success (Fig. 169.3).[17] In this model, the effectiveness of a tele-ICU program was influenced by characteristics of both target hospitals and ICUs, in addition to the telemedicine unit itself. When optimal, these characteristics may facilitate timely interventions and guideline adherence, leading to improved quality and efficiency of care. When suboptimal, telemedicine fails to change practice patterns and thus fails to improve quality.[17] Using a novel ethnographic approach to evaluate 10 telemedicine programs, this same team found that the effectiveness of a tele-ICU program was influenced by the interaction of factors within the domains of leadership of both the tele-ICU program and the facility providing remote care, the perceived value of the program by front-line care providers, and the organizational characteristics of the telemedicine program.[18]

A growing body of evidence has accumulated over the years, suggesting a decrease in mortality and better quality of life associated with implementing tele-ICU programs in the critical care process. Lilly and colleagues, in a multicenter report including 432 patients from 56 different ICUs, observed that those tele-ICU interventions with early intensivist case involvement, adherence to best ICU practices, reduced response times to alarms, and that encouraged use of performance data were associated with lower mortality and length of stay (Fig. 169.4).[19,20] Likewise, in a program led by nurses screening best practices in ICU patients, Kahn and colleagues found improvements in the quality of care and a decrease in mechanical ventilation days and length of stay but no impact on mortality.[21]

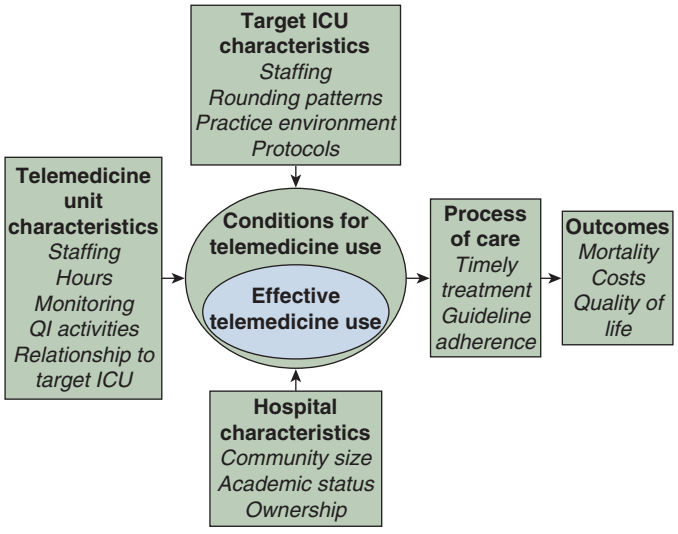

Fig. 169.3 Conceptual model for ICU telemedicine effectiveness. Under this model, the effectiveness of ICU telemedicine is determined by identifiable characteristics of the target hospital, the target ICU, and the telemedicine unit. *ICU,* Intensive care unit; *QI,* quality improvement. (From Kahn JM. ICU telemedicine: From theory to practice. *Crit Care Med.* 2015;42:2457–2458.)

Tele-ICU in Pediatric Patients

The disparity between available and needed expertise in critical care may be even more acute in children. The Institute of Medicine has reported that most children receive emergency care in general hospitals. Although children make up 27% of all emergency department (ED) visits in the United States, only 6% of these EDs are properly equipped for pediatric emergencies. This likely affects the quality of care delivered to children presenting to EDs and, more acutely, in those located in underserved and rural communities.[22]

Telemedicine consultation for pediatric critical care shares similarities with the adult setting, in addition to differences arising from the unique challenges offered by different and fragmented demographics, a wide range in patient size and physiology, and the coexistence of congenital malformations, among others. Consequently, a verbatim translation of an adult tele-ICU model for these patients may be unworkable, and proper adjustments should be made in maintaining a systematic approach in the teleconsultation format.

Reports related to the use of telemedicine in pediatric ICUs are relatively scarce, with some of them related with critical care consultation to rural and isolated populations. Heath and colleagues conducted 63 teleconsultations in 10 rural EDs. Most of the communications occurred without significant technical issues, and in 40% of them telemedicine was used to supervise the critical care transport team. A survey reported high satisfaction among consulting and referring physicians, with most of the providers perceiving telemedicine as improving patient care, being superior to telephone conversations, and allowing good provider-to-provider communication.[23] Yager and colleagues reviewed 56 consecutive telemedicine consultations for pediatric patients in the critical care setting. Communications occurred with the pediatric critical care fellow in 100%, nursing staff in 68%, and parents in 66% of their teleconsultations. Patient assessment, communication with the multidisciplinary care team, and communication with a patient's family were the outcomes most often cited that would not have been possible via telephone. A change in medical management was noted after 32% of encounters.[24]

The use of an appropriate pediatric tele-ICU can facilitate decision making in remote sites, allowing for a more selective referral of patients to tertiary centers. This is of particular interest in the neonate with cyanosis. In a study from a prospectively collected multicenter database in infants matched for gestational age, weight, and diagnosis, Webb and colleagues reported that telemedicine shortened the time to diagnosis and significantly decreased the need for transport of infants with mild or no heart disease. They also found that the length of hospitalization and intensive care stay and the use of indomethacin and inotropic support were less in telemedicine patients compared with patients in centers without the availability of telemedicine.[25]

More recently, Berrens and colleagues reported that rapid-response and code-response teams at a satellite facility supported via telemedicine by a pediatric intensivist were able to provide timely and reliable support, with no patients transferred from the satellite campus requiring a rapid escalation of care.[26]

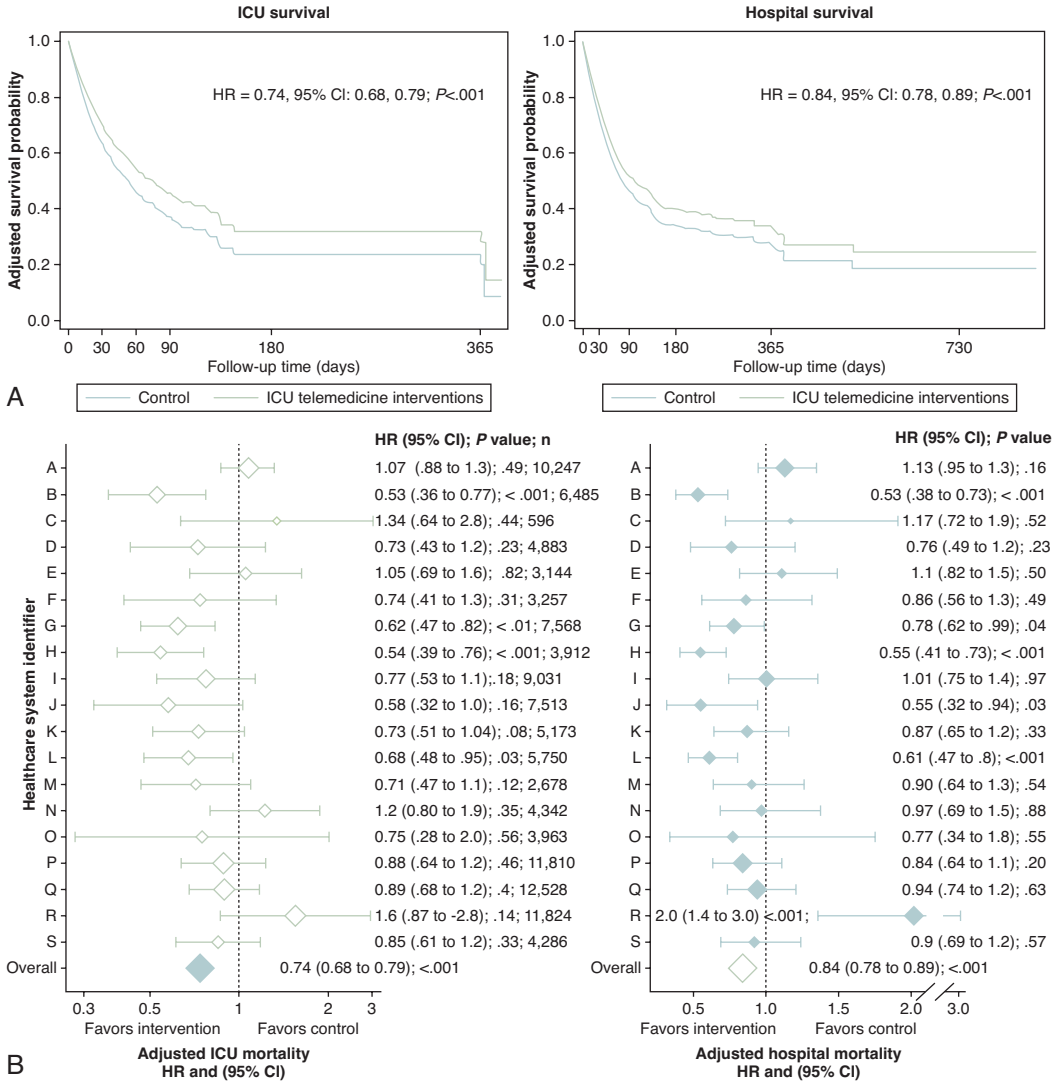

Fig. 169.4 **A,** Adjusted ICU-specific *(left)* and hospital-specific *(right)* survival estimated by Cox proportional hazards regression. Models adjusted for APACHE IV score, age, hospital, or ICU identifier (as a random effect); admission source; primary admission diagnosis; operative status; time from start of study enrollment; heart rate; admission and highest creatinine values; respiratory rate; admission hematocrit value; blood urea nitrogen; white blood cell count; Glasgow Coma Scale score; prothrombin time; anion gap; urine output (in the first 24 hours); base excess; and total bilirubin and albumin values. **B,** Adjusted ICU-specific *(left)* and hospital-specific *(right)* survival estimated by healthcare system. The *center of the diamond* represents the effect estimate, the *bars* represent 95% CIs, the *symbol size* is proportional to the number of observations for the corresponding healthcare system, and the overall effects are presented as *diamonds in the bottom row*. *CI*, Confidence interval; *HR,* hazard ratio; *ICU,* intensive care unit. (From Lilly CM, McLaughlin JM, Zhao H, et al; UMass Memorial Critical Care Operations Group. A multicenter study of ICU telemedicine reengineering of adult critical care. *Chest.* 2014;145:500–507, Fig. 2.)

We have reported our own experience with telemedicine in pediatric cardiac critical care in the international setting, eventually expanding to four hospitals in two Latin American countries. We conducted 1040 teleconsultations for 476 patients, 62% of them being in the most complex surgical patients. There was a difference in overall satisfaction, perception about telemedicine usefulness in education, and impact on medical practice among centers. We concluded that a "one-size-fits-all" approach may not be feasible in most international telemedicine settings, and prospective interventions should consider differences in staff composition, perception of needs, and patient population among centers.[27] In one of the international hospitals participating in our telemedicine program, we conducted a retrospective review of clinical records and a telemedicine database of patients admitted there during the initial 10 months of our program and compared with patients admitted during a preintervention period. We observed a shorter cardiac ICU and length of hospital stay in cardiovascular patients and a shorter preoperative and cardiac ICU length of stay in surgical patients.[28] We found also that the implementation of telemedicine-assisted interventions in their pediatric extracorporeal membrane oxygenation (ECMO) program delivered valuable diagnostic and therapeutic advice, was associated with significant changes in selection criteria and model of care, and provided a

significant increase in patient survival during the telemedicine period as compared with a historical cohort from the same institution (from 29.4% to 54.4%).[29]

Tele-ICU in Disaster Response

Probably one of the most compelling arguments for implementing a tele-ICU program is the continuous training and readiness for disaster response. In such dire situations and despite apparent preparedness, mid-course corrections or the need for improvisation is a common occurrence, including failure in logistics and communications. Although it is true that the very nature of natural or man-made disasters presents unique challenges in every new presentation, it is also true that many of these problems arise from the fact that once disaster response plans are made, they often end stored and forgotten, and the teams eventually become untrained. Reynolds and colleagues. published their experience with the use of a previously established tele-ICU program for disaster relief during the winter 2009 blizzards in the Baltimore metropolitan area. Given they had been using a telemedicine system for 5 years on a routine basis, they transitioned seamlessly to disaster response mode, conducting daily ICU rounds and coordinated care with the onsite team, assisted by robotic telepresence[30] together with remote access to EMR and imaging studies.

TELE-ICU IN THE FUTURE

Tele-ICU is an ever-growing field. The current supply-demand estimates in adult critical care project a need for tripling the capacity of ICU case days compared with 2006. This is not and will not be sustainable in the foreseeable future.[31] Hence, a different paradigm for ICU care needs to be developed. Telemedicine will undoubtedly be an integral part of this new approach, Tele-ICU programs will advance their integration with powerful artificial intelligence (AI) tools, allowing for earlier intervention and avoidance of adverse events,[10,11,32] perhaps enabling critical patients to be treated closer to their homes, family, friends, and support network while empowering local teams, providing best-evidence guidelines and quality assurance, and accelerating the decision-making process to expedite definite treatment or else more compassionate, palliative, or end-of-life care. Integration through a continuum from home and the community to the critical care environment will incorporate early preventive strategies aimed at well-being preservation and risk avoidance, rather than the current reactive approach toward already established critical care disease, connecting presently disjointed practices in ambulatory medicine and critical care.

KEY POINTS

- Tele-ICU has become a reliable strategy to enhance care in critically ill patients.
- Fields potentially affected by telemedicine include medical team organization, medical education and licensing, quality improvement, disaster response, and research.
- Tele-ICU operations should be in compliance with international, national, state, and local laws and regulations.
- A systematic approach including quality improvement interventions may yield the best results in patient survival and length of stay.
- Units with low-intensity day staffing may benefit the most from tele-ICU.
- Pediatric critical patients present unique challenges, but experience is growing rapidly.

Full references for this chapter can be found at expertconsult.com.

ANNOTATED REFERENCES

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This document was endorsed by the American Association of Critical-Care Nurses and the Society of Critical Care Medicine, laying the basic organizational principles for tele-ICU operations.

Berrens ZJ, Gosdin CH, Brady PW, et al. Efficacy and safety of pediatric critical care physician telemedicine involvement in rapid response team and code response in a satellite facility. *Pediatr Crit Care Med.* 2019;20(2):172–177.
In this cross-sectional single-center study conducted in a tertiary pediatric center and its satellite facility to evaluate a telemedicine model to provide pediatric intensivist involvement in rapid response and code teams at the satellite facility, the authors found telemedicine critical care teams were involved in satellite campus rapid-response team activations 94.6% of the time with a median response time of 7 minutes, with a similar ratio of patients transferred to the pediatric ICU (PICU) when compared with the monthly rate at their main campus. They concluded that telemedicine was a reliable, timely, and effective alternative to facilitate critical care involvement in rapid-response and code teams at satellite facilities.

Kahn JM, Rak KJ, Kuza CC, et al. Determinants of intensive care unit telemedicine effectiveness. An ethnographic study. *Am J Respir Crit Care Med.* 2019;199(8):970–979.
The authors used an innovative approach conducting a qualitative study with an ethnographic evaluation of six tele-ICU programs and 10 target ICUs, including numerous interviews and focus groups, comparing results between effective vs. less effective programs. They suggest that the effectiveness of ICU telemedicine programs may be influenced by several potentially modifiable factors within the domains of leadership, perceived value, and organizational structure. It is a useful reference for new and established tele-ICU programs.

Lilly CM, McLaughlin JM, Zhao H, et al. A multi-center study of ICU telemedicine reengineering of adult critical care. *Chest*. 2014;145(3):500–507.
In this large, multicenter, nonrandomized, pre/post assessment of telemedicine interventions in more than 100,000 adult ICU patients, the authors found that interventions that increased early intensivist case involvement, improved adherence to ICU best practices, reduced response times to alarms, encouraged the use of performance data, and were associated with lower hospital mortality and length of stay.

Lopez-Magallon AJ, Saenz L, Lara-Gutierrez J, et al. Telemedicine in pediatric critical care: A retrospective study in an international extracorporeal membrane oxygenation program. *Telemed J E Health*. 2018;24(7):489–496.
In this retrospective, pre-post intervention study in an international pediatric ECMO program, we found that the implementation of telemedicine-assisted interventions was associated with significant changes in selection criteria and model of care and increased hospital survival. Valuable diagnostic and therapeutic advice was offered, with 19% and 17% of patients receiving a recommendation for diagnostic cardiac catheterization or additional surgical intervention, respectively.

Webb C, Waugh C, Grigsby J, et al. Impact of telemedicine on hospital transport, length of stay, and medical outcomes in infants with suspected heart disease: A multicenter study. *J Am Soc Echocardiogr.* 2013;28(9):1090–1098.
This was a prospective telemedicine intervention study conducted in nine pediatric cardiology centers comparing infants born at hospitals with telemedicine access to remote cardiology consultation with those without telemedicine access as controls. Telemedicine access shortened the time to diagnosis and decreased the need for transport in infants with mild or no heart disease. Also, length of stay and need for indomethacin or inotropic support were less in the telemedicine group. An important reference in the pediatric world making the case for telemedicine—enabling expedited access to specialty care, empowerment of local teams, and allowing more patients and families to stay closer to home.

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Teaching Critical Care

Christopher K. Schott

INTRODUCTION

As a specialty, critical care medicine has many unique challenges when it comes to teaching trainees. The intensive care unit (ICU) is an environment with high stakes and time-sensitive decision making for acutely ill patients with multiple competing demands for time balanced against learners across multiple levels of training (medical students, residents, fellows) and backgrounds (internal medicine, surgery, anesthesia, emergency medicine, neurology, nurse practitioners, physician assistants, pharmacists, etc.).[1–3] Given these challenges, it is helpful to know that the skills necessary to be a high-quality, effective teacher are able to be learned with an understanding of the principles of adult learning in addition to developing a toolbox of methods to teach depending on the topic or circumstances. The goal of this chapter is to provide a review of adult learning theory and curriculum development to aid in learners' ability to acquire knowledge and skill for critical care.

THE ROLE OF THE EDUCATOR

Teaching success should be measured in terms of student performance, not the activities of the teacher. Delivering a carefully organized PowerPoint presentation, supervising problem-based workshops, or providing bedside clinical tutorials does not mean one has taught. Unless the learner has acquired new cognitive or psychomotor skills, teaching has not occurred.[4] An effective teacher takes responsibility for ensuring that students learn.

Stritter and Bowles described a model focused on the student.[4] In this model, the teacher assumes responsibility for the learner's success and creates an environment conducive to learning by managing the educational resources. The teacher as a "manager" creates specific educational objectives, motivates students, uses various educational strategies, evaluates learning, and provides effective feedback to ensure the learner achieves all the educational objectives.[4] Using this learner-centric approach, educators can start to think of themselves less as the "sage on the stage" presenting information and more as the "guide on the side" to help learners achieve success assimilating new information.[5]

ADULT LEARNING THEORIES

There are multiple theories that describe how individuals learn. In particular, there are several pillars that describe the principles of adult learning. Ôª øMalcolm Knowles's andragogy demonstrates the principles that drive adult learners: (1) learning is more self-directed; (2) learning is based on the scaffolds of prior experiences; (3) adults are more motivated to learn things directly related to their roles; (4) adult learning is more problem than topic centered; (5) there is a greater emphasis on internal or intrinsic motivation than extrinsic drivers; and (6) adults need to understand *why* there is a need to learn the material.[6,7] Kolb describes this model as "experiential learning," further supporting the need for adult learners to base new knowledge on both prior experiences and the ability to "play" with the novel concepts to help cement into more permanent learning.[8] This is essential to keep in mind when dealing with more mature learners composing a critical care team. Early learners, such as medical students or residents, may be driven more by external factors, such as a rotation evaluation or grade, compared with senior residents, fellows, or junior faculty who have more intrinsic motivation to recognize the need to learn material for their delivery of patient care.

This transitions into the importance of developing an appropriate learning environment. Learners retain more when they feel comfortable and safe as opposed to situations where there may be fear or anxiety.[7,9] This is derived from the "brain-based learning" principle of "relaxed alertness," whereby learners are inhibited from processing new information into long-term memory when the predominant emotion is a stress or fear response.[10] Therefore an optimal learning environment should strive to balance presenting learners with level-appropriate challenges in an environment where they feel safe to play, process, and retain the information they are being presented.

Together, these principles should guide educators on ways to optimize their students' or trainees' ability to successfully gain new knowledge and skills. The following sections describe different ways to deliver information and develop curricula based upon these learning theories.

CURRICULUM DEVELOPMENT

Educational objectives outline the skills and behaviors the learner will be able to demonstrate after the teacher has completed a lecture, daily bedside instruction, 1-month elective, or fellowship training. Objectives should be developed for every instructional activity because they are a road map. They guide the teacher in developing an appropriate curriculum, set unambiguous expectations for the learner, and serve as a reference for evaluation and feedback.[11,12] Developing educational objectives involves the following three steps.

First, using action verbs (e.g., defines, explains, demonstrates, identifies, summarizes, evaluates), the instructor describes a specific behavior the learner must perform to show achievement of the objective. An objective such as "teaches concepts of airway management" is not adequate because it defines what the teacher is doing and does not clearly describe what the learner should be demonstrating. Therefore it neither serves as a road map for the teacher or the student nor identifies a clear behavior the teacher can evaluate. Second, the teacher should describe the conditions under which the behaviors are to occur. For example "given a scenario using simulation, the student will evaluate the airway and demonstrate effective bag-mask ventilation." Finally,

the criteria for acceptable performance should accompany the objective—that is, "bag-mask ventilation will be followed by successful laryngotracheal intubation within 30 seconds." When written for a lesson plan or formal curriculum, the format of a learning objective should be "who" (learner) will "do what" (knowledge or skill being taught) by "when" (end of lecture, curriculum, or course) as measured by "how" (the method of evaluation).[13]

When teaching students a specific clinical skill—for example, how to manage a patient with hypotension—the teacher must establish that the learner has first mastered the lower cognitive domains, knowledge, and comprehension. This is called *scaffolding* and is based on a classical hierarchy of levels of comprehension described by Bloom.[14,15] Learners will not be able to initiate an appropriate treatment for hypotension or evaluate effectiveness of treatment unless they can first list the causes of hypotension and describe the effect of preload on stroke volume. The teacher can ask some simple questions to better understand what level of cognitive domain the student is at, as well as asking subsequent questions to advance the learner to the higher level. Using an example from the treatment of heart failure, a teacher could start with a comprehension-level question such as "What is the mechanism of action of furosemide?" This can advance to a higher level, such as analysis, with the instruction "Identify the differences in development, presentation, echocardiography, and treatment for patients with systolic versus diastolic heart failure." At the highest-level evaluation, an instruction might then be "Evaluate the evidence to support the role of angiotensin-converting enzyme inhibitors in the symptomatology, rates of hospitalization, functional status, and mortality for patients with systolic heart failure." Table 170.1 demonstrates Bloom's taxonomy, built against a hierarchy of learner competency (using the Dreyfus model of skill acquisition and the RIME framework) with example verbs to use when constructing questions for each learner level.[15-18]

Educational objectives specifically related to critical care medicine training programs should be developed in accordance with the expectations outlined in the Accreditation Council for Graduate Medical Education (ACGME) program. In addition to listing the specific cognitive and motor skills that must be taught, the ACGME has developed general core competencies that focus on patient care and not just knowledge acquisition.[19] The six competencies include medical knowledge, patient care, interpersonal and communication skills, professionalism, practice-based learning, and systems-based practice. In recent years, the ACGME has evolved from simply assessing trainees subjectively on these competencies to an evaluation system of milestones through clinical competency committees with better-defined anchors for expected progression based on each clinical specialty.[20] Examples of educational objectives for each competency and details of each specialty's milestones are available at www.acgme.org.

LEARNING EXPERIENCES

There are numerous instructional methodologies a teacher can use to achieve educational objectives. Because adult learners prefer active learning, a curriculum that requires them to process information, participate in problem solving, and defend clinical judgment increases their enthusiasm for learning.[21]

Although frequently used, traditional lectures are not an efficient learning method.[22] There are growing challenges to attending lectures with limited time and competing activities for medical trainees. Moreover, because didactic sessions are not interactive, the teacher does not have an opportunity to assess whether the learner understands the content and its applicability. In contrast, small group sessions that incorporate problem-based learning and interactive workshops are more effective because they engage the students, force them to defend their decisions, and explain how they evaluate outcomes.[22]

A more contemporary model of an efficient learning environment is that of the "flipped classroom."[23–26] A flipped classroom design is one where the students review the core content, such as renal replacement therapy, before attending the session and then use the time with the instructor to work through cases or problems and provide direct formative feedback. This provides the ability to present material individually to learners at their own pace while focusing on learner-centered activities to reinforce the new knowledge or skills in a classroom, small group, simulation, or clinical setting.[1] The growth of recording technology provides the opportunity for an instructor to prerecord core content lectures and allow their time in the classroom to be used more efficiently to answer students' questions and work through the material without needing to repeat static elements of the content. Additionally these prerecorded lectures can serve as an online reference library for students to return to for review or when they might subsequently encounter a particular topic in clinical practice.[27]

However, none of these methods teaches students or residents how to apply these skills to real-life situations. It is possible that giving students an opportunity to manage complex problems and anticipate consequences of their interventions in an environment where their mistakes do not result in untoward outcomes, where feedback is immediate, and where students can repeat their performance until they acquire these skills might improve retention of new knowledge and skills. Such instructional opportunities exist and have been available for years in the form of simulation.

Simulation is defined as any training device that duplicates artificially the conditions that are likely to be encountered in an operation and may include low tech, partial task trainers, simulated patients, computer-based simulation, and whole-body realistic patient simulation. Work in cognitive psychology and education theory suggests that more effective

TABLE 170.1 HIERARCHY OF LEARNING COMPETENCIES Comparing the RIME Framework, Dreyfus Model, and Bloom's Taxonomy With Example Verbs to Question Learners at Each Respective Level

RIME	Dreyfus's Skill Level		Bloom's Taxonomy Learner Level	Example Verbs for Questioning Learners
Educator	Expert	Master	Evaluation	Debate, Discuss, Judge
	Proficient Performer	Expert	Synthesis	Compose, Hypothesize, Predict
Manager	Competent Performer	Proficient	Analysis	Compare, Contrast, Classify
Interpreter	Advanced Beginner	Competent	Application	List, Construct
Reporter	Novice	Novice	Comprehension	Describe, Explain
			Knowledge	Who, What, When, Where, Why, How

learning occurs when the educational experience provides interactive clues similar to situations in which the learning is applied.[28,29]

What initially began as computerized software with a separate torso apparatus has evolved into complex whole-body computerized manikins. Current models, such as the Laerdal SimMan 3G simulator, provide trainees a high-fidelity manikin that can have spontaneous respirations, palpable pulses, pupils that react to light and can constrict (unequally if desired), sweat, seize, demonstrate cyanosis, and simulate various difficulties for airway management. Moreover, the trainees can practice skills such as bag-valve-mask ventilation, nasal or orotracheal intubations, cricothyroidotomy, chest tube placement, needle decompression, closed chest compressions, cardiac pacing, and electrical defibrillation, among other procedures, with real-time feedback provided.[30] These computerized human simulators require trainees to integrate cognitive and psychomotor learning along with multisensory contextual cues to aid in recall and application in clinical settings.[31,32] Several publications have demonstrated the success of using simulation to emphasize team-based, multidisciplinary models with the ability to conduct in situ to maximize authenticity for the learners.[33] Examples of learning objectives for fourth-year medical students using the simulator are listed in Table 170.2. Note that all objectives are written in terms of behaviors the student must perform, thus giving the teacher clear guidelines for evaluation.

Though no study has unequivocally demonstrated improvement in actual patient outcomes,[33] and despite not showing these results in published data to present, simulation addresses the fundamentals of adult learning discussed previously. Simulation provides hands-on experiences without any direct risk to patient safety and can simultaneously address the cognitive, psychomotor, and affective domains of learning that are essential to a successful curriculum. Moreover, organizations such as the Institute of Medicine endorse simulation as a tool to teach novice practitioners problem-solving and crisis management skills.

TABLE 170.2 Learning Objectives for Fourth-Year Critical Care Medicine Course

Respiratory Distress
- Evaluate a simulated patient in respiratory distress (tachypneic and hypoxemic).
- Initiate appropriate oxygen therapy.
- Evaluate effectiveness of therapeutic intervention.
- Demonstrate effective bag-mask ventilation.
- Insert intravenous catheter for resuscitation.
- Evaluate patient for potentially difficult airway.

Cardiovascular
- Evaluate a patient with hypotension.
- Initiate therapy for a patient with hypotension (initiate intravenous fluids).
- Order appropriate diagnostic tests for evaluation of a patient with hypotension.
- Evaluate effectiveness of therapeutic intervention.
- Evaluate a patient with sinus tachycardia, develop a differential diagnosis, and order appropriate diagnostic tests.

Arrhythmias
- Evaluate a patient with sinus tachycardia, develop a differential diagnosis, and order appropriate diagnostic tests.
- Demonstrate defibrillation of ventricular fibrillation and pulseless ventricular tachycardia.
- Demonstrate airway management and cardiovascular resuscitation for simulated patients with ventricular fibrillation, ventricular tachycardia, pulseless electrical activity, and asystole.

TEACHING SKILLS AND STRATEGIES

The high-stakes and time-sensitive environment of the ICU may place the perception of constraints on clinician-educators, resulting in a perception that it is challenging to successfully teach trainees. However, there have been several widely taught and well-published skills that can easily be done at the bedside or in the ICU with minimal preparation or consumption of time. One such skill is the "one-minute preceptor."[34]

The one-minute preceptor (OME), also referred to as the "five-step 'microskills' model," aims to guide the learner by reasoning through their understanding of a topic.[3,9,35,36] It uses structured questioning and serves as a learner-centric approach, aiding the learner to arrive at a teaching point in an efficient manner while the learner is presenting a patient or clinical quandary, particularly when the learner expresses uncertainty in their decision making. It follows the structure of (1) having the learner make a commitment, (2) probe for supporting evidence, (3) provide a general teaching point on the topic, (4) reinforce correct behaviors with positive feedback, and (5) correct errors with formative feedback.[3,9,35] This can be done over the course of only a few minutes but with lasting impact for the learner.[36] In the initial step (Step 1: Commit), the learner is unable to waffle in their decision making and must take ownership of it. Regardless of whether that decision is "correct" or not, in terms of the clinical context, this provides a starting point. The instructor can use this to explore how the learner arrived at this decision through their prior experiences and knowledge (scaffolding) to understand more about the learner's thought process (Step 2: Probe). If the learner's decision was "incorrect" in that clinical context, their thought process provides the instructor the roadmap on how they arrived at that conclusion and thus a framework to help redirect. If the learner arrived at a "correct" conclusion, the instructor can use this step to help expand the learner's understanding of the topic through additional questions, following Bloom's taxonomy, to help progress the learner to a higher level of competency. This is followed by a brief, general teaching point, made by the instructor, on the topic (Step 3: Statement). This serves as a demonstration of a teaching moment by the instructor on the topic while minimizing any misperceived judgment of the learner's sophistication. This transitions into providing reinforcement and positive feedback on what the learner did correctly (Step 4: Reinforce), helping solidify the appropriate decision making while building the learner's self-esteem. The process concludes with providing formative feedback (Step 5: Correcting errors) to provide ongoing guidance for the learner's growth. This must be done with appropriate tact so as to not judge, shame, or embarrass the learner while providing effective feedback to expand their understanding of the topic.

PROVIDING EFFECTIVE FEEDBACK

The final step in being a manager of learning is to effectively use feedback to enhance learning. Too often feedback is used to fulfill an administrative function; it is provided as a summative report once the rotation is complete. This is referred to as "evaluative feedback." Conversely, "formative feedback" is provided in real time with the goal of positively changing a learner's behavior or skills. Effective feedback enhances affective learning, but when used inappropriately or done poorly, can also inhibit learning.[37]

Students want feedback; they want to know how they are performing and how their performance can be improved. Most students receive inadequate feedback during their training. Explanations for lack of feedback include a teacher's concerns that the feedback will result in unintended consequences, will damage the student-teacher relationship, or

will result in students evaluating the teacher as having performed poorly. None of these consequences will occur if the feedback is delivered correctly. Formative feedback is the only way to ensure the success of students, telling them what they have done well and, if necessary, what they need to do to achieve an educational objective. Without effective formative feedback, the behaviors go uncorrected and the student develops a system of self-validation: "I did well because no one told me otherwise."

Often, residents may have difficulty even recognizing that they are receiving feedback when it occurs in the same context of educational sessions.[38] Therefore it is important to make it explicit to the learner that feedback is being given. This can be done through asking for an invitation ("Can I provide you feedback on how you did with that procedure?") while maintaining a safe environment for the learner and overtly using the word "feedback" when it is being delivered.

For feedback to effectively change behavior without causing unintended consequences, several rules should be followed. First, all feedback should be based on how the student performed regarding a specific goal and/or objective of the program.[37] This is another reason teachers must develop clear educational objectives. They serve not only as the framework for the curriculum but also as a reference for feedback. If feedback is provided in the context of specific performance, there should be no untoward consequence.[37] For example, if the goal is for the learner to demonstrate effective bag-mask ventilation with appropriate chest excursion and adequate oxygen saturation, then the goal was either achieved or it was not. This is a statement based on an objective and is not a personal affront unless the feedback contains judgmental language. Second, feedback must include a description of how to succeed. In the example presented, if the patient was not effectively ventilated, the teacher should suggest repositioning the head, inserting an oral airway, and performing two-person bag-mask ventilation so there is a better seal with the mask. Third, the specific behavior the learner demonstrated should be addressed and not just interpreted.[37] If students are late to rounds, do not assume they do not care or are lazy. Stating the expectation that rounds begin at 7 AM and that the expectation is for the trainee to be prepared by then assigns no judgment. Fourth, for feedback to be effective, it should be an expected component of the learning tools.[37] Therefore the key to providing feedback is for it to be timely and based on an objective behavior, not a subjective trait of the student. Students should be informed during orientation that they will receive daily feedback on their performance of the stated goals and objectives. In summary, feedback should be timely, specific, and behavioral-based with suggestions for improvement. Without successfully implementing feedback, the model of teaching described by Irby is incomplete.[21]

CONCLUSION

A teacher who begins every educational session with clear objectives, creates an environment where students want to learn, applies different educational strategies, evaluates learning, and provides formative feedback will help his or her students to successfully achieve the educational objectives. These guidelines are applicable for developing a bedside teaching session, a 1-month rotation, or a multiyear curriculum.

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KEY POINTS

- A teacher, serving as a manager, develops educational objectives, motivates students, organizes the curriculum, evaluates performance, and provides feedback.
- Educational objectives are an essential component of any instructional activity, setting clear expectations for the learner and serving as a reference for evaluation by the teacher.
- Adults prefer active learning; therefore a curriculum that requires them to analyze, solve, defend, and evaluate increases their interest in learning. Medical simulation is an innovative addition to a critical care curriculum.
- The one-minute preceptor technique provides a model of questions instructors may use to guide learners efficiently and effectively.
- Formative feedback should be provided during instructional activity to ensure the student's success.

References for this chapter can be found at expertconsult.com.

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Difficult Airway Management for Intensivists

Thomas C. Mort and F. Luke Aldo

The critically ill patient, particularly the critically ill difficult airway patient, presents unique airway challenges in emergency situations outside the operating room. The risk of life-threatening complications, including anoxic brain injury, death, and long-term disability, are exaggerated in this patient group when undergoing urgent/emergent airway management in the remote location. Physical examination of the patient is helpful to identify difficult airway characteristics, yet many remain subtle or difficult to recognize in the urgent setting. Routine assessment in the elective operating room setting is more comprehensive when compared with the agitated, hypoxic, sedated, hemodynamically unstable intensive care unit (ICU) patient suffering deterioration leading to an airway intervention. Risk factors vary but include body mass index (BMI) >30, a history of difficult airway, past or current presence of head and neck tumor ± radiation therapy to the head/neck region, history of chronic obstructive pulmonary disease (COPD), current or past tracheostomy, cervical spine limitations, airway edema, mass effect, swelling (angioedema), and airway soilage (bleeding, emesis).

Critical care provided to the ICU patient is often multidisciplinary; hence, there are a variety of approaches and schema to manage the airway. Optimally, a standardized approach for airway management should be agreed upon within your institution that reflects the concerns for all specialties. Different specialties may prefer their own algorithms or guidelines for airway management, yet it is important that a standardized approach for airway management be agreed. Despite the presence of a multitude of guidelines and algorithms from regional, national, and international sources, the vast majority reflect very similar philosophies and schema to manage the known or suspected difficult airway patient. Adherence to the American Society of Anesthesiologists (ASA) guidelines is common, but not universal. Collaboration will enhance patient care and should improve safety and outcome. Combining the ASA difficult airway algorithm/guidelines with the Chimes' Vortex approach may be beneficial to all. The Vortex approach advances one's ability to visual the progression from bag-valve-mask (BVM) ventilation, placement of supraglottic airway (SGA) or endotracheal tube (ETT) via laryngoscopy, advising the team to use no more than three attempts (or fewer), which should prompt movement to a standardized surgical technique. The incorporation of this schema has resulted in a more comprehensive application of the algorithm and improved airway management decisions.

It is imperative to mention that the use of fiber-optic techniques is a mainstay for airway management in the ICU setting and beyond. Maintaining one's fiber-optic intubation and bronchoscopy skills is crucial for patient safety. Fiber-optic methods remain a gold standard for diagnostic airway dilemmas in the ICU setting; awake intubation and select asleep airway management scenarios (bronchoscopic techniques will be addressed in other chapters). Use as a primary or rescue airway technique is universal in nearly all algorithms and guidelines. In the ICU setting, it has maintained multiple and various diagnostic and therapeutic roles that may be lifesaving.

PREOXYGENATION AND PER-OXYGENATION

Indications

Care providers should make every effort to provide a source of oxygen to the patient before and during an airway intervention:

- 100% oxygen for 2–4 minutes via a tight-fitting mask via a resuscitation bag before induction is standard. Extending this time frame may help the patient if the SpO_2 is moving in an upward trajectory. If not improving or falling, then alternative plans need to be deployed (e.g., secure the airway with an ETT or SGA).
  - High-flow nasal cannula oxygen (HFNO) is potentially valuable when used in conjunction with preoxygenation with a tight-fitting mask. It is inexpensive, is readily available, is easy to apply, and has few negative effects (15–30 L/min). The elevated hypopharyngeal oxygen may reduce the incidence of desaturation when intubation is delayed or multiple attempts are required to secure the airway.
  - If the patient is already on noninvasive ventilation (NIV: continuous positive airway pressure [CPAP], bilevel positive airway pressure [BiPAP]), this can be used as a preoxygenation method as long as the airway is patent and the patient's effort is sustainable. Assure the FiO_2 is increased to 100% on the NIV assembly.
  - If nasal NIV is present, topicalization of the oropharynx may be employed. Full-face NIV is compatible with topicalization by carefully lifting the mask from the corner of the mouth and applying local anesthesia via an atomizer or syringe.
  - During awake fiber-optic intubation, ongoing oxygen delivery via nasal cannula is recommended. If asleep fiber-optic intubation is employed as a primary or rescue method, continuous ventilation and oxygenation support, in addition to positive-pressure lateralization of periglottic tissues, can be delivered via an endoscopy mask that allows passing of the bronchoscope through the mask via a built-in portal.

SUPRAGLOTTIC AIRWAY PLACEMENT

BEFORE THE PROCEDURE

Indications

SGA use for managing the airway:

- When bag-mask ventilation is ineffective or impossible:
  - Noninvasive maneuvers such as nasal and oral airway placement, jaw thrust, chin lift, two- or three-person efforts are ineffective or fail to maintain Spo_2 >90%

- Decision to use an SGA (e.g., laryngeal mask airway [LMA]) should be made rapidly to avoid desaturation or endangering the patient's safety.

Primary use when mask ventilation difficulty is anticipated:

Decision to use an SGA may be based on a known history of difficult mask ventilation. This could be done as a first step in managing the patient. After optimal positioning preoxygenation with 100% oxygen via a tight-fitting bag-mask assembly combined with HFNO (15–30 L/min), placement of the SGA occurs immediately after pharmacologic induction. Alternatively, topical anesthesia preparation will allow placement of the SGA device; establish effective ventilation, then induce. Additionally, airway preparation with topical anesthesia would allow "awake" intubation by a variety of airway adjuncts, though bronchoscopy and video-assisted laryngoscopy (VAL) are preferred by most clinicians.

Suspected difficulty based on Langeron's criteria (two or more factors) + other factors

- Obesity
- Edentulous
- Beard
- Age >55 years
- History of snoring, obstructive sleep apnea (OSA)
- Macroglossia
- Anatomic alteration of head/neck, dressing, cervical collar
- Poor positioning

Secondary use as a rescue airway device when ineffective or impossible mask ventilation exists or after difficult or failed direct or indirect laryngoscopy:

- After induction of unconsciousness/apnea, bag-mask ventilation not effective
- Upper airway collapse/obstruction (above SGA level)
- Upper airway bleeding (e.g., tongue malignancy) to separate bleeding from lower airway
- When intubation proves difficult or fails, an SGA can be placed to support oxygenation and then removed for further attempts or used as a conduit for intubation
- Bridge to support ventilation/oxygenation while other methods are pursued, equipment is gathered, personnel are summoned:
  - Ventilation/oxygenation before direct laryngoscopy/intubation
  - Fiber-optic bronchoscopy via SGA
  - Retrograde wire intubation: passing wire up through SGA, retrieve wire, remove SGA, then advance ETT in one of three methods: (1) preferably, pass the wire through the bronchoscope portal, advance the preloaded bronchoscope over the wire to below the glottis, remove the wire and advance the bronchoscope into the trachea; (2) advance an airway exchange catheter over the wire to just below the glottis, remove wire, then advance ETT into trachea with laryngoscopy assistance; or (3) least desirable, pass ETT over the wire with laryngoscopy assistance.
  - Surgical airway (cricothyrotomy, tracheotomy) with SGA in place, supporting ongoing oxygenation and ventilation
- Semielective use for ventilation/oxygenation support for procedures where bag-mask ventilation is known or suspected to be difficult/cumbersome/patient intolerant to procedure without airway support (e.g., OSA patient for upper endoscopy with moderate sedation)
  - Bronchoscopy in patients intolerant to sedation (OSA, obese, debilitated, cardiopulmonary cripple)
  - Percutaneous tracheostomy
  - Upper endoscopy (specially designed SGA with portal to pass endoscope/transesophageal echocardiography [TEE] probe, LMA Gastro-Teleflex)
  - TEE
  - Brief procedure requiring unconsciousness and airway control

Contraindications

- Absolute
  - Airway obstruction (supraglottic, glottic, or subglottic)
  - Patient unprepared (awake, no topical anesthesia)
  - Elective use with aspiration risk or full stomach
    - Emergency short-term use for rescue of difficult airway is acceptable.
- Relative
  - Anatomic alteration of supraglottic area, glottis, hypopharynx
  - Tumor, abscess, foreign body, swelling
  - Emergency short-term use for airway rescue is acceptable
  - Pregnancy, obesity, massive/multiple-injured patient
    - Emergency short-term use for airway rescue is acceptable

Equipment

- Equipment for mask ventilation
- Induction medications, topical anesthesia medications, and equipment for intubation
- Disposable or reusable SGA device
- Lubricating jelly
- Syringe for cuff inflation/deflation (cuff pressure <60 cm H_2O pressure)
- Tape to secure SGA
- Bite block optional (second-generation SGAs have a built-in bite block and gastric drainage port)
- SGA includes models similar to the original LMA (first generation) design and second-generation models from a variety of manufacturers
- Choice of device is often based on cost, comfort with product
- Evidence-based use exists for some, but not all, product offerings
- Sizes range from neonatal to large adult and will vary by manufacturer
- SGA sizes available should meet the needs of patient populations in your facility
- Access to manometer to measure cuff pressure (<60 cm H_2O); some SGA models have a built-in manometer
- SGA access in facility may be best on code cart, difficult airway cart, rapid-response care cart, resuscitation areas in any and all areas where airway management may take place, either elective, urgent, or emergent
- In the remote hospital location, SGA devices in a transportable airway bag or tackle box carried by the airway team is an excellent alternative.

ANATOMY

Though there are a variety of SGAs that occupy the periglottic area and surround the glottic opening with a cuff, most models differ very little except in the manufactured materials, their flexibility or rigidity, ease of use, weight, and effectiveness. Most, but not all (e.g., I-gel: Intersurgical and air-Q SP: Cookgas), have an inflatable cuff that lies in the hypopharynx and essentially seals the supraglottic region from the epiglottis down the cricopharyngeal sphincter. A sealed airway allows positive-pressure ventilation to be delivered but is limited by the effectiveness of the cuff seal/periglottic mucosal surface interface. Many will allow effective airway pressurization to 10–25 cm H_2O pressure before leaking, whereas other models are specifically designed to allow much higher sealing thresholds (25–35 cm). These latter models are particularly effective in generating ventilatory support for the obese and morbidly obese patient and when confronted by low pulmonary

compliance situations (congestive heart failure, acute respiratory distress syndrome, abdominal distention, pregnancy, ascites, and pulmonary fibrosis). The recently published Difficult Airway Society guidelines recommend the second-generation SGA based on higher cuff leak thresholds, improved intubating potential, and the presence of a bite block and gastric drainage capabilities. Many manufacturers now offer SGA models with a portal that allows passage of a suction catheter or nasogastric tube (NGT) to assist with evacuation of air or gastric contents from the esophagus and stomach (second-generation SGA). Although handy, access to the aerodigestive tract is not guaranteed, nor is the emptying process. Thus the assumption that these SGA models are acceptable in nonfasting patients or those at risk for aspiration is not supported by published literature. Despite this, any patient who has a failed airway may benefit from SGA placement even if the risk of aspiration is elevated.

In general, placement of the SGA can be performed in the exaggerated "sniff" position to the other extreme, a neutral cervical spine. Many SGA models are flexible (e.g., classic LMA-Teleflex) or foreshortened, semirigid, and curved to replicate the oro-hypopharyngeal curvature (e.g., ProSeal, Fastrach, Supreme LMA, or Aura-Once-Ambu). The SGA generally can be placed effectively when faced with little to no neck flexibility. The SGA is lubricated and then passed toward the roof of the mouth across the hard to soft palate, encouraging smooth advancement along the posterior throat so as to minimize getting hung up on the epiglottis. It typically comes to lie with its distal tip in the cricopharyngeal region. Unfortunately, the cuff end may buckle over on itself, come to lie over the glottic opening, or be displaced in a contorted position that impedes effective ventilation and oxygenation. The SGA may indeed be placed incorrectly but still function in near-perfect form with effective ventilation; it is a peculiar airway device. It can be forgiving, yet it still requires skill and finesse to place it properly in most situations. Guidance by a skilled and frequent user is the best method to learn the details of its proper use. Ideally, it lies just over the glottic opening and allows access to the trachea. However, the SGA is frequently malpositioned or the epiglottis is folded over to a lesser or greater degree, partially or completely blocking the pathway to the glottic opening, yet ventilation and oxygenation remain unabated. This may be adequate for airflow to and from but not for the passage of an ETT into the glottic opening. Hence, most generic SGA models do require fiber-optic–guided placement of an ETT because of the uncertain position of the SGA and its adjacent airway structures.

AFTER THE PROCEDURE

Postprocedure Care

The SGA used in the semielective, urgent, or emergent setting is often of short duration (2–20 minutes), because the goal is typically to intubate the trachea. Hence the SGA acts as a rescue oxygenation/ventilation device and/or an intubation conduit.

Complications

Complications are not necessarily because of the SGA itself.

- Common
  - Sore throat
  - Complications inversely related to the experience or skill of operator
- Infrequent
  - Inability to properly insert
  - Inability to ventilate despite proper positioning (laryngospasm, patient biting, kinking of SGA tube), contributing to negative-pressure pulmonary edema
  - Mucosal injury, pressure-induced damage, nerve/vascular injury of airway structures
  - Arytenoid dislocation, nerve damage, venous engorgement (all rare)
- Serious, rare complications
  - Obstruction of the glottic opening
  - Regurgitation/aspiration

OUTCOMES AND EVIDENCE

The LMA design offers a relatively short learning curve for the airway novice and affords fewer episodes of desaturation, less difficulty in maintenance of a patent airway, larger tidal volume than mask ventilation, and decreased arm and hand fatigue when compared with a conventional face mask. Its value in the ICU setting for assistance during emergency airway management is undeniable, especially during difficult intubation or when ventilation is not possible with a standard bag-mask assembly. Blind or fiber-optic–assisted tracheal intubation is an extremely attractive asset that the SGA device offers the clinician and provides an entirely novel rescue approach when conventional laryngoscopy and tracheal intubation prove troublesome or impossible. It is also useful in maintaining airway support in the ICU setting for patients who require repetitive general anesthetic or heavy sedation-analgesia for brief procedures, fiber-optic bronchoscopy, or diagnostic visualization of the airway. Recent work suggests that the SGA is better tolerated and produces fewer cardiovascular side effects than tracheal intubation. Insertion in the patient with an unstable cervical spine may be far easier than direct laryngoscopy because its insertion does not absolutely require neck manipulation.

The device may be difficult to place into the hypopharynx in the presence of a small mouth, a large tongue or tonsils, hypertrophied lingual tissue, or a posteriorly displaced pharynx. However, the SGA often proves easier to use than conventional methods of airway control such as direct laryngoscopy. The threat of gastric dilatation and regurgitation/aspiration may lead some to avoid its use in the critically ill, but its excellent track record and very low incidence of regurgitation/aspiration (1/1126 emergency insertions, Hartford Hospital, TCM) support its role as a primary airway rescue device when conventional methods fail. The role of the SGA as a rescue device in the elective and emergency setting is unparalleled, but further studies into its use in the emergency setting are needed to solidify its standing as the premier rescue airway device, regardless of which model is used. All recognized algorithms and airway management guidelines include the SGA as an integral component of management. Its multiple roles as a rescue device for difficult bag-mask ventilation and difficult intubation, as a conduit for bronchoscopic-assisted intubation, and as an oxygenation/ventilation bridge during front of neck access (FONA, surgical airway) support their recommendations.

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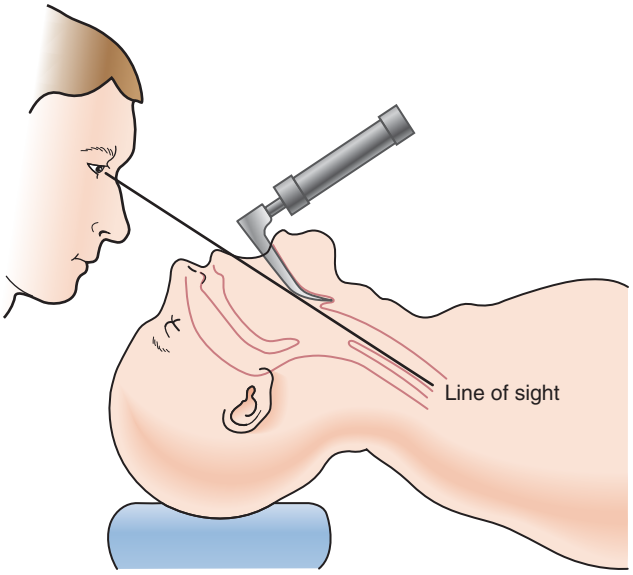

Fig. E1.1 Line of sight with direct laryngoscopy.

BOUGIE-ASSISTED INTUBATION

BEFORE THE PROCEDURE

Indications

- Exchange of ETT (Warning: most bougie models are approximately 55–65 cm in length and are shorter than the recommended airway exchange catheters. This may present a problem with maintaining control of the bougie during the exchange, owing to its length [component within the airway and the length outside the mouth available to thread new ETT]. Moreover, the bougie is typically 15F in caliber (4.7 mm diameter). Using the largest-caliber airway exchange catheter possible provides the best safety profile for ETT exchange.
- Assist with passing ETT into trachea when limited by the "line of sight"
  - Full view of laryngeal inlet (unable to pass ETT because of hang-up on cricoid ring)
  - Full grade 1 view but a restricted pathway to the glottis (e.g., boggy or edematous tissues, redundant pharyngeal mucosa). Thus when passing the ETT, the grade I view becomes partially or completely obstructed.
    - Grade II or III view of the larynx with laryngoscopy (conventional)
    - Grade II: posterior third of glottis visible (Lehane-Cormack classification) or more detailed classification (Cook-Yentis)
    - Grade III: no cords visible, only epiglottis visible; Cook-Yentis classification
      - Grade IIIa: only epiglottic edge visible
      - Grade IIIb: down-folded or floppy epiglottis is visible
    - Grade IV: no view of any airway structure; bougie use not recommended (Figs. E1.1 through E1.6)
  - Combined use with a videolaryngoscope (VAL) to assist with ETT placement
    - Channeled VAL devices (Pentax AWS, AirTraq)
    - Unchanneled VAL devices (GlideScope, McGrath, Storz C-Mac)
      - Very difficult to manipulate the standard bougie "around the corner" of the models with blades of excessive angulation (GlideScope, McGrath). These VAL models promote the likelihood of ETT delivery at an angle such that the tip impinges on the anterior tracheal wall or on the cricoid ring, thus limiting its advancement. Typically, ETT rotation will allow advancement, but bougie placement via the ETT may allow a well-lubricated bougie tip to slip off the impingement and allow ETT passage. A bougie with a maneuverable tip (anterior ↔ posterior movement) would potentially improve ETT placement through the glottic opening.
    - Excellent adjunct with conventionally shaped "Video C-Mac" and other conventional angled VAL blades.
    - Useful if ETT is located just proximal to glottic opening and the bougie is passed through the existing ETT and then manipulated into the trachea.
      - Use of the bougie to determine the location of the ETT (esophagus vs. trachea).
  - Hang-up test (Cheney sign).
  - Bougie tip will hang up on carina or mainstem bronchus, as opposed to simply passing unimpeded into the esophagus. Typically, a depth of 28–32 cm (carina) or deeper (32–36 cm, second bronchi) will allow confirmation of the bougie within the airway vs. the esophagus.
  - Useful in cardiac arrest or clinical situations in which it is difficult to discern proper ETT placement (i.e., cardiac arrest with no detectable $ETCO_2$ or access to such devices).

Contraindications

- Unfamiliar with its use
- Recent tracheobronchial reconstruction

Equipment

- A tracheal tube introducer "bougie" is an inexpensive, disposable, easily transportable airway device that requires minimal setup time, no battery or electrical power, and is noted on all the major airway management algorithm lists of desired airway devices that should be immediately available.
- A variety of manufacturers offer bougie models in 55- to 65-cm lengths, usually 14–15F in size.
- Solid and hollow bougie models are offered by some manufacturers.
- Distinct black markings along the length of the bougie assist the clinician with the depth of insertion.

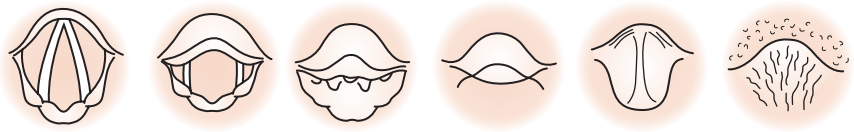

Fig. E1.2 Lehane-Cormack laryngeal view grading system with the Cook-Yentis modifications, grades I → IV.

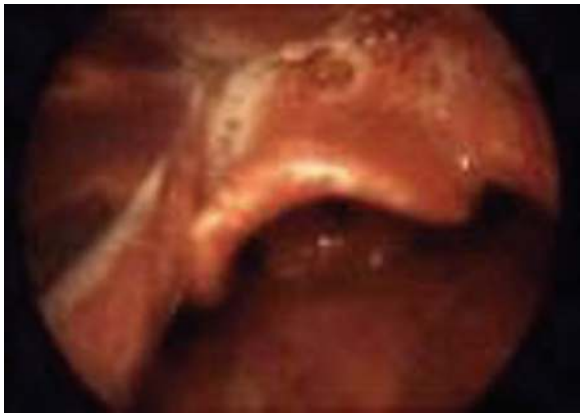

Fig. E1.3 Cook-Yentis grade IIb laryngeal view with direct laryngoscopy achieves a very high success rate with bougie-assisted intubation.

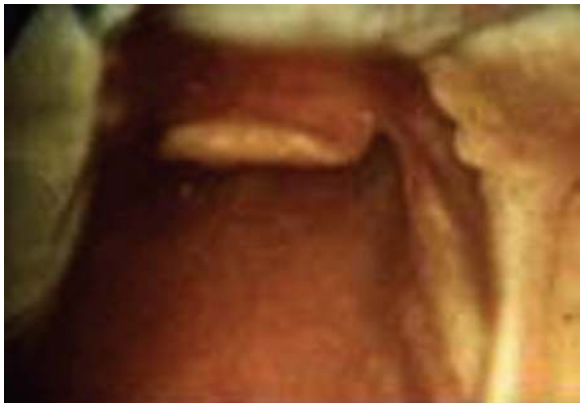

Fig. E1.4 Cook-Yentis grade IIIa view with direct laryngoscopy achieves a respectable success rate with bougie-assisted intubation, especially when compared with blind passing of the endotracheal tube "around the corner."

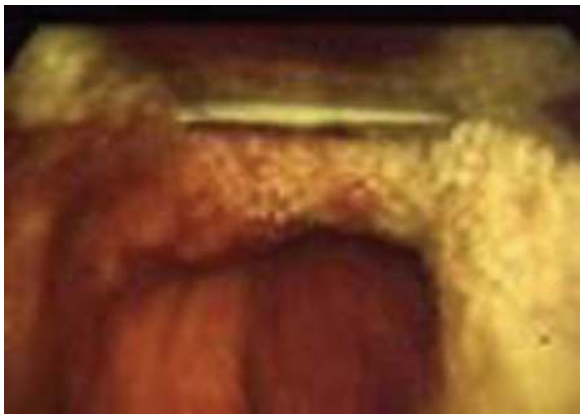

Fig. E1.5 A grade IV view, essentially no view at all of the laryngeal structures. The bougie is not indicated for a grade IV view, though in experts' hands and after failure of other techniques, careful blind passage combined with detection of tip hang-up (carina, mainstem bronchus) may allow blinded intubation. This is a last-ditch effort maneuver and is not recommended as a routine approach. It is best handled with an SGA, flexible fiber-optic bronchoscopy (FFB), or video-assisted laryngoscopy (VAL).

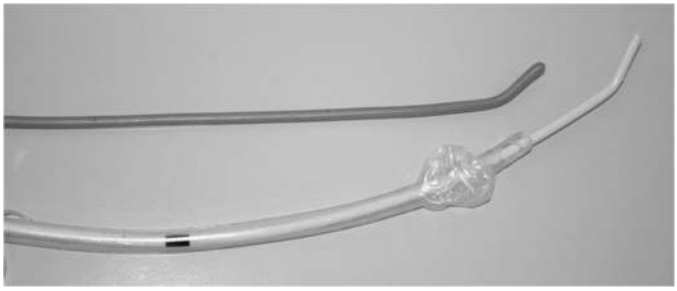

Fig. E1.6 Two bougie models are shown (tracheal tube introducer). Note the characteristic 30-degree angle. The Coude tip allows manipulation of the bougie underneath the epiglottis to increase its rate of passage through the laryngeal opening.

ANATOMY

Though the bougie is capable of assisting intubation in nearly all airway situations except when "no view" is possible, it is most commonly used as an adjunct with grade IIb, IIIa, and IIIb laryngeal views. Even when the laryngoscopy reveals a full view (grade I), the bougie may be useful when the mouth opening is small or narrow and/or the hypopharyngeal opening is narrow (OSA, obesity, swelling) and passing the ETT may actually obstruct the view of the glottic opening. In this case, the narrower, more colorful tracheal tube introducer can be passed into the trachea with little visual obstruction taking place. Conversely, the floppy epiglottis is a challenge that may be technically difficult with many different airway adjuncts. The bougie may either be used to elevate the floppy epiglottis or be maneuvered around by virtue of the Coude tip. Though useful, the success rate is often less than 50%, and other airway device alternatives may be needed (intubating laryngeal mask airway [ILMA], VAL, flexible fiber-optic bronchoscope [FFB] (Fig. E1.7).

PROCEDURE

- The bougie is grasped in the intubator's right hand at the 20- to 25-cm mark.
- It is passed alongside the laryngoscope with the 30-degree angled tip (Coude) anteriorly.
- The tip is advanced anterior to the arytenoids and into the larynx (grade IIa, IIb).

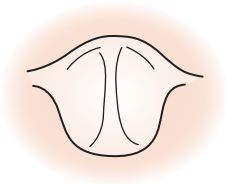

Fig. E1.7 A grade IIIb view; floppy or overhanging epiglottis may be difficult to navigate around with a variety of airway adjuncts. The bougie may be used to elevate the epiglottis and navigate into the trachea, but the success rate is substantially lower in the grade IIIb setting (30%–50%) compared with a grade IIIa (only leading edge of epiglottis visible, 80%–90%).

- The tip is then advanced underneath the epiglottis and past the vocal cords blindly (grade IIIa).
- The tip lifts the floppy epiglottis and is then advanced blindly past the vocal cords (grade IIIb).
- Advancement into the trachea to a depth of 22–26 cm in an average adult
  - Tip may "bounce" or "click" past the tracheal rings, suggesting tracheal placement.
  - This is a helpful sign but does not guarantee intratracheal placement.
  - Conversely, the lack of "clicks" does not guarantee the position of the bougie, nor does it rule out location within the trachea.
  - Ten to fifty percent of bougies passed into a grade III airway may enter the esophagus
    - Grade IIIa: 5%–12% may enter the esophagus
    - Grade IIIb: 30%–50% may enter the esophagus
      - Quickly deploy backup strategy (SGA, FFB, VAL)
      - Some may consider the bougie a poor choice in grade IIIb view
  - Tip may be gently advanced farther (28–36 cm) to contact carina/mainstem bronchus of second bronchi
    - Tip hang-up provides tactile feedback during blind passage
    - Detection of carina/bronchus is reassuring to operator
    - Advancement past 35–40 cm without hang-up strongly suggests the bougie is in the esophagus
    - Using hang-up or Cheney sign lowers the incidence and dangers of passing the ETT into the esophagus, bougie should be retracted to 23-25 cm depth, held securely then ETT may be advanced over the bougie
    - Eliminates the delay of verifying the ETT location by insufflation, capnography, auscultation
  - Decision time: passing the ETT
    - If time permits, generously lubricate the ETT
    - Smaller-sized ETTs pass over the bougie more easily than larger ones
    - Maintain tongue displacement with laryngoscopy/hand grasp
    - Pass the ETT, but do not force the advancement (an assistant should grasp the proximal end of the bougie to stabilize it)
    - Anticipate resistance at 16- to 17-cm depth because of impingement on arytenoid/vocal cord (two methods to remedy this) (Fig. E1.8).
      - Preemptively advance ETT while rotating in the counterclockwise (CCW) direction to allow ETT bevel tip to avoid impingement on the glottic structure.
      - If resistance is encountered, stop and withdraw ETT 1–2 cm and then rotate CCW and advance the ETT into the airway.
      - If ETT fails to pass, the patient may be ventilated and oxygenated with bag-mask ventilation (move the bougie to the corner of the mouth).

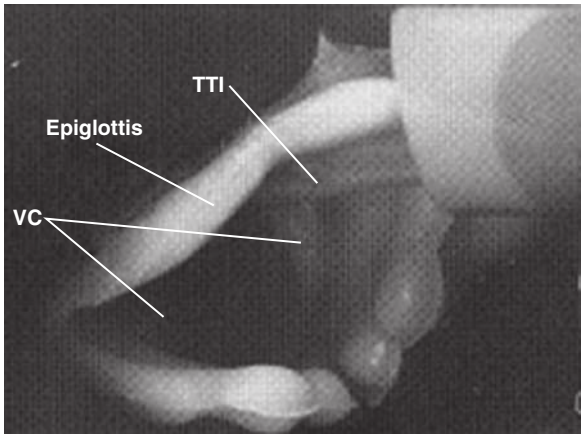

Fig. E1.8 Endotracheal tube (ETT) being passed over tracheal tube introducer (TTI, bougie) and getting hung up on the epiglottis and arytenoid. Continued advancement should be discouraged. Simply withdraw 1–2 cm, rotate ETT counterclockwise about 90 degrees, and readvance. *VC,* Vocal cord.

      - Change to a smaller-diameter ETT (to ease advancement over the bougie) and assume the glottic opening may be swollen, impeding entry.

AFTER THE PROCEDURE

Postprocedure Care

- After advancement of ETT into the trachea, stabilize the ETT in position, and remove the bougie. Be sure to hold the ETT in place as the bogie is removed.
- Standard methods of determining the ETT position are required.

Complications

- Inability to pass the bougie underneath the epiglottic edge (grade IIIa) or inability to lift the down-folded or floppy epiglottis (grade IIIb).
  - Depending on the skill and experience of the operator and the condition of the patient, time spent advancing the bougie should be limited so as not to endanger the patient's condition (SpO_2).
  - If unsuccessful, quickly move to another accessory device to secure the airway.
- Infrequent complications:
  - Minor tissue injury, airway trauma
  - Esophageal placement of bougie
  - Esophageal intubation (the hang-up test should eliminate this hazard)
- Serious, rare complications:
  - Mucosal laceration, bronchial/carina perforation if extreme force is applied to bougie advancement or the patient's underlying airway anatomy is compromised/diseased

OUTCOMES AND EVIDENCE

The simplicity of the trachea tube introducer makes it an attractive option for assisting with trachea intubation in the situation when a restricted laryngeal view is available with laryngoscopy. A variety of uses for the bougie make it a desirable addition to the difficult airway

cart or bag, made accessible at the bedside in the ICU and other remote locations in the hospital. The bougie is a suggested option in the management algorithms offered by anesthesiology societies in the United States, Canada, the United Kingdom, Germany, and many other countries.

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INTUBATING MODEL OF THE SGA FOR EMERGENCY AIRWAY RESCUE (LMA MODEL [FASTRACH] INTUBATING LMA [ILMA] WILL SERVE AS AN EXAMPLE BUT OTHER BRANDS ARE AVAILABLE)

BEFORE THE PROCEDURE

Indications

- Emergency rescue of the airway when tracheal intubation is the goal
  - Failed conventional intubation attempts
  - Failed bougie-assisted intubation
  - Failed VAL intubation
  - May be a substitute for conventional SGA device after its failure to secure successful ventilation/oxygenation

Contraindications

- Inexperienced operator/airway team
- Major risk for regurgitation/aspiration (relative; loss or lack of airway is worse)
- Oral cavity inaccessible/trismus
- Similar to other SGA devices

Equipment

- Equipment for mask ventilation
- Induction medications, topical anesthesia medications, and equipment for intubation
- Disposable or reusable models of the ILMA, ETT, and stabilizing rod
- Lubricating jelly
- Syringe for cuff inflation/deflation
- Tape to secure SGA
- Bite block not needed
- Manometer to measure cuff pressure (<60 cm H_2O)

ANATOMY

The ILMA is similar to other SGA devices that occupy the periglottic area and surround the glottic opening with a cuff. Passing the ILMA into the oral cavity is easier than the comparative standard LMA, because it is designed with an intrinsic curve easing passage into the hypopharynx. The inflatable cuff lies in the hypopharynx and essentially seals the supraglottic region from the epiglottis down to the cricopharyngeal (upper) sphincter. The rigid construction of the ILMA is limited by its diameter, so adequate mouth opening is a prerequisite. The sealed ILMA allows positive-pressure ventilation to be delivered. Occasionally, the ILMA will afford effective ventilation if the standard LMA model fails, and vice versa (as could other brands).

In general, placement of the ILMA can be performed in the exaggerated "sniff" position or the other extreme, a neutral cervical spine. In the presence of cervical spine immobility, it is best to maintain stabilization yet remove the front collar to improve oral access. After cuff deflation, the ILMA is lubricated and then passed along the roof of the mouth across the hard to soft palate, encouraging smooth advancement along the posterior throat so as to minimize getting hung up on the epiglottis or causing its down-folding. The distal tip of the ILMA typically comes to lie in the cricopharyngeal region. Unfortunately, the cuff end may buckle over on itself, come to lie over the glottic opening, or be displaced in a contorted position that impedes effective ventilation and oxygenation (Figs. E1.9–E1.16).

PROCEDURE

- The ILMA is placed into the airway in a similar fashion as other SGA products. However, the shortened length of the ILMA model and its handle may be easier to place than the standard SGA model. Placement is augmented by passing it along the hard to soft palate posteriorly into the hypopharynx, posterior to the epiglottis. It too comes

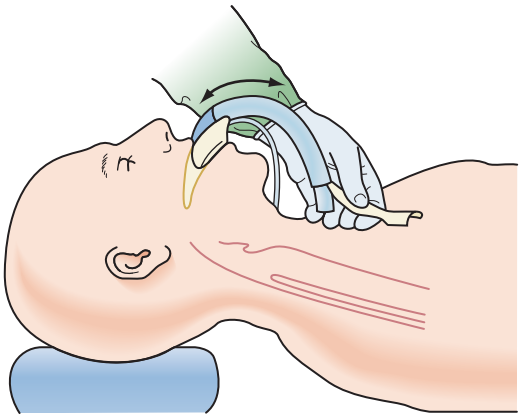

Fig. E1.9 Deflate the cuff, and lubricate with a water-soluble lubricant on the posterior surface. The lubricated intubating laryngeal mask airway is passed over the hard to soft palate along the posterior pharyngeal wall to the point where gentle resistance is felt.

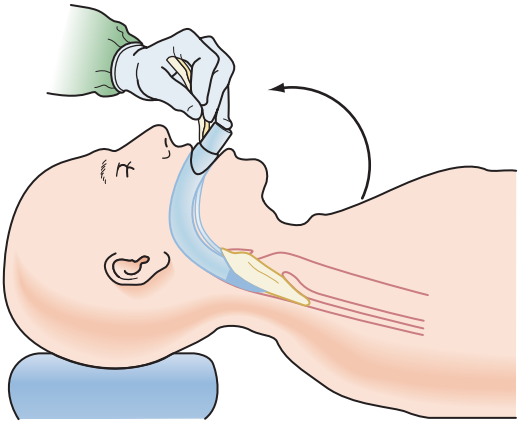

Fig. E1.10 Swing the mask into place in a circular movement, maintaining contact against the palate and posterior wall of the pharynx. Do not use the handle as a lever.

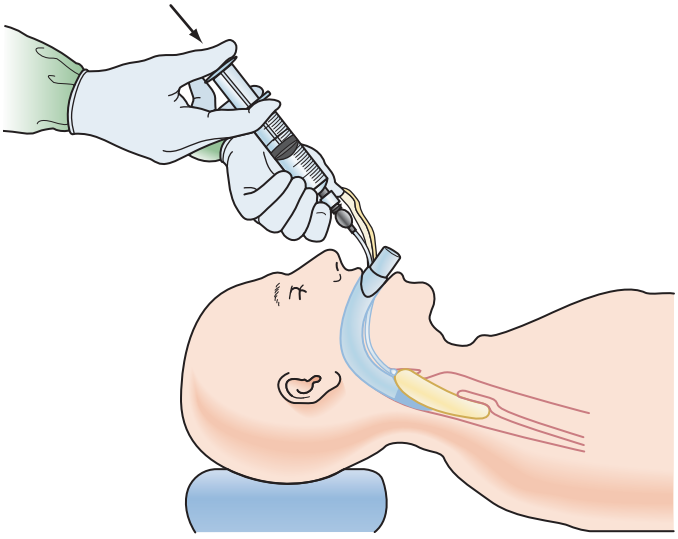

Fig. E1.11 Inflate the mask, without holding the tube or handle, with approximately 10–20 mL of airway to seal the airway. Apply a manual bag or anesthesia circuit and verify ventilation. If no ventilation (leak or resistance), assume misplacement of ILMA or down-folding of the epiglottis. Manipulate the ILMA in an up-and-down or in-and-out maneuver to optimize position. Recheck ventilation, and adjust location of the ILMA to optimize ventilation. Do not attempt to pass the endotracheal tube until effective ventilation is ensured.

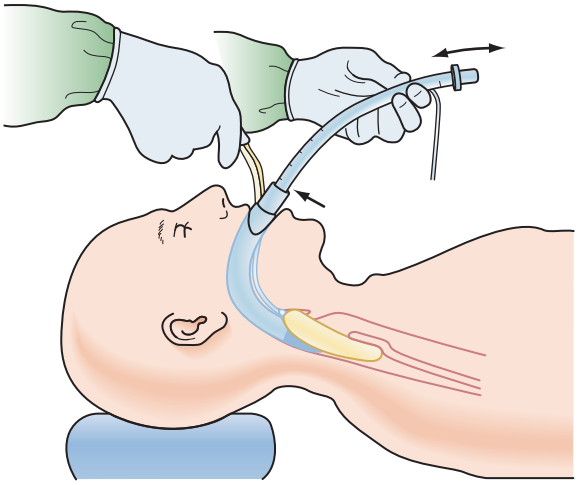

Fig. E1.12 Hold the ILMA handle while gently inserting the lubricated endotracheal tube (ETT) into the airway shaft. The provided ILMA-ETT is best suited for this, though a well-lubricated standard ETT may be used with fiber-optic guidance or may be used (with proper training and experience) blindly by inserting it "backward," meaning the concave curve of the ETT faces the nose as it is advanced into the ILMA shaft.

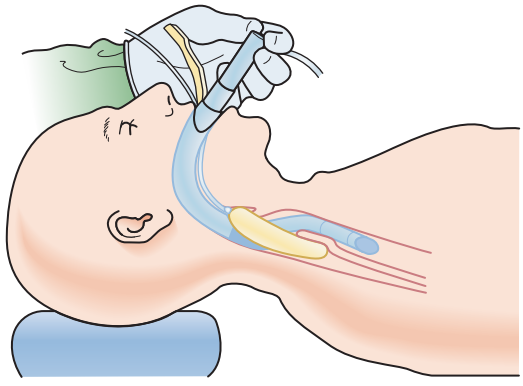

Fig. E1.13 Advance the ETT, inflate the cuff, and confirm intubation. If unable to pass, ensure adequate lubrication. If resistance is felt, the ILMA may be malpositioned or may have entrapped the epiglottis and thus block ETT advancement. Try the in-and-out maneuver to reposition the ILMA and free up the epiglottis if applicable.

to lie with its tip atop the cricopharyngeal area posterior to the arytenoids/glottis. The tip may fold over or under and impede air exchange or be sensed by an incomplete cuff seal (leak). This can be remedied by performing the "in-and-out" or "up-and-down" maneuver (simply moving the ILMA slightly inward and outward to free up the distal tip). Cuff inflation is followed by positive-pressure oxygen delivery. Successful placement allows the chest to rise and $ETCO_2$ detection, with no audible air leak, to approximately 15–25 cm H_2O pressure applied to the ILMA. Always confirm ventilation before attempting ETT advancement via the ILMA.

- Two maneuvers are handy to improve success in ILMA placement and intubation:
  - After ILMA placement, the Chandy maneuver #1 involves using the ILMA handle to optimize the positioning of the ILMA within the airway, with the goal of maximizing tidal volume, $ETCO_2$, and the feel of "bagging." The ILMA is held in this position in preparation for passing a lubricated ETT. The included LMA brand wire-reinforced ETT is an excellent ETT for passing, but it is suboptimal for long-term use in the ICU airway (if duration of intubation is >24–48 hours, one should consider changing the ETT over an airway exchange catheter to the standard ICU ETT model).
  - Limiting SGA insertion attempts to two to three is suggested by several sources. Once effective ventilation/oxygenation is established, passing an ETT may be the next objective. With the ILMA in the best ventilating position (Chandy #1), the Chandy maneuver #2 involves using the ILMA handle to slightly elevate or "lift" the ILMA (handle toward forehead, ILMA distal tip anteriorly) to improve the success rate of passing the ETT into the trachea, based on the ILMA portal being tilted toward the

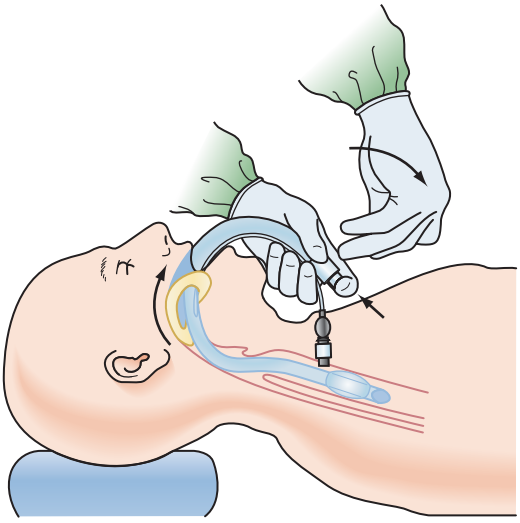

Fig. E1.14 Remove the ETT connector, and place the provided stabilizing rod onto the end of the ETT. Then ease the ILMA over the existing ETT and rod by gently swinging the handle caudally (keeping the ETT stable in position) until the ETT can be grasped at the level of the incisors.

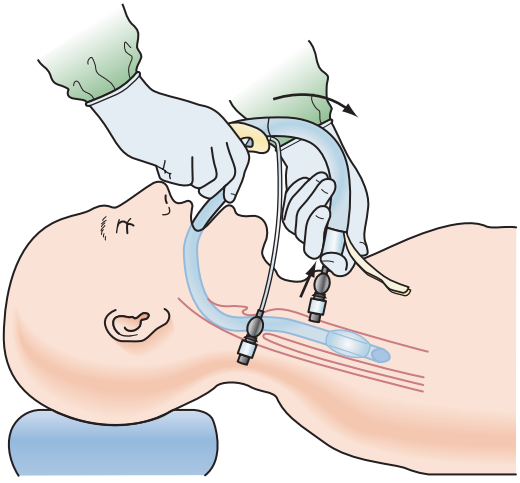

Fig. E1.15 Remove the stabilizing rod, and gently unthread the inflation line and pilot balloon of the ETT. Replace the ETT connector, and confirm ventilation and position per standard intubation procedures. If the ILMA has been used on a very challenging airway or the patient is unstable, delay removal of the ILMA from the existing ETT until stabilization takes place. Extubation of the airway is possible, so this maneuver should only be performed by those skilled in its execution.

glottic opening and away from the esophagus. This lift increases seal pressure and improves the alignment of the ILMA to the glottic opening and corrects any flexion the mask has undergone after its placement. Malposition or flexion of the mask while in the ventilating position may alter the pathway of the ETT as it exits the ILMA. Generous lubrication of the ETT to ease passage through the ILMA lumen is absolutely essential. Intubation of the trachea may be performed blindly or with fiber-optic assistance. The skill to successfully intubate the trachea is attained by practice coupled with instruction by an experienced individual. Practicing the technique before an emergency situation arises is in the best interest of patient care.

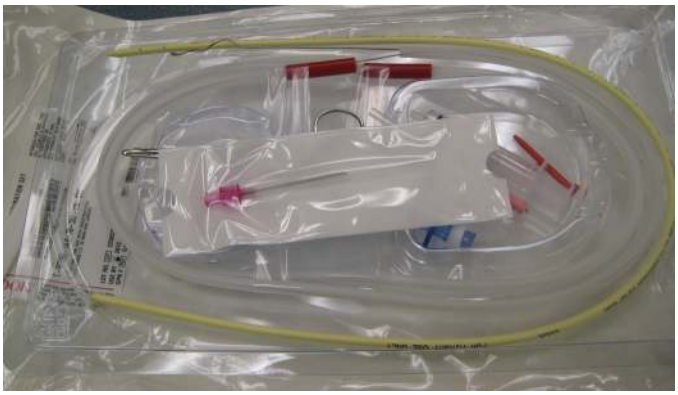

Fig. E1.16 Cook Critical Care prepackaged retrograde wire intubation kit. Use of the ILMA should be learned before its deployment in an emergency airway crisis. Training on a mannequin or humans under elective conditions by a skilled practitioner is best.

- Troubleshooting in the event of failure to intubate (typically caused by a down-folded epiglottis, ETT impaction on the periglottic tissues, too large or too small ILMA, or patient is resisting intubation because of inadequate sedation/analgesia/muscle relaxation/anesthesia).
  - If resistance is felt approximately 2 cm beyond the black transverse line marked on the ILMA ETT (or 15–16 cm marking on a standard ETT), the down-folded epiglottis may be blocking ETT advancement, as may the vestibular wall. Rotation of the ETT may allow passage if impeded by the vestibular wall. A down-folded epiglottis may need to be addressed by performing the "up-and-down" maneuver. This is a partial withdrawal of the inflated ILMA to a maximum of 6 cm, followed by reinsertion. This often frees the epiglottis from its down-folded position. Otherwise, FFB assistance is needed, or a different size ILMA may be tried.
  - If the ETT meets immediate resistance at 15–16 cm (black mark) or at a 4- to 5-cm depth past the black mark, then the ILMA is too large, and downsizing may help.
  - If resistance is encountered at 3 cm past the black mark, the ILMA may be too small. If an alternative-size ILMA is not available, external manipulation of the larynx either downward or caudally may assist with passing the ETT. Likewise, ETT rotation may be helpful.
  - The ILMA has an "epiglottis elevator bar" to assist in lifting the epiglottis up to afford improved ETT passage into the laryngeal inlet. When using bronchoscopic-guided ETT advancement, using the ETT tip to elevate the bar is best because the bronchoscope typically is not rigid enough to do so by itself.
  - Another miscellaneous yet quite important clinical situation that may prohibit intubation is excessive periglottic/glottic edema when viewing with the FFB. Massive airway edema may preclude advancement of the FFB-ETT owing to the inability to clearly identify the glottic opening; caution must be exercised to not advance the FFB tip into unrecognizable tissue planes. Excessive force on the FFB or ETT may lead to tissue injury and thus threaten the current airway patency by inducing further bleeding, edema, or swelling. Attaching a bronchoscopic swivel adapter to the ILMA itself or via the ETT may allow active application of positive pressure to the airway and promote lateralization of the edematous glottic tissues. This is analogous to the use of CPAP in OSA patients. The bronchoscopic adapter is too

narrow to allow an ETT to pass through it. To remedy this, an Aintree catheter (bougie-type catheter with a lumen that allows a proper-sized FFB to be placed within the catheter) is sized to fit through the adapter and its diaphragm. The Aintree-FFB assembly may be passed through the bronchoscopic adapter, down the ILMA, and used to visualize the glottic opening. Once advanced into the trachea, the Aintree remains within the trachea as the FFB is withdrawn. The ILMA is then removed over the Aintree, and the ETT is advanced over the Aintree catheter in similar fashion to a bougie, tube exchanger, or FFB.

- Blind intubation via the ILMA is useful and generally successful (90% within three attempts in the Hartford Hospital database for emergency intubations). Recent guidelines have leaned toward deploying bronchoscopic guidance for intubation so as to avoid blind insertion in the difficult airway situation. Moreover, recent societal recommendations have moved away from the ILMA toward the second-generation SGA models, despite an impressive track record of success with the classic SGA model (LMA) and the ILMA model design.

AFTER THE PROCEDURE

Postprocedure Care

- After "blind" intubation of the trachea, standard methods to confirm ETT position are pursued (chest auscultation, $ETCO_2$ detection, ETT misting, chest rise, etc.).
- After fiber-optic–assisted intubation, the same clinical confirmation of ETT position should be pursued, even though visualization of the ETT within the trachea with FFB is considered failsafe. The caveat here is that FFB confirmation, though failsafe under ideal conditions, may be limited by secretions, edema, soilage, operator inexperience, faulty battery power, and other limitations seen in the ICU airway.
- With the ETT-ILMA assembly in place, the ILMA has to be carefully removed from the patient while leaving the ETT within the trachea. Accidental tracheal extubation during ILMA removal could be disastrous.
- Step-by-step removal of the ILMA is outlined later.
- If one is unfamiliar with ILMA removal, a more experienced team should be summoned to assist with this task. Conversely, if the patient's clinical condition needs to be stabilized before its removal, at a minimum, the air should be removed from the ILMA cuff (leaving the ETT cuff inflated) to reduce the pressure effect on the pharyngeal mucosa.

Complications

- Common
  - As outlined under SGA
  - Inability to establish ventilation/oxygenation
  - Inability to intubate the trachea
  - Esophageal intubation
  - Obstructed advancement of the ETT through the ILMA
- Infrequent
  - Dental damage, mucosal injury
- Serious, rare complications
  - Regurgitation/aspiration (very rare)

OUTCOMES AND EVIDENCE

- The use of the ILMA has revolutionized airway management, especially in the emergency setting. It is an accepted component in the ASA airway management algorithm, in addition to all other algorithms offered by medical societies throughout the world. The presence of VAL has potentially altered the ILMA's role as a logical and rational first step toward airway rescue when conventional methods fail or are inappropriate. However, the clinician must be familiar with this device and have it readily available as a backup for VAL difficulties or failures.
- In the elective setting, the ILMA has an excellent track record for a high level of successful ventilation coupled with blind and FFB-assisted intubation. Its successful deployment in the acute care setting in the ICU, emergency department, or other remote locations outside of the operating room has been well received, though the success rate for both ventilation and intubation is tempered to a more realistic success rate of nearly 8–9 out of 10 patient encounters (Hartford Hospital database, TCM). Thus a backup plan must be in place to deal with ILMA failure and establish effective ventilation/oxygenation, and ultimately tracheal intubation, either blindly or with FFB assistance.

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RETROGRADE WIRE INTUBATION

BEFORE THE PROCEDURE

Indications

- Secure the airway in the elective setting with the patient awake, with adequate local anesthesia topicalization or nerve blocks
  - Trismus, severe temporomandibular joint (TMJ) disease, limited cervical range of motion
  - Known difficult mask ventilation, intubation
- Secure the airway emergently in the setting that mask ventilation/oxygenation is effective
  - Retrograde wire-guided intubation, in the best situation, may require 2–5 minutes to complete; hence one must be able to maintain successful ventilation/oxygenation.
- Considered an effective airway rescue in the nonemergent pathway on the ASA difficult airway algorithm (*cannot* intubate, *can* ventilate) when oral or nasal intubation is impossible or failed for a variety of conditions
  - Any reason the patient is a "difficult airway"
  - Massive oral, nasal, or pharyngeal hemorrhage (must be able to locate wire)
  - Trismus (must open at least one fingerbreadth)
  - TMJ abnormalities limiting mouth opening (must open at least one fingerbreadth)
  - Structural deformities of oropharynx, congenital or acquired
  - Mass (cancer, tumor, polyp, or other if not directly in line of wire advancement)
  - Traumatic injuries making oral/nasal tracheal intubation difficult or impossible
    - Maxillofacial injuries
    - Cervical spine instability
- Secure the airway electively when difficult airway factors are known or suspected to exist and intubation by other means may be difficult or impossible.

Contraindications

- Absolute contraindications
  - Transection of trachea with retraction of distal end into the mediastinum
  - Fracture or other significant injury of the larynx or cricoid cartilage
  - Infection, cancer, mass at site of wire insertion (cricothyroid membrane) or in pathway of wire advancement
  - Unfamiliarity with the procedure
- Relative contraindications*
  - Infants and toddlers (<3 years)
  - Bleeding diathesis
  - Patients with massive neck edema, lack of landmarks

Equipment

- Guidewire (suggested >60 cm) matched to appropriate needle size allowing advancement
- 20-, 18-, 16-, or 14-gauge cutting needle on a syringe
- Cuffed 6.0 endotracheal tube
- Hemostat or Kelly clamp
- Alternative: manufactured retrograde wire intubation kit (Cook Critical Care) (see Fig. E1.16)
- Optional: FFB

ANATOMY

The cricothyroid membrane is located between the superior thyroid cartilage and the inferior cricoid ring. The cricothyroid membrane is located just 1.5–2 cm below the vocal cords, so care must be practiced when advancing a needle caudad, as the underside of the vocal cords could be impaled. Passing the ETT over the wire or obturator/wire may be met with resistance at the 16- to 17-cm depth, as the ETT tip may impinge on the vocal cords or arytenoids. This is the inherent danger of passing the ETT blindly over the wire or obturator/wire assembly. The location of the distal tip (having met resistance) may or may not be at the position below the vocal cords. This is the challenge of the retrograde wire method; knowing the location of the ETT tip is unknown when the decision is made to remove the wire. If the ETT tip is erroneously positioned above the glottis, then the access to the airway is denied with wire removal; hence, the advantage of using the FFB as an intubation guide (Fig. E1.17).

PROCEDURE

- Retrograde tracheal intubation
  - Needle insertion directed cephalad; operator should approach with dominant hand more caudad (e.g., right-handed operator on right side of patient)

*Relative contraindications may be overlooked in the emergency situation.

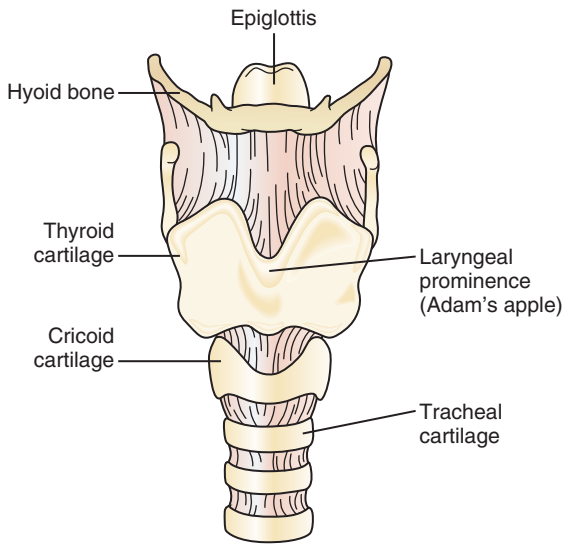

Fig. E1.17 Anatomic landmarks for access to the cricothyroid membrane.

- Puncture cricothyroid membrane with needle directed cephalad (Fig. E1.18). Aspirate air with syringe to locate air column (1–2 mL of saline in syringe; allow bubbles to percolate to verify the air column).
- Pass the guidewire through the needle aimed superiorly so that the distal end of the wire may be retrieved from the mouth (or if desired, nose) of the patient. Withdraw needle off wire.
  - Pull majority of wire out of the mouth (or naris)
  - Secure distal end of wire by clamping hemostat at the level of the cricothyroid membrane (Figs. E1.19 and E1.20).
- Three choices to pass ETT down the wire into the airway (nasal or oral): (1) wire assisted, (2) wire with obturator to reinforce wire, (3) flexible bronchoscope (loaded with ETT) passed over wire into airway
  - Wire assisted
    - Load lubricated ETT over oral (or nasal) end of wire, passing wire into tube through the Murphy eye.
    - Pull wire relatively taut and straight.
    - Advance ETT over wire into trachea to cricoid area and then, gradually relaxing cricothyroid end of wire, advance ETT to appropriate intratracheal location.
    - Release cricothyroid end of wire, and withdraw wire out of ETT.
    - Confirm ETT position (auscultation/capnography).
  - Wire with obturator to reinforce wire (Fig. E1.21)
    - Pass obturator over wire into airway until resistance is felt.
    - See manufacturer's instructions for Cook retrograde intubation kit.
    - Load lubricated ETT over oral (or nasal) end of wire/obturator.
    - Advance ETT into trachea to cricoid area.
    - Remove wire from cricothyroid membrane end, and then advance obturator distally into trachea.
    - Advance ETT to appropriate intratracheal location.
    - Confirm ETT position (auscultation/capnography).
  - FFB (loaded with smaller-sized ETT [6–7 mm]) (Fig. E1.22)
    - Advance wire through the suction portal of the FFB.
    - Grasp wire end from top of FFB.
    - Advance FFB down wire, observing the airway structures as you advance (Fig. E1.23).
    - Advancing the FFB to distal end of wire will occlude view and appear "pink" (backside of cricothyroid membrane). Correct position may be verified by darkening the room to transilluminate the cricothyroid membrane puncture site (Fig. E1.24).

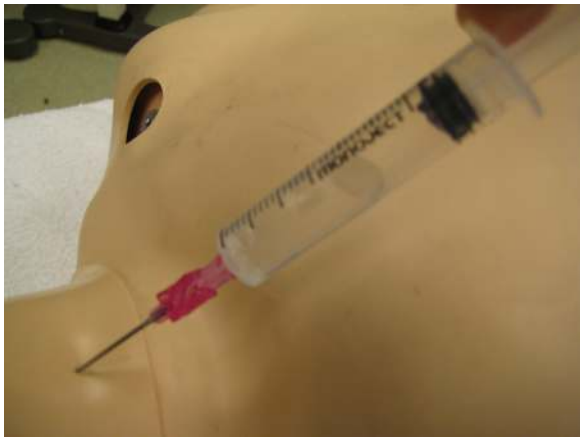

Fig. E1.18 Puncture of cricothyroid membrane, with air aspiration reflected in bubbling in saline-filled syringe.

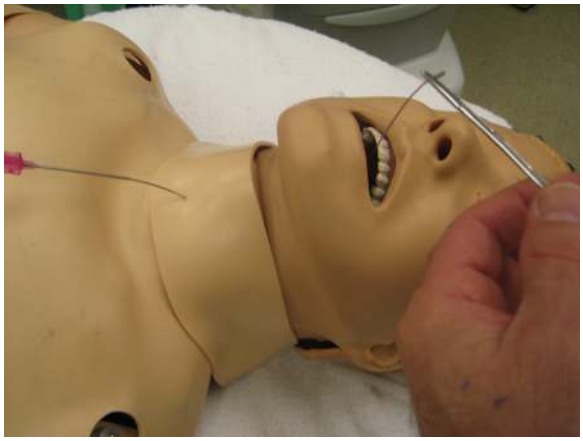

Fig. E1.20 Advancing the wire from the neck to the oral cavity.

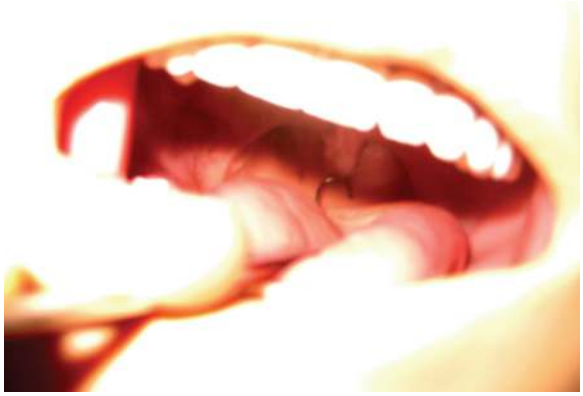

Fig. E1.19 Locating and retrieving the retrograde wire within the oral cavity.

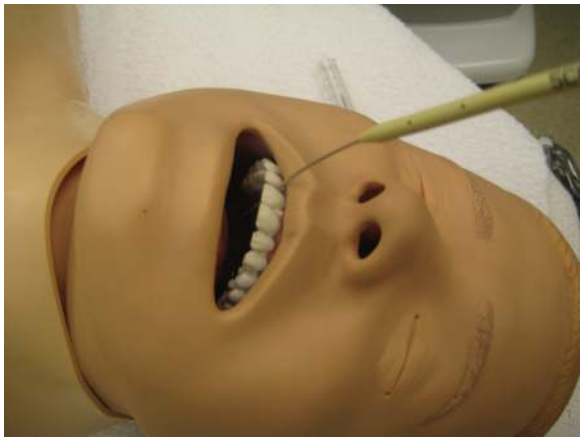

Fig. E1.21 Passing the Cook obturator over the retrograde wire to reinforce the wire to allow ease of passing the ETT into the airway.

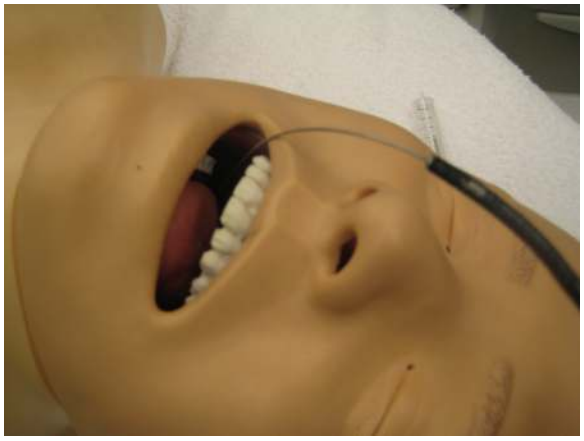

Fig. E1.22 A better choice than the obturator is the FFB passed over the wire via the suction port of the fiber-optic bronchoscope.

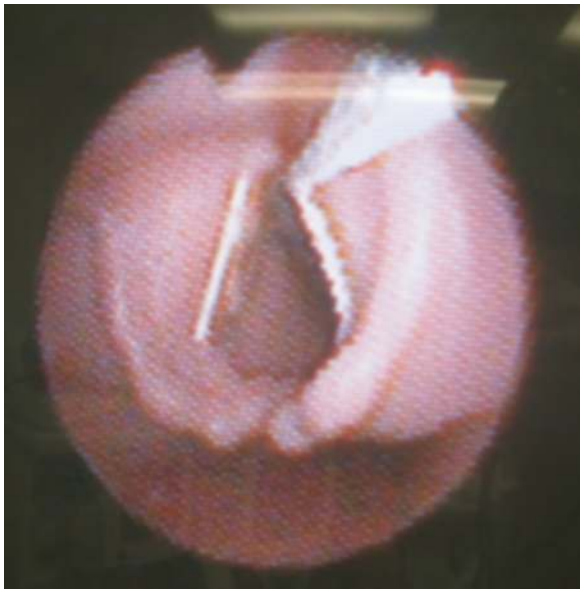

Fig. E1.23 Retrograde wire seen emerging from glottis.

- Once the FFB is below the vocal cords, the cricothyroid end of wire may be released as the fiberscope is advanced to the carina and wire and then pulled out of the fiberscope.
- Or the wire may be pulled out inferiorly through the cricothyroid puncture and fiberscope and advanced into the trachea.
- Advance the FFB tip into distal trachea, and advance the ETT into position and confirm.

AFTER THE PROCEDURE

Postprocedure Care

- After advancement of ETT into the trachea, stabilize the ETT in position.
- Standard methods of determining the ETT position are required.

Complications

- Inability to locate wire in oral cavity/nose
  - Use light (e.g., laryngoscope) to assist locating wire
  - Pick up wire with hemostat

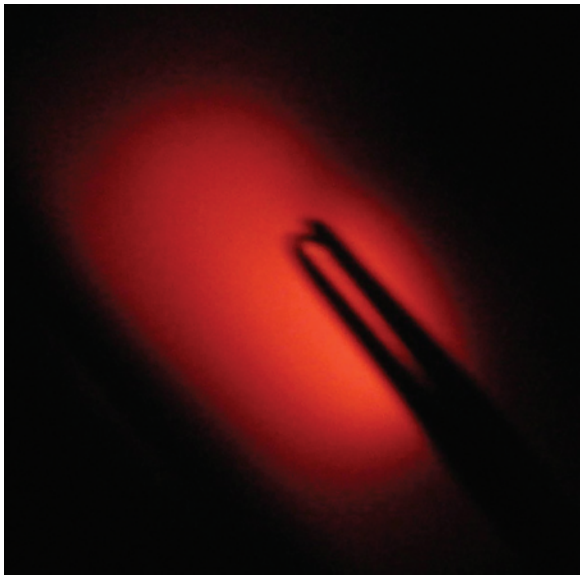

Fig. E1.24 Flexible fiber-optic bronchoscope (FFB) passed over retrograde wire, with tip of FFB at wire insertion site at the cricothyroid membrane, with transillumination of light from the FFB.

- Infrequent
  - Tissue injury when picking up wire with hemostat
  - Hematoma from injury to the cricothyroid artery
  - Subcutaneous emphysema
  - Infection at site of insertion (rare)
  - False tract from passing wire
- Serious but rare complications
  - Possible airway obstruction, loss of airway, laryngospasm

OUTCOMES AND EVIDENCE

Retrograde intubation, once a prominent adjunct before today's many varied airway devices, retains an important position in managing the difficult airway, but it has been relegated to a much less prominent role. It is important for clinicians to maintain the ability, knowledge, and equipment to perform this specialized method of securing the airway. Even in the best of clinical situations and manned by an experienced team, this method remains a relatively time-consuming technique that limits it to the nonemergency pathway, where ventilation/oxygenation is possible with either bag-mask ventilation or SGA or the patient is awake and breathing spontaneously.

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NEEDLE CRICOTHYROTOMY WITH TRANSTRACHEAL JET VENTILATION

BEFORE THE PROCEDURE

Indications

Similar to cricothyrotomy.

- Impossible or failed oral or nasal endotracheal intubation owing to any of the following:
  - Difficult or impossible intubation (cannot ventilate, cannot intubate [CVCI])
  - Massive oral, nasal, or pharyngeal hemorrhage
  - Massive regurgitation or emesis
  - Masseter spasm, clenched teeth, TMJ limitations
  - Structural deformities of oropharynx, congenital or acquired
  - Stenosis/narrowing of upper airway
  - Mass (cancer, tumor, polyp, or other) with partial obstruction
- Airway obstruction (partial but not complete) above cricothyroid membrane
  - Nontraumatic versus traumatic
    - Oropharyngeal edema
    - Mass (cancer, tumor, polyp, or other) (Fig. E1.25)
  - Traumatic
    - Foreign body obstruction
    - Stenosis
- Traumatic injuries making oral or nasal endotracheal intubation difficult or potentially hazardous
  - Maxillofacial injuries
  - Cervical spine instability

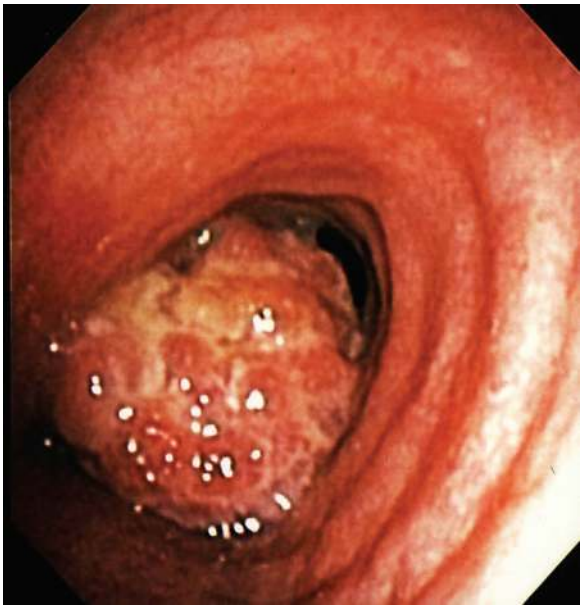

Fig. E1.25 Classic example of when not to incorporate transtracheal jet ventilation (TTJV). This intratracheal tumor mass occludes more than 85% of the tracheal lumen. Providing high-pressure TTJV supports oxygen transfer into the pulmonary tree, but overpressurization of the thorax will likely occur, because egress of the transmitted pressure may be blocked by the mass and its potential ball-valve effect. Likewise, a glottic or subglottic mass (above the site of needle insertion) may equally disallow egress or relief of the pressure buildup with high-pressure TTJV, thus leading to barotrauma.

Contraindications

- Absolute contraindications
  - Endotracheal intubation can be accomplished easily and quickly, and no contraindications to endotracheal intubation are present.
  - Transection of trachea with retraction of distal end into the mediastinum
  - Fracture or other significant injury of the larynx or cricoid cartilage
  - Lack of egress of pressurized airflow (exhalation, must ensure good air in, bad air out) resulting in inability to relieve pressured insufflation from trachea
- Relative contraindications*
  - Infants and toddlers (<3 years)
  - Bleeding diathesis
  - Patients with massive neck edema or lack of landmarks
  - Acute laryngeal disease

Equipment

- Sanders handheld high-pressure ventilator
- 12-/14-gauge Jelco IV catheter on a syringe
- Optional: wire-reinforced needle-catheter (e.g., Cook Critical Care)
- Alternatively: ENK oxygen modulator system by Cook Critical Care (low-pressure choice). Requires 15 L/min oxygen supply. Oxygen delivery is derived by finger occlusion of the portals on the plastic assembly. Delivered in similar ratio as high-pressure transtracheal jet ventilation (TTJV). Newer products are being developed that allow more accurate pressure delivery and air egress in the hopes of improving oxygenation, reducing barotrauma, and improving patient safety.
  - Newer technology has advanced TTJV to help lower the risk of barotrauma during "jetting." The Ventrain (Ventinova Medical) is a single-use ventilation device designed to allow ventilation via small-gauge lumens. Its ventilation is not based on the continuous high pressure as the standard TTJV assembly, but on continuous and bidirectional gas flow for both inspiration and expiration, thus allowing gas flow during inspiration but actively removes gas from the trachea with expiration ventilation assistance (EVA). This assists the clinician when dealing with rescue catheter ventilation but also when the airway is obstructed.

ANATOMY

The thyroid cartilage consists of two approximately quadrilateral-shaped laminae of hyaline cartilage that fuse anteriorly to form the laryngeal prominence. The anterior superior edge of the thyroid cartilage, the laryngeal prominence, is known as the *Adam's apple* and is

* Relative contraindications may be overlooked in the true emergency situation, because it is more important to obtain an airway and avoid hypoxemia.

usually easily seen in men. It is probably the most important landmark in the neck when performing a cricothyrotomy. The cricoid cartilage is shaped like a signet ring with the shield located posteriorly and forms the inferior border of the cricothyroid membrane. The thyroid cartilage forms the superior border of the cricothyroid membrane.

The cricothyroid membrane is a dense fibroelastic membrane located between the thyroid cartilage superiorly and the cricoid cartilage inferiorly; the cricothyroid muscles bound it laterally. The cricothyroid membrane covers an area that is trapezoidal in shape. The average size of the cricothyroid membrane in the adult is approximately 22–30 mm wide and 9–10 mm high. Palpating a notch, a slight indentation or dip in the skin inferior to the laryngeal prominence, can identify the cricothyroid membrane. The cricothyroid membrane is located approximately 2–3 cm below the laryngeal prominence in an adult.

PROCEDURE

- Place the patient in supine position (shoulder roll to extend cervical spine forward if possible).
- Prep neck area if time permits.
- Locate cricothyroid membrane.
- Using a 12- or 14-gauge needle on a syringe, puncture the skin midline and directly over the cricothyroid membrane (2–3 mL saline in 5- or 10-mL syringe will assist visualizing bubbles when withdrawing syringe barrel to verify needle tip in "air space").
- Direct the needle at a 45-degree angle caudally, and carefully insert it through the upper half of the cricothyroid membrane, aspirating as the needle is advanced. Aspiration of air signifies entry into the tracheal lumen.
- Secure the needle (assign one person to maintain catheter position), and attach Luer-Lok end of high-pressure ventilator.
- Administer low-pressure airflow (5–10 psi initially) bursts of positive-pressure ventilation.
- Six to ten breaths per minute to maximize exhalation time (I/E ratio >1:5).
- Adjust pressure upward with the goal of visible chest wall excursions and life-sustaining saturation.
- Continue efforts to maintain airway patency to ensure egress of pressurized air (exhalation)
  - Jaw thrust, chin lift, neck extension
  - Oral airway, nasal airway, tongue retraction
  - SGA device, laryngoscopy
- TTJV is a short-term oxygen delivery strategy during airway management difficulties.
  - Alternative airway management methods should be pursued.
  - Continue efforts to secure the airway from above if feasible.
  - Pressurization of airway may allow previously failed rescue methods to succeed (i.e., drive airway upward through the glottis, thus revealing an otherwise collapsed, edematous, or unrecognizable airway).
- NOTE: Placing the catheter via the cricothyroid membrane before airway intervention (anticipating difficulty) is acceptable, because placement during a crisis is often hindered by a lack of landmarks, suboptimal positioning, and inexperience. If placed but not used, it can be simply removed with little consequence.

AFTER THE PROCEDURE

Postprocedure Care

- TTJV is considered a short-term "fix" to supplement oxygenation in a lifesaving fashion; ventilation (CO_2 exchange) may be limited.
- Continued efforts to secure the airway with advanced techniques (FFB, VAL, SGA) should be pursued.
- Creation of a surgical airway (tracheostomy) is possible with active TTJV taking place.
- Removal of the catheter is quick and usually with little consequence.

Complications

- Common
  - Kinking of the catheter (use wire-reinforced catheter)
  - Blockage or obstruction of the catheter (redirect or withdraw slightly)
- Infrequent
  - Subcutaneous emphysema of neck, thorax, face
  - Minor bleeding
  - Infection (rare)
  - Incorrect or unsuccessful catheter placement
- Serious but rare complications
  - Damage to the laryngeal cartilage
  - Serious hemorrhage because of severed blood vessel
  - Posterior wall perforation (concerning), but if followed by TTJV, devastating consequences may take place
  - Pressurization of intratracheal airway leading to barotrauma, pneumothorax or, worse, tension pneumothorax, pneumomediastinum, and pneumopericardium

OUTCOMES AND EVIDENCE

- Patient outcomes after TTJV are related to their coexisting condition
  - Recognized as lifesaving maneuver in many airway management algorithms
  - Lack of training, lack of practice, low frequency make it high risk
  - Successful catheter placement may be fraught with incorrect I:E ratio, excessive delivery of breaths (>12/min), lack of pressure egress
- Owing to the emergency nature of the procedure, randomized controlled studies in humans are not possible in the emergency setting.
  - The DART program at Johns Hopkins does not push TTJV because it interferes with the performance of a surgical airway (FONA) if subcutaneous emphysema results from TTJV. The ASA Closed Claim Analysis and the NAP4 suggested that TTJV is associated with significant complications and morbidity. Moreover, such complications detract from the effective pursuit of a surgical alternative.
- Technique used successfully in elective setting with proper equipment, trained and knowledgeable personnel performing TTJV.

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NEEDLE AND SURGICAL CRICOTHYROTOMY

BEFORE THE PROCEDURE

Indications

- Impossible or failed oral or nasal endotracheal intubation because of any of the following:
  - Very difficult/impossible intubation (ventilation/oxygenation possible)
  - CVCI airway; can't intubate, can't oxygenate (CICO, UK version)
  - Massive oral, nasal, or pharyngeal hemorrhage
  - Massive regurgitation or emesis
  - Masseter spasm
  - Clenched teeth
  - Structural deformities of oropharynx, congenital or acquired
  - Stenosis of upper airway
  - Laryngospasm
  - Mass (cancer, tumor, polyp, or other)

FONA

- Airway obstruction (partial or complete) that cannot be cleared
  - Nontraumatic
    - Oropharyngeal edema
    - Laryngospasm
    - Mass (cancer, tumor, polyp, or other away from insertion site)
  - Traumatic
    - Foreign body obstruction (above level of insertion)
    - Supraglottic, glottic, or subglottic stenosis/narrowing (above insertion site)
  - Traumatic injuries making oral or nasal endotracheal intubation difficult or potentially hazardous
    - Maxillofacial injuries
    - Cervical spine instability
  - Elective versus urgent versus emergent
    - Elective: critical airway situation noted before induction, patient hemodynamically stable, oxygenation/ventilation adequate
    - Urgent: critical airway situation noted before or during induction, patient's hemodynamics and/or oxygenation/ventilation compromised
    - Emergent: critical airway situation during induction, patient hemodynamically unstable and/or oxygenation/ventilation deterioration

Contraindications

- Absolute contraindications
  - Endotracheal intubation can be accomplished easily and quickly, and no contraindications to endotracheal intubation are present.
  - Transection of trachea with retraction of distal end into the mediastinum
  - Fracture or other significant injury of the larynx or cricoid cartilage
- Relative contraindications*
  - Infants and toddlers (<3 years)
  - Bleeding diathesis
  - Patients with massive neck edema, lack of landmarks
  - Acute laryngeal disease (mass, tumor, infection over cricothyroid membrane)

Equipment

- Homemade
  - Guide wire
  - #20 scalpel blade
  - 14-, 16-, or 18-gauge cutting needle on a syringe (depending on wire gauge)
  - Cuffed 6.0 ETT on a dilator (with lumen)
  - Optional: cuffed, nonfenestrated, #4 and #5 tracheostomy tubes
  - Scalpel, #11
  - Trousseau dilator
  - Tracheal hook
  - 4 × 4 gauze sponges
  - Optional equipment: two small hemostats, surgical drapes, 1% lidocaine with syringe and needle
- Prepackaged (e.g., Melker Cricothyrotomy, Cook Critical Care) (Fig. E1.26)

ANATOMY

The thyroid cartilage consists of two approximately quadrilateral-shaped laminae of hyaline cartilage that fuse anteriorly to form the laryngeal prominence. The anterior superior edge of the thyroid cartilage, the laryngeal prominence, is known as the *Adam's apple* and is usually easily seen in men. It is probably the most important landmark in the neck when performing a cricothyrotomy. The cricoid cartilage is shaped like a signet ring with the shield located posteriorly and forms the inferior border of the cricothyroid membrane. The thyroid cartilage forms the superior border of the cricothyroid membrane (Fig. E1.27).

The cricothyroid membrane is a dense fibroelastic membrane located between the thyroid cartilage superiorly and the cricoid cartilage inferiorly; the cricothyroid muscles bound it laterally. The cricothyroid membrane covers an area that is trapezoidal in shape. The average size

*Relative contraindications may be overlooked in the true emergency situation, because it is more important to obtain an airway and avoid hypoxemia.

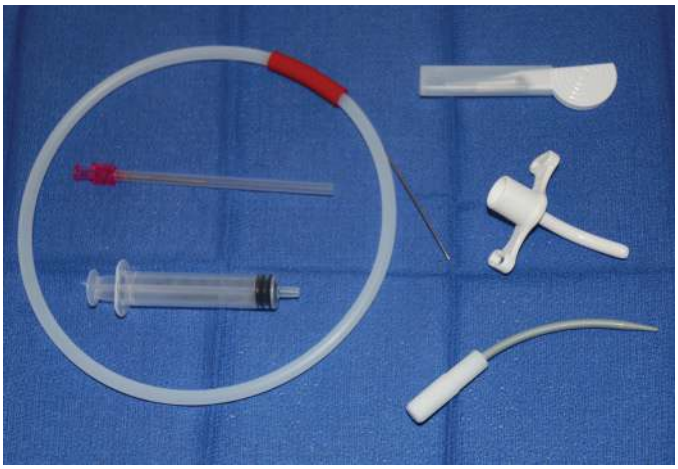

Fig. E1.26 Prepackaged surgical kit.

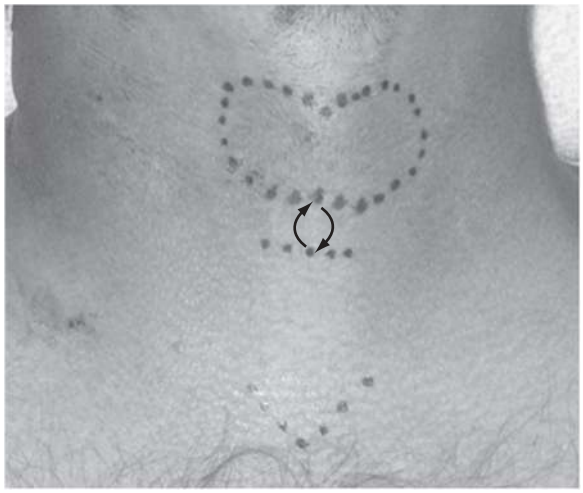

Fig. E1.27 Anatomic outline shows the sternal notch (lower "V"), the straight line (cricoid ring), and the two curved arrows that overlie the cricothyroid membrane, with the outline of the thyroid cartilage above the cricothyroid membrane.

of the cricothyroid membrane in the adult is approximately 22–30 mm wide and 9–10 mm high. Palpating a notch, a slight indentation or dip in the skin inferior to the laryngeal prominence, can identify the cricothyroid membrane. The cricothyroid membrane is located approximately 2–3 cm below the laryngeal prominence in an adult.

PROCEDURE: CONVENTIONAL APPROACH

- Place the patient in a supine position, hyperextended neck with shoulder roll if possible.
- Surgically prep the area using antiseptic solution (if applicable, time permitting).
- Palpate the cricothyroid membrane anteriorly, between the thyroid cartilage and cricoid cartilage.
- Immobilize the larynx—in the right-handed operator, the thumb and long fingers of the left hand are used to grasp the thyroid cartilage.
- Incise the skin—vertical and midline, approximately 2–3 cm in length from the depth of the thyroid cartilage, membrane, and cricoid cartilage.
- Prepare subcutaneous tissue—dissect down to the cricothyroid membrane.
- Incise the membrane—transverse, midline, and at least 1.5 cm long to facilitate ETT placement.
- Place tracheal hook on lower edge of thyroid cartilage and lift upward and cephalad.
- Alternatively, place tracheal hook on upper edge of cricoid ring and lift upward and caudad.
- Place ETT or tracheostomy tube—smaller diameter preferred (5.0–6.5 mm)
- Inflate cuff and confirm placement using auscultation and/or capnography.
- Secure the tube.
- Optional: FFB evaluation

PROCEDURE: STYLET-DILATOR METHOD

- Place the patient in a supine position, hyperextended neck with shoulder roll if possible.
- Surgically prep the area using antiseptic solution (if applicable, time permitting).
- Palpate the cricothyroid membrane anteriorly, between the thyroid cartilage and cricoid cartilage.
- Using a 14-gauge needle on a syringe, puncture the skin midline and directly over the cricothyroid membrane.
- Direct the needle at a 45-degree angle caudally, and carefully insert it through the upper half of the cricothyroid membrane, aspirating as the needle is advanced. Aspiration of air signifies entry into the tracheal lumen.
- Secure the needle, and advance the flexible end of the wire first.
- Once a sufficient amount of the wire is introduced into the trachea, remove the needle.
- Using a 20-blade scalpel, make a deep horizontal puncture.
- Insert the dilator and endotracheal tube assembly onto the wire, and gently advance through the cricothyroid membrane with a continuous downward twisting motion.
- Remove the dilator, inflate the endotracheal cuff, and connect the breathing circuit.
- Secure ETT, auscultate breath sounds, and confirm the return of CO_2.
- Optional: FFB evaluation of airway

PROCEDURE: SELDINGER TECHNIQUE—MELKER COOK CRITICAL CARE

- Supine position, hyperextended neck with shoulder roll if possible
- Surgically prep the area using antiseptic solution (if applicable, time permitting).
- Palpate the cricothyroid membrane anteriorly, between the thyroid cartilage and cricoid cartilage.
- Immobilize larynx as described earlier.
- Puncture the skin and the cricothyroid membrane with the puncture cannula with connected syringe.
- Aspiration of air confirms entry into trachea with needle directed caudad.
- Disconnect syringe from needle, pass the wire caudad into airway, and remove needle.
- Incise skin 0.5–1 cm on each side of the wire guide.
- Insert the dilator together with deflated airway catheter over the wire, through the skin, and into the trachea.
- Remove dilator, inflate cuff, and confirm correct tube placement.
- Secure ETT, auscultate breath sounds, and confirm the return of CO_2.

- Optional: FFB evaluation of airway

PROCEDURE: SURGICAL APPROACH—RAPID 4-STEP, MODIFIED 3-STEP (BOUGIE-ASSISTED) TECHNIQUE

- Supine position, hyperextended neck with shoulder roll if possible
- Surgically prep the area using antiseptic solution (if applicable, time permitting).
- Palpate the cricothyroid membrane anteriorly, between the thyroid cartilage and cricoid cartilage.
- Immobilize larynx as described earlier.
- Incise skin and cricothyroid membrane transversely with scalpel blade.
- Insert a tracheal hook through the incision; secure the cricoid cartilage with the hook.
- Move to a more ventral and caudal position (outward and downward direction with hook).
- Insert smaller-diameter ETT into opening of trachea.
- Three-step technique with Bougie assistance:
  - Midline incision into the skin followed by horizontal division of cricothyroid membrane
  - Advancement of elastic bougie through tracheal space into right mainstem bronchus
  - Advancement of ETT over bougie, removal of bougie
  - Secure ETT, auscultate breath sounds, and confirm the return of CO_2

AFTER THE PROCEDURE

Postprocedure Care

- Postprocedure care should include the insertion of an orogastric or nasogastric tube in cases of full stomach.
- Revision of the cricothyrotomy may be needed as soon as the patient is stable.
- Most cases have previous laryngeal damage or postobstruction pulmonary edema and will require ventilation in the ICU.

Complications

- Common
  - Kinking of the catheter, wire
  - Blockage or obstruction of the catheter
- Infrequent (potentially life-threatening)
  - Kinking of the catheter
  - Aspiration
  - Creation of false passage into the tissue
  - Subglottic stenosis
  - Laryngeal stenosis
  - Hemorrhage/hematoma
  - Esophageal/tracheal laceration
  - Mediastinal emphysema
  - Vocal cord injury
  - Minor bleeding
  - Infection
  - Incorrect or unsuccessful catheter placement
- Serious but rare complications
  - Damage to the laryngeal cartilage
  - Serious hemorrhage because severed blood vessel
  - False passage, loss of airway
  - Pneumothorax, tension component

OUTCOMES AND EVIDENCE

- Patient outcomes after needle cricothyrotomy are related to coexisting conditions.
  - Lowest survival rates are associated with cricothyrotomy undertaken during cardiac arrest (only 6%), compared with 76% for any other reason.
- Most common causes of death are patient comorbidities, followed by failure to achieve an airway, and last, by the procedure itself. Many airway-related deaths are caused by the lack of attempting surgical access at all or attempting it too late in the airway crisis. Move to a surgical airway sooner rather than later.
- Owing to the emergency nature of the procedure, randomized controlled studies in humans are not likely to be performed.
- Because cricothyroidotomy is a rarely performed but potentially lifesaving procedure of last resort in the patient with a failed airway, clinicians responsible for airway management must retain familiarity with the necessary equipment and relevant anatomy.
  - Gaining needle access to the CTM followed by high-pressure oxygen delivery is fraught with failure. It may derail efforts to access the airway via a surgical incision. Alterations of the FONA (e.g., subcutaneous air) may interfere with gaining access from the anterior neck region.
- Clinicians responsible for advanced airway management should review the anatomy and practice with the equipment needed for cricothyroidotomy several times per year.
- At the very least, clinicians should know who to call for assistance with gaining surgical access to the airway.
- Immediate access to needed equipment is imperative to optimize patient safety.
- Delay in starting surgical access, lack of equipment, and inexperience with the technique are the most common underlying reasons for poor outcome.
- Although an emergency surgical airway may be glamorized to be done rapidly, given common anatomic and positioning restraints (cervical collar, cardiopulmonary resuscitation [CPR], ongoing BVM, poor positioning, obese thick neck devoid of landmarks), it is the exception that it can be performed accurately in less than 45 seconds. Clinical experience suggests >1–3 minutes and well beyond this time frame in many instances.
  - The two main concerns with surgical airway access is that it is not tried at all or it is attempted too late.
  - If placing an ETT via the surgical access route, beware of depth of the ETT. It can easily be placed past the carina leading to mainstem bronchus intubation. Approximate depth should be 10 cm, and verification by bronchoscopy is recommended.

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ESOPHAGEAL-TRACHEAL COMBITUBE: ALTERNATIVELY, THE RUSCH EASY TUBE (SMALLER—LATEX-FREE COMBITUBE LOOK-ALIKE AND THE KING LT-LARYNGEAL TUBE-SINGLE LUMEN, ESOPHAGEAL PLACEMENT, ONE SYRINGE FOR DUAL CUFF INFLATION)

BEFORE THE PROCEDURE

Indications

- Emergency airway device in the CVCI pathway
  - Provides rapid control of airway when intubation is impossible and other techniques of securing the airway fail
- Airway management when the patient situation disallows laryngoscopy or bag-mask ventilation because of positioning, confinement
  - Example: trapped in a car after motor vehicle crash and inability to perform laryngoscopy

Contraindications

- Absolute
  - Pediatrics or patients less than 4 feet tall
    - Pediatric sizes unavailable[36]
  - Airway obstruction (supraglottic and below)
  - Intact gag reflex
  - Recent upper esophageal surgery (i.e., Ivor Lewis esophagogastrectomy)
  - Caustic ingestion
  - Latex allergy
    - Combitube includes latex in its construction
    - Alternative product: EasyTube, Rusch Medical (latex free); similar in design to Combitube
- Relative
  - Elective/nonemergent situations

  Example: easy intubation, easy bag-mask ventilation
  - Esophageal pathology (proximal third, upper portion)
    - Example: patient with known esophageal varices; however, if patient is hypoxic and no other airway is possible, benefits clearly outweigh risks. Variceal location tends to be in the lower half of the esophagus.
  - Anatomic alteration of supraglottic area, glottis, hypopharynx
    - Tumor, abscess, foreign body, swelling
    - Emergency short-term use for airway rescue is acceptable.
  - King laryngeal tube
    - Responsive patients with an intact gag reflex
    - Patients with known esophageal disease
    - Patients who have ingested caustic substances

Equipment

- The Esophageal-Tracheal Combitube (Kendall-Sheridan, Argyle, NY) is available in two sizes: 41F (large adult) and 37F. It is a double-lumen soft plastic tube that is inserted into the mouth with or without laryngoscopy and advanced blindly into either the trachea or esophagus (>90% pass into the esophagus). The Combitube has two inflatable cuffs: a smaller distal cuff similar to that of a conventional ETT and a larger proximal cuff designed to seal the pharynx. Once placed, the practitioner must ventilate the proper conduit to deliver oxygen into the trachea. Understanding the Combitube's design is imperative to its successful use and fosters the ability to troubleshoot difficulties. The Combitube is joined by its recently introduced cousins: the Rusch EasyTube and King laryngeal tube (LT). The Rusch EasyTube is a latex-free alternative that is offered in a large model (similar to the Combitube 41F) and a smaller adult version (35F). The Combitube enters the esophagus in over 95% of cases; ventilation is through lumen #1 (blue connector). End-tidal CO_2 detection, pulse oximetry, and other confirmatory measures must be confirmed for all placements. The occasional placement in the trachea requires ventilation of the lungs through lumen #2 (Fig. E1.28).
- Another airway device that is gaining popularity for in-hospital and prehospital use is the King LT, which is blindly inserted into the hypopharynx with the distal tip inserted past the cricopharyngeal opening of the esophagus (not in the trachea). The ventilation portal comes to rest posterior and inferior to the epiglottis in proximity to the open glottis. It has two high-volume, low-pressure inflatable balloons similar to the Combitube (one that occludes the esophagus and one that inflates in the posterior oropharynx) yet requires fewer steps, because it is reliant on only a single site of inflation. The distal cuff is designed to seal the esophagus. The proximal cuff is intended to seal the oropharynx. Ventilation is achieved via a 15-mm connector (single portal as opposed to the Combitube's two) for attachment to a standard breathing circuit or

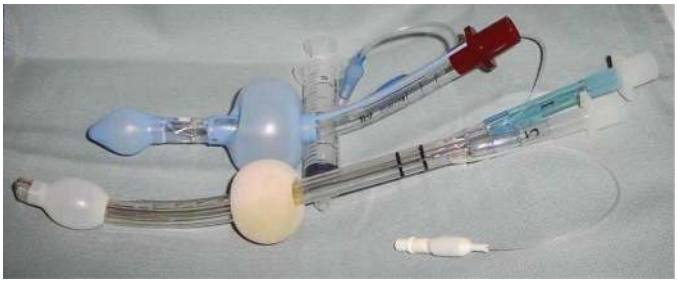

Fig. E1.28 King laryngeal tube (LT) *(upper)* and Combitube *(lower)* are both dual-balloon airway devices. Combitube has a long track record of excellent performance but is being challenged by the smaller-sized King LT, with its single pilot valve/dual cuff design and single ventilation portal.

resuscitation bag. The patient may breathe spontaneously via the King LT. CO_2 detection is adaptable to all three devices (Fig. E1.29).

ANATOMY

An understanding of basic airway, tracheal, and esophageal anatomy is required to interpret which lumen should be used to ventilate the patient. Also, if ventilation is unsuccessful, it is important to understand that the positioning of the Combitube may not be ideal, and it may have to be advanced or withdrawn slightly.

PROCEDURE: COMBITUBE

- The Combitube is an emergency airway management device for patients requiring rapid control of the airway, particularly when poor laryngoscopic visualization of the larynx makes tracheal intubation impossible.
- Insert appropriate-sized Combitube into patient's mouth, with or without laryngoscopy (the smaller-sized Combitube [37F] may be used in all adults <6 feet, 5 inches tall).
- Advance the Combitube blindly into either the trachea or esophagus.
- Stop advancing once the proximal depth indicator (two black rings) is at the level of the teeth.
- Inflate the smaller distal cuff and the larger proximal cuff that seals the pharynx.
- Ventilate through the proximal (blue, #1) lumen first, because 95% of Combitube placements result in an esophageal position and auscultate the lungs and stomach.
- If breath sounds are not heard but gastric sounds are, the Combitube has likely been placed in the trachea.
- Simply change ventilation to the distal (clear, #2) lumen, and recheck for breath sounds.
- If breath sounds are still not detectable by auscultation, the Combitube has likely been advanced too deeply into the esophagus, and the pharyngeal cuff is obstructing the glottis.
- If this occurs, deflate the pharyngeal cuff, withdraw the Combitube a few centimeters, and recheck for breath sounds.
- Once the appropriate lumen has been selected and ventilation appears adequate, confirm with capnography.

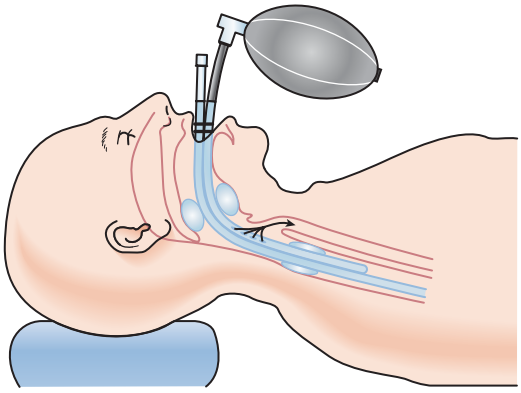

Fig. E1.29 Combitube in the esophageal position with both balloons inflated. Proper positioning of the eight side ventilation portals allow oxygen delivery into the glottis. If resistance is met when bagging, it is typically caused by two factors: (1) Combitube is positioned too deep, so some or all of the ventilation portals are occluded by esophageal mucosa (solution: withdraw Combitube to a more proximal position); or (2) upper inflated cuff has forced the epiglottis downward and is partially or completely obstructing the glottic opening (solution: withdraw Combitube to a more proximal position).

PROCEDURE: KING LARYNGEAL TUBE

The King LT is a supraglottic airway that uses two cuffs to create a supraglottic ventilation seal similar to the Combitube (hypopharynx and esophageal level). The King LT has a single ventilation port (15-mm connector) and a single valve and pilot balloon that simultaneously inflate both the pharyngeal and the esophageal balloons.

- Assuming the operator is familiar with the King LT, lubrication is applied and preoxygenation is completed.
- Sniffing position if possible, but not required.
- Hold the King LT at the connector with dominant hand. With nondominant hand, hold mouth open and apply chin lift.
- With the King LT rotated laterally 45–90 degrees such that the blue orientation line is touching the corner of the mouth, introduce tip into mouth and advance behind base of tongue.
- As tube tip passes under tongue, rotate tube back to midline (blue orientation line faces chin).
- Without exerting excessive force, advance tube until base of connector is aligned with teeth or gums.
- Inflate via the single pilot valve until sealed (40–80 mL, depending on King LT size).
- Gently ventilate to assess position (free-flowing I/E, large V_T).
- Depth markings give an indication of the distance from the vocal cords to the teeth.
- Confirm proper position by auscultation, chest movement, and verification of CO_2.
- If ventilation is met with high resistance, slowly withdraw device until ventilation improves.
- Intubation may be accomplished with the FFB-Aintree combination (Figs. E1.30 and E1.31).

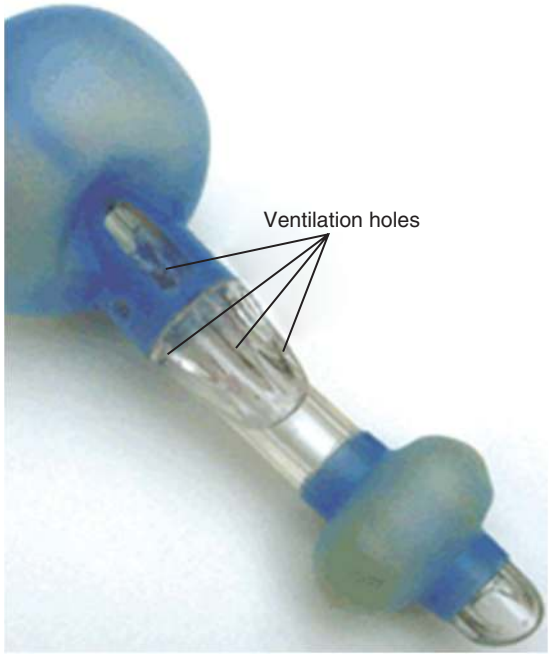

Fig. E1.30 Close-up view of King laryngeal tube and the ventilation holes that come to lie posterior to the glottic opening. The upper opening will emit an FFB or FFB-Aintree combo to visualize/intubate the trachea. (With permission from Ambu, Inc., Glen Burnie, Maryland.)

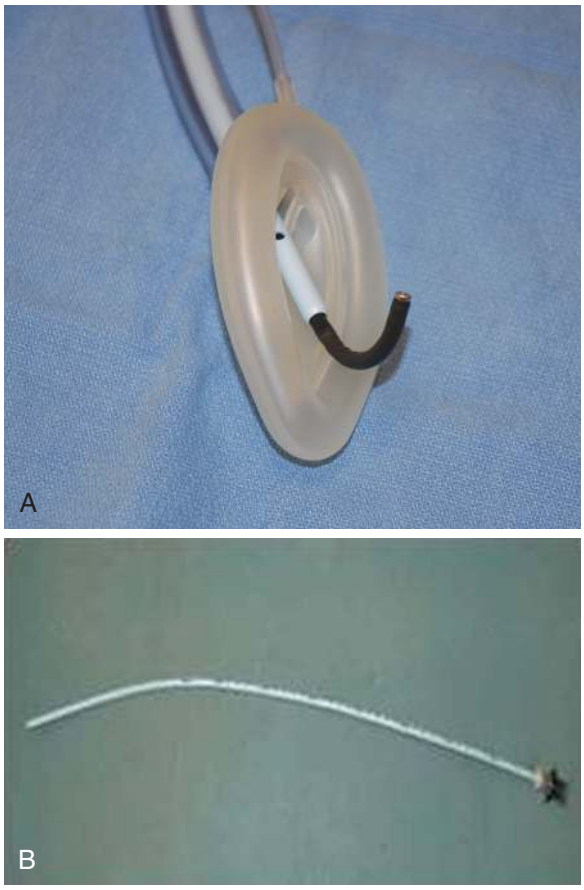

Fig. E1.31 A, The Cook-brand Aintree catheter acts as a "jacket" around the flexible fiber-optic bronchoscope (FFB), which is then passed (in this case) via the laryngeal mask airway to assist in visualizing the glottic opening. The Aintree-FFB combo can be passed via the ventilation portal of the King laryngeal tube (LT) to allow passage into the trachea. After removal of the FFB from the Aintree (which remains in the trachea), the King LT is removed over the Aintree. A lubricated endotracheal tube (ETT) is then passed over the Aintree, as it acts as a bougie. **B,** The Aintree catheter, a 56-cm-long, hollow catheter.

- The Rusch EasyTube is another alternative to these two products. It is available in two sizes: 41F and 28F, has a single lumen at the distal end, two separate cuffs for inflation (as does the Combitube), and a latex-free balloon and offers access to the upper airway (via a suction catheter, airway exchange catheter, or flexible bronchoscopy).

AFTER THE PROCEDURE

Postprocedure Care

- Once patient is stabilized and adequately ventilated and oxygenated, a more definitive airway should be secured.
  - It is an acute emergency airway device.
  - The three products are not intended for extended use in the emergency patient.
  - Intubation of the trachea is favored in most patients, so a plan should be developed to change to an ETT.
  - Changing to an ETT may be performed with the use of conventional and advanced airway devices.
  - If exchange is considered to be dangerous and risky (desaturation, massive edema, poor pulmonary compliance) or it proves to be impossible to identify the glottic opening, securing the airway surgically may be the best (or only) alternative.
  - When the three devices are in the esophageal position, surgical entrance into the trachea is not impeded by the airway device.

Complications

- Common
  - Difficulty maintaining a cuff seal to provide adequate positive-pressure ventilation
  - Regurgitation and aspiration would ideally be limited, but complete protection is not guaranteed.
- Serious but rare complications
  - Lacerations to the esophageal wall or pyriform sinus
    - Can result in subcutaneous emphysema, pneumomediastinum, pneumoperitoneum, and esophageal rupture
  - Ischemia of tongue/airway edema if left in place for long duration

OUTCOMES AND EVIDENCE

These devices, though relatively simple and timely to place, do require complete familiarization with their placement, cuff inflation features, and limitations. The King LT is popular as an elective airway support device and as a useful rescue airway device in cases of an unexpectedly difficult airway. Anecdotally, clinicians may prefer the King LT based on its smaller size and simplicity with one inflation portal. In essence, these devices can be considered "secondary SGA devices" in the rescue schema. Though each could serve as a rescue technique for failed DL ± Bougie or VAL, most guidelines recommend SGA such as a first- or second-generation SGA (i-gel, LMA Proseal, LMA Supreme, Ambu Aura, Fastrach LMA). Hence, the Combitube and others would serve as a reserve backup rescue for other SGAs (which have potential as an intubation conduit).

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EVALUATION OF A CUFF LEAK IN THE ICU

BEFORE THE PROCEDURE

Indications

- Audible cuff leak in an intubated patient may represent a variety of problems
  - Tear/microperforation or macroperforation of ETT cuff
    - Remedy: exchange ETT
  - Broken pilot balloon line
    - Remedy: occlude line perforation, inflate cuff, clamp line with Kelly/hemostat (temporary, low risk)
    - Remedy: cut line, attach new pilot balloon/valve/line assembly, reinflate balloon (less temporary, may perform well long-term, low risk)
    - Change ETT (high risk) (Fig. E1.32).
  - Incompetent valve/pilot balloon perforation/dysfunction
    - Remedy: cut line, attach new pilot balloon/valve/line assembly, reinflate balloon (less temporary, may perform well long-term, low risk)
    - Remedy: inflate cuff, clamp line with Kelly/hemostat (temporary)
    - Remedy: change ETT (high risk)
- ETT cuff/tracheal wall incongruity (tracheomalacia, tracheal softening, tracheitis, overstretched poorly compliant cuff)
  - Remedy: advance ETT/cuff to alternative level in trachea (temporary, low risk)
  - Remedy: change ETT (high risk) or change tracheostomy to larger size, length, or cuff shape/design (moderate or high risk if trach >10 days old)
  - Presence of foreign body within trachea leading to airway leak (temperature probe, NGT, feeding tube)
    - Presence of tracheoesophageal fistula (TEF), bronchoesophageal fistula (BEF), or bronchogastric fistula (BGF). Often this condition is known to the care providers. Adjusting the depth of the ETT may be required. If a new diagnosis of a fistula is made, this may be a surgical emergency because of the potential for mediastinal spillage.
  - Dislocation of ETT (partial or complete extubation of the trachea) is typified by three potential locations within the airway:
    - Cuff between vocal cords (partial extubation)
    - ETT tip at level of vocal cords (complete extubation)
    - ETT tip/cuff in hypopharynx (complete extubation) (Figs. E1.33 through E1.35)
- Partial/complete extubation of the airway, masquerading as an ETT with a cuff leak, must be identified
  - It is imperative to check the status of the pilot balloon.
  - If the pilot balloon appears to be intact (holds insufflated air), the ETT tip/cuff location is likely not intratracheal.
  - If the "cuff" leak is erroneously identified as a malfunctioning ETT cuff and the airway team passes an airway exchange catheter (AEC), the misplaced distal tip of the ETT may allow passage of the AEC to areas external to the trachea (e.g., esophagus, pyriform sinus)

Fig. E1.32 Commercially available pilot balloon repair kit. Blunt needle is inserted into the cut end of the pilot valve line.

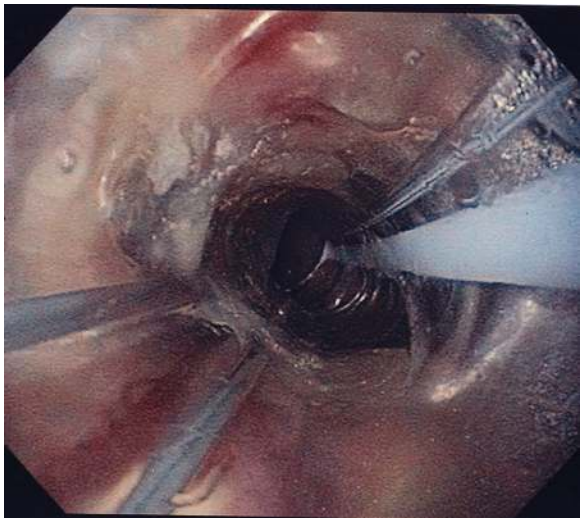

Fig. E1.33 This patient had a continuous "cuff leak" while supported on mechanical ventilation. The endotracheal tube (ETT) depth was 25 cm at the dentition, yet the ETT tip is just below the vocal cords when viewed with the FFB. The barely visible white vocal cords are "stretched" by the ETT and are located laterally in the picture. In the upper-right corner is the bluish edge of the lower portion of the ETT cuff. Distally at the ETT, one can see with the FFB that the posterior wall of the thyroid cartilage is visible (not seen in this picture).

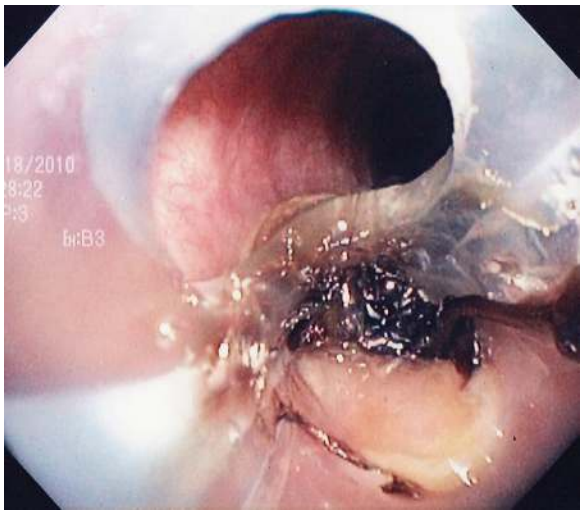

Fig. E1.34 The ICU physician was called to evaluate an intermittent "cuff leak," difficulty passing the suction catheter, and waxing/waning oxygen saturation. The pilot balloon was intact and inflated. Flexible fiber-optic bronchoscopic examination found the endotracheal tube (ETT) tip was impaled on the vocal cord, with a view of the subglottic area via the Murphy eye of the ETT. The FFB was passed into the trachea via the Murphy eye, and the ETT was gently advanced into the trachea.

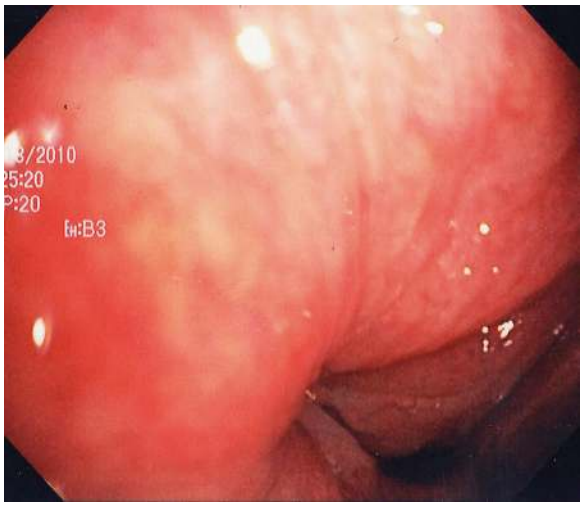

Fig. E1.35 The intensive care unit team was called to investigate a continuous "cuff leak" in this patient. The pilot balloon was intact; the fiber-optic bronchoscopic (FFB) view of the vocal cords from the tip of the endotracheal tube (ETT) reveals that the ETT tip is well above the glottic opening. The FFB was advanced into the trachea, and the ETT was then returned to the tracheal position.

- Two methods are strongly recommended to diagnostically and therapeutically manage the possible ETT tip/cuff dislocation:
  - First choice: FFB to diagnose the tip location and therapeutically allow reintubation of the trachea if possible (85% likely at authors' institution)
  - Second choice: laryngoscopy, preferably VAL versus direct laryngoscopy (DL), so as to allow improved visualization of the airway and possibly improve the margin of safety in this potentially life-threatening consequence of the intubated ICU patient
- Caveat: How reliable is the level of the ETT at the dentition line in determining where the tip is located (based on a database of 245 cases of partial extubation at the authors' institution)?
  - ETT at <20 cm at the dentition line: 55% were above the glottis
  - ETT at >20 cm: 73% at level of glottis or above glottis (hypopharynx)
  - Conclusion: There appears to be little correlation of ETT markings at the dentition line and the location of the ETT tip.
  - Overall, 51% of ETT tips were above the vocal cords, 32% were at the level of the vocal cords, and in 17%, the cuff was located between the vocal cords on examination.
- Caveat: Is there any difference in the incidence of complications when using FFB versus DL to diagnose and manage a dislocated ETT?
  - Managing this clinical situation with DL alone was fraught with complications such as severe hypoxemia, esophageal intubation, loss of the airway, bradycardia, and cardiac arrest.
  - Diagnostic and therapeutic management with FFB was an overall excellent choice, but it was not without its own problems. The ETT tip that was above the vocal cords was often centralized and easily advanced into the trachea, but approximately 15%–20% of these cases had the ETT tip abutting the vocal cords, pharyngeal wall, or other tissues that made it very difficult to advance the FFB into the trachea. Several of these ETTs had to be moved more proximal to allow FFB advancement, but this was not always successful.
  - Alternative airway management schema beyond the FFB must be available to rescue the airway in the event difficulty is encountered.

Contraindications

- Absolute
  - Difficult intubation and ETT can be salvaged by some other means than replacing it (e.g., repair of pilot balloon or clearing of obstructive luminal secretions via the CAM Resqu-Cath) (Figs. E1.36 through E1.38).
- Relative
  - Unprepared
    - Unless the situation is truly emergent, ETT exchange should not be attempted without properly preparing the patient and without having immediate access to difficult airway supplies.
  - ETT is not damaged
    - If the reason for exchange is for "cuff leak," for example, but the leak is the result of supraglottic positioning, not a damaged cuff, then adjustment of the ETT and not ETT exchange is appropriate. However, an overdistended ETT cuff may suffer from altered compliance because of stretching. Thus a new ETT may be advantageous.

Equipment

- Conventional intubation equipment
- Advanced airway rescue devices, including FFB and VAL
- Miscellaneous equipment
  - Kelly clamp/hemostat
  - Replacement pilot balloon kit

PROCEDURE

- Place patient on 100% oxygen.
- Review patient history, problem list, medications, level of ventilatory support.

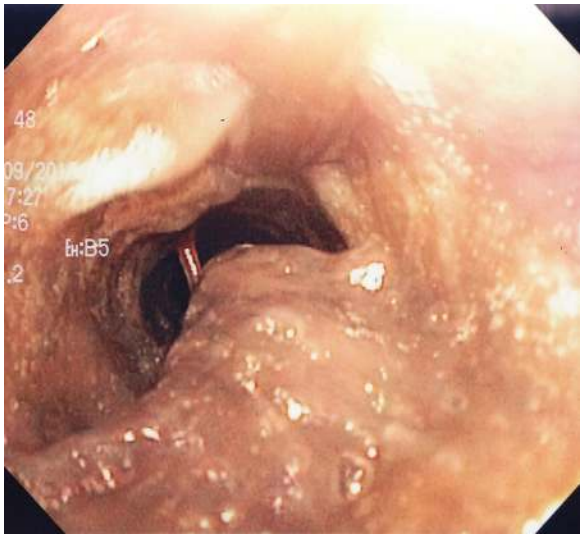

Fig. E1.36 This patient immediately failed a continuous positive airway pressure (CPAP) trial. Investigation with fiber-optic bronchoscopy (FFB) found significant biofilm accumulation at several levels of the endotracheal tube (ETT) lumen. A choice of exchanging to a new ETT was contemplated, but the patient was a known difficult airway. A catheter with an inflatable cuff (similar to a Fogarty catheter) that had a mesh covering for "traction" was passed and was able to remove 90% of biofilm blockage in less than 90 seconds on two passes.

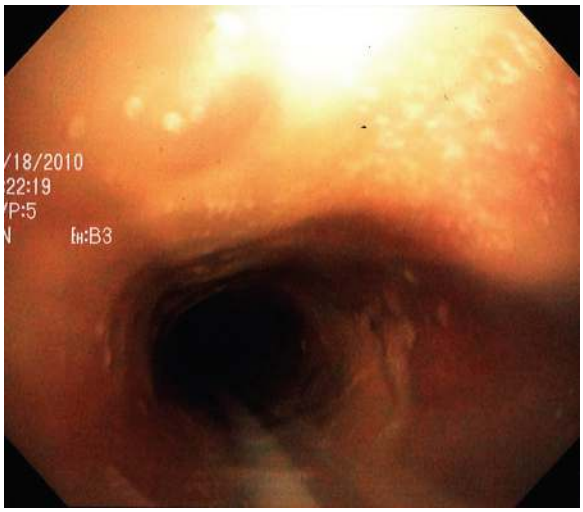

Fig. E1.37 The same endotracheal tube (ETT) as in Fig. E1.36, after a single pass of the biofilm removal catheter.

- Assemble conventional and rescue airway equipment, including capnography.
- Initiate sedation/analgesia if not already present, with or without muscle paralysis.
- Optimize positioning, perform FFB to determine level of the ETT tip if appropriate, and then advance the ETT over the FFB into the trachea.
  - Alternative rescue methods, personnel should be immediately available
- Second choice: examination of the airway (laryngoscopy, video-based preferable)
  - Extra caution when advancing laryngoscope blade into oropharynx, as the tip may puncture the overinflated ETT cuff in the "back" of the throat.

Fig. E1.38 **A,** A large biofilm plug removed following a single pass of the biofilm removal system. **B,** Close-up of the mesh-covered catheter cuff used to remove the tracheal lumen obstruction of biofilm.

- Consideration should be given to replacing the ETT when its cuff has undergone overinflation and may have altered compliance.

AFTER THE PROCEDURE

Postprocedure Care

- Reconfirm endotracheal placement with capnography.
- Assess depth of ETT with breath-sound auscultation, bronchoscopy, chest radiograph (delayed).

Complications

- Common
  - Inability to advance new ETT owing to tip embedded in the upper airway tissues
  - Hypoxemia
- Serious but rare complications
  - Loss of difficult airway
    - Most feared and worst outcome
    - Can be reduced by using FFB versus DL
    - Use VAL over DL
    - Ensure airway team has adequate supportive staff and immediate access to advanced airway equipment (including surgical staff)

OUTCOMES AND EVIDENCE

Partial extubation of the airway can be a life-threatening consequence of tracheal intubation in the ICU patient. Misdiagnosis or lack of understanding of this situation may lead to patient

morbidity and mortality. Being prepared, as is the case for any ICU airway situation, is in the best interest of patient safety. Running through the differential diagnosis of a "cuff leak" is imperative. The simplest task to complete is to inquire about the characteristics of the cuff leak (duration, amount of air placed in cuff, etc.) and to check its integrity. If the pilot balloon appears intact, it is reasonable to assume the ETT tip cuff is displaced at or above the vocal cords, and one should consider FFB for diagnostic and therapeutic management. Again, VAL is invaluable as both a diagnostic and therapeutic option.

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EXTUBATION OF THE DIFFICULT AIRWAY

BEFORE THE PROCEDURE

Indications

- To optimize the safety of the ICU patient being readied for extubation, with special emphasis on the difficult airway patient
- Known difficult airway
  - Known difficult mask ventilation
  - Known difficult laryngoscopy
  - Known difficult intubation
- Suspected difficult airway
  - Obesity
  - Cervical spine precautions, hard collar, halo vest, limited range of motion
  - Edema, swelling, airway trauma, systemic reaction (sepsis, blood transfusion reaction, anaphylaxis)
  - Massive volume resuscitation
  - Evolving head/neck trauma, pathology, injury
  - Any limitation to the mouth/oral cavity/oropharynx
  - Excessive secretions, bleeding, bandages, alterations to anatomy
- *Difficult extubation* is defined as the clinical situation when a patient presents with known or presumed risk factors that may contribute to difficulty reestablishing access to the airway.
  - The subsequent intolerance of the extubated state poses an increased risk to patient safety.
  - An extubation strategy should be developed that allows the airway manager to (1) replace the ETT in a timely manner and (2) ventilate and oxygenate the patient while the patient is being prepared for reintubation and during the reintubation itself.
  - The practitioner should assess the patient's risk on two levels: the patient's predicted ability to tolerate the extubated state and ability (or inability) to reestablish the airway if reintubation becomes necessary. Weaning criteria and extubation parameters will not be discussed because they vary by locale, practitioner, and the patient's clinical situation.

Contraindications

- Absolute contraindications
  - When the clinical assessment of the patient is suggestive of a high risk for difficulty establishing an airway and airway management personnel with an expertise of handling such a patient are not present or they are not properly equipped to handle such a patient.
  - Patient fails routine accepted extubation parameters for your facility.
  - When the full complement of ICU personnel are unavailable for the extubation trial (e.g., nursing staff, respiratory therapy staff, airway team members).
  - When a backup plan/strategy has not been developed or the equipment/personnel to execute such a strategy are not available.
- Relative contraindications*
  - Establishing a surgical airway (tracheostomy) would be a better choice.
  - Delaying the extubation trial would be in the patient's best interest.

Equipment

- Conventional airway management equipment
- Advanced airway rescue equipment (difficult airway cart/bag)
  - FFB
  - Advanced VAL equipment
  - Airway exchange catheters
- Nursing staff
- Respiratory therapy staff
- Surgical assistance for a surgical airway (if indicated)
- Sedation/analgesia/muscle relaxant medications
- Postextubation oxygen delivery system
  - Nasal cannula
  - Face mask
  - CPAP, BiPAP

ANATOMY

- Patient assessment must be completed before the decision whether or not to extubate.
- Review of the patient's stay in the ICU, medications, problem list, surgeries, procedures, previous airway interventions, and current clinical condition would be standard to provide needed information to develop an understanding of the patient's current predicament.
- This evaluation would be supported by a clinical assessment of the patient's airway to evaluate inability to tolerate extubation from such causes as:
  - Airway obstruction (partial or complete)
  - Hypoventilation syndromes
  - Hypoxemic respiratory failure
  - Failure of pulmonary toilet
  - Inability to protect airway

*Based on personal preference, experience, and the patient's clinical condition.

- Evaluate for potential difficulty reestablishing the airway
  - Difficult airway
  - Limited access to the airway
  - Inexperienced personnel pertaining to airway skills
  - Airway injury, edema formation
- Risk factors for difficult extubation
  - Known difficult airway
  - Suspected difficult airway based on the following factors:
    - Restricted access to airway
    - Cervical collar, halo vest, limited range of motion
    - Head and neck trauma, procedures, or surgery
    - ETT size, duration of intubation
    - Head and neck positioning (e.g., prone vs. supine)
    - Traumatic intubation, self-extubation
    - Patient bucking or coughing
    - Drug or systemic reactions
      - Angioedema
      - Anaphylaxis
      - Sepsis-related syndromes
      - Excessive volume resuscitation
- ASA Practice Guidelines and other societies have suggested that a preformulated extubation strategy should include:
  - A consideration of the relative merits of "awake" extubation versus extubation before the return of consciousness (more applicable to the operating room setting)
  - An evaluation for general clinical factors that may produce an adverse impact on ventilation after the patient has been extubated
  - The formulation of an airway management plan that can be implemented if the patient is not able to maintain adequate ventilation after extubation
  - A consideration of the short-term use of a device that can serve as a guide to facilitate intubation and/or to facilitate ventilation/oxygenation

PROCEDURE

- Suggested three-step patient assessment
  - Review history, current conditions, medications, mental status as previously stated.
  - Assess airway; external evaluation supplemented with internal evaluation
    - Conventional laryngoscopy has limited clinical utility in the ICU patient.
    - In most patients, VAL allows the ability to "see around the corner," thus providing a view of the periglottic airway to determine if the airway is suitable for extubation; also provides valuable information regarding the ease or difficulty of viewing the airway anatomy in the event reintubation is needed after extubation.
  - Develop strategy for extubation, delay extubation, or secure via surgical means; extubation choices include
    - Conventional extubation (directly to oxygen source)
      - Extubation over an airway exchange catheter to maintain airway access
      - FFB-assisted airway evaluation/extubation
        - Transition to LMA until patient is "safe" to lose "airway access" (Fig. E1.39)
        - It may be appropriate to relocate the extubation procedure to the operating room. Requesting the presence of personnel capable of rapidly performing surgical access (Difficult Airway Response Team [DART], surgical airway team, etc.) may be appropriate in some instances.

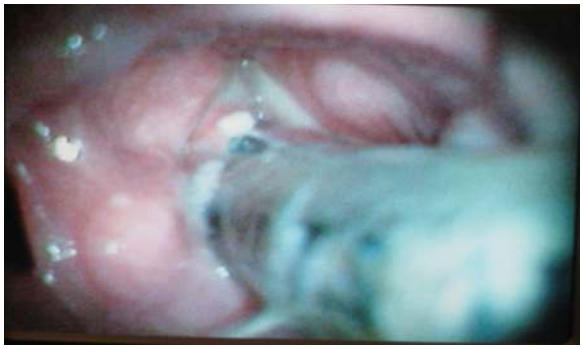

Fig. E1.39 Laryngoscopic view (GlideScope) of a patient with a known difficult airway who is ready for an extubation trial. The airway was assessed to determine two factors: (1) the ease or difficulty of reintubating the trachea if extubation is poorly tolerated and (2) the status of the periglottic tissues (edema, swelling, and trauma) and whether they are compatible with tolerance of the extubated state. This airway view demonstrated residual edema and swelling, in addition to secretion buildup.

- Clinical decision plan for the difficult extubation
  - A variety of methods are available to assist the practitioner to maintain continuous access to the airway after extubation, each with its limitations and restrictions.
  - Though no method guarantees control and the ability to resecure the airway at all times, the LMA offers the ability for fiberoptic–assisted visualization of the supraglottic structures while serving as a ventilating and reintubating conduit, but is hampered by a limited time frame.
  - FFB is useful for periglottic assessment after extubation but requires advanced skills and minimal secretions. Moreover, it offers only a brief moment for airway assessment and continuous access to the airway after extubation.
  - Conversely, the AEC allows continuous control of the airway after extubation but without visualization, is well tolerated in the vast majority of patients, and serves as an adjunct for reintubation and oxygen administration. Patient intolerance, accidental dislodgment, and mucosal and tracheobronchial wall injury have been reported but are rare. Several brands of AECs are available in a variety of sizes. Cook Medical offers adult-appropriate sized AECs in 11F (3.7 mm diameter, 14F (4.7 mm), and 19F (6.3 mm). The best tolerated in adults is the 11F. However, reintubation over this AEC may be difficult with the larger-caliber, adult-sized ETT (7.0–9.0 mm internal diameter [ID]). Thus it is suggested to reintubate with a smaller 6.0 ETT to ease advancement into the trachea. This is only a short-term solution for most adults because they would be best served with a larger-caliber ETT. Thus tackling this problem is straightforward. If reintubation is required, pass a lubricated Aintree catheter (19F) over the 11F or 14F indwelling AEC. This will improve the ability to "railroad" a larger-caliber ETT into the trachea. Reintubation is best performed with laryngoscopic assistance to open the pathway to the glottic opening.
  - Carinal irritation may be treated with proximal repositioning, instillation of topical agents to anesthetize the airway, plus explanation and reassurance. Dislodgment may occur because of an uncooperative patient or a poorly secured catheter.
  - Observation in a monitored environment with experienced personnel should be given top priority, as should the immediate availability of difficult airway equipment in the event of extubation intolerance.

- Suggested extubation procedure for the difficult airway patient:
  - Acquire advanced airway rescue equipment.
  - Assemble personnel (respiratory therapist, nursing staff, and surgical staff).
  - Prepare circumferential tape to secure the airway catheter after extubation. Other ETT-holding devices may be adapted to secure an AEC.
  - Discussion with patient/family/airway care team.
  - Position patient upright; suction internal and external to ETT.
  - If obese, ramped position recommended.
  - Pass lubricated AEC to 23- to 26-cm depth (shorter adults <5 ft. tall may require a depth of 20–22 cm).
  - Remove the ETT while maintaining the AEC in its original position.
  - Wipe excess lubrication/secretions from the AEC before taping.
  - Secure the AEC with tape (circumferential) and mark AEC "airway only."
  - Oxygen: nasal, mask, or humidified oxygen.
  - Maintain NPO (nothing by mouth), provide pulmonary toilet.
  - Ensure availability of smaller-caliber ETT (6.0) for reintubation if needed. Aintree catheter to place over 11F or 14F AEC to increase caliber of catheter to augment the advancement of the ETT into the trachea
  - Maintain patient in monitored setting with skilled personnel available (Fig. E1.40).
- Clinical judgment and the patient's cardiopulmonary and other systemic conditions, combined with the airway status, should guide the clinician in establishing a reasonable period for maintaining a state of "reversible extubation" with the indwelling AEC. Table E1.1 shows a suggested time frame for maintaining the well-tolerated AEC. If significant head/neck and/or laryngeal/periglottic edema precludes extubation, several maneuvers may be implemented to assist in decreasing swelling and edema
  - Raise head of bed as much as tolerated.
  - Maintain even to negative in/out fluid balance.
  - Diurese if volume overloaded (common in ICU).
  - Pretreatment (12–24 hours before extubation) with corticosteroids if appropriate (controversial but may reduce postextubation stridor, breathing difficulties, reintubation, and laryngeal edema overall).
  - SAFETY NOTE: Administration of oxygen (low flow 1–2 L/min, medium flow 3–6 L/min, or high-pressure "jet" delivery) via the AEC cannot be recommended unless preparing for emergency reintubation (short-term only). Without proper egress of insufflated oxygen, even low-flow oxygen may lead to barotrauma and life-threatening consequences. Thus oxygen delivery around, not through, the AEC lumen, is recommended. Many experts favor not applying "jet" pressurized oxygen via the AEC because of (1) the rarity that most clinicians use jet ventilation and (2) the hazards of its use during an emergency.

TABLE E1.1 Time Frame* for Maintaining the Well-Tolerated Airway Exchange Catheter

Difficult airway only, no respiratory issues or airway swelling	1–4 hours
Difficult airway, no direct respiratory issues, potential for airway swelling	2–6 hours
Difficult airway, cardiopulmonary issues, multiple extubation failures	2–24 hours

*Time frame will vary according to patient condition, airway assessment, and tolerance of the presence of the airway exchange catheter.

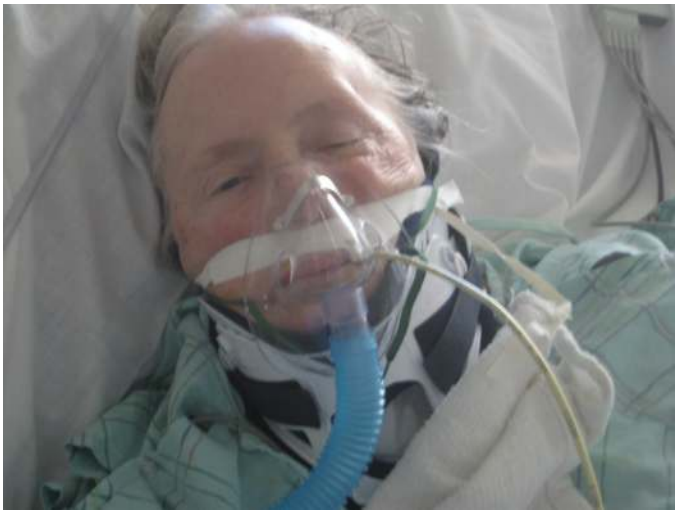

Fig. E1.40 Patient on postoperative day 2 after an anterior-posterior four-level cervical fusion, laminectomy, and discectomy at two levels. She required an "awake" flexible fiber-optic bronchoscopy (FFB) intubation to allow induction of anesthesia. Being a known difficult airway to start with, her airway status only worsened with postoperative swelling and the addition of the halo vest that further restricted cervical movement. She was extubated over an airway catheter but developed rapid deterioration because of stridor, requiring emergency passage of a new endotracheal tube (ETT) over the airway catheter, which was accomplished in less than 20 seconds. A smaller-bore ETT was used (6.0) based on the assumption that airway swelling was the cause of the stridor and a smaller ETT would most likely pass more easily into a swollen airway.

AFTER THE PROCEDURE

Postprocedure Care

- Optimize patient positioning, pulmonary toilet, minimize sedation.
- Continuous close observation by trained personnel and immediate access to an experienced airway management team
- Failure to tolerate the extubated state may vary from 2% to 25% of all patients over a variable timeline such as 12–48 hours.
- The ICU setting is unpredictable. Patients may fail extubation because numerous alterations in the patient's condition can take place unexpectedly (e.g., new-onset dysrhythmia, flash pulmonary edema, acute neurologic changes, systemic reactions, aspiration).
  - Maintain AEC in place for 1–2 hours, at least. Some patients will tire or suffer deterioration in the 2- to 24-hour time frame. Extending the time the "reversible extubation" is maintained is recommended; however, it remains unpredictable for many patients.

Complications

- Patient intolerance of AEC (10%)
  - Assure distal tip is not irritating the carina/bronchus.
  - Hand holding, explanation may improve tolerance.
  - Local anesthetic application via AEC
- Infrequent
  - Removing AEC too early and reintubation required later
  - AEC is removed by patient or falls out inadvertently
  - Inability to reintubate tracheal via AEC (recommend laryngoscopic assistance, may require alternative strategy)

- Esophageal intubation if AEC is displaced
- Serious but rare complications
  - Possible airway obstruction, loss of airway, laryngospasm, mucosal damage
  - Distal tip of AEC, if advanced too distally, may perforate the tracheobronchial tree, tip misplacement into the aerodigestive tract
  - Barotrauma because of oxygen insufflation via the AEC

OUTCOMES AND EVIDENCE

The difficult airway patient being readied for extubation warrants a strategy that allows a predictable reintubation in a timely manner, and thus a "reversible extubation." Though regional or national guidelines that outline specific management schema for dealing with this clinical situation are not readily available, this outline offers "safety first" for the patient. Much emphasis is focused on placing the ETT into the trachea, yet the more difficult issue is replacing the ETT in a recently extubated airway, typically under adverse clinical conditions. Patient morbidity and even mortality (i.e., brain injury from anoxia) are real consequences of extubation of the patient with a difficult airway and should be respected and approached cautiously.

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VIDEOLARYNGOSCOPE-ASSISTED INTUBATION

BEFORE THE PROCEDURE

Indications

Video-Assisted Laryngoscopy

- Routine tracheal intubation
- Emergency tracheal intubation
- Rescue of other failed intubation methods
- Viewing airway structures for educational/training purposes
- Exchange of tracheostomy tube
- Evaluation of airway structures for foreign body, trauma, edema, cuff leak
- Extubation evaluation of airway
- Assistance with advancement of TEE probe, feeding tube, NGT, esophageal dilator
- Evaluate ETT position in situ
- Types of VAL blades
  - Conventional angle (20–30 degrees) versus acute angle (60–70 degrees)
  - Channeled versus nonchanneled
  - Hybrid
- Advantages of VAL versus conventional DL (Figs. E1.41 and E1.42)
  - Full view of laryngeal inlet in majority of cases
  - Typically transforms laryngeal view one to two grades lower (better view)
    - Grade III view of the larynx with DL (grade III: no cords visible, only epiglottis visible) improves to grade I or II with VAL

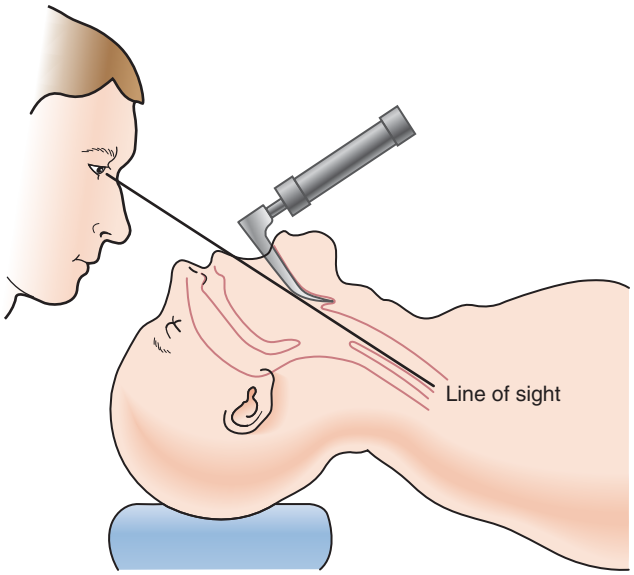

Fig. E1.41 Line of sight with direct laryngoscopy.

Fig. E1.42 Lines of sight for direct laryngoscopy (DL) versus videolaryngoscopy (VAL). There is approximately 30 degrees between the two methods that accounts for the ability to "see around the corner" when the laryngeal view is restricted with DL. Several manufacturers offer both conventional and acute angle blades. Conventional angle blades afford gaining experience with a "MacIntosh" blade combined with the advantage of video assisted visualization.

- Grade IV (no view of any airway structure) often improves to grade II (enough to allow ETT advancement)
- Improved line of sight of naked eye with DL, as operator must peer via the mouth opening around dentition, tongue, and the like; view is often restricted, even more so when the ETT is passed into the airway

Contraindications

- Unfamiliar with its use
- Recent tracheobronchial reconstruction
  - Inappropriate deployment because of trismus, oral cavity restrictions

Equipment

Five basic choices (not all-inclusive of models available, multiple manufacturers) (Figs. E1.43 through E1.50)

- Channeled VAL devices (groove or channel that is preloaded with ETT to assist with its passing)
  - Pentax AWS, AirTraq, King Vision
- Unchanneled VAL devices (must manipulate ETT freehand into trachea)
  - GlideScope, McGrath, Storz C-Mac, APA, VividTrac, Storz DCI Video Laryngoscope
- Acute angle blade assembly (e.g., 60–70 degrees, GlideScope, McGrath, Storz)
- Normal angle blade assembly (e.g., 20–35 degrees, GlideScope, McGrath, Storz)
- Hybrid blade (offering both styles)
- Alternatively, video optical stylet (ETT loaded on stylet, video-assisted intubation)
  - Clarus Shikani/Levitan/Pocket Scope Storz Brambrink, AincA, APA, Insight, J-Wand, Safe-CamVideo, SensaScope, and VivaSigt SL
- A variety of manufacturers offer models from disposable models (Airtraq-Prodol) to reusable models that range from $1500 (single device) to $30,000 (well-stocked cart).

Fig. E1.43 The Airtraq, a portable yet disposable channeled videolaryngoscope (VAL) device that offers excellent laryngeal viewing, given its relatively inexpensive cost and simple external design. (With permission from Prodol Meditec S.A.,Vizcaya, Spain.)

Fig. E1.44 The Pentax AWS, a portable, reusable channeled videolaryngoscope (VAL) with a disposable (clear) blade that has an adjustable video screen (black portion in photo) that adapts to various patient positions. An endotracheal tube (ETT) is preloaded into the channel of the blade to ease advancement into the larynx.

- Reusable models typically offer a disposable blade cover or video baton sleeve to speed its reusability between patient encounters.
- Most are easily transportable in an airway cart or bag or attached to an IV pole with wheels.

ANATOMY

Periglottic airway anatomy is typically visualized on a video-based screen, which equates to a much larger view as compared with the restricted view of the operator looking through the patient's mouth. Depending on the VAL device, the quality is excellent overall. Even the disposable model offers good color distinction, reasonable detail, and

Fig. E1.45 GlideScope AVL shown with video screen and two of several sizes of disposable video baton blades designed for neonatal to large adult. The optional specially shaped stylet that conforms to the blade's extreme 60 allows the operator improved access to advance the endotracheal tube to the laryngeal opening. (With permission from Verathon, Inc., Bothell, Washington.)

Fig. E1.46 The McGrath portable videolaryngoscope is easily transported and offers excellent video-quality images but on a smaller screen. To ease placement in patients with restricted oral access (e.g., halo vest, large chest/breasts, short neck), the device features a disposable clear blade and an adjustable video arm that can be disarticulated to allow the blade to be placed into the mouth and then reattached to the handle.

differentiation of various tissue pathologies. The more expensive models offer excellent quality, color, and detail, and some offer recording capabilities. Secretions, blood, and fogging may impede visualization. Adequate mouth opening is required to allow placement of the blade assembly. Moreover, adequate space between the chest, neck, chin, and mouth opening must be present to allow manipulation of the blade

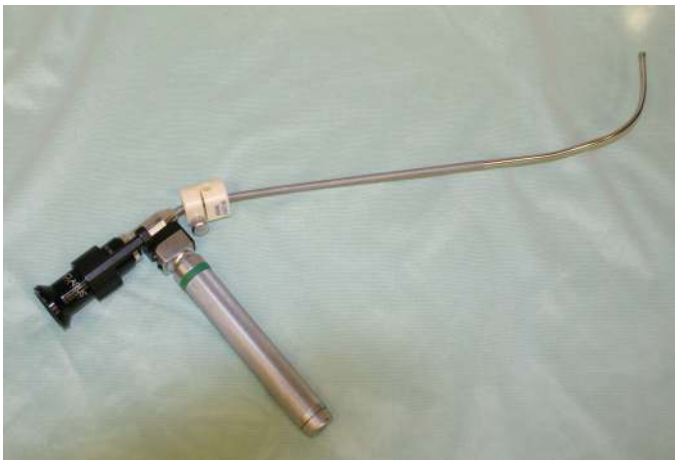

Fig. E1.47 The Levitan FPS Scope is an optical stylet that assists the operator with visualization of the airway structures via the eyepiece. Elevation of the mandible-tongue complex with a manual jaw thrust or combining the optical stylet with direct laryngoscopy allows the stylet–endotracheal tube to be passed underneath the epiglottis and into the trachea.

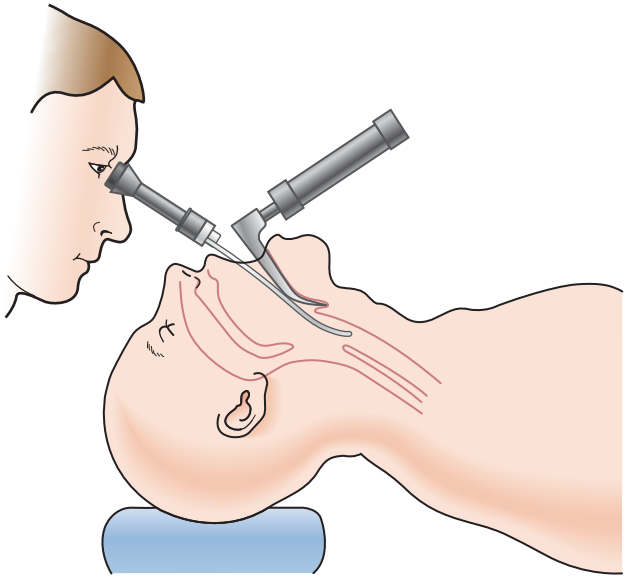

Fig. E1.48 Combining direct laryngoscopy with the optical stylet to achieve laryngeal visualization.

into the correct position to view the airway. The McGrath scope offers a disarticulating blade handle that allows placement of the blade followed by attachment of the handle, thus easing its placement in the restricted airway.

PROCEDURE

- Because of the variety of devices, the operator must be well versed in the individual device's limitations, indications and contraindications, method of placement, angulation within the oral cavity, video characteristics, and more.
- Because of the bulkiness of the VAL's blade, a minimum mouth opening is required to allow device placement into the oral cavity. Further, for the nonchanneled models, adequate space must exist to afford ETT manipulation.

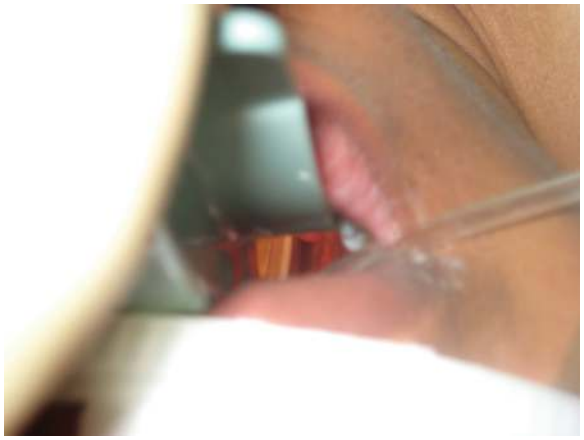

Fig. E1.49 The view offered by a conventional laryngoscope; limited view of glottis structure owing to dependency of operator's line of sight.

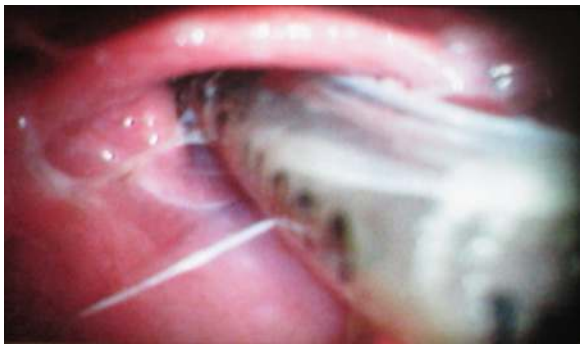

Fig. E1.50 Same patient as Fig. E1.49 but with videolaryngoscope-assisted view, allowing operator full view of epiglottis, arytenoids, and glottic opening.

- Preparation of the patient for intubation will vary by the patient's condition, airway status, hemodynamic profile, equipment choice(s), and airway team's judgment and preference. One option for the patient with a known or suspected difficult airway or hemodynamic compromise (hypotension, cardiac tamponade, tension pneumothorax, pulmonary embolism, low ejection fraction, cardiogenic or any shock state), may be topical preparation followed by gentle intubation (with or without light sedation). Adequate topicalization or nerve blocks that will allow bronchoscopic-assisted intubation would allow VAL-assisted intubation. This is now a viable option in the high-risk patient because of airway or hemodynamic concerns.

- Use of any of these devices is a four-step process:
  - Placement into the oral cavity and advancement into the orohypopharynx
  - Optimizing the glottis view
  - Advancing the ETT either via the channel, freehand over a stylet that approximates the curve of the device's blade (nonchanneled), or advancing the ETT-optical stylet assembly to the glottic level and then advancing the ETT into the trachea
  - Smooth and gentle advancement into the mouth is required when manipulating the device, because the operator's attention is typically focused on the "view" and not the patient's dentition or airway tissues.

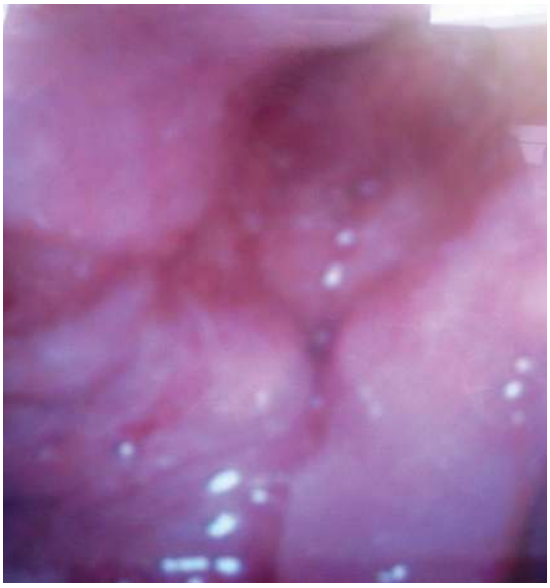

Fig. E1.51 Videolaryngoscope (VAL) view of a massively swollen airway. No features were discernible via direct laryngoscopy. VAL revealed massive edema but enough detail to allow placement of an endotracheal tube.

- Additional caveat for using VAL for airway management (Fig. E1.51)
  - Proper removal of the device to minimize patient injury and avoid extubation
  - Fundamentals of airway management must be practiced, even when use of high-tech equipment is incorporated. VAL may be able to overcome the lack of fundamentals.
    - Proper positioning is an absolute must (e.g., ramping the obese patient)
    - Secretions, vomitus, bleeding impede viewing.
    - Do not use equipment you are not trained to use.
    - Do not try a new technique or device in an emergency (do what you do best).
    - Remove the front of a hard cervical collar (maintain midline stabilization).
    - Secure the head to the bed frame for immobilization with 2-inch tape ± sandbags; this frees up valuable space that would otherwise be occupied by a colleague trying to maintain a midline position, which could interfere with airway management efforts.
    - If the airway should be secured awake, then do so (FFB, VAL, SGA).
    - Always have a backup plan for any VAL difficulty or failure.
    - VAL is only as good as the person holding it.
    - Do not practice in a cavalier manner just because you have VAL available.
    - The SGA has been displaced by VAL; SGA is an excellent VAL rescue device.
    - Never apply excessive force to the device "to make it fit."
    - Avoid forcing the advancement of the ETT with VAL (there is no visualization of the ETT until it passes the distally placed video chip).
    - Apply lubrication to the blade as needed, and to the ETT, to ease passage (this is particularly apropos for the patient with dry mucous membranes, e.g., CPAP or BiPAP therapy, mouth breather).
    - If VAL is your first choice and fails, consider trying DL in some cases.

    - An infamous quote regarding the use of VAL: VAL will often make a difficult airway an easy one, but it can make an easy airway a difficult one.
        - If you are applying excessive force or you are "just trying too hard," then you should change something, not try harder.
- To review the use of any individual VAL device, please refer to the product's website and review it through educational offerings.
- Review of the technique (which varies with each device) and its indications, contraindications, and limitations is imperative for operator confidence and patient safety.
- Practice on mannequins with proper instruction. Instruction by experienced personnel on the elective, healthy, normal-airway patient is a prerequisite to use in the difficult airway or emergency setting.
- Decision time: passing the ETT
    - If time permits, generously lubricate the ETT.
    - Smaller-sized ETTs pass over the bougie more easily than do larger ones.
    - Maintain tongue displacement with laryngoscopy/hand grasp.
    - Pass the ETT, but do not force the advancement (an assistant should grasp the proximal end of the bougie to stabilize it).

AFTER THE PROCEDURE

Postprocedure Care

- After advancement of ETT into the trachea and reverifying its position, stabilize the ETT in position, and remove the device.
- Though the video attributes allow observation that the ETT is through the glottis, removing the device may jeopardize its position. Once the device is removed, one is unable to confirm its position without again passing the device. Standard methods of determining the ETT position, such as capnography and chest auscultation, are recommended.

Complications

- Difficulty or failure achieving adequate laryngeal view (2%–10%)
    - Inadequate mouth opening, limited mandibular hinge movement
    - Secretions, blood, vomitus, fogging
    - Power failure (battery, electrical, system failure)
- Difficulty or failure to intubate trachea (2%–10%)
    - Inability to manipulate ETT correctly
    - Operator inexperience
    - Altered/traumatized/edematous/mass/distorted anatomy
    - Unable to pass ETT tip past glottis/cricoid ring: use bougie (through the ETT) for assistance
- Infrequent
    - Tissue injury, airway trauma (palatal or tonsillar pillar wall perforation, pharyngeal wall laceration/perforation)
    - Esophageal placement of ETT
    - Dental damage
- Serious but rare complications
    - Mucosal and tissue laceration/perforation leading to mediastinitis/pharyngeal abscess

OUTCOMES AND EVIDENCE

- The addition of the VAL technology is not new, but the era of lower-cost, more accessible models is afoot. DL is now being challenged as a first-line approach to airway management. Whether VAL replaces DL as the primary method of management is difficult to say, primarily because of economic issues.
- The overall usefulness of video-based visualization of the "easy" airway is questionable except for evaluation and educational purposes. However, its use for the restricted laryngeal view with DL, for the difficult airway (either known or presumed), and for its role as a rescue device for failed DL is without question a welcome addition to our airway arsenal.
- VAL serves a variety of roles in airway management in the ICU setting, well beyond simply tracheal intubation. Extubation evaluation, ETT exchange, rescue of DL failures, and its use as a primary management choice are but a few.
- The impact VAL imparts on ICU airway management is not currently reflected in the management algorithms offered by anesthesiology societies in the United States, Canada, the United Kingdom, Germany, and many other countries.
- Likewise, its presumed improvement in patient care is intuitive, but it must be proven through research and be evidence-based to warrant its ubiquitous inclusion in ICU airway management as a standard of care. The airway team must use it with caution, practice basic airway fundamentals, and develop a rescue strategy for VAL difficulty or failure, because they will occur regularly, especially in the high-risk ICU patient population.

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ETT EXCHANGE

BEFORE THE PROCEDURE

Indications

Common Reasons in the ICU Setting

- Dysfunctional ETT (cuff, pilot balloon, narrowed lumen, biofilm, obstruction)
- Change location (nasal-to-oral, oral-to-nasal)
- Change size or type of ETT (7.0 → 8.0, double-lumen to single-lumen ETT)
- Similar clinical circumstances with tracheostomy tube exchange
- ETT exchange has been mentioned under other headings as it pertains to airway management procedures
- Elective versus urgent versus emergent conditions
  - May affect one's ability to accurately evaluate the airway situation
  - Primary reason to have trained personnel and an appropriately stocked difficult airway cart in the ICU setting
- Time permitting, review current patient medical/surgical history, airway procedures
  - Current ventilator settings
  - Current sedatives, analgesics, vasoactive agents
    - ETT secretion status, ETT patency, reason for exchange (clarify request) and substantiate that it is legitimate given the risks versus benefits.
    - Examine current ETT depth, size, patency, location.
    - Evaluate sedative-analgesic needs, cardiopulmonary response to procedure.
    - Assemble nursing, respiratory therapy, physician assistance as needed.
    - Assure immediate access to difficult airway cart, code cart, resuscitative drugs.
    - An imperative action by the airway team is a preexchange airway assessment. Performed externally and internally, this assessment will allow risk stratification, assessment of airway status, and planning of the exchange procedure. Preexchange laryngoscopy affords airway assessment as a segue to improved airway care. Assessment, best performed with VAL, may uncover partial/total ETT extubation masquerading as a "cuff leak" or offer a vital glimpse when there is overwhelming airway edema and secretions that render a high-risk warning for the exchange. In the case of elective ETT exchange (i.e., change of size or location), an alternative may be to delay or abort the exchange or choose to perform a surgical airway. Urgent or emergent exchanges (i.e., cuff perforation, narrowed lumen) may proceed but with a clear understanding of the airway status to optimize procedural planning.

Contraindications

- Inadequate equipment, personnel in high-risk patients
- Delay or abort exchange or alternatively, perform a surgical airway

Equipment

Equipment needs include all contents of the difficult airway cart, capable suction apparatus. and airway exchange catheters (AEC, various diameters) (see Figs. E1.43 through E1.50).

ANATOMY

Periglottic airway anatomy has been reviewed in previous sections. The primary concerns for an ETT exchange are access to the oral cavity via the nose or mouth and the patency of the airway in regard to adequate room to place the new ETT across the supraglottic, glottic, and subglottic regions. VAL offers a clear advantage over conventional DL or FFB methods.

PROCEDURE

- Multiple choices exist for ETT exchange. Currently, the safest method would be to maintain continuous access to the airway via an indwelling AEC or placement of both the existing and new ETT across the glottic opening. The latter is occasionally possible when, for example, the existing ETT is small (e.g., 6.0) in a tall male patient (relatively large glottic opening).
- Options for ETT exchange (oral to oral)
  - Blinded ETT removal followed by DL, VAL replacement (may be required with ETT obstruction or damage)
  - DL placement, ETT removal, and freehand replacement
  - FFB assisted (either passing FFB through glottis with or without existing ETT present)
  - AEC assisted (without the benefit of laryngoscopy to open the airway to provide a pathway for advancement)
  - Combined DL + AEC
  - VAL placement followed by removal and ETT replacement
  - Combined VAL + AEC
  - Combined VAL + FFB ± AEC
- ETT exchange options (nasal to oral, oral to nasal)
  - Similar to previous exchange options
  - Safest method for a location change would offer continuous airway access, thus, for example, VAL assessment followed by passing an AEC via the nasally placed ETT, backing out existing ETT above the glottis via the AEC, optimize VAL view, and then freehand ETT advancement. Once the ETT is in position, the AEC may be removed. Conversely, an ETT may be delivered via FFB or DL if visualization is adequate.
  - Maintaining continuous access affords "backtracking" if advancement of the new ETT is disrupted. Either the existing ETT or a new ETT may be readvanced into the airway over the indwelling AEC.
  - Fundamentals of airway management must be practiced, even when use of high-tech equipment is incorporated.
    - Proper positioning is an absolute (e.g., ramping the obese patient).
    - Secretions, vomitus, bleeding impede viewing. Apply suction to optimize view.
    - Assemble equipment and staff and discuss primary and backup plans.
    - 100% oxygen, suction ETT if applicable
    - Provide appropriate sedatives and analgesics and consider the pro/cons of neuromuscular blocking agents.
    - Before the exchange, assign tasks to team members to assure each is aware and comfortable with his or her role in the exchange.

  - Apply liberal lubrication to the blade and ETT to ease passage.
  - Double-glove for procedure. If gloves become slippery from lubrication, assistant can remove outer glove(s).
- "Mind the gap" between the ETT and the airway exchange catheter. An attempt to minimize the gap is imperative. The ETT will pass with less "wobble" and reduce hang-up on airway tissues. In some instances, a smaller AEC is the only option (double-lumen tube, existing small-caliber ETT, luminal narrowing or kink). The replacement ETT (e.g., 8-mm ETT) must be advanced over a smaller AEC with an increased risk of ETT hang-up, multiple attempts, delay in oxygenation, and other airway and hemodynamic complications. The smaller AEC may "bow" laterally in the airway when force is applied to the advancing ETT. The ETT may veer laterally and impinge on airway tissues, particularly the epiglottis, arytenoid, and vocal cords. Resistance may ensue. This major point promotes two important concepts: minimize the gap and deploy VAL to optimize viewing capabilities.
- If clinical conditions dictate that a smaller-diameter AEC be used, the Cook brand Aintree catheter (19F) can be used as a "jacket" for the 11F and 14F Cook AEC. Its placement on the AEC will reduce wobble, narrow the gap, and increase the "rigidity" of the AEC.
- Beware of the depth markings on the AEC and coordinate them with those markings on the ETT. It is imperative that personnel be assigned to stabilize the AEC during removal and replacement of the ETTs. Awareness of the AEC depth is important to minimize distal or proximal migration; both could have devastating consequences.
- The exchange method with the highest first-pass success rate, fewest attempts, lowest incidence of desaturation, and overall success is combining VAL and AEC, particularly in the known or suspected difficult airway patient.
- Further, data from the Hartford Hospital Exchange database strongly suggests that incorporating the larger-diameter AEC will markedly improve first-pass success and reduce desaturation and other airway-related complications. Thus there is an increasing incidence of complications when using the small-caliber AEC (14F and especially the 11F). If conditions dictate that the smaller-caliber AEC must be used, then augmenting the diameter of the 11F or 14 F AEC with the 19F Aintree catheter is recommended.

AFTER THE PROCEDURE

Postprocedure Care

- After advancement of ETT into the trachea and reverifying its position, stabilize the ETT in position, and remove the AEC.
- Standard methods of determining the ETT position, such as capnography and chest auscultation, are recommended. FFB may also be helpful.

Complications

- Passing an AEC into an ETT without knowledge of its relative location (e.g., intratracheal versus supraglottic position in unrecognized extubation masquerading as a "cuff leak") could lead to esophageal intubation, interruption of oxygen delivery, or loss of the airway. Hence, a preexchange laryngoscopy, preferably VAL based, is recommended.
- Airway-related.
  - Desaturation, esophageal intubation, regurgitation, aspiration
  - Mainstem bronchus intubation, mucosa injury, tracheobronchial wall injury, pneumothorax
  - Loss of airway, need for accessory devices
  - Lip, dental, tongue, pharyngeal injury
  - Tracheobronchial and/or ETT obstruction from distal soilage/secretions
- Hemodynamic-related
  - Tachycardia, bradycardia
  - Hypertension, hypotension
  - Dysrhythmia, cardiac arrest

OUTCOMES AND EVIDENCE

- Despite the serious clinical implications of ETT exchange, there is a relative paucity of evidence-based literature regarding best practice for ETT exchange. Maintaining continuous access to the airway is, however, a consistent recommendation. Many serious and potentially life-threatening complications can accompany exchange procedures. Recent evidence suggests patients with a known/suspected difficult airway or poor visualization offered by DL during the preexchange airway assessment may benefit greatly by incorporating VAL + AEC.
- The value of a preexchange airway assessment (VAL) is demonstrated in its ability to diagnose otherwise unrecognized partial/complete tracheal extubation masquerading as a cuff leak.
- Exchanging a double-lumen tube (DLT) to a single-lumen tube (or vice versa) typically is more difficult because of (1) the larger diameter, angled DLT possibly being difficult to place in general and (2) AEC-assisted exchange often entailing the use of a smaller-caliber AEC because the DLT's smaller luminal diameter will not accept the larger AEC.
- The overall usefulness of video-based visualization of the "easy" airway is questionable except for evaluation and educational purposes. However, its use for the restricted laryngeal view with DL, for the difficult airway (either known or presumed), and for its role as a rescue device for failed DL is, without question, a welcome addition to our airway arsenal.
- VAL serves a variety of roles in airway management in the ICU setting, well beyond simply tracheal intubation. Extubation evaluation, ETT exchange, rescue of DL failures, plus its use as a primary management choice are but a few.

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Bedside Ultrasonography

Yanick Beaulieu and John Gorcsan III

Advances in ultrasound technology continue to enhance its diagnostic applications in daily medical practice. Constantly evolving, this tool has become invaluable for properly trained cardiologists, anesthesiologists, intensivists, surgeons, obstetricians, and emergency department physicians. Ultrasound can enable rapid, accurate, and noninvasive diagnosis of a broad range of medical conditions. Patients in the intensive care unit (ICU) present daily diagnostic and therapeutic challenges to the medical team. The availability of ultrasound instrumentation in critical care units has facilitated greatly the rapid evaluation and treatment of patients with a wide spectrum of conditions. Although transthoracic and transesophageal echocardiography (TEE) have been generally available for years for evaluating ICU patients, advances in ultrasound imaging, including harmonic imaging, digital acquisition, and contrast for endocardial enhancement, have improved the diagnostic yield. Modern techniques are simple and safe to use. Ultrasound devices continue to become even more portable than in the past, and hand-carried devices now are readily available for everyday clinical use (point-of-care ultrasound [POCUS]). The spectrum of POCUS is quite broad, and many of its key imaging applications are discussed elsewhere. In this chapter we place emphasis on echocardiography and cardiovascular diagnostics. The use of bedside ultrasound to facilitate central line placement and to aid in the care of patients with pleural effusions and intraabdominal fluid collections also is addressed.

USE OF BEDSIDE ULTRASONOGRAPHY IN THE INTENSIVE CARE UNIT

General Indications

Ultrasonography has become an invaluable tool for managing critically ill patients. Its safety and portability allow for use at the bedside to provide rapid, detailed information regarding the cardiopulmonary system[1] and to assess the function and anatomy of certain internal organs. It also can be used by the clinician to interrogate the pleural and intraabdominal spaces and to perform some invasive procedures safely. General indications for the performance of echocardiography in the ICU are listed in Box E2.1. Box E2.2 lists major indications for performance of primary TEE in the ICU. Other indications for the use of bedside ultrasonography by the intensivist in critically ill patients are listed in Box E2.3.

Technical Aspects

Acoustic Window in a Critically Ill Patient

The practical value of bedside ultrasonography in the management of critically ill patients is now widely accepted, despite the inherent limitations of the technique.[2] These limitations arise primarily from the suboptimal imaging conditions commonly encountered when performing studies of the critically ill. The constrained physical environment of the ICU also can compromise the quality of the images obtained. For an ultrasound study to be deemed adequate, a good acoustic "window" is required to allow accurate analysis. Ultrasonography uses the physical principle that sound is reflected from tissue interfaces, allowing a two-dimensional (2D) image of the anatomic structure studied to be constructed.[3] Anything hindering the reflection of this acoustic signal—air, bone, calcium, foreign body, or other interposed structure—interferes with ultrasound transmission and diminishes the overall quality of the examination. In the ICU, many patients are mechanically ventilated. In these patients, adequate imaging can be limited by complications such as pneumothorax, pneumomediastinum, or subcutaneous emphysema.[2] Other important factors limiting quality data acquisition in critically ill patients are related to surgical wounds and dressings, tapes, tubing, obesity, and chronic obstructive pulmonary disease. In addition, lack of patient cooperation and the impossibility of moving some patients into the optimal position for the desired examination contribute to a high prevalence of technically inadequate studies.[2]

Although ultrasonography permits evaluation of the structure and function of the heart and other important organs and structures, acquisition of data and interpretation of results are fraught with potential traps.[4] Performing an ultrasound examination requires a thorough knowledge of anatomy and instrumentation, including attention to gain control, grayscale settings, Doppler velocity settings, and transducer placement.

Preparation of the Patient

Before starting an ultrasound examination at the bedside in the ICU, certain important criteria should be met. The criteria vary, depending on the type of examination being performed (transthoracic echocardiography [TTE]; TEE; vascular, abdominal, or thoracic ultrasound) and on certain patient-related factors (e.g., presence or absence of mechanical ventilation, nasogastric tube, or surgical dressings).

An awake patient should be informed about the importance of the ultrasound investigation and should be provided with an explanation of how the clinician will perform the examination.[3] These steps are especially important when the examination uses the transesophageal route.

Positioning

Proper positioning of the patient is important for obtaining an adequate image. For performance of TTE and TEE in patients who are not mechanically ventilated, optimal imaging usually is obtained by having the patient in the left lateral decubitus position. Taking the extra 5 minutes to position the patient on his or her left side for TTE often

BOX E2.1 General Indications for Performance of an Echocardiographic Examination in the Intensive Care Unit

- Hemodynamic instability
  - Ventricular failure
  - Hypovolemia
  - Pulmonary embolism
  - Acute valvular dysfunction
  - Cardiac tamponade
  - Complications after cardiothoracic surgery
- Infective endocarditis
- Aortic dissection and rupture
- Unexplained hypoxemia
- Source of embolus

BOX E2.2 Major Indications for Performance of Primary Transesophageal Echocardiography Study in the Intensive Care Unit

- Diagnosis of conditions in which the superior image quality is vital (e.g., aortic dissection, assessment of endocarditis and its complications, intracardiac thrombus)
- Imaging of structures that may be inadequately seen by TTE (e.g., thoracic aorta, left atrial appendage, prosthetic valves)
- Echocardiographic examinations of patients with conditions that prevent image clarity with TTE (e.g., severe obesity, emphysema, mechanical ventilation with high level of PEEP, presence of tubes, surgical incisions, dressings)
- Acute perioperative hemodynamic derangements

PEEP, Positive end-expiratory pressure; *TTE,* transthoracic echocardiography.

BOX E2.3 Other Indications for Use of Bedside Ultrasonography by the Intensivist

- Central line placement
- Assessment of pleural effusions and intraabdominal fluid collections
- Urinary bladder scan
- FAST
- Intraaortic balloon counterpulsation
- Ventricular assist devices

FAST, Focused assessment of the trauma patient.

results in much improved image quality and minimizes aspiration risk. Adequate positioning of the patient depends on the structures being assessed (e.g., pleural space, peritoneal cavity, vascular structures, or bladder). Care must be taken when positioning a critically ill patient in bed, because these patients often have multiple vascular catheters, an endotracheal tube, drains, and other tubes or devices connected to them. When the ultrasound examination is performed to localize and mark pleural or abdominal fluid collections for subsequent drainage, it is crucial that the patient be placed in the same position used during the actual drainage of the collection. Risks of perforating surrounding organs (e.g., heart, spleen, liver, lungs, or bowel) and inducing significant morbidity are increased if the drainage is performed in a position different from the one used during marking.

Sedation

To optimize the ultrasound examination, the patient must be cooperative and nonagitated. Noninvasive procedures such as TTE and abdominal ultrasound usually are well tolerated, and additional sedation rarely is needed to perform them. When performing TEE, however, certain precautions need to be taken. Patients should fast (or have their tube feeds stopped) for at least 4 hours before the procedure. Topical anesthesia of the oropharynx also is helpful before insertion of the TEE probe, especially in patients who are not endotracheally intubated.[3] Even if adequate topical anesthesia is provided, insertion of the TEE probe still can cause significant discomfort and anxiety, so providing adequate sedation and analgesia is important. Frequently used sedative or analgesic agents include intravenous (IV) midazolam, fentanyl, and propofol. Dosing should be titrated according to clinical parameters, including arterial blood pressure, minute ventilation, and arterial oxygen saturation.[3] Sedative-induced hypotension is a frequent problem in patients with depressed ventricular function or decreased systemic vascular resistance, and occasionally patients may require transient support with IV volume infusion or vasopressor agent. If the patient is extremely uncooperative and biting, increased sedation, transient paralysis, and mechanical ventilation may be required to perform TEE safely.

Monitoring During the Procedure

Most ICU patients are monitored continuously for key respiratory, cardiac, or hemodynamic parameters. At a minimum, it is essential that patients undergoing an ultrasound examination in the ICU be monitored with noninvasive recording of blood pressure, pulse oximetry, and electrocardiogram. Even TTE or abdominal ultrasound examinations can be associated with inadvertent pulling of tubes or drains, and anxiety can be encountered during the procedure. Because of its more invasive nature, insertion of the TEE probe may induce discomfort and complications such as increased agitation and respiratory distress. These effects can be associated with substantial changes in blood pressure and ventilatory status. Administration of sedatives and sometimes paralytic agents can further alter hemodynamic and respiratory status.[3,5]

Safety

Performance of ultrasound examinations in the ICU provides data that previously required transport to the radiology suite. This is an important advantage for the critically ill patient, because transport out of and back to the ICU is known to be associated with an increased risk of complications.[6] Performance of bedside TTE ultrasound and of other noninvasive ultrasound examinations is safe and not associated with significant risks to the patient. Performance of the semiinvasive bedside TEE also is associated with a low incidence of serious complications (<0.5% in the general population and the elderly).[5] The reported mortality rate associated with TEE is 0.01%–0.03%.[7] Most patients undergoing TEE examinations in the ICU are receiving mechanical ventilation and have continuous monitoring of arterial blood pressure, electrocardiogram, and oxygen saturation.[8] Transient hypotension, typically attributable to administration of sedative medications, usually can be treated with vasopressors or IV fluids or both. The risk of injury to the pharynx or esophagus is greater in anesthetized and endotracheally intubated critically ill patients than in awake patients, because anesthetized patients cannot assist with probe insertion by swallowing and do not resist when insertion proves difficult.[8] Increased difficulty in directing the TEE probe also can be encountered in the presence of a nasogastric tube. Coagulopathy and thrombocytopenia, common problems in critically ill patients, can increase the risk of hemorrhage resulting from mucosal injury during blind insertion of the TEE probe. Daniel and colleagues[9] reported significant complications related to TEE in 18 (0.18%)

of 10,218 examinations. In 11 studies reporting on 943 patients undergoing TEE, the rate of complications was 1.7%.[5] Serious complications occurred in only two patients (0.2%). Colreavy and colleagues[8] studied the safety and utility of TEE performed by ICU physicians in 255 critically ill patients and reported that TEE was associated with a complication rate of only 1.6%. It is reasonable to conclude that bedside TEE is associated with few complications, given the high severity of illness.[5] Close monitoring of hemodynamic and oxygenation parameters is essential. Box E2.4 lists specific contraindications to the insertion of a TEE probe.

BEDSIDE ECHOCARDIOGRAPHY IN A CRITICALLY ILL PATIENT

Echocardiography can provide diagnostic information noninvasively regarding cardiac structure and mechanical function. The supplementary information provided by this technique can help determine the cause of hypotension refractory to inotropic support or vasopressor infusions.[3] It also can help in the diagnosis of a wide spectrum of other cardiovascular abnormalities (e.g., endocarditis) and guide therapeutic management. An adequate understanding of the proper use of echocardiography is a prerequisite for the intensivist. General indications for performance of an echocardiographic examination in the ICU are listed in Box E2.1.

Transthoracic Versus Transesophageal Echocardiography in a Critically Ill Patient

Accurate and prompt diagnosis is crucial in the ICU. The easiest and least invasive way to image cardiac structures is TTE.[3] This noninvasive imaging modality is of great value in the critical care setting because of its portability, widespread availability, and rapid diagnostic capability. In the ICU, TTE may sometimes fail to provide adequate image quality because of factors that potentially can hinder the quality of the ultrasound signal, as described previously. The failure rate (partial or complete) of TTE in the ICU has been reported to be 30%–40%.[10,11] Nonetheless, improvements have been made in transthoracic imaging (e.g., harmonics and contrast and digital technologies), resulting in a progressively lower failure rate of TTE in the ICU (currently 10%–5% in our institution).

TEE is particularly useful for evaluation of suspected aortic dissection, prosthetic heart valves (especially in the mitral position), detecting cardiac emboli, valvular vegetations, possible intracardiac shunts, wall motion abnormalities, and unexplained hypotension. TEE allows better visualization of the heart than TTE, especially of the posterior structures, owing to the proximity of the probe and favorable acoustic transmission.[1] Despite its limitations, TTE may provide complementary information. For example several areas of the heart and great vessels are difficult to visualize by TEE. The view of the left ventricular apex often is foreshortened with TEE, and an apical left ventricular clot can be missed. TTE usually is superior for visualization of the apex. Because of interposition of the left mainstem bronchus, the superior portion of the ascending aorta is another important area that may not be well visualized with TEE. The transducer position and angulation of TEE are constrained by the relative positions of the esophagus and heart. The relatively fixed relationship between the position of the probe and the heart often makes it impossible to align the Doppler beam parallel to the flow of interest (e.g., to evaluate the jet of blood resulting from aortic stenosis). In addition, the 2D imaging planes of TEE often make standard anatomic measurements more difficult to obtain.

As a result of the significantly improved technical quality of TTE, most ICU patients can be studied satisfactorily with this modality alone. Immediate TEE is still preferable, however, in certain specific clinical situations in which TTE is likely to fail or prove suboptimal.[11] The major indications for primary TEE in the ICU[12,13] are listed in Box E2.2. Even when TEE is necessary, data from the TTE examination are often essential for the final clinical interpretation.

BOX E2.4 Contraindications to Insertion of Transesophageal Echocardiography Probe

Absolute Contraindications
Esophageal pathologies
Stricture
Mass or tumor
Diverticulum
Mallory-Weiss tear
Dysphagia or odynophagia not previously evaluated
Cervical spine instability

Relative Contraindications
Esophageal varices
Recent esophageal or gastric surgery
Oropharyngeal carcinoma
Upper gastrointestinal bleeding
Severe cervical arthritis
Atlantoaxial disease

Hemodynamic Evaluation

Ventricular Function

Left ventricular systolic function. Evaluation of left ventricular performance by echocardiography is often paramount in the ICU. Accurate and timely assessment of systolic function should be an integral part of the medical management of hemodynamically unstable critically ill patients. Global assessment of left ventricular contractility includes the determination of ejection fraction (EF), circumferential fiber shortening, and cardiac output.

The simplest quantitative approach is to measure the mid–left ventricular short-axis dimension at end diastole and end systole to determine the percentage of fractional shortening. Fractional shortening is related directly to EF; normal fractional shortening is 30%–42%.[1]

$$\text{Fractional shortening} = \frac{\text{End-diastolic dimension} - \text{End-sytolic dimension}}{\text{End-diastolic dimension}}$$

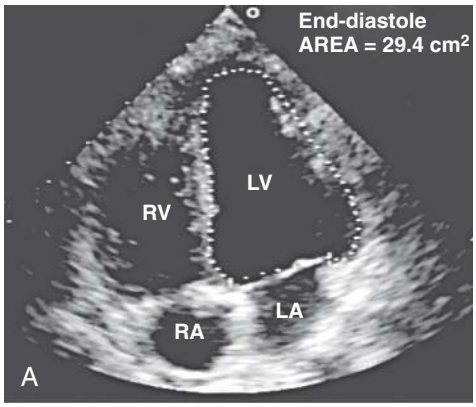
In the setting of regional wall motion abnormalities, fractional shortening may underestimate or overestimate global ventricular function and must be interpreted in light of what is seen in all of the 2D imaging planes of the ventricle.[14]

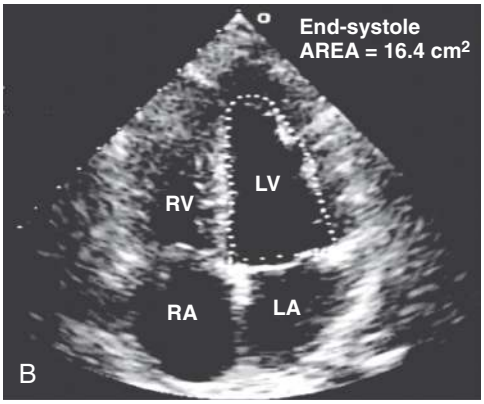
Global systolic ventricular function also can be assessed quantitatively by fractional area change (normal value is 36%–64%)[15] and by EF (normal value is 55%–75%) (Fig. E2.1):

$$\text{Fractional area change} = \frac{\text{End-diastolic area} - \text{End-sytolic area}}{\text{End-diastolic area}}$$

$$\text{Ejection fraction} = \frac{\text{End-diastolic volume} - \text{End-systolic volume}}{\text{End-diastolic volume}}$$

These measurements require good image quality, because endocardial border contours must be traced (see Fig. E2.1). Machine-integrated



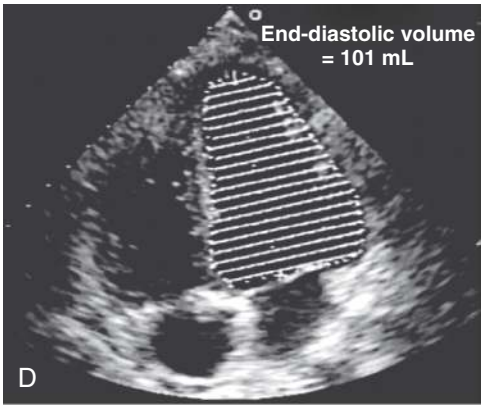


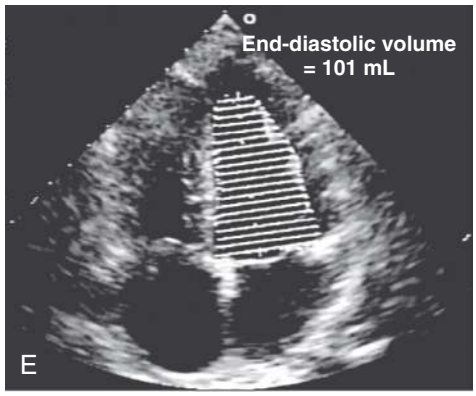
$$\text{Fractional area change} = \frac{\text{End-diastolic area} - \text{end-systolic area}}{\text{End-diastolic area}}$$

$$= \frac{29.4\ \text{cm}^2 - 16.4\ \text{cm}^2}{29.4\ \text{cm}^2}$$

$$= 44\%$$

C





$$\text{Ejection fraction} = \frac{\text{End-diastolic volume} - \text{end-systolic volume}}{\text{End-diastolic volume}}$$

$$= \frac{101\ \text{mL} - 39\ \text{mL}}{101\ \text{mL}}$$

$$= 61\%$$

F

Fig. E2.1 Fractional area change and ejection fraction calculation. Endocardial contour of the left ventricular cavity is traced at end diastole **(A)** and at end systole **(B)** in the transthoracic apical four-chamber view. Machine-integrated software computes the data and gives corresponding end-diastolic and end-systolic areas. Fractional area change can be calculated with these data **(C)**. Normal values are 36%–64%.[15] Corresponding end-diastolic **(D)** and end-systolic **(E)** volumes are computed using the modified Simpson method. The data are used to calculate the ejection fraction **(F)**. Normal values are 55%–75%. *LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle.

software uses the data to determine volumes, areas, and the resultant EF (see Fig. E2.1). In patients with regional wall motion abnormalities, more precise measures of stroke volume can be made by approximating ventricular volumes as a stack of elliptical disks on biplane imaging (modified Simpson method).[1,15]

In the critical care setting, defining the endocardial border may be suboptimal because of poor image quality.[10,16,17] In these cases, global ventricular function often is assessed qualitatively by visual inspection alone. This method has been found to be reliable when used by experienced clinicians.[18] By simple visualization of the kinetics and size of the cardiac cavities in real time, an experienced intensivist with a sufficient echocardiographic background can establish a functional diagnosis immediately.

Analysis of regional wall motion includes a numeric scoring system to describe the movement of the different regions of the left and right ventricles (1 = normokinesia; 2 = hypokinesia; 3 = akinesia; 4 = dyskinesia; 5 = aneurysmal change).[15] Visualized from the short-axis view of the left ventricle, a complete overview of myocardial areas perfused by the three major coronary arteries can be obtained (Fig. E2.2). If the TTE examination is technically difficult and the endocardium is poorly visualized, harmonic imaging and possibly contrast, if needed, can dramatically improve endocardial border visualization and subsequent evaluation of global systolic function (as discussed further later in this chapter). For the remaining few technically challenging cases with suboptimal TTE, performance of TEE allows for more precise evaluation of ventricular function in most critically ill patients because of the higher image quality that can be obtained with this echographic modality.

Left Ventricular failure in the intensive care unit. In a critically ill patient with unexplained hemodynamic instability, determination of cardiac function is an integral part of the medical management. Echocardiography is valuable in this setting because the clinical examination and invasive hemodynamic monitoring often fail to provide an adequate assessment of ventricular function. In a study by Fontes and colleagues[19] that compared pulmonary artery (Swan-Ganz) catheterization with TEE, the overall predictive probability for conventional clinical and hemodynamic assessment of normal ventricular function was 98%, whereas for abnormal ventricular function (EF <40%), it was 0%. Several other studies have reported similar results.[20–22] Assessment of

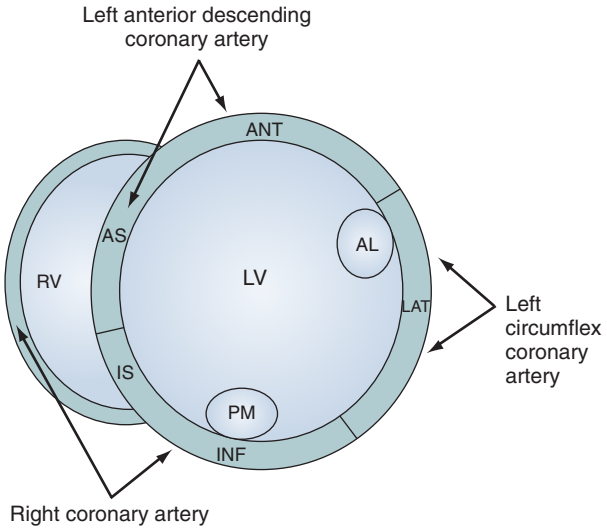


Fig. E2.2 Transthoracic short-axis echocardiographic view of the left ventricle (LV) and right ventricle (RV) at the midpapillary muscle level. In this tomographic view of the heart, areas of myocardium and papillary muscles (*AL,* anterolateral; *PM,* posteromedial) supplied by all three major coronary arteries are represented. *ANT,* Anterior; *AS,* anteroseptal; *INF,* inferior; *IS,* inferoseptal; *LAT,* lateral.

biventricular function is one of the most important indications for echocardiography in the ICU. In a study by Bruch and colleagues,[23] 115 critically ill patients were studied by TEE. The most common indication for TEE was hemodynamic instability (67% of patients). Of these hemodynamically unstable patients, 20 (26%) were found to have significant left ventricular dysfunction (EF <30%). In a study by McLean[24], the most common reason to request a TEE in the ICU was to assess left ventricular functioning. In most patients, left ventricular function was assessed adequately by TTE before TEE. In a study by Vignon and colleagues,[17] TTE allowed adequate evaluation of global left ventricular function in 77% of mechanically ventilated ICU patients. Although TEE was needed for most other indications, TTE was shown to be an excellent diagnostic tool for assessment of left ventricular function in the ICU (Fig. E2.3), even in the presence of positive end-expiratory pressure.

Several important points should be emphasized: (1) significant left ventricular dysfunction occurs commonly in critically ill patients; (2) ventricular function should be assessed in all patients with unexplained hemodynamic instability because this information is particularly important for guiding resuscitation and informing decisions regarding subsequent medical or surgical management; (3) it is now possible to obtain adequate information about ventricular function in most ICU patients using TTE, but TEE improves accuracy in patients with suboptimal imaging by TTE.

Sepsis-related cardiomyopathy. Classically, septic shock has been considered an initially "hyperdynamic" state characterized by normal or high cardiac output. Yet echocardiographic studies indicate that ventricular performance often is markedly impaired in patients with sepsis.[25–27] Parker and colleagues[28] were among the first to describe left ventricular hypokinesis in septic shock. They reported that survivors manifested severely depressed left ventricular EF, but that adequate left ventricular stroke output was maintained as a result of acute left ventricular dilation.[29] Jardin and colleagues[25] studied 90 patients with septic shock and performed daily bedside assessments of left ventricular volume and left ventricular EF using TTE. They observed that left ventricular EF was significantly depressed in all patients, resulting in severe reductions in left ventricular stroke volume. Of these patients, 34 (38%) eventually were weaned from hemodynamic support and showed gradual improvement in left ventricular EF and ultimately recovered. The remaining 56 patients (62%) eventually died of early circulatory failure or late multiple organ failure. In this subset, the degree of left ventricular dysfunction was actually less than in survivors but failed to improve over time. The severity of left ventricular dysfunction does not predict outcome. A paradoxical relationship between the degree of left ventricular dysfunction and the likelihood of recovery also has been described by others.[25,28,30,31] Among patients who survive, left ventricular dilation and systolic dysfunction usually are reversible.

Left ventricular EF might not be a reliable index of left ventricular systolic function in patients with early septic shock because this is a state characterized by low systemic vascular resistance that unloads the left ventricle.[25] Normal or supranormal EF in early sepsis might lead clinicians to make the wrong inference about cardiac reserve because

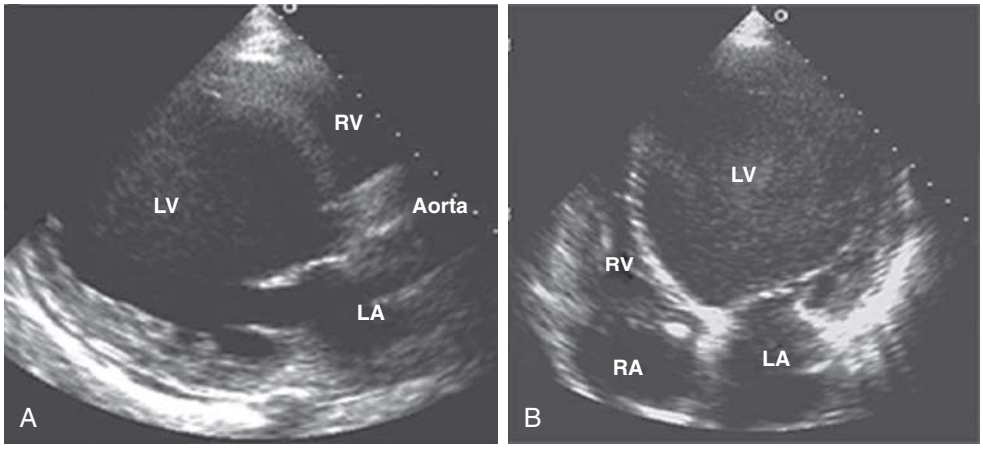


Fig. E2.3 Dilated cardiomyopathy. Transthoracic examination of a severely dilated left ventricle (LV) in the parasternal long-axis **(A)** and apical four-chamber **(B)** views. The 65-year-old patient presented with flash pulmonary edema and later was found to have severe diffuse coronary artery disease. *LA,* Left atrium; *RA,* right atrium; *RV,* right ventricle.

left ventricular EF might decrease when afterload is increased by the administration of vasopressor agents.

Left ventricular diastolic function. In the ICU, diastolic dysfunction should be suspected when ventricular filling pressure (pulmonary capillary wedge pressure) is elevated and EF is normal or supranormal.[1] The diastolic properties of the ventricle often are assessed by evaluating Doppler echocardiographic mitral inflow and pulmonary venous flow patterns. Mitral inflow, as measured by pulsed-wave Doppler directed at the tips of the mitral leaflets, is characterized by an early filling phase (E wave) followed by atrial systole, resulting in additional filling (A wave) (Fig. E2.4). The transmitral Doppler pattern always should be interpreted in conjunction with pulsed-wave Doppler of the pulmonary venous flow, which is characterized by a systolic phase (S), a diastolic phase (D), and an atrial phase (AR) from reversal of flow into the pulmonary veins during atrial contraction (Fig. E2.5). These filling patterns are related to the intrinsic diastolic properties of the myocardium and are influenced by many different factors, particularly left atrial pressure, heart rate, ischemia, ventricular hypertrophy, and valvular pathologies. Only modest correlation has been found between Doppler indices of diastolic function and parameters measured using more invasive means.[32,33] Integrated interpretation of mitral and pulmonary venous flow patterns may be useful for diagnosing abnormal myocardial relaxation (e.g., owing to hypertensive heart disease, hypertrophic cardiomyopathy, or coronary ischemia) or restrictive pathology (e.g., owing to cardiomyopathy, constrictive pericarditis, coronary artery disease, cardiac transplantation, or dilated cardiomyopathy). Nevertheless, these findings must be interpreted with caution when caring for critically ill patients, given the many different factors that can acutely influence flow patterns in this population of patients.

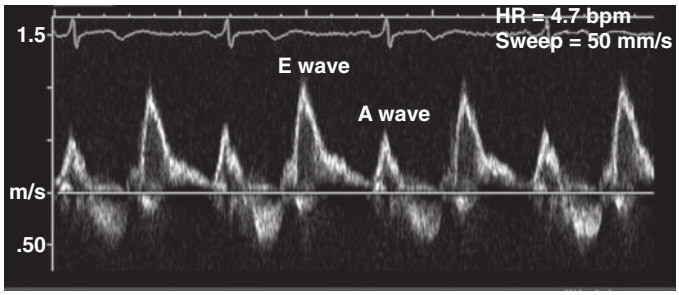


Fig. E2.4 Normal mitral inflow profile as measured by transthoracic pulsed-wave Doppler at the tips of the mitral leaflets. It is characterized by an early filling phase (E wave) followed by atrial systole (A wave), which results in additional filling. These filling parameters are related to intrinsic diastolic myocardial properties and can be influenced by many different factors (see text).

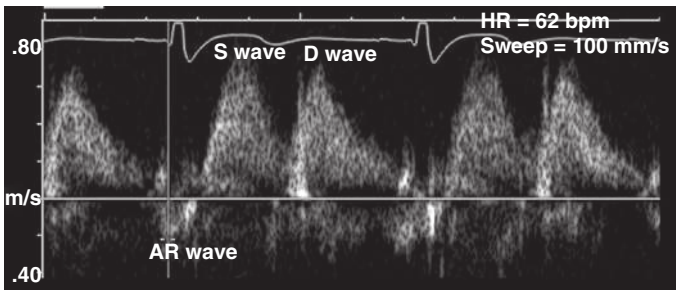


Fig. E2.5 Normal pulmonary venous flow profile as measured by transthoracic pulsed-wave Doppler with the sample volume placed in the right superior pulmonary vein. It is characterized by a predominant systolic wave (S), a diastolic wave (D), and an atrial wave (AR) (from reversal of flow into the pulmonary veins occurring during atrial contraction). The pulmonary venous flow profile always should be interpreted in conjunction with the transmitral Doppler pattern to have a more complete assessment of diastolic function.

Right ventricular function and ventricular interaction. Abnormal right ventricular function often plays an important and sometimes underestimated role in the pathogenesis of critical illness.[34–36] Based on an echocardiographic definition,[37] massive pulmonary embolism and acute respiratory distress syndrome are the two main causes of acute cor pulmonale in adults.[38] In the critical care setting, right ventricular function also can be altered by any other perturbations that increase right ventricular afterload, such as positive end-expiratory pressure or increased pulmonary vascular resistance (from vascular, cardiac, metabolic, or pulmonary causes). Depressed right ventricular systolic function is also often associated with right ventricular infarction, most commonly in the setting of inferior myocardial infarction. Acute sickle cell crisis, air or fat embolism, myocardial contusion, and sepsis are other causes of acute right ventricular dysfunction.

Adequate assessment of right ventricular function is important when caring for hemodynamically unstable, critically ill patients, specifically patients with massive pulmonary embolism and acute respiratory distress syndrome, because the diagnosis of concomitant right ventricular dysfunction may alter therapy (e.g., fluid loading, use of vasopressors, use of thrombolytics) and provide information about prognosis.[38,39] Echocardiographic examination of the right ventricle requires primarily an assessment of the size and kinetics of the cavity and septum.[37,40] Normally the right ventricle appears somewhat flattened. As it dilates, the apical region of the right ventricle becomes more rounded (Fig. E2.6). In the short-axis view, the right ventricle, which usually has a crescentic shape, becomes ovoid because of septal displacement and bulging of the right ventricular free wall (see Fig. E2.6).[1] Right ventricular size and function generally are evaluated by visual comparison with the left ventricle. Right ventricular diastolic dimensions can be obtained by measuring right ventricular end-diastolic area in the long axis, from an apical four-chamber view, using either TTE or TEE.

Because pericardial constraint necessarily results in left ventricular restriction when the right ventricle acutely dilates (i.e., there is ventricular interaction), one of the best ways to quantify right ventricular dilation is to measure the ratio between the right ventricular and left ventricular end-diastolic areas, an approach that compensates for individual variations in cardiac size.[37,40] Moderate right ventricular dilation corresponds to a diastolic ventricular ratio greater than 0.6; severe right ventricular dilation corresponds to a ratio greater than or equal to 1.0.[37,40] Right ventricular diastolic enlargement usually is associated with right atrial dilation, inferior vena caval dilation, and tricuspid regurgitation. When pressure in the right atrium exceeds pressure in the left atrium, the foramen ovale may open. Pressure and volume overload of the right ventricle can distort left ventricular geometry and produce abnormal motion of the interventricular septum. With conditions of high strain imposed on the right ventricle (volume or pressure overload or both), the interventricular septum flattens, and the left ventricle assumes a "D" shape (see Fig. E2.6).[4,37] This "paradoxical" septal motion also is seen at the interatrial level.

Because the two ventricles are enclosed within the relatively stiff pericardium, the sum of the diastolic ventricular dimensions must remain constant.[41] Acute right ventricular or left ventricular dilation can occur only if it is associated with an acute and proportional reduction in left ventricular or right ventricular diastolic dimension (i.e., ventricular interaction). With acute right ventricular dilation, septal displacement impairs left ventricular relaxation; the opposite occurs with acute left ventricular dilation. In these situations, the pressure-volume

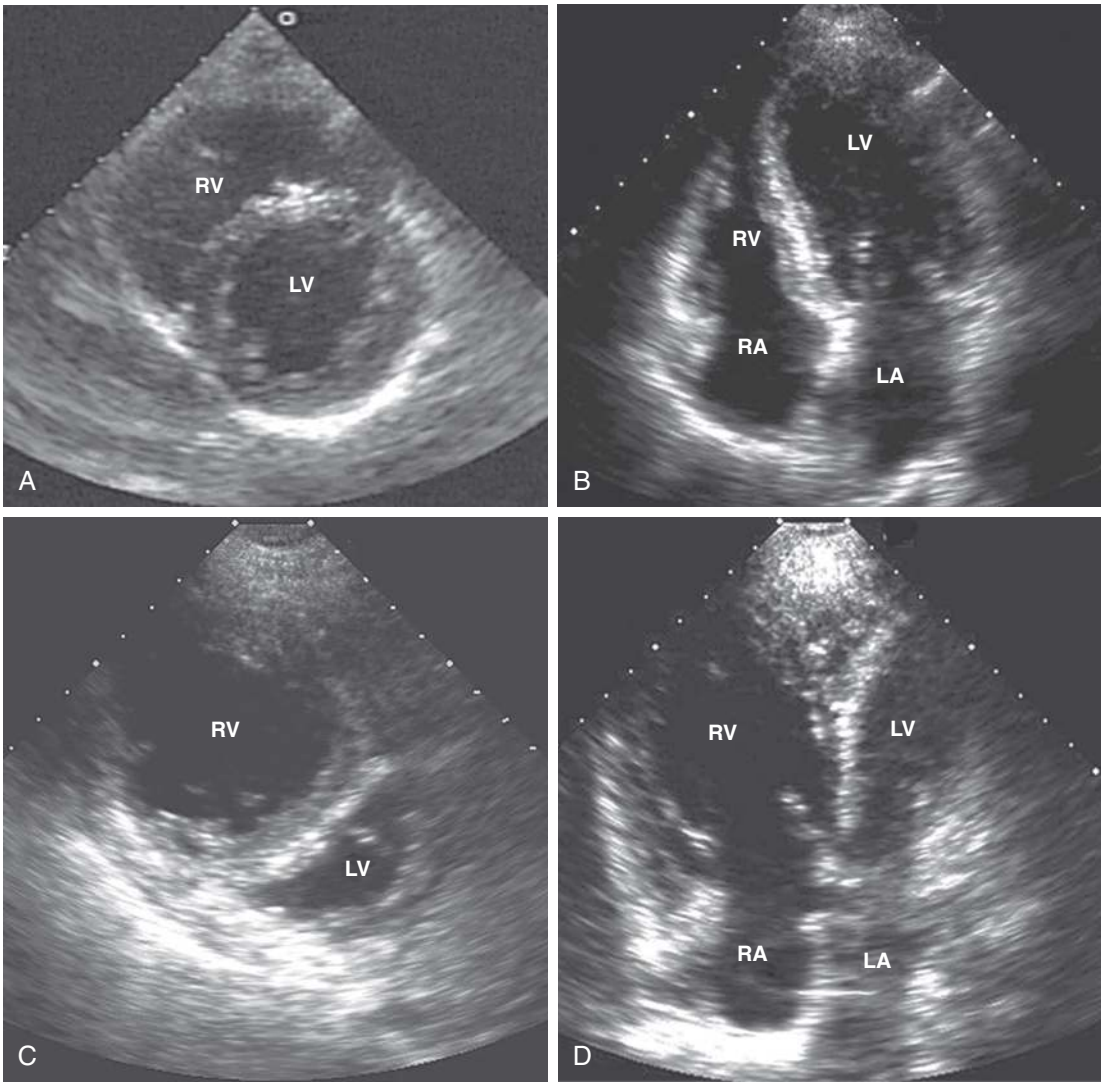


Fig. E2.6 Severe right ventricular failure and dilation. **A,** Normal transthoracic parasternal short-axis view of the left ventricle (LV) and right ventricle (RV) at the midpapillary muscle level. **B,** Normal transthoracic apical four-chamber view of the LV and RV. These pictures of a normal heart depict the relationship between the LV and RV, with the LV being normally larger than the RV and the interventricular septum bulging slightly toward the RV. **C,** Transthoracic parasternal short-axis view of the LV and RV in a patient with severe right ventricular failure and dilation. The right ventricular cavity is seen to be much larger than the left ventricular cavity. Because of the high volume and pressure in the RV, the interventricular septum is bulging toward the left. This gives the LV a characteristic "D" appearance. **D,** Transthoracic apical four-chamber view of the same patient shows the inverse relationship between the left ventricular and right ventricular sizes. The right ventricular dilation can occur only if associated with a proportional reduction in LV diastolic dimension ("ventricular interaction"). This reduction in left ventricular diastolic dimension significantly impairs left ventricular relaxation and changes the pressure-volume relationship of the left heart chambers. *LA,* Left atrium; *RA,* right atrium.

relationships of the left and right heart chambers are altered, and information obtained from a pulmonary artery catheter could be misleading (e.g., high filling pressures are recorded despite normal or even low circulating volume).

Pulmonary Embolism

Hemodynamic instability that arises from acute *cor pulmonale* is often a consequence of massive pulmonary embolism and occurs relatively commonly in the critically ill. Until fairly recently, contrast pulmonary angiography generally was regarded as the gold standard for the diagnosis of pulmonary embolism. Angiography is an invasive procedure, however, and carries the risk of major complications in patients with circulatory failure.[42] Contrast-enhanced helical computed tomography (CT) is an accurate and noninvasive test that has essentially replaced angiography for the diagnosis of pulmonary embolism. Even CT requires transportation of patients to a location outside of the ICU, however, and transport alone is associated with significant risks. Echocardiography is well suited for diagnosing pulmonary embolism because it can be initiated and completed within minutes at the bedside. Detection by TTE of acute right ventricular dilation and dysfunction (acute cor pulmonale) has good positive predictive value for massive pulmonary embolism and its consequences.[43,44] The finding of right

ventricular dilation and dysfunction is not specific for pulmonary embolism, however, because these findings may be observed with a variety of other conditions associated with increased right ventricular strain. In a study by McConnell and colleagues,[45] patients with acute pulmonary embolism were found by TTE to have a distinct regional pattern of right ventricular dysfunction characterized by akinesia of the mid–free wall but normal motion at the apex. These findings contrasted with findings obtained in patients with primary pulmonary hypertension who had abnormal wall motion in all regions. Regional right ventricular dysfunction had a sensitivity of 77% and a specificity of 94% for the diagnosis of acute pulmonary embolism; positive predictive value was 71%, and negative predictive value was 96%. Therefore the presence of regional right ventricular dysfunction that spares the apex should raise the level of clinical suspicion for the diagnosis of acute pulmonary embolism.

Central pulmonary emboli are present in approximately half of all patients with findings suggestive of pulmonary embolism and acute cor pulmonale on TTE.[5] Emboli lodged in the proximal pulmonary arteries usually cannot be visualized directly.[5] Because other clinical conditions can produce acute cor pulmonale in the ICU, better visualization of the pulmonary arteries is needed to achieve high accuracy for the diagnosis of pulmonary embolism. This goal can be achieved by using TEE. TEE has good sensitivity for detecting emboli lodged in the main and right pulmonary arteries, but has limited capability to detect more distal or left pulmonary emboli.[5,46,47] If an embolus is visualized, the diagnosis is made. If the study is negative when the index of suspicion for pulmonary embolism is high, however, TEE must be followed up by a more definitive test such as angiography or helical CT. Also, when there is high clinical suspicion for pulmonary embolism but no thrombi are visualized using TEE, the potential for nonthrombotic causes of pulmonary embolism (e.g., air or fat emboli) must be kept in mind.

The demonstration of acute cor pulmonale with echocardiography has important prognostic and therapeutic implications.[48,49] The presence of cor pulmonale with massive pulmonary embolism is associated with increased mortality incidence, whereas the absence of right ventricular dysfunction is associated with a better prognosis.[39] There is no consensus on the precise indications for administration of thrombolytics in massive pulmonary embolism complicated by acute cor pulmonale.[50,51] A safe and reasonable strategy for managing critically ill patients with suspected massive pulmonary embolism is as follows:

1. Initially perform bedside TTE, looking for the presence of regional right ventricular dysfunction, as described earlier. If the TTE examination is suboptimal, TEE should be performed.
2. If echocardiography is inconclusive or negative and the clinical suspicion of a pulmonary embolism remains high, a definitive confirmatory radiologic test (preferably helical CT with contrast) should be performed.

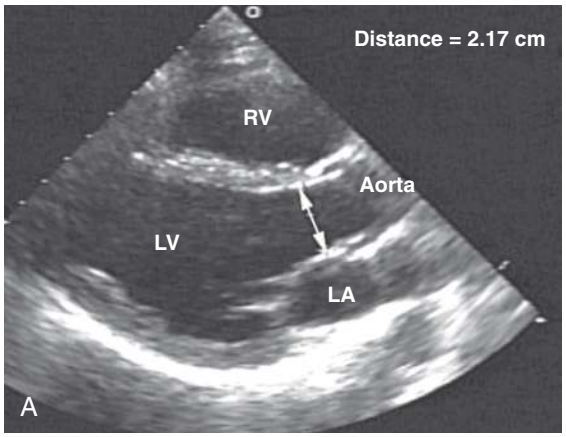
Assessment of Cardiac Output

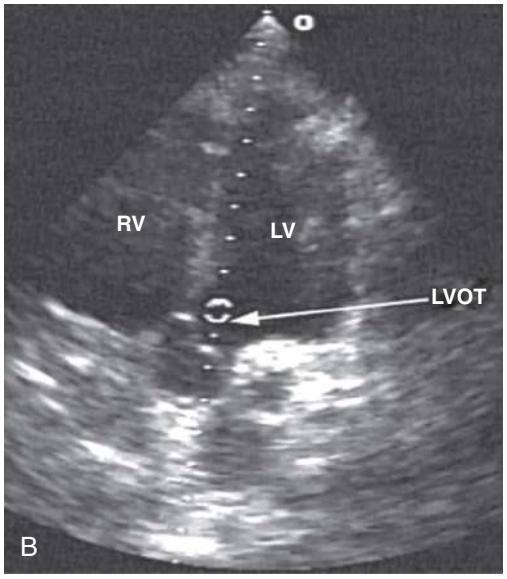
Measurement of cardiac output remains a cornerstone in the hemodynamic assessment of critically ill patients. Thermodilution is considered the gold-standard approach for determining cardiac output in most ICUs. Measurement of cardiac output using thermodilution requires placement of a pulmonary artery catheter (or at least central venous and arterial catheters)—an invasive and potentially inaccurate method. Unreliable values are particularly common in the presence of tricuspid regurgitation related to high pulmonary artery pressure. Several methods for determining cardiac output have been described using 2D imaging and Doppler echocardiography. With this technique, stroke volume and cardiac output can be determined directly by combining Doppler-derived measurements of instantaneous blood flow velocity through a conduit with the cross sectional area of the conduit. Blood flow can be calculated through various cardiac structures, including the pulmonary valve,[52] mitral valve,[53,54] and aortic valve.[55–58] In the absence of intracardiac shunts, blood flow through these structures should be the same (continuity equation).[59] Of these methods, the one using the left ventricular outflow tract and aortic valve as the conduit is probably the most reliable and most commonly used. There is excellent agreement with thermodilution in most situations.[55–58] The left ventricular stroke volume is obtained by measuring the cross sectional area of the left ventricular outflow tract (area [cm^2] = (left ventricular outflow tract diameter [cm^2]) × (π/4), assuming that just below the aortic annulus, the left ventricular outflow tract is circular) multiplied by the transaortic flow velocity time integral derived from a spectral Doppler tracing. The stroke volume obtained is multiplied by the heart rate to give the cardiac output: cardiac output = cross sectional area × velocity time integral × heart rate (Fig. E2.7). With TTE, the left ventricular outflow tract diameter usually is obtained from the parasternal long-axis view, just below the insertion of the aortic valve leaflets. The Doppler interrogation is performed through the aortic valve from the apical view (see Fig. E2.7). With TEE, the left ventricular outflow tract diameter usually is obtained from the five-chamber view of the left ventricle. The transgastric view usually is used to obtain an apical long-axis view of the aortic valve through which Doppler interrogation is performed.[60] With either TTE or TEE, obtaining an accurate left ventricular outflow tract diameter and Doppler signal is essential to have an accurate cardiac output calculation. Because the measure of the left ventricular outflow tract diameter has a second-order relationship with the cross sectional area (see previous formula), it is crucial that this measure be determined precisely. For the Doppler signal to be reliable, the Doppler sample must be parallel to the transaortic flow with an angle of incidence not exceeding 20 degrees so as to avoid underestimation of transaortic velocity. Using TTE in critically ill patients, McLean and coworkers[61] showed an excellent correlation (r = 0.94) between cardiac output determined by the left ventricular outflow tract Doppler method and the thermodilution method. Other studies have shown similar results.[55] In a study by Feinberg and colleagues,[58] cardiac output determined by TEE Doppler imaging was obtainable in 88% of 33 critically ill patients, and there was good correlation (r = 0.91) with the thermodilution method. Descorps-Declere and colleagues[60] also showed transgastric pulsed Doppler measurement across the left ventricular outflow tract with TEE to be a clinically acceptable method for cardiac output measurement in critically ill patients (r = 0.975 compared with the thermodilution method).

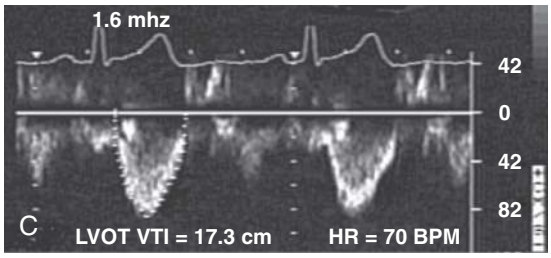
Another promising ultrasound-based technology for estimating cardiac output noninvasively in adults uses a small transesophageal Doppler probe to measure blood flow velocity waveforms in the descending aorta combined with a nomogram (based on height, weight, and age) that estimates aortic cross sectional area. This minimally invasive esophageal probe can be inserted easily in sedated patients and left in place safely for several days to provide continuous monitoring of cardiac function.[62,63] Several technical problems can limit the accuracy of cardiac output measurements by esophageal Doppler monitoring,[62] however, and although initial results are promising,[64–66] more studies are needed to make a decision regarding the accuracy of this technique in critically ill patients.

Assessment of Filling Pressures and Volume Status

Adequate determination of preload and volume status is important for the proper management of critically ill patients. Invasive pressure measurements to assess left ventricular filling are commonly used at the bedside to make inferences regarding left ventricular preload. These pressure measurements correlate only weakly with left ventricular volume, however.[67] Data from invasive monitoring using pulmonary







D

$$\text{LVOT CSA (cm}^2) = \text{LVOT diameter (cm)}^2 \times \pi/4$$
$$= (2.17)^2 \times \pi/4$$
$$= 5.859 \times 0.785$$
$$= 4.599\ \text{cm}^2$$

$$\text{SV} = \text{LVOT CSA} \times \text{VTI}$$
$$= 4.599 \times 17.3$$
$$= 79.56\ \text{mL}$$

$$\text{CO} = \text{SV} \times \text{heart rate}$$
$$= 79.56 \times 70$$
$$= 5.569\ \text{mL/min}$$

Fig. E2.7 Calculation of the stroke volume and cardiac output from the left ventricular outflow tract (LVOT). **A,** LVOT diameter obtained from the transthoracic parasternal long-axis view, just below the insertion of the aortic valve leaflets. In this example, the LVOT diameter is 2.17 cm. **B,** Doppler interrogation (with pulsed-wave Doppler) is performed from the apical view with the sample volume being placed in the LVOT, just below the aortic valve. **C,** Spectral Doppler tracing from the LVOT from which the transaortic flow velocity time integral (VTI) is derived. In this example, the VTI is 17.3 cm. **D,** The left ventricular stroke volume (SV) is obtained by measuring the cross sectional area (CSA) of the LVOT (area [cm^2] = LVOT diameter [cm^2] × $\pi/4$) and multiplying by the transaortic VTI derived from the spectral Doppler tracing. The stroke volume obtained is multiplied by the heart rate to give the cardiac output (CO). *LA,* Left atrium; *LV,* left ventricle; *RV,* right ventricle.

artery catheterization may be misleading because ventricular compliance is altered secondary to numerous factors.[68,69] Differences in diastolic compliance among patients may account for the weak correlation between pressure and volume and may limit the ability to use pressure measurements alone to derive information concerning left ventricular preload, a volume-based variable.[14] Parameters that can be measured using 2D echocardiographic imaging are left ventricular end-diastolic volume and left ventricular end-diastolic area. Using Doppler interrogation, additional information—mainly transmitral diastolic filling pattern and pulmonary venous flow—can be evaluated.

Two-dimensional imaging. Echocardiography has been validated for left ventricular volume measurements.[15] Subjective assessment of left ventricular volume by estimating the size of the left ventricular cavity in the short-axis and long-axis views is often adequate to guide fluid volume therapy at the extreme ends of cardiac filling and function. More precise quantitative values are desirable, however, and can be obtained by using endocardial border tracing (as described earlier). The normal left ventricular end-diastolic volume as determined by echocardiography is 80–130 mL,[15] and the normal left ventricular end-diastolic volume index is 55–65 mL/m^2.[15] Left ventricular end-diastolic area measured in the left parasternal short-axis view at the level of the midpapillary muscle is commonly used to estimate volume status (Fig. E2.8). The normal values for left ventricular end-diastolic area in the short-axis view are 9.5–22 cm^2.[15]

Two-dimensional TTE evaluation of ventricular dimensions has been found to be useful in assessing preload and optimizing therapy.[25,70] Nevertheless, suboptimal image quality may preclude adequate visualization of the endocardial border by TTE. This potential limitation of TTE has been partially circumvented in recent years with the advent of harmonic imaging and contrast echocardiography (see later). In cases in which endocardial border visualization remains suboptimal, TEE is the modality of choice. With TEE, left ventricular volume can be estimated rapidly by subjective assessment of the left ventricular size. Quantitatively, it is estimated most often by determining the left ventricular cross sectional area at the end of diastole, most commonly using the transgastric short-axis view at the level of the midpapillary muscle. This section is used because of the reproducibility of the view and because changes in left ventricular volume affect the

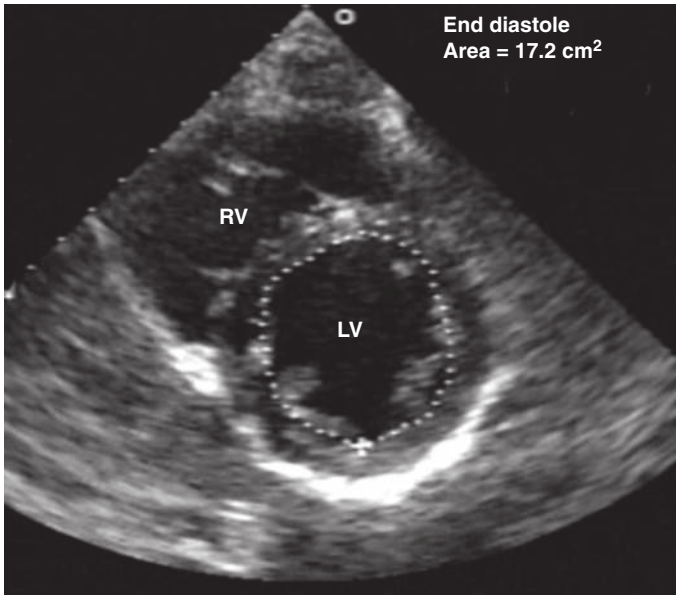


Fig. E2.8 Calculation of left ventricular end-diastolic area in the transthoracic short-axis view at the level of the midpapillary muscle by endocardial contour tracing. Values of normal left ventricular end-diastolic area in the short axis range from 9.5 to 22 cm^2.[15] The level of the midpapillary muscle is used because of the reproducibility of the view and because changes in left ventricular volume affect the short axis of the ventricle to a greater degree than the long axis. *LV,* Left ventricle; *RV,* right ventricle.

short axis of the ventricle to a greater degree than the long axis.[14] The end-diastolic area must be measured consistently from the same reference section. End-diastolic area measured with TEE correlates well with left ventricular volume determined by radionuclide studies.[70]

Systolic obliteration of left ventricular cross sectional area accompanies decreased end-diastolic area and is considered to be a sign of severe hypovolemia (Fig. E2.9). Although a small end-diastolic area generally indicates hypovolemia, a large end-diastolic area does not indicate adequate preload in patients with left ventricular dysfunction. Also, when systemic vascular resistance is low, as in early sepsis, left ventricular emptying improves because of reduced afterload. In these situations, it may be difficult to differentiate hypovolemia from low systemic vascular resistance by echocardiography alone, because both conditions are associated with decreased end-diastolic area. Knowledge of left ventricular end-diastolic volume or absolute preload does not allow for accurate prediction of the hemodynamic response to alterations in preload.[71] Tousignant and colleagues[72] investigated the relationship between left ventricular stroke volume and left ventricular end-diastolic area in a cohort of ICU patients and found only a modest correlation ($r = 0.60$) between single-point estimates of left ventricular end-diastolic area and responses to fluid loading. Based on the assumption that changes in end-diastolic area occur because of changes in left ventricular volume, the determination of this area and its subsequent degree of variation after a fluid challenge could help better assess preload responsiveness. Studies have shown that changes in end-diastolic area measured by TEE using endocardial border tracing are closely related to changes in cardiac output and are superior to measurements of pulmonary artery occlusion pressure for predicting the ventricular preload associated with maximal cardiac output.[73]

Circulating volume status also can be assessed by 2D echocardiography by indirectly estimating right atrial pressure; this is often done by assessing the diameter and change in caliber with inspiration of the inferior vena cava (Fig. E2.10). This method has been shown to discriminate reliably between right atrial pressures either less than or greater than 10 mm Hg.[74] A dilated vena cava (diameter >20 mm) without a normal inspiratory decrease in caliber (>50% with gentle sniffing) usually indicates elevated right atrial pressure. In mechanically ventilated patients, this measure is less specific because of a high prevalence of inferior vena cava dilation.[75,76] A small vena caval dimension reliably excludes the presence of elevated right atrial pressure in these patients.[75,76]

Doppler flow patterns. Analysis of the Doppler signal at the level of the mitral valve and pulmonary vein offers additional information about preload.[77,78] These Doppler profiles can be obtained by either

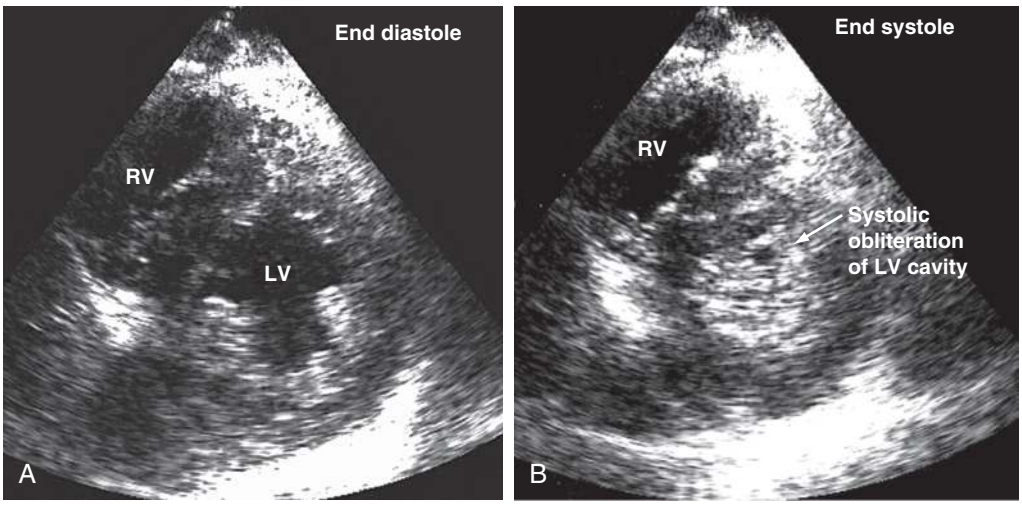


Fig. E2.9 Systolic obliteration of the left ventricle (LV) in a patient with severe left ventricular hypertrophy and dehydration. This transthoracic parasternal short-axis view shows the LV at end diastole **(A)** and at end systole **(B)**. Nearly complete obliteration of the left ventricular cavity is seen at end systole. Systolic obliteration of the cross sectional area accompanies decreased end-diastolic area and is considered to be a sign of severe hypovolemia. In this case, the patient presented with hypotension and was found to be severely dehydrated because of a viral gastroenteritis. *RV,* Right ventricle.

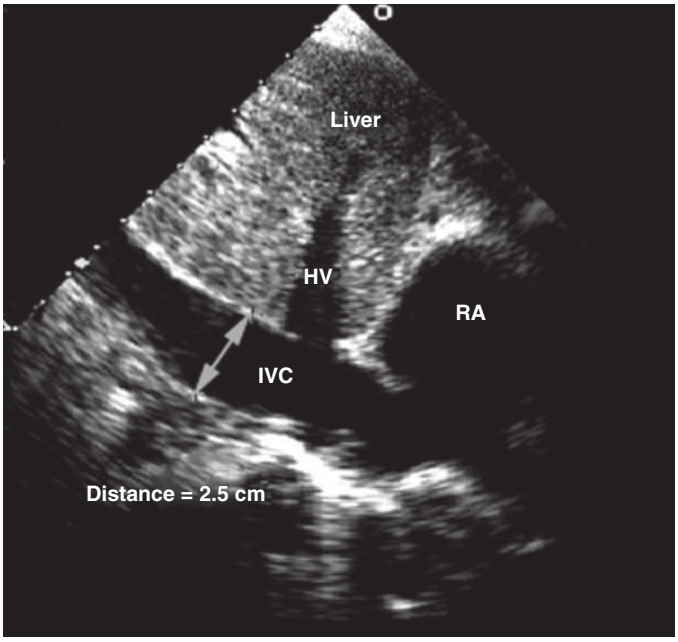


Fig. E2.10 Indirect assessment of circulating volume status on two-dimensional echocardiography by assessing the diameter and change in caliber with inspiration of the inferior vena cava (IVC). This method has been shown to discriminate reliably between right atrial pressures of less than or greater than 10 mm Hg. A dilated vena cava (>20 mm) without the normal inspiratory decrease in caliber (>50% on gentle sniffing) usually indicates elevated right atrial pressure. A small vena cava reliably excludes elevated right atrial pressure in these patients. In this case, the IVC was dilated at 2.5 cm with minimal respiratory variation in a patient spontaneously breathing. The right atrial pressure was estimated to be approximately 10–15 mm Hg. Images were obtained in the subcostal view. *HV,* Hepatic veins; *RA,* right atrium.

TTE or TEE. Transmitral parameters that have been studied include the relation of early to late transmitral diastolic filling (E/A ratio), isovolumetric relaxation time, and the rate of deceleration of early diastolic inflow (deceleration time).[1]

A decrease in preload causes a significant reduction in the E wave (early filling flow wave) velocity at the mitral level in conjunction with a decrease of the S wave (systolic flow wave) in the pulmonary vein. In clinical practice, the E/A ratio is easy to assess; the normal value of this ratio is approximately 1.[1,3] In conjunction with normal left ventricular contractility, a low E/A ratio is usually characteristic of inadequate preload.[79]

Pulmonary venous flow also can be used to assess left atrial pressure. A normal pulmonary venous flow pattern showing a predominance of flow during systole (S phase) compared with early diastole (D phase) usually indicates that left atrial pressure is less than 8 mm Hg, whereas the opposite predominance of flow (in the absence of significant mitral regurgitation) usually indicates elevation of left atrial pressure.[1]

Transmitral and pulmonary vein Doppler patterns strongly depend on intrinsic and external factors and are not affected purely by the loading conditions of the left ventricle. It is crucial that interpretation of Doppler parameters be done in conjunction with a global analysis of cardiac function and other available hemodynamic or anatomic variables.

Hypovolemia in the Intensive Care Unit

Precise and rapid assessment of volume status is crucial when caring for hemodynamically unstable ICU patients. Hypovolemia is one of the most common causes of hypotension in the ICU. As was discussed in detail earlier, bedside echocardiography offers a quick and reliable way of estimating volume status by evaluating cardiac dynamics and left ventricular dimensions and area. The finding of end-systolic cavity obliteration offers a reliable sign of hypovolemia. Other changes in the volume status are usually associated with subtle changes in left ventricular cavity size, so only this extreme is reliable to make the diagnosis of hypovolemia by echocardiography. In general, TTE has good sensitivity for diagnosing the presence of a small hyperdynamic left ventricle, the most typical finding in hypovolemic patients with underlying normal cardiac function; TEE is particularly useful in the immediate postoperative setting (Video E2.1).

When dynamic left ventricular obstruction is present, cardiac output is often low, and even in the presence of marked hypovolemia, pulmonary artery occlusion pressure is typically high. Paradoxical worsening of hypotension after intravascular volume loading may be the first clue to dynamic left ventricular obstruction in critically ill patients. It is important that this entity be recognized early and that the pathophysiologic process be well understood, because inadequate management of this condition can lead rapidly to worsening of hemodynamic status and death. Dynamic obstruction of the left ventricle can present in different forms. One of these forms is dynamic left ventricular outflow tract obstruction. Although dynamic left ventricular outflow tract obstruction is often seen in association with asymmetric septal hypertrophy, it also can occur in other situations.[80,81] Dynamic left ventricular outflow tract obstruction is thought to be caused by the Venturi effect. This effect results when excessive acceleration of blood through a conduit produces a decrease in its lateral distending pressure. In the left ventricular outflow tract, such a decrease in pressure leads to a suction phenomenon that draws the anterior mitral leaflet and chordae inward toward the interventricular septum.[82] This systolic anterior motion of the mitral valve leads to contact between the mitral leaflet and the septum that creates an obstructive subaortic pressure gradient and distortion of the mitral valve leaflet coaptation (Fig. E2.11).[82] By 2D echocardiography, the left ventricle appears to be small and hyperdynamic, and there is motion of the anterior leaflet (or chordae, or both) toward the septum in systole (see Fig. E2.11). With color Doppler, a "mosaic" pattern of flow is seen in the left ventricular outflow tract, owing to the high velocity and turbulence. Variable degrees of asymmetric mitral regurgitation also may be present (see Fig. E2.11). Continuous-wave Doppler shows the presence of a significant gradient in the left ventricular outflow tract. Dynamic left ventricular obstruction also can be present without systolic anterior motion. In the presence of reduced afterload, dehydration, or significant catecholaminergic stimulation, patients with a small hypertrophied left ventricle (typically seen in elderly patients with chronic hypertension) can develop midventricular obstruction because of hyperdynamic systolic obliteration of the left ventricular cavity (see Fig. E2.9).[83] These physiologic factors may predict the development or worsening of left ventricular dynamic obstruction. Interplay of these factors with preexisting ventricular hypertrophy predisposes the patient to develop cardiogenic shock from this combined loss of preload and presence of dynamic left ventricular obstruction. Dynamic left ventricular obstruction has also been described in patients with acute myocardial infarction, mostly in association with apical infarction.[81,84,85]

In a study by Chenzbraun and colleagues,[85] four ICU patients with hemodynamic instability were found to have a small hyperdynamic ventricle on TEE. Of these four patients, three had pulmonary artery occlusion pressure greater than 20 mm Hg. A study by Poelaert and colleagues[20] that evaluated the diagnostic value of TEE compared with pulmonary artery catheterization showed that pulmonary artery catheterization failed to diagnose the presence of hypovolemia in 44% of patients when TEE showed systolic obliteration of the left ventricular cavity, supporting a

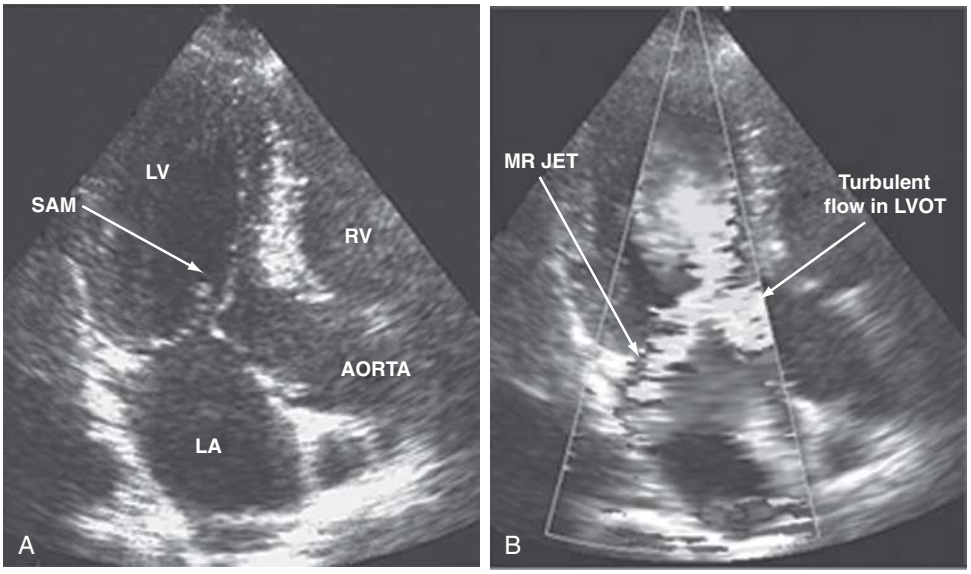


Fig. E2.11 Systolic anterior motion (SAM) of the mitral valve in a patient with asymmetric left ventricular hypertrophy and dehydration. Two-dimensional transthoracic apical long-axis view shows movement of the anterior leaflet of the mitral valve *(arrow)* toward the interventricular septum during systole **(A)**. This creates a subaortic dynamic obstruction. The resulting high velocity and turbulence in the left ventricular outflow tract (LVOT) gives a "mosaic" pattern of flow on color Doppler **(B)**. A variable degree of asymmetric mitral regurgitation (MR) also may be present secondary to the systolic anterior motion, as shown in this example. *LA,* Left atrium; *LV,* left ventricle; *RV,* right ventricle.

diagnosis of hypovolemia. TTE and TEE have been shown to play key roles in making the diagnosis of hypovolemia and left ventricular dynamic obstruction, leading to a dramatic impact on therapy.[19,21,22,82–85]

Assessment of Pulmonary Artery Pressure

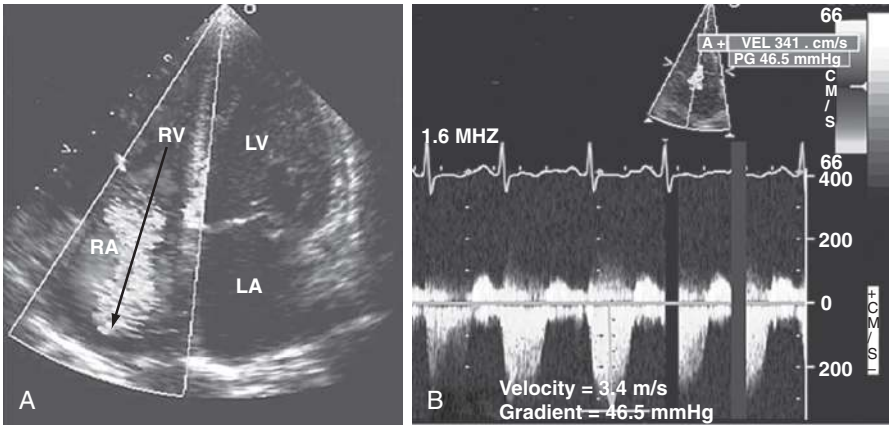
Pulmonary hypertension occurs commonly in critically ill patients and is a manifestation of various pulmonary, cardiac, and systemic processes. Pulmonary hypertension is said to be present when systolic pulmonary pressure exceeds 35 mm Hg, diastolic pulmonary pressure is greater than 15 mm Hg, and mean pulmonary pressure is greater than 25 mm Hg.[59] Many helpful echocardiographic methods have been validated for noninvasive estimation of pulmonary artery pressure.[59,86] Systolic and diastolic pulmonary artery pressures are determined from the tricuspid and pulmonary regurgitation velocities (some degree of regurgitation is essential to be able to obtain a Doppler signal and subsequently estimate pulmonary artery pressure). Tricuspid regurgitation is present in more than 75% of healthy adults[59] and in approximately 90% of critically ill patients.[87] Peak tricuspid regurgitation velocity, usually obtained by continuous-wave Doppler from the right ventricular inflow or the apical four-chamber view position, reflects the pressure difference during systole between the right ventricle and the right atrium (Fig. E2.12).[88–90] Peak systolic pulmonary artery pressure is determined from the peak tricuspid regurgitation Doppler velocity using the modified Bernoulli equation[91]: $\Delta P = 4 \times$ (peak tricuspid regurgitation velocity).[2] To this peak systolic pressure gradient between right ventricle and right atrium is added the estimated right atrial pressure (see previous section) to obtain the peak right ventricular systolic pressure. In the absence of pulmonic stenosis or right ventricular outflow obstruction, peak right ventricular systolic pressure equals systolic pulmonary artery pressure (see Fig. E2.12). Echocardiography also can determine diastolic pulmonary artery pressure by applying the modified Bernoulli equation using the regurgitant Doppler velocity of the pulmonary valve to obtain the gradient between the pulmonary artery and the right ventricle at end diastole. To this is added the estimated right atrial pressure (equivalent to right ventricular end-diastolic pressure in the absence of tricuspid stenosis) to obtain end-diastolic pulmonary artery pressure: end-diastolic pulmonary artery pressure $= 4 \times$ (peak pulmonary regurgitation velocity)^2 + estimated right atrial pressure. Approximately 70% of critically ill patients have an adequate Doppler signal of pulmonic insufficiency for this calculation.[92] Tricuspid and pulmonary regurgitation are present simultaneously in more than 85% of subjects.[93]

Assessment of Valvular Function and Integrity

Attention has been drawn to the limitations of the physical examination for the detection of cardiovascular abnormalities.[94,95] This problem is enhanced in acutely ill patients in the ICU, and many cardiovascular abnormalities may be concurrent with noncardiac illness without being clinically suspected.[96] Significant valvular abnormalities are a good example of such cardiovascular pathologies that can be present in a critically ill patient without being clinically recognized.[96] Even with invasive monitoring, significant valvular pathologies may be missed. The most common indications for bedside echocardiography for evaluation of valvular apparatus in the ICU patient population are for suspected endocarditis,[8,24] acute aortic or mitral valve regurgitation,[97,98] and prosthetic valve dysfunction.[16] Echocardiography is uniquely suited to the evaluation of valvular heart disease because of its ability to help determine the etiology and severity of valvular lesions. In the ICU, TTE can provide valuable information concerning valvular integrity and function,[16] but it may be suboptimal and not sensitive enough to detect endocarditis, a dysfunctional mitral valve, or prosthetic valve dysfunction; TEE is often warranted. TEE is especially important for the fine detail of mitral valve pathology, such as a torn chordae tendineae and flail scallop (Video E2.2).

Valvular Regurgitation and Prosthetic Valve Dysfunction

In a patient with unexplained hemodynamic instability and a grossly normal TTE examination, performance of subsequent TEE is



$$\text{Systolic PAP} = 4 \times (\text{peak TR velocity})^2 + \text{estimated RA pressure}$$
$$= 4 \times (3.41)^2 + 10$$
$$= 46.51 + 10$$
$$= 56.5 \text{ mm Hg}$$

C

Fig. E2.12 Calculation of systolic pulmonary artery pressure (PAP). **A,** Color Doppler transthoracic apical four-chamber view showing a significant tricuspid regurgitation (TR) jet from right ventricle (RV) to right atrium (RA). The peak TR velocity is measured by placing the continuous-wave Doppler in the center of the TR jet *(arrow).* **B,** Spectral continuous-wave Doppler profile of the TR jet. Peak TR velocity (3.41 m/s) and peak systolic PAP gradient (46.5 mm Hg) can be obtained with this modality. **C,** Peak systolic PAP also can be determined from the peak TR Doppler velocity using the modified Bernoulli equation: $\Delta P = 4 \times (\text{peak TR velocity})^2$. To this peak systolic pressure gradient between right ventricle and right atrium is added the estimated right atrial pressure (determined to be 10 in this example) to obtain the peak right ventricular systolic pressure. In the absence of pulmonic stenosis or right ventricular outflow obstruction, peak right ventricular systolic pressure is equal to systolic PAP. *LA,* Left atrium; *LV,* left ventricle.

important to rule out the presence of significant undetected valvular pathology. Common valvular pathologies that can be missed are mitral regurgitation and prosthetic valve dysfunction. In some situations, TTE may provide better imaging than TEE for evaluation of anterior structures such as the aortic valve (native or prosthetic) and for Doppler measurements. TEE is clearly superior to TTE for evaluation of mitral valve pathologies (native and prosthetic). In a study of ICU patients by Alam,[16] TTE compared with TEE was shown either to miss or to underestimate the severity of regurgitation of St. Jude and bioprosthetic valves in the mitral but not in the aortic position.

With acute severe mitral regurgitation, the diagnosis may be clinically difficult because the murmur is often of short duration and low intensity (because of rapid pressure equalization between the left ventricle and the relatively noncompliant left atrium). By TTE, the size of the regurgitant jet in acute mitral regurgitation may appear small and lead to underestimation of severity.[99] Because of its close anatomic proximity, TEE provides a more precise evaluation of the degree of mitral regurgitation (Fig. E2.13) and provides crucial diagnostic information regarding the cause for mitral regurgitation. The diagnosis of acute mitral regurgitation represents a medical emergency that may necessitate urgent surgery, so the threshold to perform a TEE when this entity is suspected should be low.[8,10,97] Also, several investigators have confirmed the superior accuracy, sensitivity, and reliability of TEE over TTE for dysfunction of mitral prostheses, in which ultrasonic shadowing of the left atrium often occurs with the standard transthoracic studies.[100–103] TEE may be especially useful to detect obstruction of prosthetic valves from thrombus (Video E2.3).

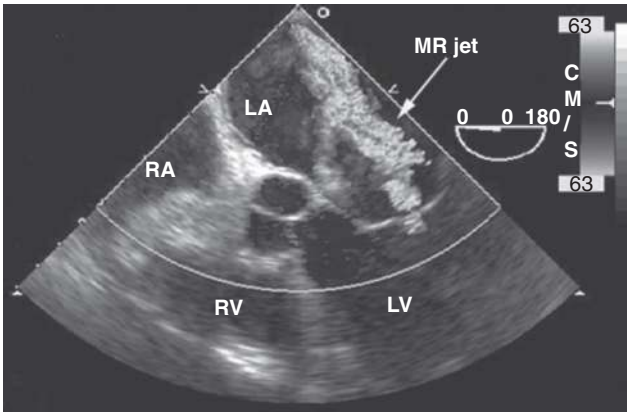


Fig. E2.13 Severe mitral regurgitation (MR). Transesophageal five-chamber view shows severe MR with a large regurgitant jet *(arrow)* going far posteriorly in the left atrium (LA). In this case, systolic flow reversal in the pulmonary veins (another echocardiographic sign of severe MR) also was present (not shown on this picture). Because of its close anatomic proximity, transesophageal echocardiography is an excellent tool for the precise evaluation of the degree of MR. *LV,* Left ventricle; *RA,* right atrium; *RV,* right ventricle.

Traumatic Valvular Injuries

Traumatic valvular injuries associated with myocardial injury may present as acute regurgitation. Bedside exclusion of major damage to the aorta, valves, and myocardium is important in the posttrauma context.[104,105] Valvular injuries may occur as a consequence of blunt or penetrating injury. Most frequently the aortic valve is injured; less commonly the mitral and tricuspid valves are injured.[106] Valvular dysfunction is usually the result of a torn leaflet or rupture of a papillary muscle or chordae.[106] In trauma patients, TEE is the bedside imaging modality of choice to detect these pathologies.[104,105] In a study by Chirillo and colleagues assessing the usefulness of TTE and TEE in the

recognition and management of cardiovascular injuries after blunt chest trauma, TTE provided suboptimal imaging in 62% of patients, and the poor quality of images obtained was the main cause for the low sensitivity of TTE compared with TEE.[105a]

Evaluation of the Pericardial Space

Echocardiography is an essential instrument for the diagnosis of pericardial disease. In the ICU, the most common clinical indication for assessment of the pericardial space is suspected tamponade. The pericardium is a potential space that can become filled with fluid, blood, pus, or, uncommonly, air. Presence of fluid in this compartment is detected as an echo-free space. Pericardial fluid usually is detected easily with TTE. The parasternal long-axis and short-axis views together with the apical views usually reveal the effusion (Fig. E2.14). In many critically ill patients with suboptimal TTE image quality, the subcostal view is often the only adequate window available to detect the presence of a pericardial effusion. In these ICU patients with poor acoustic windows and in the postcardiac surgical setting, TEE may be needed to assess the pericardial space adequately.

In addition to assisting in the diagnosis of pericardial effusion and tamponade, 2D echocardiography can assist in its drainage, as pericardiocentesis can be performed safely under 2D echocardiographic guidance.[107,108] By determining the depth of the effusion and its distance from the site of puncture, it is possible to optimize needle placement. Echocardiography also can be used for immediate monitoring of the results of the pericardiocentesis.

Cardiac Tamponade in the Intensive Care Unit

The most common causes of cardiac tamponade in the ICU are listed in Box E2.5. Echocardiographic 2D signs of tamponade are a direct consequence of increased pericardial pressure, leading to diastolic collapse of one or more cardiac chambers (usually on the right side first)

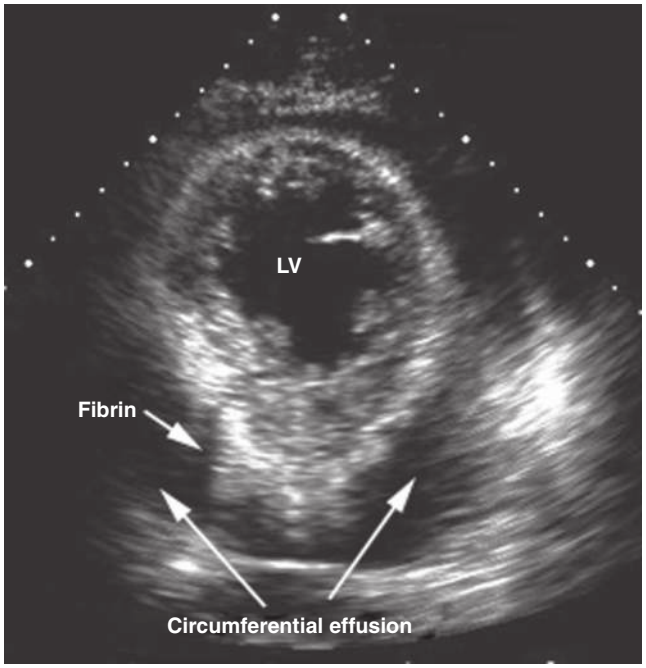


Fig. E2.14 **Large pericardial effusion.** Transthoracic parasternal short-axis view shows a large, predominantly echo-free space around the left ventricle (LV). This space represents fluid in the pericardium. In this case, the large circumferential pericardial effusion was bloody at pericardiocentesis. Particulate matter (e.g., fibrin and clots) can be visualized as denser echoes around the heart and floating in the effusion.

BOX E2.5 Most Common Causes of Cardiac Tamponade in the Intensive Care Unit

- Myocardial or coronary perforation secondary to catheter-based intervention (i.e., after intravenous pacemaker lead insertion, central line placement, or percutaneous coronary interventions)
- Compressive hematoma after cardiac surgery
- Proximal ascending aortic dissection
- Blunt or penetrating chest trauma
- Complication of myocardial infarction (e.g., ventricular rupture)
- Uremic or infectious pericarditis
- Pericardial involvement by metastatic disease or other systemic processes

(Fig. E2.15). Usually, collapse of the right ventricular free wall is seen in early diastole, and right atrial wall collapse is seen in late diastole.[14] This latter sign is sensitive but not specific for tamponade. It is, however, specific for a hemodynamically significant effusion if the right atrial collapse lasts longer than one-third of the R-R interval.[14,109] In the presence of a massive effusion, the heart may have a "swinging" motion in the pericardial cavity. This finding is not always present in cardiac tamponade, because the amount of fluid in the pericardial space may be small but still cause tamponade physiology, depending on the acuity with which the effusion accumulates and the compliance of the pericardium. In post-sternotomy patients, tamponade may be missed by TTE (even in cases in which imaging quality seems adequate) because hematomas causing selective cardiac chamber compression are often in the form of loculated clots located in the far field of the ultrasound beam in the posterior heart region (even when the anterior pericardium is left open).[110] The right atrium and right ventricle may be spared in such cases secondary to postoperative adhesions or tethering of the right ventricle to the chest wall anteriorly.[110]

Another (indirect) sign of a hemodynamically significant pericardial effusion on 2D imaging is plethora of the inferior vena cava with blunted respiratory changes.[1] The latter sign is less valuable in mechanically ventilated patients, because they often have a stiff, dilated inferior vena cava even in the absence of a pericardial effusion (Video E2.4).

Doppler findings of cardiac tamponade are based on characteristic changes in intrathoracic and intracardiac hemodynamics that occur with respiration. Because of ventricular interaction, mitral inflow velocity (E wave) decreases after inspiration and increases after expiration. Reciprocal changes occur with respect to tricuspid inflow velocity. With tamponade, the exaggerated inspiratory-expiratory variation of the inflow velocity (E wave) over one respiratory cycle should be greater than 40% on the left and greater than 80% on the right.[111] In critically ill patients, however, mechanical ventilation, bronchospasm, significant pleural effusion, and respiratory distress can alter intrathoracic and intracardiac hemodynamics and make these Doppler findings less reliable. A significant pleural effusion sometimes causes significant respiratory Doppler variations of the inflow velocities that disappear when the effusion is drained.[112] The presence of arrhythmia also makes the Doppler findings difficult to interpret. In some circumstances, echocardiographic signs of tamponade may be subtle or absent, so one must keep in mind that the diagnosis of tamponade remains a clinical one and that the echocardiographic signs must be analyzed in conjunction with the clinical findings.

Complications After Cardiac Surgery

Bedside echocardiography has proved to be of particular value in the critical care management of patients with hemodynamic instability after cardiothoracic operations.[7,8,83,113–115] TTE is often severely limited in this group of patients.[5,8] TEE is the modality of choice in this setting

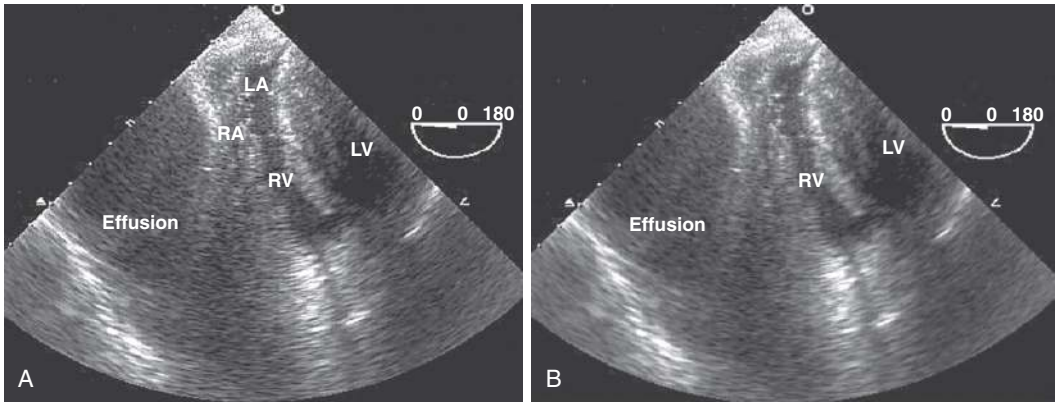


Fig. E2.15 Cardiac tamponade. Transesophageal four-chamber view **(A)** shows the presence of a large effusion that severely compresses the right atrium (RA) and right ventricle (RV), which appear slitlike. The left ventricle (LV) also is small because of indirect compression and underfilling. Transgastric short-axis view **(B)** of the same patient shows the large pericardial effusion and severely compressed ventricular chambers. This postcardiotomy patient was in profound shock and was brought back to the operating room emergently for reexploration and drainage of the effusion. *LA,* Left atrium.

because it provides detailed information that can help determine the cause of refractory hypotension. The most frequent echocardiographic diagnoses encountered in these patients are left ventricular or right ventricular failure, tamponade, hypovolemia, and valvular dysfunction. Schmidlin and colleagues[116] studied 136 patients after cardiac surgery and showed that a new diagnosis was established or an important pathology was excluded in 45% of patients undergoing TEE. A therapeutic impact was detected in 73% of cases. The main indications for TEE in this study were control of left ventricular function (34%), unexplained hemodynamic deterioration (29%), suspicion of pericardial tamponade (14%), cardiac ischemia (9%), and "other" (14%). Reichert and colleagues.[113] performed TEE in hypotensive patients after cardiac surgery. Left ventricular failure was found in 27% of patients, hypovolemia in 23%, right ventricular failure in 18%, biventricular failure in 13%, and tamponade in 10%. Comparison with hemodynamic parameters showed agreement on diagnosis (hypovolemia versus tamponade versus cardiac failure) in only 50% of the cases. Echocardiography identified two cases of tamponade and six of hypovolemia that were not suspected based on standard hemodynamic data. In five patients with hemodynamic findings suggesting tamponade, unnecessary reoperation was prevented because TEE ruled out this diagnosis. Costachescu and colleagues[22] also showed the superiority of TEE compared with conventional monitoring with pulmonary artery catheterization in diagnosing and excluding significant causes of hemodynamic instability in postoperative cardiac surgical patients.

Infective Endocarditis

In the ICU, occurrence of infective endocarditis is not uncommon, and rightfully is considered quite often in the differential diagnosis of febrile patients. Suspicion of infective endocarditis was the second most common indication for performance of an echocardiogram among centers reporting their experience, as summarized in a review article by Heidenreich.[5] Nearly all critically ill patients are at risk for iatrogenic infection, bacteremia, and subsequent endocarditis because of the presence of multiple indwelling catheters, severe underlying diseases, malnutrition, and prolonged mechanical ventilation. Classic clinical findings suggesting endocarditis[106] are unusual among this patient population. Echocardiography is the test of choice for the noninvasive diagnosis of endocarditis. Fowler and colleagues[117] studied patients with *Staphylococcus aureus* bacteremia referred for TEE and showed that endocarditis ultimately was diagnosed in 25%. Only 7% of these patients had physical findings suggesting endocarditis. Absence of clinical stigmata is especially likely if the infection presents acutely. Because the consequences of untreated endocarditis are devastating and often ultimately fatal, it is important that the infection and its complications be recognized promptly and treated appropriately.[59]

The echocardiographic features typical for infective endocarditis are[59,118] (1) an oscillating intracardiac mass on a valve or supporting structure or in the path of a regurgitant jet or an iatrogenic device, (2) abscesses, (3) new partial dehiscence of a prosthetic valve, or (4) new valvular regurgitation. Sensitivity for the echographic diagnosis of endocarditis is 58%–62% for TTE and 88%–98% for TEE.[119,120] TEE is particularly useful for detecting small vegetations[121] and detecting vegetations on prosthetic valves. TEE also has been shown to be superior to TTE for diagnosing complications of endocarditis such as aortic root abscess, fistulas, and ruptured chordae tendineae of the mitral valve.[16] Among ICU patients, sensitivity of TTE for the diagnosis of endocarditis is often poor because the quality of the transthoracic study is commonly suboptimal. The sensitivity of TEE for suspected infective endocarditis usually is excellent in the ICU (Fig. E2.16). In a study by Font and colleagues,[97] a search for vegetations was the indication for 51 (46%) of 112 TEE studies performed for critically ill patients. TEE increased the detection rate by 27% compared with TTE. Suspicion of endocarditis represented 29% of the indications for TEE in a study of ICU patients by Chenzbraun and colleagues[85]; 9 (27%) of 31 patients with suspected infective endocarditis had a positive study for endocarditis. All positive studies were in patients who had an increased likelihood for infective endocarditis before the examination, as indicated by the presence of fever, positive blood cultures, new-onset murmur, prosthetic valve, or new-onset heart failure (alone or in combination). None of the patients with native valves and no clinical features of endocarditis produced a TEE study diagnostic of infective endocarditis, and in none of them was the diagnosis of infective endocarditis made subsequently. The findings from this study indicate that TEE is not useful as a screening procedure in septic patients without high clinical likelihood for endocarditis. The clinical probability of endocarditis should guide the use of TEE. Clinical factors considered "high risk" include intracardiac prosthetic material, positive blood cultures (in particular, *S. aureus*), evidence of peripheral emboli, and history of previous endocarditis[8,16] (Video E2.5).

As concluded by Colreavy and colleagues,[8] performance of TEE in the ICU for suspicion of infective endocarditis should be (1) cases associated with a clinical likelihood of endocarditis and a negative TTE examination, (2) suspected prosthetic valve endocarditis,

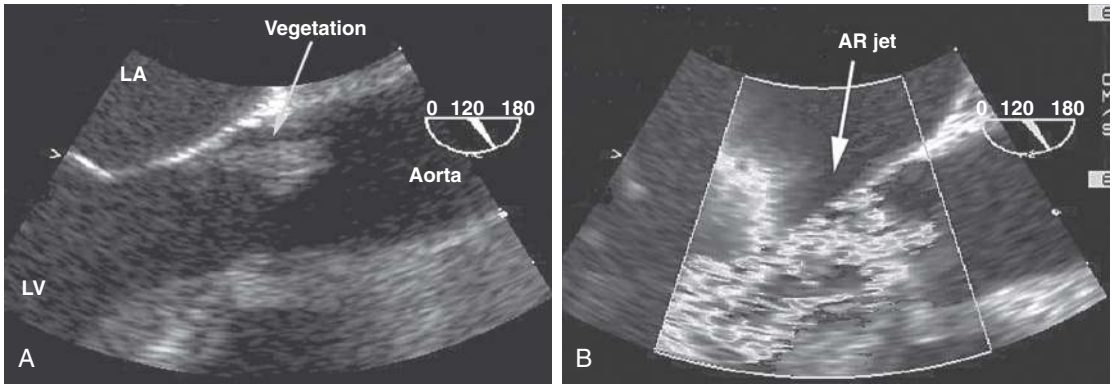


Fig. E2.16 Infective endocarditis of the aortic valve. A 55-year-old patient was admitted to the ICU with fever, chills, hypotension, and respiratory distress for which he had to be intubated. He had 4/4 positive blood cultures for *Staphylococcus aureus*. Transthoracic echocardiography was performed initially, but the quality was suboptimal, and no definite conclusion could be reached. Subsequent transesophageal echocardiography revealed a large vegetation on the left aortic coronary cusp, as seen in the midesophageal view at 120 degrees **(A)**. Color Doppler examination **(B)** revealed the presence of associated severe aortic regurgitation (AR). The patient was treated with antibiotics and emergent aortic valvular surgery. *LA,* Left atrium; *LV,* left ventricle.

(3) assessment of complications in known cases of endocarditis, and (4) cases of *S. aureus* bacteremia when the source is unknown or blood cultures remain positive despite antibiotic therapy. When assessing a patient for infective endocarditis by echocardiography, one must keep in mind the noninfectious causes of vegetations that may result from tumors, myxomatous degeneration, marantic endocarditis, Lambl excrescences, valve thrombus, and suture material in patients with repaired native or prosthetic valves.

Assessment of the Aorta

In the ICU, use of bedside echocardiography for assessment of suspected aortic pathologies provides many advantages over CT or aortography: there is no need for IV contrast administration, there may be less time delay, there is no need for transportation of a critically ill patient, and cardiac morphology and function can be evaluated at the same time.[3] For many years, aortography has been the gold standard for the investigation of suspected injuries of the aorta.[3] The advent of noninvasive modalities such as CT, magnetic resonance imaging (MRI), and TEE with their excellent sensitivity and specificity to diagnose aortic pathologies has decreased the need for aortograms.

Suspected aortic pathologies can be encountered in different ICU settings. The aorta may have to be imaged to rule out dissection, rupture, aneurysm, aortic debris, or aortic abscess. TTE is a good initial imaging modality for evaluation of the proximal aorta (ascending aorta and arch),[59] but the descending thoracic aorta cannot be adequately assessed and visualized with this modality. Because of the close anatomic relationship between the thoracic aorta and the esophagus, TEE allows optimal visualization of the entire thoracic aorta (Fig. E2.17). As described earlier, a blind spot exists in the distal portion of the ascending aorta and the proximal portion of the transverse aorta where its imaging can be suboptimal.[122,123]

Aortic Dissection and Rupture

Patients presenting with suspected aortic dissection need emergency diagnosis and treatment. Different noninvasive tests have been advocated for evaluation of suspected aortic dissection, including

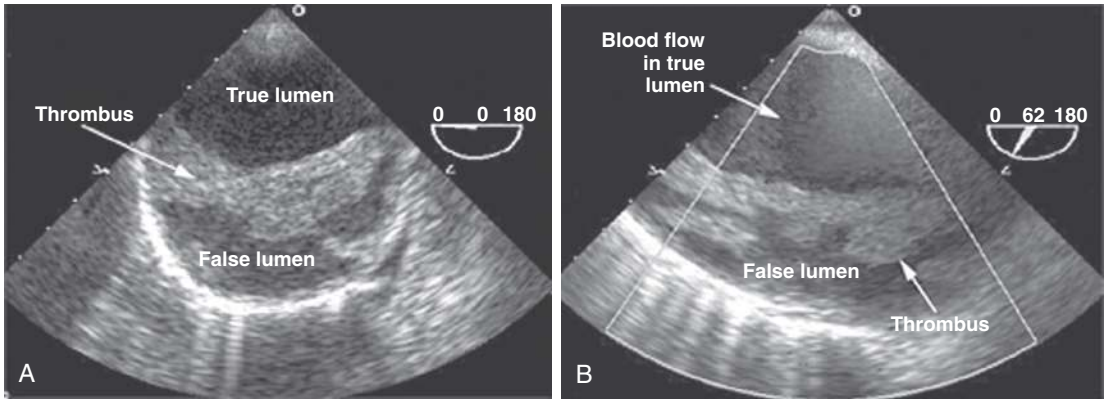


Fig. E2.17 Dissecting thoracic aortic aneurysm. A 65-year-old patient presented to the emergency department with severe ripping chest pain radiating to the back. The initial electrocardiogram was unremarkable, and the chest x-ray showed a widened mediastinum. The patient underwent transesophageal echocardiography, which revealed the presence of a large dissecting aneurysm of the descending thoracic aorta. The short-axis view **(A)** revealed the presence of a large aneurysm with a true and a false lumen. The false lumen was filled with thrombus *(arrow).* On the longitudinal view with color Doppler **(B)**, blood flow in the true lumen is visualized. The patient was taken emergently to the operating room.

TEE, CT, and MRI.[5,124] Nienaber and colleagues[124] compared all three modalities and found that they had similar sensitivities (98%). MRI had higher specificity than TEE (98% vs. 77%). A limitation of the study was that single-plane TEE was used. With multiplane TEE, specificity is improved to greater than 90% (see Fig. E2.17).[122] TTE was compared with CT and aortography in a multicenter European cooperative study,[125] it was shown that TEE was superior compared with both alternative modalities for the diagnosis of aortic dissection (sensitivity 99%). Other studies have confirmed the high accuracy of TEE.[125–128] A negative TEE examination for the diagnosis of aortic dissection, even in a high-risk population, has high negative predictive value.[129] Most centers use contrast CT scanning as the first choice for suspected aortic dissection, but TEE is an option in patients who cannot receive contrast, such as those who have advanced renal disease or are too unstable to be transported to the CT scanner (Video E2.6).

Another common indication to perform emergency aortic imaging in the ICU is to assess patients with blunt or penetrating chest trauma.[3] These patients are at high risk of life-threatening aortic injuries such as traumatic dissection and rupture, and prompt diagnosis and treatment are critical. Exclusion of major trauma to the ascending and descending aorta at the bedside is important in this context.[105] The value of TEE on admission for trauma patients with enlarged mediastinum and hemodynamic instability, with or without a combination of several other symptoms (e.g., pleural effusion, decreasing hematocrit, thoracic vertebral fracture), has been stressed by many authors.[130–133] Patients usually have a contained hematoma around the aortic dissection.[131] Transection of the thoracic aorta usually is seen at the level of the ligamentum arteriosum.

Additional helpful features of TEE in evaluating aortic pathologies are the ability to detect or assess extension of dissection into the proximal coronary arteries; the presence of pericardial or mediastinal hematoma or effusion; the presence, severity, and mechanism of associated aortic valve regurgitation; the point of entry and exit between the true and false lumens; the presence of thrombus in the false lumen; and ventricular function.[16] When TEE findings are equivocal or negative in cases of suspected thoracic aortic disease, other imaging modalities such as aortography, CT, or MRI should still be performed.

Assessment for Intracardiac and Intrapulmonary Shunts

In critically ill patients, clinical suspicion for an intracardiac or intrapulmonary shunt most often is raised in the context of unexplained embolic stroke or refractory hypoxemia. In such cases, the presence of a right-to-left shunt must be excluded. Common origins of right-to-left shunt are atrial septal defect or patent foramen ovale at the cardiac level[5] and arteriovenous fistula at the pulmonary level.[5] To be able to detect the presence of such a shunt at the bedside, a contrast study often is needed, because the shunt is usually not well visualized with 2D echocardiography alone. Color-flow imaging increases the detection rate of intracardiac shunt to some extent, but usually only when the shunt is large. Accordingly, a contrast study should be performed routinely as part of a TEE or TTE examination when evaluating a patient with unexplained embolic stroke or refractory hypoxemia in the ICU. For this purpose, agitated saline contrast is usually used. Approximately 0.5 mL of air is mixed with 10 mL of normal saline and is vigorously agitated back and forth between two syringes connected to the patient by a three-way stopcock. After an adequate echocardiographic view of the right and left atrial cavities has been obtained, the agitated saline is forcefully injected IV. After injection, the contrast is seen in the vena cava, right atrium, right ventricle, and pulmonary artery. In the absence of a shunt, only a minimal amount of contrast should be seen in the left-sided cavities, because most of the microbubbles from the agitated saline are unable to pass through the pulmonary capillaries. If an intracardiac shunt is present, such as an atrial septal defect or patent foramen ovale, left-sided contrast is observed immediately after right-sided opacification, and the contrast is seen going through the interatrial septum (Fig. E2.18). Performance of a Valsalva maneuver by the patient during contrast injection increases the sensitivity of the bubble study to detect right-to-left shunting. In mechanically ventilated patients, a maneuver equivalent to a Valsalva may be performed by inducing sudden release of sustained airway pressure previously achieved by inflating the lungs manually. This maneuver reverses the atrial transseptal gradient and may help

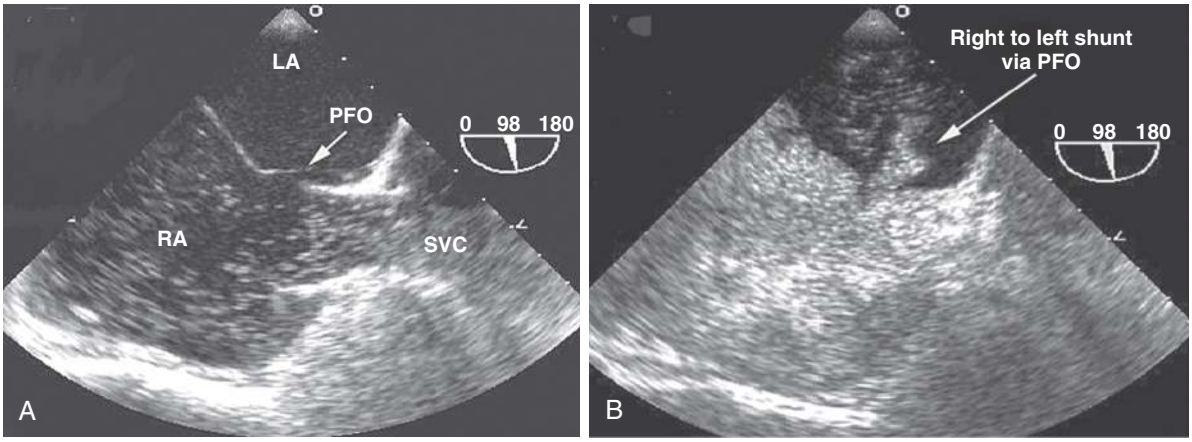


Fig. E2.18 Positive bubble study shows the presence of a right-to-left shunt via a patent foramen ovale (PFO). Transesophageal echocardiography was performed in a patient hospitalized in the ICU for pneumonia. He presented with refractory hypoxemia that was out of proportion to the underlying minor pulmonary process. Transesophageal echocardiography was obtained (multiplane transducer at 98 degrees) and showed the presence of a PFO with a significant right-to-left shunt caused by elevated right atrial pressure. Soon after contrast injection **(A)**, the bubbles are seen arriving in the right atrium (RA) from the superior vena cava (SVC). A few seconds later **(B)**, a complete opacification of the right atrium is reached, and the bubble contrast is clearly seen shunting through the PFO from the right atrium to left atrium (LA).

uncover a patent foramen ovale that would not have been seen otherwise. Right-to-left shunting also can be caused by the presence of pulmonary arteriovenous fistulas. These often are associated with end-stage liver disease (hepatopulmonary syndrome). With this type of shunt, contrast is seen to appear in the left atrium from the pulmonary veins instead of through the atrial septum; this finding is best detected by TEE, which usually permits visualization of all four pulmonary veins. The characteristic of intrapulmonary versus intracardiac shunt is that there is a longer delay (three to five cardiac cycles) for contrast to migrate from the right- to the left-sided cavities in the presence of an intrapulmonary shunt.[5]

Other types of intracardiac shunts also can be encountered in the ICU. After myocardial infarction, patients can develop cardiogenic shock resulting from acute development of a ventricular septal defect and resultant left-to-right shunt. Physical examination and invasive hemodynamic monitoring (pulmonary artery catheterization) sometimes can miss this diagnosis. Echocardiography reveals a disrupted ventricular septum with a high-velocity left-to-right shunt. This kind of shunt usually is well visualized without use of contrast. The diagnosis can be established by 2D and Doppler TTE in approximately 90% of cases.[134] Penetrating cardiac trauma is often associated with intracardiac and extracardiac shunts, and TEE is becoming the preferred tool for perioperative early identification of occult shunts.[14] Identification of these shunts is paramount in these critically ill patients, because missing them may lead to cardiac tamponade and rapid death. TEE has been shown to be superior to angiography and TTE to visualize these lesions.[135–137]

Unexplained Hypoxemia

Patent foramen ovale is present in 25%–30% of healthy individuals.[59,106] Usually it allows only minimal and intermittent right-to-left shunting. When the right atrial pressure is disproportionately increased and exceeds left atrial pressure, the patent foramen ovale can widen and significantly raise the importance of the right-to-left shunt, with resultant significant hypoxemia. In a critically ill patient, this increase in right-sided pressure can occur from pulmonary hypertension secondary to acute respiratory distress syndrome or pulmonary embolism, right ventricular failure (from infarction or pulmonary hypertension), or severe tricuspid regurgitation, which is often seen in the ICU for a variety of reasons. In critically ill patients, TEE is in general more useful than TTE for evaluation of patent foramen ovale, atrial septal defect (see Fig. E2.18), and pulmonary arteriovenous fistula[138] because of the close proximity of the lesion to the ultrasound transducer.

Patients with patent foramen ovale and persistent refractory hypoxemia despite ventilator and hemodynamic manipulation sometimes need to have catheter-based septal defect closure devices inserted. TEE is crucial to assist in the performance of this procedure.[139]

Source of Embolus

In the setting of acute unexplained stroke, echocardiography often is required to determine whether a potential embolic source of cardiac origin is present. TEE is the modality of choice for this purpose. Possible cardiac sources of emboli to the arterial circulation include left atrial or appendicular thrombus, left ventricular thrombus, thoracic atheromatosis, and right-sided clots (from right atrium, right ventricle, vena cava) combined with a right-to-left intracardiac shunt (leading to a paradoxical embolus). Cardiac tumors and vegetations are other potential sources of emboli from cardiac origin that must be considered.

When cardioversion is considered for a critically ill patient with atrial fibrillation or flutter, performance of TEE is helpful in evaluating the left atrium and appendage for the presence of thrombus (Fig. E2.19). If no intracardiac clots are documented, cardioversion can be performed with minimal embolic risks.

USE OF CONTRAST AND HARMONIC TECHNOLOGY TO ENHANCE TRANSTHORACIC EXAMINATIONS WITH POOR IMAGE QUALITY IN A CRITICALLY ILL PATIENT

Using standard echocardiographic methods, endocardial delineation is suboptimal in approximately 30% of cases.[140] However, two developments in ultrasound have improved the quality of endocardial border definition: harmonic imaging and IV contrast echocardiography.[141] Dramatic improvements in image quality have been achieved with the development of harmonic imaging. This technology exploits the formation of ultrasound signals that return to the transducer at a multiple of the transmitted (fundamental) frequency, referred to as the *harmonic frequency*.[1] Signals are received by the ultrasound transducer at twice the transmitted frequency. This "second harmonic imaging" results in images with better contrast between the myocardium and cardiac chambers and improved endocardial definition compared with fundamental imaging.[142–144] Most current ultrasound equipment includes harmonic imaging as a standard feature.

In critically ill patients with poor acoustic windows, endocardial visualization still may be inadequate despite the use of second harmonic imaging.[140] In these patients, contrast agents capable of producing left ventricular cavity opacification with an IV injection can be helpful in delineating endocardial borders. Several contrast agents are currently available that contain albumin microspheres filled with perfluorocarbon gas, allowing for the passage of contrast through the lungs with appearance of contrast in the left ventricle.[1] The chamber is opacified by the contrast agent within 1 minute of administration and

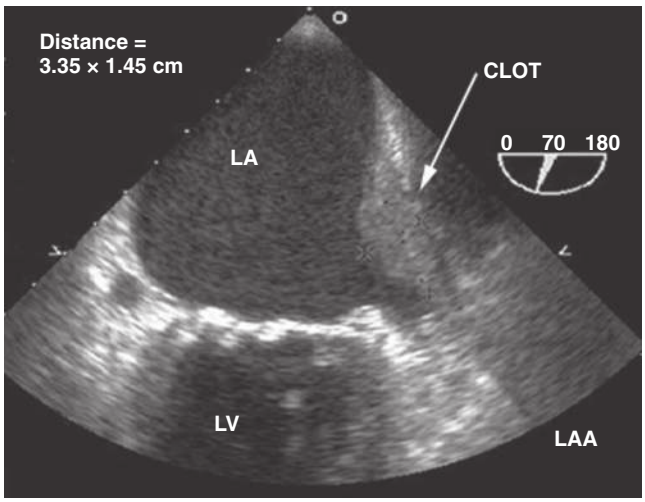


Fig. E2.19 Large clot in the left atrial wall and left atrial appendage (LAA). A 72-year-old patient hospitalized in the ICU for urosepsis developed rapid atrial fibrillation. She was initially anticoagulated and rate-controlled. Despite resolution of the septic picture, she remained in atrial fibrillation 4 days after its onset. The patient underwent transesophageal echocardiography before undergoing a planned electrical cardioversion. The midesophageal view with multiplane transducer at 70 degrees revealed the presence of a large clot (3.35 × 1.45 cm) in the posterolateral wall of the left atrium (LA) extending into the LAA. With these findings, the patient's anticoagulation regimen was intensified, and the cardioversion was not performed. *LV,* Left ventricle.

allows improved endocardial border detection. The presence of contrast also enhances Doppler signals.[145] Studies have examined the impact of these newer modalities of harmonic imaging and contrast in the ICU. Reilly and colleagues[146] assessed the benefits of contrast echocardiography for the evaluation of left ventricular function in 70 unselected ICU patients; 22 patients (31%) were receiving mechanical ventilation. Left ventricular EF could not be obtained at all in 23% of patients with standard imaging, but when harmonic imaging was employed, left ventricular EF was unobtainable in only 13% of patients. When contrast imaging was employed, left ventricular EF was measurable in all the patients. EF was confidently determined in 56%, 62%, and 91% of patients with standard imaging, harmonic imaging, and contrast imaging. In this study, contrast imaging was safe and dramatically improved the capacity to evaluate left ventricular EF and regional wall motion reliably compared with fundamental and harmonic imaging. Yong and colleagues[141] extended these observations by comparing the results of harmonic and contrast imaging with an independent standard (i.e., TEE) in 32 consecutive critically ill patients who were considered technically very difficult. Estimation of EF was possible in 31%, 50%, and 97% with fundamental imaging, harmonic imaging, and contrast imaging. Quantification of EF by contrast enhancement correlated best with TEE ($r = 0.91$).

In critically ill patients with suboptimal TTE image quality, contrast echocardiography combined with harmonic imaging provides a noninvasive and safe alternative to TEE for determination of regional and global left ventricular function (Fig. E2.20).[140] It is a rapid and simple technique that can be performed at the bedside in the ICU, with positive impact on interpretation of left ventricular function. Before using TEE, this technique should be considered in critically ill patients when simple TTE is inadequate for the evaluation of left ventricular function.[140]

COMPARISON BETWEEN BEDSIDE ECHOCARDIOGRAPHY AND PULMONARY ARTERY CATHETER IN THE INTENSIVE CARE UNIT

Since its introduction into clinical practice in 1970, pulmonary artery catheterization has been a standard hemodynamic monitoring technique for critically ill patients in the ICU.[147–149] Pulmonary artery catheterization provides clinicians with indices of cardiovascular function to assist in therapeutic decision making. Pulmonary artery catheterization can be a useful diagnostic tool, aiding in the management of critically ill patients. Nevertheless, misinterpretation of the data it provides can lead to excessive morbidity and mortality.[63,147,150,151] Conventional monitoring using a pulmonary artery catheter has been shown to be limited in the evaluation of global ventricular function,[19,21] and echocardiographic studies have established that pulmonary artery occlusion pressure often does not allow accurate assessment of left ventricular preload.[26,152,153] The frequent changes in ventricular compliance and loading conditions occurring in critically ill patients can affect systolic and diastolic function. In such cases, conventional monitoring does not enable early detection of acute changes in function, and it does not allow the clinician to discern systolic from diastolic changes.[19]

In critically ill patients, echocardiography, particularly TEE, has the ability to clarify diagnosis and define pathophysiologic process more precisely than pulmonary artery catheterization. In a prospective study of limited scope, Benjamin and colleagues[21] found that TEE-derived data disagreed with the pulmonary artery catheterization evaluation of intracardiac volume in 55% of cases and with the pulmonary artery catheterization assessment of myocardial function in 39% of cases. These authors also reported that the post–pulmonary artery catheterization therapeutic recommendations were different from the

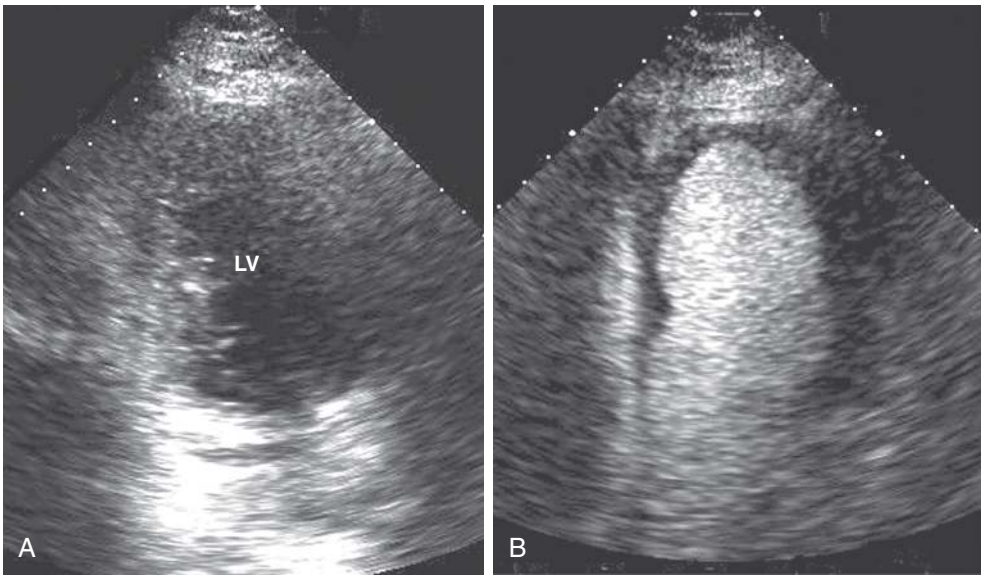


Fig. E2.20 Use of contrast agent to improve endocardial border delineation in a critically ill patient with suboptimal transthoracic image quality. A suboptimal transthoracic apical two-chamber view **(A)** of the left ventricle (LV) obtained from a ventilated ICU patient with hemodynamic instability. The poor endocardial resolution makes regional and global ventricular function hard to assess. Same transthoracic two-chamber apical view **(B)** in the same patient after contrast injection. A dramatic improvement in endocardial border definition is noted. Contrast echocardiography combined with harmonic imaging provides a noninvasive, safe alternative to transesophageal echocardiography for determination of regional and global left ventricular function.

post-TEE therapeutic recommendations in 58% of patients. In a retrospective analysis of 108 critically ill patients who underwent a TEE, Poelaert and colleagues[20] found that of 64% of patients with pulmonary artery catheterization, 44% underwent therapy changes after TEE (41% in the cardiac and 54% in the septic subgroup). Also, these investigators found that in 41% of patients without pulmonary artery catheterization, TEE led to a change in therapy. They concluded that TEE produced a change in therapy in at least a third of ICU patients, independent of the presence of pulmonary artery catheterization.[20]

Another significant advantage of echocardiography in the ICU is the speed with which it can be performed relative to pulmonary artery catheterization. In the study by Benjamin and colleagues,[21] TEE was performed in 12 ± 7 minutes versus 30 minutes or more for pulmonary artery catheterization insertion. In a study by Kaul,[154] the average time required to place a pulmonary artery catheter and record the data was 63 ± 45 minutes versus 19 ± 7 minutes to complete bedside TEE. Reported complications of pulmonary artery catheterization include pneumothorax, hemothorax, bacteremia, sepsis, cardiac arrhythmias, pulmonary artery rupture, cardiac perforation, and valvular damage.[21] Compared with pulmonary artery catheterization, bedside echocardiography has a better safety profile, as discussed previously in this chapter.

A major advantage of pulmonary artery catheterization versus TEE, however, is that the catheter can more easily serve as a continuous monitoring technique to assess the response to a therapeutic intervention.[21] Of course, this potential advantage may provide little benefit in patients in whom the information is misinterpreted or inadequate. In some ICUs, echocardiography has completely replaced pulmonary artery catheterization for assessment of circulatory status of mechanically ventilated patients.[38]

Despite having multiple limitations, pulmonary artery catheterization still has a role in the ICU and remains a useful diagnostic tool when used by physicians who have extensive experience with it.[20,155] A combination of invasive pressure monitoring and TEE probably offers the most complete bedside evaluation of morphology and intracardiac hemodynamics and provides a more precise pressure-volume evaluation of left ventricular and right ventricular function and filling.[20,22]

IMPACT OF BEDSIDE ECHOCARDIOGRAPHY ON DIAGNOSIS AND MANAGEMENT IN A CRITICALLY ILL PATIENT

Echocardiography often provides unexpected diagnoses in critically ill patients. Compared with TTE and invasive hemodynamic monitoring, TEE frequently provides different or additional information. This information often is important for adequate and optimal adjustment of therapy. Several studies have examined the impact of bedside echocardiography, particularly TEE, on the management of critically ill patients. Published studies have reported changes in management after TEE in 30%–60% of patients,[17,20,156,157] leading to surgical interventions in 7%–30%.[17,98,157,158] Impact varies depending on the type of ICU population being studied. Several studies have reported the clinical impact of urgent TEE in hemodynamically unstable patients.[157,159,160] In a prospective study of surgical ICU patients by Bruch and colleagues,[23] echocardiography altered management in 50 (43%) of 115 patients. Alterations in medical management induced by TEE included administration of fluids and initiation or discontinuation of inotropic agents, anticoagulants, or antibiotics. These findings are similar to those reported in patients in medical or coronary care ICUs.[10,158] In a retrospective study done by Colreavy and colleagues[8] of a mixed medical and surgical ICU population, TEE findings led to a significant change in management in 32% of all studies performed. In a prospective study by Heidenreich and colleagues[161] of 61 critically ill patients with unexplained hypotension, new diagnoses not made with TTE were made in 17 patients (28%), leading to surgical intervention in 12 (20%). Prospective randomized trials to study the ultimate impact of bedside echocardiography on mortality and morbidity in the ICU are needed. Such studies would be difficult to do, however, given the growing use and importance of this technology in the critical care setting.

OTHER APPLICATIONS OF BEDSIDE ULTRASONOGRAPHY IN THE INTENSIVE CARE UNIT

Central Line Placement

Central venous catheterization is performed frequently in critically ill patients. Placement of a central venous catheter is not without risk and can be associated with adverse events that are hazardous to patients and expensive to treat.[162–164] Complications can be seen in 15%–20% of cases.[165–167] As described in a review by McGee and Gould,[168] complications related to central venous line placement are most often mechanical (arterial puncture, local hematoma, hemothorax, pneumothorax), infectious (catheter colonization and related bloodstream infection), and thrombotic. Complications are influenced by patient factors (obesity, coagulopathy, previous failed catheterization), site of attempted access, and operator experience.[169] As previously reported, only approximately 38%–65% of patients are cannulated on the first attempt using a blind method.[170,171]

The use of ultrasound guidance during central venous catheterization has been well shown to reduce the risk of complications, mostly so for the internal jugular route. Ultrasound guidance also speeds catheter placement, decreases the number of attempts before successful placement, and improves the overall rate of successful placement. Ultrasound can be used to help localize and define the anatomy of the vein, with subsequent placement of the central venous catheter by the standard use of anatomic landmarks at the site identified by ultrasound, using the knowledge that a vein is patent and of adequate size. Ultrasound also can be used to provide real-time 2D ultrasound guidance to locate the vein and subsequently introduce the needle through the skin and into the vessel. Multiple studies have reported the superiority of ultrasound-assisted cannulation of the internal jugular vein in ICU patients, compared with the external landmark–guided technique.[170–172] Trials looking at ultrasound guidance after failure by the landmark method reported success rates ranging from 33% to 100%.[169,173–175] A meta-analysis[175] of the literature comparing guidance using anatomic landmarks only versus guidance using ultrasound for the placement of central venous catheters indicated that ultrasound guidance significantly decreases placement failure by 64%, decreases related complications by 78%, and decreases the need for multiple placement attempts by 40%. Data showing superiority of the ultrasound guidance technique are consistent and strong for the internal jugular vein approach, but less so for subclavian venous catheterization.[175–177]

Some patients can be identified in whom cannulation may be more difficult or in whom consequences of a complication could be more serious.[169] In these patients (Box E2.6), central venous cannulation may be laborious and risky, and ultrasound guidance should be considered. Hatfield and Bodenham[169] showed the benefit of portable ultrasound when central venous access was difficult. As suggested by this study and others,[178] ultrasound guidance is particularly beneficial when used in difficult cases or when a competent operator fails after a few attempts using surface landmarks.

BOX E2.6 Criteria for Difficult Central Venous Access

- Limited access sites for attempts (e.g., local infection, other catheters present)
- Difficult-to-identify surface landmarks (e.g., local swelling or deformity, severe obesity)
- Previous complications (e.g., pneumothorax, arterial puncture)
- Previous catheterization difficulties (e.g., multiple sites attempted, failure to gain access, >3 punctures at one site)
- Uncorrected coagulopathy (APTT >1.5×; INR >1.8; platelets <50,000/μL)
- Patient unable to tolerate supine position
- Known underlying vascular anomalies

APTT, Activated partial thromboplastin time; *INR,* international normalized ratio.

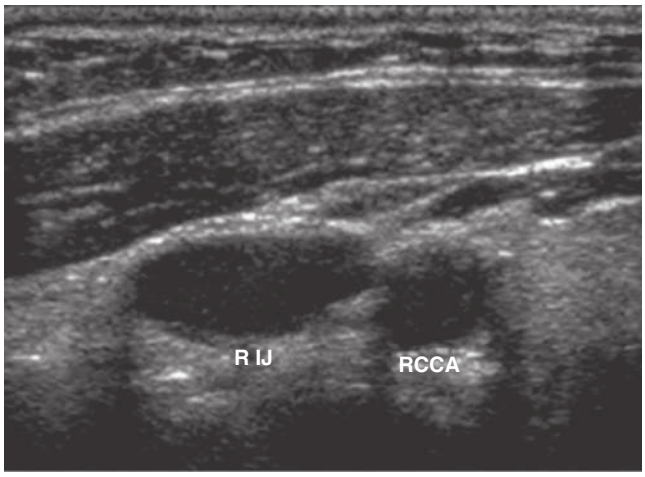


Fig. E2.21 Transverse view of normal anatomy of the right internal jugular (RIJ) vein and right common carotid artery (RCCA). Ultrasound examination helps determine the anatomic relationship, size, and patency of the vessels. Knowledge of these important vessel characteristics helps determine if the anatomy is suitable for central vein catheterization at a low risk. If the vessel anatomy is normal and the operator is experienced, subsequent venous catheterization can be done by the surface landmark technique or under real-time ultrasound guidance. If high-risk characteristics are identified (see Box E2.6), however, real-time ultrasound guidance (or selection of a different access site) would be preferred. (Courtesy Dr. Kurian Puthenpurayil.)

Ultrasound guidance is useful for operators with varying levels of experience.[169,175] The technique is easy to learn and can be self-taught with some practical assistance from radiologists or other experienced sonographers.[169,179,180] Familiarity with the anatomy and equipment is easy to obtain safely at the bedside.

Most large vessels that are catheterized usually can be imaged by ultrasound. Different types of ultrasound modalities can be used to help guide central vessel cannulation, including 2D ultrasound, Doppler transducer, Doppler with the probe in the needle, and fingertip pulse Doppler. With 2D imaging, fluid such as blood in vessels is black because there is nearly complete transmission of ultrasound.[169] Color Doppler mode helps delineate the flow patterns in vessels. Doppler-only equipment that provides no images has shown equivocal results in studies of vascular access.[176,181]

With 2D imaging, arteries are characteristically small, pulsatile, and difficult to compress with the probe.[169] Veins are usually larger, are nonpulsatile (except in the presence of severe tricuspid regurgitation), easily compressible, and distend when the patient is placed with the head down or when a Valsalva maneuver is performed.[169]

Vessels can be examined in the transverse and longitudinal views. The transverse view permits identification of the vein and arteries based on the sonographic characteristics mentioned earlier and clarifies their positions relative to one another (Fig. E2.21). The transverse and longitudinal views enable the sonographer to monitor in real time the passage of the needle through the skin and the anterior vessel wall. Ultrasound guidance also ensures detailed and accurate control of the needle (Fig. E2.22).[169]

During vessel examination, the sonographer specifically should assess the presence and patency of the vein (Fig. E2.23), the distensibility and compressibility of the vein, the position of the vein relative to the surrounding arteries (Fig. E2.24), and the presence of a thrombus in the vein (Fig. E2.25).[169] Ultrasound identification of certain anatomic characteristics such as small vessel size (<5 mm), intraluminal thrombus, and anterior location of the artery relative to the vein helps the physician identify unfavorable vessel anatomy and choose another catheterization site. A study by Levin and colleagues[182] indicated that 2D ultrasound guidance for the insertion of radial artery catheters was easy to use and increased the rate of success of insertion at first attempt. It was determined to be a useful adjunct to arterial catheter insertion. More studies are needed in the use of ultrasound for cannulation of peripheral arterial conduits.

Assessment of Pleural Effusions and Intraabdominal Fluid Collections

In critically ill patients, atelectasis and pleural effusions are frequent and often are present at the same time. Patients in the ICU are most often supine, and chest x-rays performed in this position offer limited sensitivity for the diagnosis of pleural effusion.[183] In many instances, neither atelectasis nor infiltration can be differentiated from pleural effusion. An alternative diagnostic method is needed to provide better results. Decubitus chest radiographs may show if fluid is free flowing, but this approach cannot localize or characterize the effusion precisely. CT of the chest shows the amount and distribution of fluid and is superior to plain lateral decubitus films. CT also can differentiate fluid from atelectasis and reveal information about the lung parenchyma. Chest CT requires transport to the radiology suite, however, which can be hazardous in unstable critically ill patients. Ultrasound examination of the pleural space has proved to be valuable for diagnosis of effusion.[184–188] The value of ultrasound for localizing fluid before catheter drainage or simple thoracentesis is well recognized. Ultrasound is especially valuable for localizing loculated or small effusions before a drainage procedure. In mechanically ventilated patients, blind thoracentesis can be hazardous, especially if the effusion is small or if the patient is on a high level of positive end-expiratory pressure.[189] Lichtenstein and colleagues[189] evaluated the feasibility and safety of ultrasound-aided thoracentesis in 40 mechanically ventilated patients. No complications occurred in the 45 ultrasound-aided thoracenteses, all performed by ICU physicians.

Basic skill required to detect a pleural effusion may be acquired in minutes and improves with experience.[190] In most instances, the pleural tap does not have to be done under real-time ultrasound guidance. A critically ill patient first must be positioned adequately on the back or on the side. Scanning of the pleural space is performed with the ultrasound probe. The probe must be oriented upward and downward, laterally and medially, and anteriorly and posteriorly so as to obtain a complete anatomic assessment of the area. The pleural fluid is usually hypoechogenic and appears black. The surrounding solid structures (soft tissue, diaphragm) and organs (lung, liver, heart, spleen) are visualized as structures with different degrees of echogenicity around the

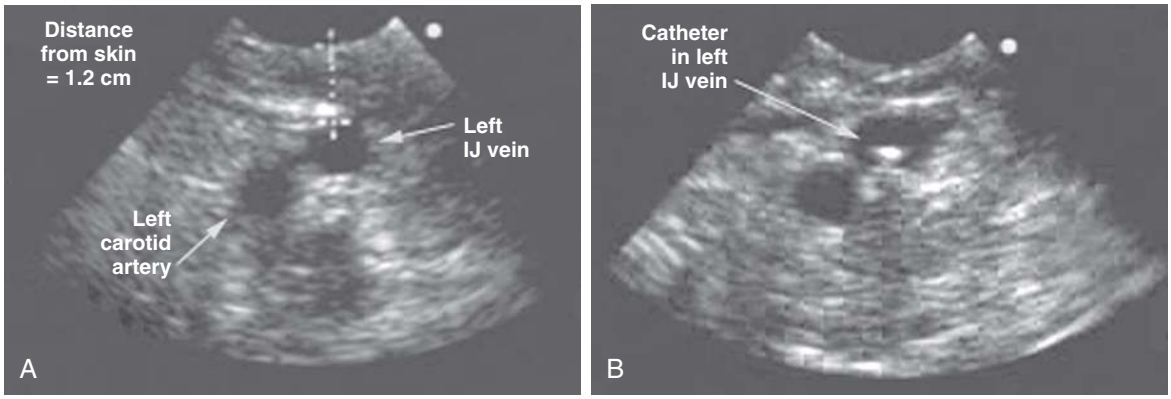


Fig. E2.22 Transverse view of left carotid artery and left internal jugular (IJ) vein. The distance from the skin to the anterior wall of the vein is measured before insertion of a central venous catheter **(A)**. Knowledge of this distance prevents the operator from going too deep with the needle when searching for the vein; this helps decrease the incidence of pneumothorax. After insertion, the catheter position in the jugular vein is confirmed **(B)**.

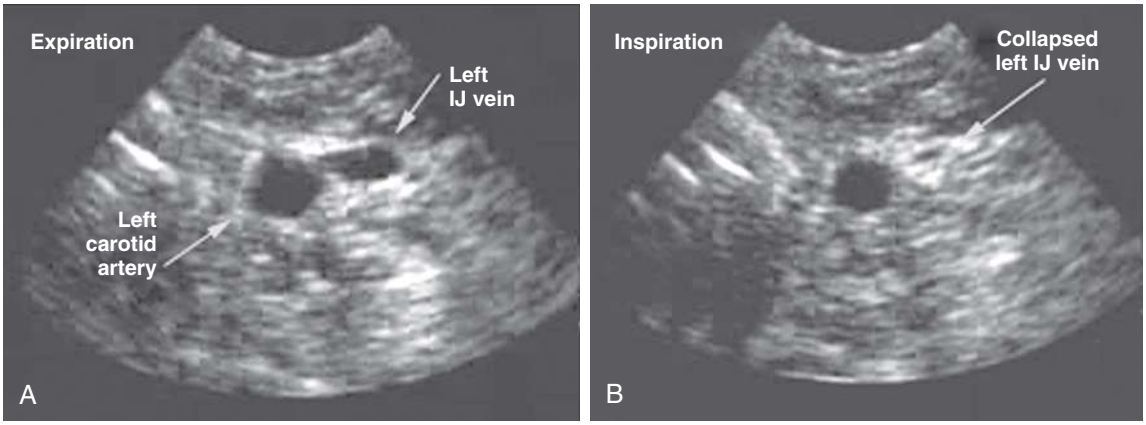


Fig. E2.23 Transverse view of the left carotid and internal jugular (IJ) vein in a spontaneously breathing patient sitting in bed at a 30-degree angle. The patient was febrile and dehydrated. A near-total collapse of the vein (which is of small caliber) can be appreciated on inspiration **(B)** compared with expiration **(A)**.

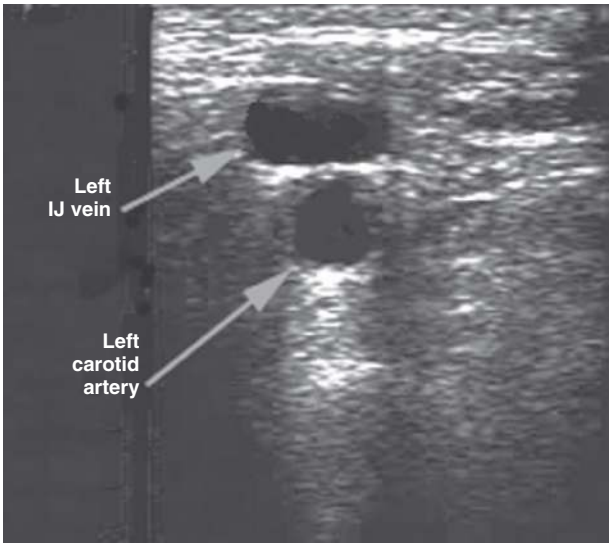


Fig. E2.24 Transverse view of left internal carotid artery and left internal jugular (IJ) vein. Notice the relative position of the jugular vein directly overlying the carotid artery. This type of anatomy is common on the left side and, when present, significantly increases the risk of procedure failure or arterial puncture.

effusion (Fig. E2.26). The presence of an aerated lung causes "airy artifacts." Ribs usually yield artifactual anechoic images. When the effusion has been well assessed, one must determine the feasibility of safely doing a thoracentesis. One must check for the absence of interposition of lung, heart, liver, or spleen during the respiratory cycle[189] to avoid puncturing these organs, which potentially can cause catastrophic complications. When an optimal and safe position for thoracentesis has been determined, the skin should be marked and disinfected, and the patient should remain in the exact same position as was used during the ultrasound examination. Optimally, the puncture should be done within seconds to minutes of the marking.

The same diagnostic and therapeutic procedures described earlier can be applied for intraabdominal fluid collections in a critically ill patient. Evaluation for intraabdominal fluid collection or abscess is restricted to areas that are not impeded by gas-filled structures[191] and include the regions around the liver and gallbladder, spleen, kidneys and lateral retroperitoneal areas, and pelvis around the uterus and bladder.[191] Fluid that does not change shape with probe pressure or patient positioning most likely represents a loculated collection.[191] Echogenic material and diffuse echoes on ultrasound within a fluid collection suggest the presence of particulate matter (e.g., fibrin or clots) and may represent an exudate or blood collection. As with pleural effusions, intraabdominal fluid collections can be percutaneously

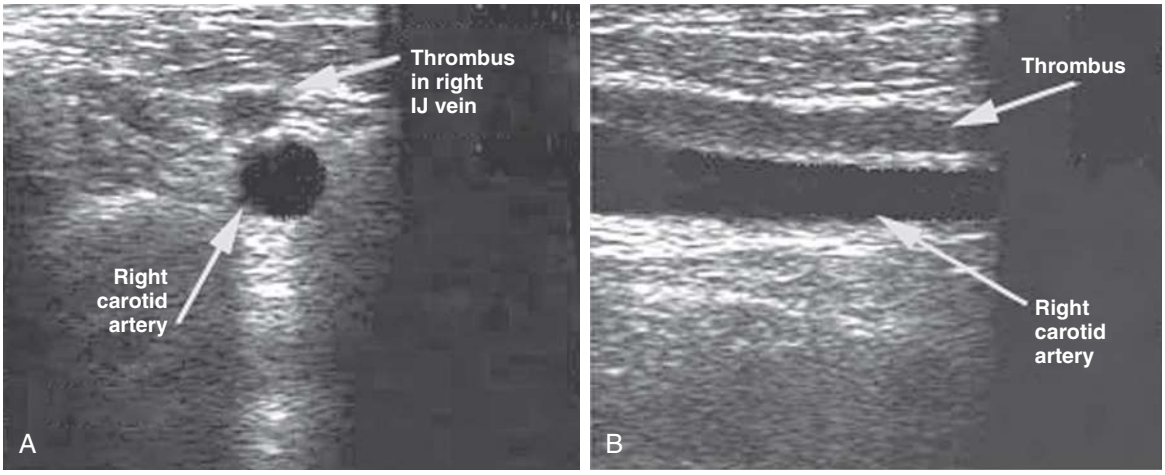


Fig. E2.25 Transverse **(A)** and longitudinal **(B)** views of the right carotid artery and right internal jugular (IJ) vein. Complete thrombosis of the right IJ vein can be appreciated. Notice the small caliber of the thrombosed vein and the increased echogenicity of the thrombotic material within it. The vessel could not be compressed by probe pressure.

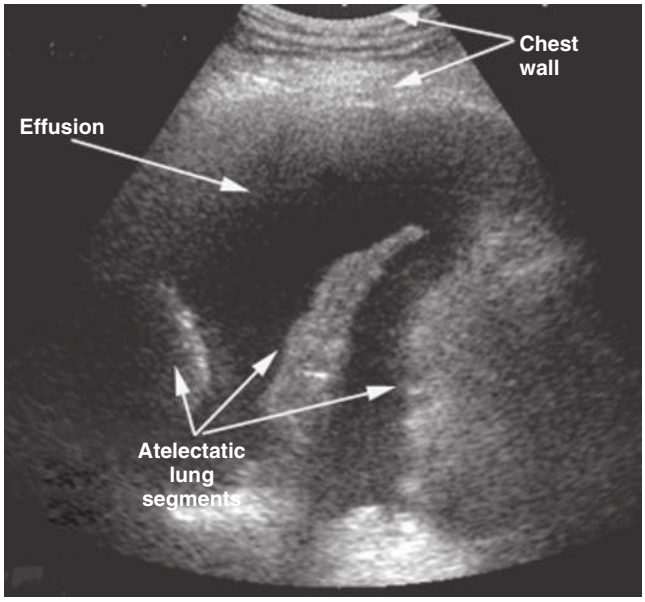


Fig. E2.26 Transverse view of a right pleural effusion. Collapsed atelectatic lung is well visualized "floating" in the effusion. (Courtesy Dr. Kurian Puthenpurayil.)

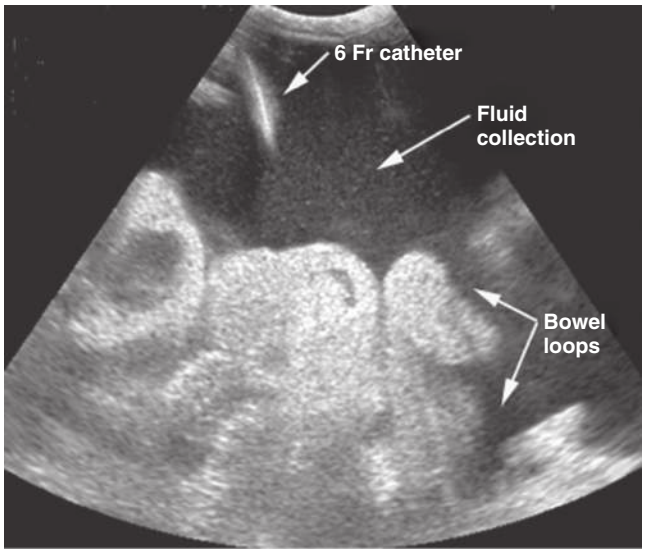


Fig. E2.27 Transverse view of a left lower quadrant abdominal collection. Echogenic, particulate material can be seen floating in the collection. Loops of bowel also are well visualized. A 6F catheter was inserted under ultrasound guidance to drain the collection, which was found to be chylous. Fluid collection with echogenic material and diffuse echoes on ultrasound are suggestive of particulate matter (e.g., fibrin or clots) and may represent an exudate or blood collection. (Courtesy Dr. Kurian Puthenpurayil.)

sampled or drained safely at the bedside under real-time ultrasound guidance (Fig. E2.27).

Urinary Bladder Scan

Bladder scanning devices are portable units that can provide a measurement of urine volume in the bladder (Fig. E2.28) and avoid bladder overdistention and reduce the need for unnecessary catheterization.[191,192] Studies have shown that frequent catheterization is a major risk factor for urinary tract infections that can be costly to medical centers.[193–195] Use of a portable bladder scanning device to reduce the incidence of nosocomial urinary tract infections was described by Moore and Edwards.[196] Bedside ultrasound assessment of volume in the urinary bladder also can be helpful to evaluate oliguria or anuria to rule out obstruction of the urinary catheter.

Focused Assessment of the Trauma Patient

Since the early 1990s, bedside ultrasound has been used in the United States as an additional diagnostic modality for use in determining the presence of intraabdominal injury after blunt trauma.[197] It is performed in the trauma bay during the secondary survey (as described in Advanced Trauma Life Support) or as part of the primary survey in hemodynamically unstable patients.[191,198–202] The focused assessment for sonographic examination of trauma (FAST) should be performed for a specific purpose, usually identification of hemoperitoneum, hemothorax, or tamponade.[191] FAST seeks to determine the presence of fluid in four areas: (1) the subxiphoid region in the pericardial sac,

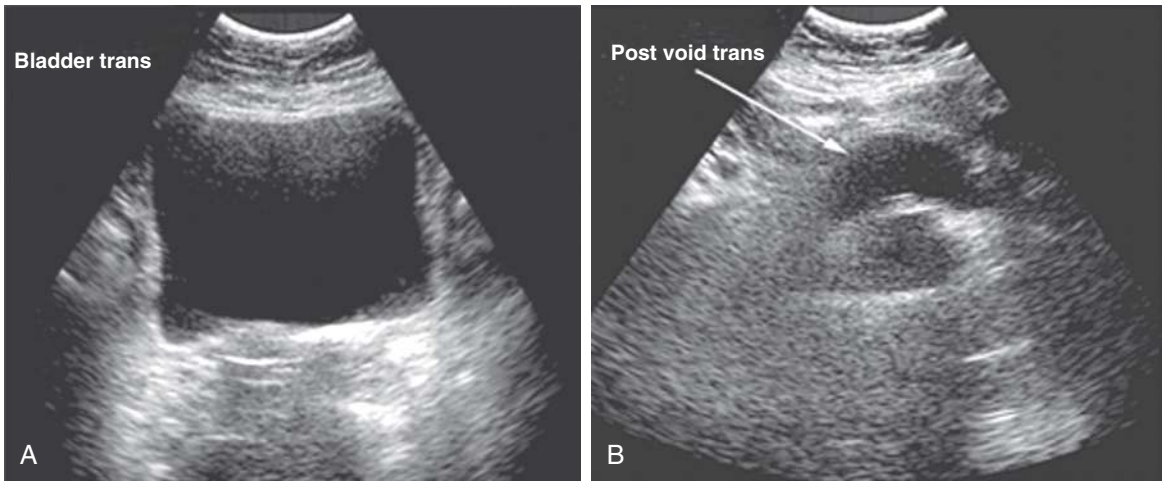


Fig. E2.28 Urinary bladder. Suprapubic transverse view of a full urinary bladder **(A)**. This "square" appearance of the bladder with a concave superior wall is typical of a moderately full bladder. When overdistended (i.e., in the presence of a low urinary tract obstruction), the bladder is large and adopts a round, globular shape (not shown). Suprapubic transverse view of an empty bladder **(B)**. When empty, the bladder can become small and commonly may be difficult to identify. (Courtesy Dr. Kurian Puthenpurayil.)

(2) the right upper quadrant in the Morison pouch, (3) the left upper quadrant in the splenorenal recess, and (4) the pelvis in the pouch of Douglas or rectovesical space (Fig. E2.29).[19] Because the FAST examination is noninvasive and quickly performed at the bedside, it is ideal for detecting intraabdominal injury in the resuscitation area. It has now been incorporated into the trauma resuscitation algorithm of most level I trauma centers in the United States.[191,203]

Use of the FAST examination has been shown to diminish the need for more invasive diagnostic measures such as diagnostic peritoneal lavage and subsequent exploratory laparotomy.[204,205] The FAST examination has been shown to be most accurate when performed for evaluation of hemodynamically unstable patients.[203,206–208] Studies have suggested that its use as a screening tool for blunt abdominal injury in hemodynamically stable trauma patients may result in underdiagnosis of intraabdominal injuries.[202,203,209]

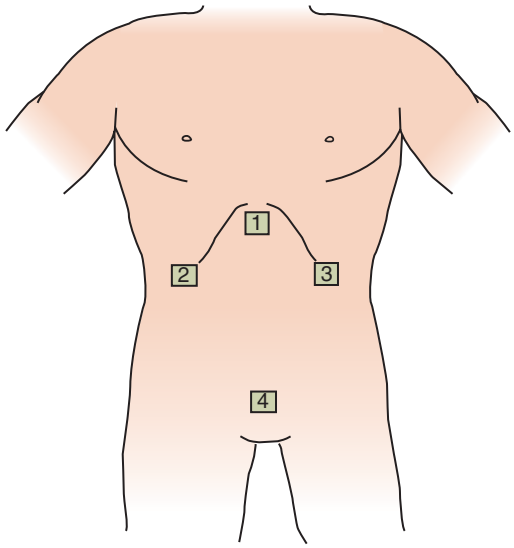


Fig. E2.29 Focused assessment for sonographic examination of trauma (FAST). The FAST examination seeks to determine the presence of fluid in four areas: (1) the subxiphoid region in the pericardial sac, (2) the right upper quadrant in the Morison pouch, (3) the left upper quadrant in the splenorenal recess, and (4) the pelvis in the pouch of Douglas or rectovesical space.

Intraaortic Balloon Counterpulsation

Bedside TEE may be helpful in different aspects of intraaortic balloon counterpulsation management. Before insertion, TEE can rule out the presence of significant aortic regurgitation, which would represent a contraindication to intraaortic balloon counterpulsation use. After insertion, TEE can confirm the position of the intraaortic catheter in the descending thoracic aorta, ensure correct functioning of the balloon (visualization of inflation and deflation), and rule out the presence of important complications of aortic catheter insertion (e.g., aortic dissection). TEE also may be used for monitoring of the ventricular function while separating the patient from the intraaortic balloon counterpulsation device.

Ventricular Assist Devices

Different complications are likely to occur after ventricular assist device implantation, such as bleeding and hemodynamic instability. Maintenance of ventricular assist device flow is a key indicator of the overall status of the system. In the postoperative period, low ventricular assist device flow is usually the result of hypovolemia and right ventricular dysfunction. TEE can be helpful for the diagnosis and monitoring of both of these conditions. Right ventricular failure has been shown to occur in approximately 20%–25% of patients being supported with an isolated left ventricular assist device.[210] With prosthetic circulatory support devices, there can be dramatic changes in ventricular volumes and hemodynamic conditions and substantial direct and indirect changes to the contralateral ventricle because of ventricular interactions. TEE can help the clinician monitor and understand these ventricular interactions.[211] It also can help assess adequacy of flow and the patency of the inflow and outflow cannulas to eliminate the presence of a thrombus and collapse or displacement of the cannulas. It also can motivate an urgent return to the operating room if a cardiac tamponade is diagnosed. If hypoxemia supervenes in the ICU, the presence of a patent foramen ovale has to be ruled out. For patients placed on extracorporeal membranous oxygenation

support, bedside TEE also can be used to monitor ventricular function during weaning of the circulatory assistance.

Performance of Bedside Ultrasonography by the Intensivist

In acute situations in the ICU, it may be difficult to have a cardiologist or sonographer available on immediate call on a 24-hour basis to perform a bedside ultrasound examination. The value of immediate bedside echocardiography for aiding in the diagnosis and management of acute hemodynamic disturbances has been well shown in the literature in the ICU and the emergency department.[212,213]

Ultrasound technologies are not exclusive to the radiologist or cardiologist. Appropriately trained emergency department physicians, surgeons, anesthesiologists, and ICU specialists have been using ultrasound devices with great success. Anesthesiologists were instrumental in many of the pioneering studies of TEE in the operating room and ICU.[4,22,214,215] Successful performance of bedside echocardiography by noncardiologist intensivists also has been well shown in the literature.[8,21,216] A study by Benjamin and colleagues[21] showed that a limited TEE examination performed and interpreted by intensivists (after training under the supervision of two cardiologists) is feasible and provides rapid, accurate diagnostic information that can have a dramatic impact on the treatment of critically ill patients.[21] The safety and utility of performance of bedside ultrasound by the intensivist for various other purposes in the ICU (central venous cannulation, thoracentesis, paracentesis) also have been well shown.[170–172,189]

With the increasing popularity of ultrasound devices—particularly lightweight, portable, handheld devices—there is controversy regarding the advisability and use of noncomprehensive "goal-directed" examinations performed by clinicians without cardiology or radiology training.[104] Studies with these portable devices that provide basic 2D and Doppler flow imaging showed they can provide important anatomic information[216–220] but that even in highly skilled hands, they may provide suboptimal imaging or diagnostic capabilities in the ICU.[218] Inappropriate interpretation or application of data gained by a poorly skilled user may result in adverse medical, ethical, and social consequences.[104] To avoid misusing the technology, adequate training is essential.

The era of a technology-extended physical examination[219] seems to have arrived, and there seems to be a role for a user-specific, focused ultrasound examination.[104,221] An examination said to be "targeted," "focused," and "limited" may often equate with "incomplete," "inadequate," or "inaccurate." Training must be individualized and tailored to specific needs, and appropriate user-specific application depends directly on the training and expertise of the user.[104] Provided that adequate expert backup is available, the training of intensivists in performing focused or more comprehensive bedside ultrasound examinations is not only feasible but also can be done safely and rapidly and yield information pertinent to the management of critically ill patients. General guidelines in training for TTE and TEE have been developed by the American Society of Echocardiography in association with the American Heart Association and the American College of Cardiology.[222] Since 1996 the American Society of Anesthesiologists and Society of Cardiovascular Anesthesiologists also have developed practice guidelines for perioperative TEE.[223] The importance of adequate training and subsequent maintenance of competence cannot be overemphasized; inappropriate use or misapplication potentially could temper the acceptance and limit the value of performance of bedside ultrasonography by the intensivist.

Training of intensivists and emergency department physicians in the performance of emergency bedside ultrasonography should facilitate acquisition of answers to clinical questions that may strongly affect medical and surgical management decisions. As has been mentioned by different authors,[190,224] training in echocardiography and general ultrasonography should be incorporated into the critical care fellowship, with special emphasis on TEE as part of the training program.

KEY POINTS

- As a result of improvements in transthoracic imaging, most ICU patients now can be adequately studied with TTE.
- TEE is particularly useful in the ICU for the assessment of unexplained hypotension, suspected aortic dissection, valvular vegetations, source of cardiac or aortic emboli, prosthetic heart valves (especially mitral), and detection of intracardiac shunts.
- The use of ultrasound guidance during central venous catheterization has been well shown to reduce the risk of complications, improve rapidity of catheter placement, and improve overall success of the procedure.
- Successful performance of bedside ultrasonography by intensivists in a limited examination has been shown to be feasible and potentially to provide rapid diagnostic information that can have a dramatic impact on the treatment of critically ill patients.
- Adequate training and maintenance of competence is crucial for the intensivist to perform bedside ultrasonography safely and efficiently, because inappropriate interpretation or application of data gained by a poorly skilled user may result in adverse consequences.

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Benjamin E, Griffin K, Leibowitz AB, et al. Goal-directed transesophageal echocardiography performed by intensivists to assess left ventricular function: comparison with pulmonary artery catheterization. *J Cardiothorac Vasc Anesth*. 1998;12:10–15.
This prospective blinded study shows that intensivists can be trained to perform limited-scope, goal-directed TEE rapidly and safely that can yield pertinent data for the management of a critically ill patient.

Colreavy FB, Donovan K, Lee KY, et al. Transesophageal echocardiography in critically ill patients. *Crit Care Med.* 2002;30:989–996.
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Central Venous Catheterization

Judith L. Pepe and Jennifer L. Silvis

BEFORE THE PROCEDURE

Indications

- Inability to achieve the clinical goal by peripheral intravenous catheterization
  - Relatively fast flow rate is required
  - Rapid, massive intravascular volume resuscitation
    3.5-inch, 8.5F introducer catheter offers the fastest flow rate. However, a 2-inch, 16-gauge peripheral catheter has a faster flow rate than the longer 16-gauge, centrally inserted triple-lumen catheter.
  - Peripheral venous access cannot be found
- Cardiopulmonary resuscitation and shock states
  - Peripheral catheters are often difficult to place in shock states
  - Drug administration is often more effective by central infusion
- Administration of agents irritating to peripheral veins
  - Concentrated potassium and sodium chloride solutions
  - Total parenteral nutrition solutions
  - Chemotherapy agents
  - Vasopressors and inotropes
- Central venous pressure monitoring
- Pulmonary artery pressure monitoring
- Transvenous pacemaker insertion
- Hemodialysis
- Plasmapheresis
- Venous access for frequent blood sampling or for measurements of central venous oxygen saturation ($ScvO_2$)
- Inferior vena cava filter placement
- Extracorporeal life support cannulation

Contraindications

- No absolute contraindications if experienced or supervised operator unless skin infection located at planned insertion site(s)
- Relative contraindications
  - Severe coagulopathy (including thrombocytopenia): Consider a femoral vein central catheter or peripherally inserted central catheter (PICC)
  - Local skin infection
  - Ipsilateral arteriovenous fistula
  - Ipsilateral venous thrombosis
  - Inferior vena cava filter: Avoid passing the guide wire beyond 20 cm during central line insertion from the jugular site in order to prevent entanglement

Equipment

- Ultrasound with small linear array probe (5–15 MHz)
- Sterile sheath, gel, and needle guide for ultrasound
- Catheter size and length appropriate for the site, side and indication (e.g., 16 cm for right internal jugular and right subclavian, 20 cm for left internal jugular or subclavian, single lumen, multilumen, 8.5F introducer)
- Insertion kit, including 10-mL syringes, needles, guide wire, suture material, and local anesthetic
- Sterile saline flush solution
- Sterile fenestrated barrier drape for head-to-toe patient coverage
- Four sterile towels
- 2% Chlorhexidine gluconate sterile prep stick
- Sterile gown and gloves for the operator and assistant(s)
- Cap to cover hair and mask with a face shield or protective glasses for the operator and assistant(s)
- Sterile central line dressing kit
- Shoulder roll (for subclavian vein catheterization)

Anatomy

The pertinent anatomy varies depending on the chosen site of central venous catheterization and is important to thoroughly understand, even when using ultrasound guidance. All relevant landmarks should be included in the sterile field. For internal jugular venous catheterization, identification of the triangle formed by the two heads of the ipsilateral sternocleidomastoid (SCM) muscle is imperative. It is also important to note the location of the angle of the mandible, the clavicle, and the sternal notch (situated between the medial ends of the right and left clavicles). The carotid artery pulse should be located and protected during placement of the needle tip into the internal jugular vein. For subclavian vein catheterization, the middle portion of the clavicle, insertion point of the clavicular head of the ipsilateral SCM muscle, and sternal notch should be identified. Femoral vein catheterization requires identification of the junction of the middle and distal third of an imaginary line drawn from the pubic tubercle to the anterior superior iliac spine to define the course of the inguinal ligament. The ipsilateral femoral arterial pulse should be located as well.

Ultrasound

Ultrasound should be used to facilitate internal jugular and femoral venous access if the equipment and expertise are available. Use of anatomic landmarks generally is the preferred approach for accessing the subclavian vein. Ultrasound guidance allows for a higher rate of first-pass success, reduced procedural time, and decreased complications. Ultrasound of the chosen site, which can be supplemented with the use of color Doppler, identifies surrounding structures, landmarks, and their spatial relationships with the targeted vessel. Color Doppler imaging can aid with distinguishing venous from arterial structures. Real-time, dynamic ultrasound guidance assists the practitioner in obtaining precise venipuncture and is preferred over using ultrasound merely

for static marking of the insertion site. Complete imaging of the guide wire tract is accomplished by following the wire from the point of skin insertion to venipuncture and visualizing the wire within the lumen of the vein in both short (cross sectional view) axes and long (longitudinal view). The short-axis view (Fig. E3.1) is obtained by placing the ultrasound probe perpendicular to the course of the targeted vessel. The long-axis view (Fig. E3.2) is then obtained by rotating the ultrasound probe 90 degrees.

Procedure

Internal Jugular Vein (Middle Approach)

- See Video E3.1.
- Obtain informed consent from the patient or surrogate decision maker.
- Gather all necessary equipment.
- Place the patient in the supine position.

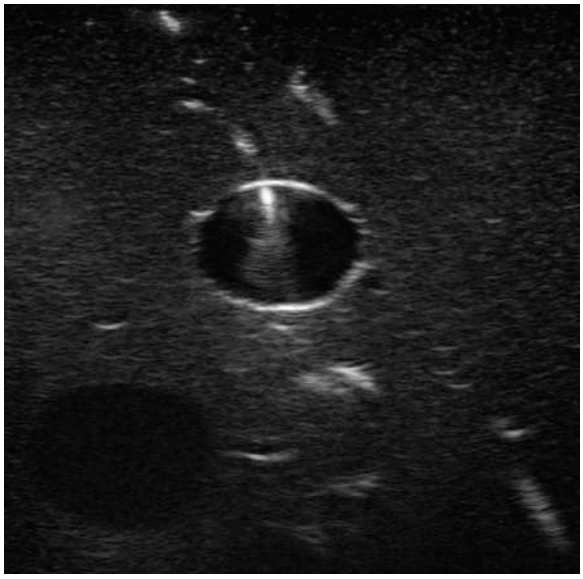

Fig. E3.1 Short-axis view demonstrating guide wire inside vein.

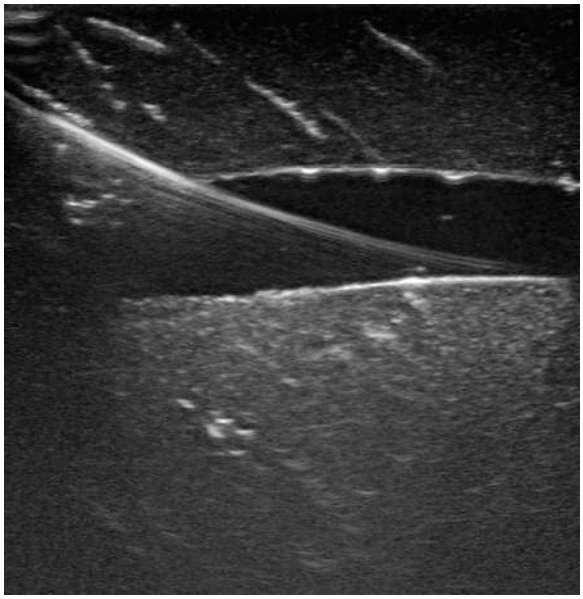

Fig. E3.2 Long-axis view confirming guide wire in vein.

- Position the bed at a comfortable height, with 15–30 degrees Trendelenburg.
- Rotate the patient's head away from the side of insertion.
- Perform a "time out" to verify patient, procedure, laterality, and consent.
- Perform nonsterile ultrasound to confirm the patency and depth of the internal jugular vein and the location of surrounding structures.
- Open the equipment using sterile technique.
- Wash hands and don a cap, face shield mask, sterile gown, and pair of gloves.
- Use a 2% chlorhexidine "prep stick" to prepare the area bounded by the ear lobe, mandible, chin, neck, and sternal notch past the midline; 2 cm inferior to the clavicle; and 2 cm posterior to the sternal head of the SCM muscle.
  - Preparing a wide area is preferred to facilitate conversion to the ipsilateral subclavian approach if the internal jugular approach proves unsuccessful.
- "Square off" (frame) the sterile area with four sterile towels.
- Place the head-to-toe fenestrated sterile drape.
- Place the ultrasound probe in a sterile sheath with gel, and position the correct needle guide on the probe.
- Find these anatomic landmarks: apex of the triangle formed by two heads of the SCM muscle, sternal notch, clavicle, and carotid pulse.
- Maintain awareness of anatomy while using ultrasound to guide needle insertion.
- Locate the internal jugular vein with the ultrasound probe in the short axis, and confirm that the vessel collapses easily with compression and is nonpulsatile.
- Inject local anesthetic into the skin and surrounding region at the proposed insertion site.
- Ensure that all materials needed for catheter placement are within easy reach on the sterile field.
  - Flush all catheter lumens, and then place caps on all ports except the distal port.
- Place the access needle with attached syringe onto the needle guide of the ultrasound probe.
- Advance the needle into the internal jugular vein under direct vision using ultrasound while applying gentle aspiration pressure on the syringe.
- Confirm the presence of the needle within the vein lumen by ultrasound imaging and by aspiration of free-flowing, nonpulsatile, venous-colored blood. Note that mild pulsations may be transmitted from the artery in close proximity.
- Remove the needle from the needle guide on the ultrasound probe.
- If ultrasound is unavailable, insert the needle at the apex of the SCM triangle (middle approach) and advance the needle toward the ipsilateral nipple at a 30- to 45-degree angle while applying gentle aspiration pressure on the syringe.
- Place the curved end of the guide wire through the syringe and/or needle into the vein. Never lose control of the distal end of the guide wire.
- Using ultrasound, confirm the course of the guide wire in the internal jugular vein in both the long and short axes.
- Remove the syringe and needle over the guide wire.
- Using a scalpel, make a small nick in the skin at the wire insertion site.
- Place a dilator over the wire, and advance the dilator into the soft tissues to establish a tract.
- Remove the dilator, leaving the guide wire in place.
- Place a catheter (single lumen or multilumen) over the wire into the vein:
  - 16 cm for the right internal jugular
  - 20 cm for the left internal jugular

- Remove the guide wire and place a cap on the distal port.
- Aspirate blood via all catheter lumens, and then flush each lumen with sterile saline.
- Secure the catheter to the skin with suture material.
- Place a sterile dressing.
- Clean up and safely discard all sharp objects into a "sharps" container.
- Order a chest x-ray to check catheter position.
  - Skilled operators may use ultrasound to confirm normal post-procedure lung sliding, assess for pneumothorax, and confirm catheter tip location.

Subclavian Vein (Infraclavicular Approach)

- See Video E3.2.
- Obtain informed consent from the patient or surrogate decision maker.
- Gather all necessary equipment.
- Perform a "time out" to verify patient, procedure, laterality, and consent.
- Place the patient in the supine position with the ipsilateral arm adducted.
- Place a shoulder roll under the patient, positioned vertically between the scapulae.
- Position the bed at a comfortable height, with 15–30 degrees Trendelenburg.
- Rotate the patient's head away from the side of insertion. Perform a time-out to verify correct patient, procedure, and consent.
- Open the equipment using sterile technique.
- Wash hands and don a cap, face shield mask, sterile gown, and pair of gloves.
- Use a 2% chlorhexidine prep stick to prepare the area bounded by the ear lobe, mandible, chin, neck, and sternal notch past the midline; 2 cm inferior to the clavicle; and 2 cm posterior to the sternal head of the SCM muscle.
  - Preparing a wide area is preferred to facilitate conversion to the ipsilateral internal jugular approach if the subclavian approach is unsuccessful.
- "Square off" (frame) the sterile area with four sterile towels.
- Place the head-to-toe fenestrated sterile drape.
- Find these anatomic landmarks: midportion of ipsilateral clavicle and sternal notch.
- Inject local anesthetic into the skin and surrounding region at the proposed insertion site.
- Ensure all materials needed for catheter placement are in easy reach within the sterile field.
  - Flush all catheter lumens and place caps on all ports except the distal port.
- Insert the needle (beveled edge in caudad direction) with attached syringe into the skin 2 cm inferior to the midportion of the clavicle, directing the needle slightly cephalad toward the clavicle in the direction of the sternal notch.
- "Walk" down the clavicle with the needle until it advances just deep to the inferior surface of the clavicle.
- While applying gentle aspiration pressure on the syringe, continue to advance the needle in the direction of the sternal notch until aspiration of free-flowing, nonpulsatile, venous-colored blood occurs, signaling entry into the subclavian vein.
- Introduce the curved end of a guide wire through the syringe and/or needle into the vein. Never lose control of the distal end of the guide wire.
- Remove the syringe and needle over the guide wire.
- Using a scalpel, make a small nick in the skin at the wire insertion site.
- Place the dilator over the guide wire, and advance the dilator into the soft tissues to establish a tract.
- Remove the dilator, leaving the wire in place.
- Place a catheter (single lumen or multilumen) over the wire into the vein.
  - 16 cm for the right subclavian
  - 20 cm for the left subclavian
- Remove the wire and place a cap on the distal port.
- Aspirate blood via all catheter lumens, and then flush each lumen with sterile saline.
- Secure the catheter to the skin with suture material.
- Place a sterile dressing.
- Clean up and safely discard all sharp objects into the "sharps" receptacle.
- Order a chest x-ray to check the catheter position.
  - Skilled operators may use ultrasound to confirm normal lung sliding and to assess for pneumothorax and catheter tip location

Femoral Vein

- Obtain informed consent from the patient or surrogate decision maker.
- Gather all necessary equipment.
- Perform a "time out" to verify patient, procedure, laterality, and consent.
- Place the patient in the supine position with the ipsilateral thigh in slight abduction.
- Reverse Trendelenburg position may assist vein visualization and access in hypovolemic shock.
- Perform nonsterile ultrasound to confirm patency and depth of the femoral vein and the location of surrounding structures.
- Open the equipment using sterile technique.
- Wash hands and don a cap, face shield mask, sterile gown, and pair of gloves.
- Use a 2% chlorhexidine "prep stick" to prepare an area bounded by the lateral midthigh, medial midthigh, and pubis in the midline, extending 2 cm superior to an imaginary line connecting the pubis and anterior superior iliac spine.
- "Square off" (frame) the sterile area with four sterile towels.
- Place the head-to-toe fenestrated sterile drape.
- Place the ultrasound probe into a sterile sheath with internal conducting gel and position the correct needle guide on the probe.
- Find these anatomic landmarks: pubic tubercle, anterior superior iliac spine, and femoral artery pulse.
- Inject local anesthetic into the skin and surrounding region at the proposed insertion site.
- Ensure that all materials needed for catheter placement are in easy reach within the sterile field.
  - Flush all catheter lumens and place caps on all ports except the distal port.
- While applying gentle aspiration pressure on the syringe under ultrasound guidance, insert the needle at a 90-degree angle into the skin medial to the femoral artery pulse in a short-axis ultrasound view.
  - The femoral vein will be located caudal to the junction of the middle and medial thirds of an imaginary line drawn from the pubic tubercle to the anterior superior iliac spine.
- Continue to apply gentle aspiration pressure to the syringe during needle advancement under ultrasound guidance until the needle is present within the vein on ultrasound and a return of free-flowing, nonpulsatile, venous-colored blood is present.
- Place the curved end of the guide wire through the syringe and/or needle and into the vein. Never lose control of the distal end of the guide wire.

- Using ultrasound, confirm the presence of the guide wire in the femoral vein in both the short and long axes.
- Remove the syringe and needle over the guide wire.
- Using a scalpel, make a small nick in the skin at the wire insertion site.
- Place the dilator over the guide wire, and advance the dilator into the soft tissues to establish a tract.
- Remove the dilator, leaving the guide wire in place.
- Place the catheter (single lumen or multilumen) over the guide wire into the vein.
- Remove the wire and place a cap on the distal port.
- Aspirate blood via all lumens, and then flush each lumen with sterile saline.
- Secure the catheter to the skin with suture material.
- Place a sterile dressing.
- Clean up and safely discard all sharp objects into the "sharps" receptacle.

AFTER THE PROCEDURE

Postprocedure Care

- Obtain a chest x-ray.
  - To confirm the location of the internal jugular and subclavian venous catheter tip at the atriocaval junction
  - To rule out the presence of a hemothorax, pneumothorax, or apical cap
- Inspect the catheter insertion site daily to detect the development of infection.
- Monitor for arrhythmias, as catheter migration may occur.
- Maintain proper local dressing care to minimize complications.
- Access all ports in a sterile manner at all times.

Complications

- Common
  - Cardiac arrhythmias
  - Arterial puncture
  - Hematoma
  - Catheter malposition
  - Venous thrombosis
  - Catheter-related bloodstream infection
- Infrequent
  - Pneumothorax
  - Hemothorax
  - Chylothorax (thoracic duct injury)
    More common with left internal jugular or subclavian vein catheterization
  - Local nerve injury
  - Entanglement with vena cava filter
  - Tracheal perforation
  - Endotracheal tube cuff rupture
- Serious, rare complications
  - Air embolus
  - Cardiac tamponade

Outcomes and Evidence

- Femoral vein catheters have a higher incidence of infectious and thrombotic complications compared with subclavian vein catheters.
- Lowest infection rates are associated with subclavian vein catheters.
- Infection of central venous catheters is diminished by paying careful attention to sterile insertion technique.
- Antibiotic-treated, noncuffed central venous catheters are associated with a lower rate of device-related bloodstream infection than nontreated catheters but a higher rate when compared with PICCs.
- Use of ultrasound to guide insertion is beneficial in reducing mechanical complications and in improving rates of successful cannulation, especially when accessing the internal jugular and femoral vein or when the operators are inexperienced in the mechanics of the procedure.
- For many purposes, PICCs may be more cost-effective and have lower complication rates than centrally inserted venous catheters.
- Deep venous thrombosis caused by PICCs may relate to catheter diameter.

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Arterial Cannulation and Invasive Blood Pressure Measurement

Phillip D. Levin and Yaacov Gozal

Peripheral artery cannulation is one of the most commonly performed invasive procedures in the intensive care unit (ICU),[1] and the resulting arterial line is an integral part of intensive care patient management. Arterial line usage varies according to unit type, patient age, and severity of illness, ranging from approximately 22% of medical ICU patients to over 50% of surgical ICU patients. There are three main indications for arterial line insertion: (1) to allow continuous beat-to-beat monitoring of blood pressure; (2) to provide pain-free, convenient, and repeated access to arterial blood for the assessment of pulmonary and cardiovascular function (including measures of pulse pressure variation and semi-invasive cardiac output measurements using transpulmonary thermodilution); and (3) to provide a source of blood for blood tests as required without the need for repeated venipuncture, including continuous measures of blood chemistry (such as continuous glucose measurement). A review of the relevant anatomy, equipment, and techniques for arterial line placement is provided in this chapter along with some of the more common complications.

SITES OF INSERTION

An arterial line can be inserted into almost any palpable peripheral artery. The most common sites in clinical practice are the radial artery (employed in up to 78% of ICU patients), the femoral artery (employed in up to 45%), and the dorsalis pedis artery. Axillary and ulnar artery cannulations are performed somewhat more rarely; brachial and temporal artery cannulation is not recommended. Cannulation of the carotid arteries is absolutely contraindicated for obvious reasons. Each arterial site has advantages and disadvantages.

The Radial and Ulnar Arteries

The radial artery originates in the antecubital fossa at the level of the neck of the radius as a terminal branch of the brachial artery. The artery runs down the length of the forearm laterally. For the distal part of its course, it is covered only by fascia and skin and lies above the radius, where it is easily palpated. At the level of the wrist the artery winds laterally around the radius and enters the posterior aspect of the hand. It terminates by dividing into the superficial and deep palmar arches, which are anastomosed with the ulnar artery. The radial artery lies near the superficial branch of the radial nerve in its distal course.

The ulnar artery is the other terminal branch of the brachial artery, also originating in the antecubital fossa at the level of the radial neck. It is usually larger than the radial artery. The ulnar artery runs medially along the length of the forearm. As opposed to the radial artery, for most of its course the ulnar artery lies deep to the muscles of the forearm, becoming superficial only toward the wrist. The ulnar artery lies close to the ulnar nerve in its distal course.

When compared with the ulnar artery, the radial artery is superficial for a longer part of its course, is easily palpated above the radius, and is less closely associated with neural structures. It is, however, a smaller artery. The radial artery is cannulated within a few centimeters of the anterior wrist creases, where it lies conveniently over the radius.

Advantages

Advantages of radial artery cannulation include huge experience and safety, peripheral position, double blood supply to the dependent territory (by the ulnar artery), and easy compression in the event of bleeding.

Disadvantages

Disadvantages include technical difficulties because of the small size of the vessel or vasoconstriction (the radial artery pulse may not be palpable when blood pressure is less than 80 mm Hg) and inaccurate blood pressure measurements (when compared with the central circulation).

The modified Allen test has been proposed as a screening tool before radial artery cannulation to ensure the presence of adequate distal collateral circulation. The Allen test has, however, been found to have high interobserver variability and to lack sensitivity and specificity.[2] It is not widely used. Radial artery catheterization for coronary angiography has been compared in patients with normal and abnormal Allen tests with no significant adverse events occurring in patients with an abnormal Allen test.[3] It might be prudent, however, to avoid insertion of an arterial catheter into the radial or ulnar artery when the other artery is known to be absent or occluded.

Positioning for Cannulation

The forearm should be supine and the wrist slightly extended and supported (Video E4.1).

The Axillary and Brachial Arteries

The axillary artery is a continuation of the subclavian artery, beginning at the outer border of the first rib. The artery is surrounded by the cords of the brachial plexus. Its position relative to the other structures

of the axilla varies according to the position of the arm. The artery ends at the inferior border of the teres major muscle, where it becomes the brachial artery. The brachial artery runs down the upper arm to the elbow. Initially, it is medial to the humerus, but distally it spirals anteriorly to end as the radial and ulnar arteries approximately 1 cm distal to the elbow. The brachial artery lies near the ulnar and median nerves in its proximal course and near the median nerve in its distal course.

Advantages

The axillary artery is a large artery, and pressure measurements reflect the central circulation.

Disadvantages

The arm position required for axillary artery cannulation may be contraindicated or difficult for some patients. Care should be taken if a long catheter is used, because its tip might be proximal to the origin of the brachiocephalic artery/left common carotid artery. In this case embolic material from the line (i.e., air bubbles or thrombus) could be introduced into the brain. The risk of line infection may also be higher relative to other sites.

Positioning for Cannulation

For axillary artery cannulation, the arm should be bent at the elbow and raised above the head (abducted and flexed to 90 degrees). The pulse can then be palpated in the axilla.

The brachial artery is punctured where it is palpable medially on the anterior aspect of the elbow. Generally, cannulation of the brachial artery is not recommended, because it is associated with specific and potentially severe complications (see later). Despite this, large case series with low complications rates have been published.[4]

The Femoral Artery

The femoral artery originates as a continuation of the external iliac artery at the level of the inguinal ligament. At the level of the inguinal ligament, it lies midway between the anterior superior iliac spine and the symphysis pubis. Distal to the inguinal ligament, the artery lies medial to the femoral nerve and lateral to the femoral vein and is superficial, being covered only by fascia, fat, and skin. The femoral artery runs down the thigh and terminates as the popliteal artery in the knee.

Advantages

The femoral artery is a large artery that is easier to locate and puncture than the radial artery. Blood pressure measurements reflect central blood pressure, and the femoral artery is palpable at a lower blood pressure than the radial artery. The femoral arterial line has a lower rate of catheter malfunction and greater longevity (compared with the radial artery).

Disadvantages

In obese subjects, adipose tissue and skin folds may create difficulties in the approach to the groin. The skin over the puncture site also can be compromised by chronic inflammatory changes or fungal infections, and the artery itself may be very deep and difficult to locate. The insertion site also may be difficult to keep clean and well dressed. The risk of hemorrhage into the retroperitoneal space (which may initially be undetectable clinically) is unique to this site. Hemorrhage (either retroperitoneal or percutaneous) is also a risk when removing femoral artery catheters, particularly in patients with deranged clotting. The femoral artery is a common site for vascular surgery in the leg, and this represents a strong relative contraindication to arterial cannulation.

Position for Cannulation

In a supine patient, assistance may be required in retracting abdominal and thigh adipose tissue to allow access to the groin.

Dorsalis Pedis

The dorsalis pedis artery begins anterior to the ankle as a branch of the anterior tibial artery. The artery runs distally in the foot between the tendons of the extensor digitorum longus and extensor hallucis longus. It terminates as it turns in to the foot toward the sole between the first two metatarsal bones. During its course over the foot the artery is covered only by fascia and skin and is easily palpable.

Advantages

The dorsalis pedis is an easily accessible, compressible small artery.

Disadvantages

This artery is the most distant from the central circulation. Vasoconstriction can affect the quality of the arterial signal. In addition, the distance from the central circulation may result in an artificially elevated systolic pressure reading that is caused by interaction of the arterial pressure wave on smaller and smaller arteries.

Position for Cannulation

The foot is placed in a neutral position with slight extension of the ankle.

Additional Considerations

From this discussion of relative anatomy, the features of the arteries commonly used for monitoring become clear: all are superficial, covered only by fascia and skin, easily palpable, and easily compressible. The specific artery chosen for insertion of an arterial line should be influenced by the experience of the operator, ease of palpation, contraindications, and limitations in positioning.

After adequate positioning, the chosen arterial line insertion site should be cleaned and sterilized with a solution containing >0.5% chlorhexidine in 70% alcohol. For femoral or axillary artery insertion, maximum sterile barrier precautions should be used—cap, mask, sterile gown, sterile gloves, and full body sterile drapes. For insertion of peripheral artery cannulas, the operator should, at a minimum, don a cap, mask, and sterile gloves and use a small sterile fenestrated drape at the insertion site.[5] Local anesthesia (approximately 1 mL of 1%–2% lidocaine *without epinephrine*) should be infiltrated around the insertion site using a small-gauge (24- to 26-gauge) needle. Epinephrine should be avoided as an additive to the local anesthetic in order to prevent arterial spasm.

EQUIPMENT

Before actually inserting the arterial cannula, the monitoring equipment, cables, arterial line setup, and adhesive tape/sutures should all be prepared and checked. Beyond the arterial cannula, the arterial line setup consists of noncompliant tubing; three-way taps (stopcocks), a pressure-transducing device, a flush system, and the monitor. The arterial cannula is connected to a short length of tubing and then to at least one three-way tap. This tap is used for blood sampling and may also be used for zeroing the setup. The three-way tap is, in turn, connected to the pressure-transducing device, which is connected to the monitor. The pressure transducer is also connected to the flush system. The flush system consists of a bag of intravenous fluid under pressure from which all air has been removed. The fluid bag is compressed to a pressure greater than the arterial pressure using a pressure bag or cuff. The flush system maintains a continuous but slow (3 mL/h) flow of fluid

through the system and into the artery to maintain cannula patency. The arterial line system may include additional three-way taps, connections to other pressure monitoring sites (e.g., central venous pressure), and damping devices as required.

Sets for Arterial Cannulation and Insertion Technique

A multiplicity of arterial cannulation sets exists, falling into three main groups: sets based on a cannula-sheathed needle (equivalent to the normal intravenous catheter) with or without an additional wire, sets based on the Seldinger technique, and sets used for direct arterial cutdown techniques.

The simplest technique for arterial line insertion employs a 20-gauge catheter-over-needle arrangement. A simple 20-gauge intravenous cannula can be used, although catheters specifically made for arterial puncture are available. Such a catheter is suitable for the smaller arteries (radial or dorsalis pedis). After appropriate positioning, the patient's pulse is palpated with the nondominant hand and the cannula inserted at an angle of 45–60 degrees to the skin and into the artery using the dominant hand. The cannula and needle may be advanced until blood flashback is seen in the needle, and then the cannula is threaded into the artery (in a manner similar to intravenous insertion). Alternatively a through-and-through technique can be employed. In this technique, the needle and cannula are inserted directly through both the front and back walls of the artery without seeking blood flashback. The needle is withdrawn partially or fully from the cannula. The cannula is then slowly drawn back until the blood flashback is seen and subsequently threaded into the artery. In the event that blood flashback is not seen, the needle should not be reinserted into the cannula because it may perforate the side or cut off a distal segment.

Occasionally, difficulty may be found in inserting the cannula despite good backflow of blood through it. In this circumstance, the arterial line wire may be of use. The wire fits through the cannula (after the needle has been removed) and may be manipulated into the artery. The wire need only be inserted a few centimeters beyond the catheter tip (into the artery), and the cannula can then be threaded. As a precondition to wire insertion, good backflow of blood must be noted through the cannula, and under no circumstances should the wire be inserted with force, because this can lead to perforation or dissection of the artery.

Some cannula-over-needle sets include a wire that is preconnected to the needle/cannula apparatus. These sets are available for both smaller and larger arteries and represent a combination of the guide wire and Seldinger techniques. The artery is punctured by one of the techniques described earlier using the needle and cannula assembly. Blood flashback is seen in the tube housing the wire. Once blood is seen to return, the wire is advanced through the needle while it is still (at least partially) within the cannula and into the artery. The cannula is then advanced over the wire into the artery.

For larger or deeper arteries (femoral and axillary), sets based on the Seldinger technique are available. Using this technique, the artery is punctured with a needle, the wire is inserted through the needle, the needle is removed, and the catheter is inserted over the wire. This differs from the wire technique described earlier, because the wire is inserted through the needle, and then the needle is removed before the cannula is inserted.

Arterial cannulation can be very challenging, especially in patients with severe peripheral vascular disease or low blood pressure. Under these circumstances, additional equipment may be required to help locate the artery. Both Doppler and ultrasound probes may be useful.

The Doppler probe provides an auditory signal corresponding to blood flow. The characteristic arterial pulse form is easily distinguished from venous blood flow. The point of maximal Doppler response lies directly above the artery and may help in directing the needle to localize the artery.

By using ultrasound with a high-frequency probe the artery may be visualized. On short axis it is seen as a pulsating echogenic (white) ring on cross section. The arterial catheter needle can also be seen on ultrasound (as a straight echogenic line) and can thus be directed into the artery. Needle insertion can be performed either out of plane using the short-axis image or in-plane using the long-axis view. Two recent meta-analyses demonstrated that use of ultrasound increases the chances of first-time success and decreases the time required for insertion.[6,7]

Cutdown techniques are rarely required in adults. This issue for pediatric patients is addressed in Chapter 228.

Once inserted, the arterial cannula should be well fixed to the patient to prevent accidental removal and connected to the flush/pressure transduction system. Consideration can be given to using a sterile semipermeable dressing to cover the insertion site with the addition of adhesive tape. Once the presence of an adequate waveform on the monitor has been confirmed, the next step is to zero the system.

Zeroing

The importance of accurate zeroing cannot be overstated—zeroing problems reflect one of the most common sources of error in pressure-transduction systems. Zeroing has two main functions: the first is to equilibrate the monitor, and the second is to correct for the contribution of the fluid column in the pressure-transduction system between the patient and the pressure transducer.

The pressure transducers in use today are rugged, inexpensive, and accurate. They convert pressure applied from the artery via the fluid-filled tubing to the transducer into electrical energy. The electrical signal generated by the transducer is then amplified in the monitor to produce a waveform on the screen and a numeric measure of blood pressure. The conversion of mechanical pressure into an electrical signal requires an "excitation voltage" to be provided by the monitor to the transducer. The standard responsiveness of the transducer is 5 μV/V excitation voltage/mm Hg, and atypical excitation voltage is 6 V. Therefore the pressure transducer produces 30 μV/mm Hg pressure applied from the artery. Typically, this signal is amplified 1000 times by the monitor, so that for each 100 mm Hg of blood pressure, the monitor output is 3 V. Before their first use, and periodically during their use, the interaction of the excitation current, the transducer response, and the monitor amplification requires resetting—in the first instance to standardize the system and thereafter to compensate for any drift. This calibration is achieved by zeroing or standardizing the measurement to atmospheric pressure, which thereafter is the zero reference point for further measurement. With current semiconductor equipment, calibration to a mercury manometer is not required.

The arterial line is zeroed by exposing the pressure transducer to atmospheric pressure, for example, by turning one of the three-way taps such that it is closed to the patient and the transducer is open to room air. The zero procedure is activated on the monitor and the system left untouched for a few seconds until a flat line appears on the arterial monitor tracing and the monitor reads zero. The three-way tap is then closed to air and opened to the patient, and blood pressure can be measured. The zero point (the three-way tap used for zeroing) can be near to the patient or near to the transducer. It is important to consider that the pressure measured by the monitor will represent the patient's arterial pressure plus any contribution made by the column of fluid in the pressure tubing between the patient and the zero point.

To illustrate this point, consider the change in pressure reading if the pressure transducer is lowered by 100 cm to the floor. In addition to the patient's blood pressure acting on the pressure transducer, a column of water 100 cm long is present and contributes to the pressure

reading. The blood pressure reading is in millimeters of mercury, so it will increase by 100/1.36, or by 73 mm Hg. If the pressure transducer is raised relative to the patient, then the pressure recorded by the monitor will decrease in a similar manner. Appropriate zeroing of the pressure transducer can compensate for these differences. Continuing the example provided earlier, while the transducer is 100 cm lower than the patient, the three-way tap near the patient's radial artery is closed to the artery and opened to room air. The monitor is rezeroed. Now the zero incorporates the contribution made by the 100-cm column of water in the tubing, and when the arterial pressure is measured again, it will once more be accurate. Although this example is extreme, smaller changes in relative position are common; the transducer is attached to the patient at the level of the shoulder while supine. The patient is subsequently repositioned from supine to sitting. The shoulder is raised by 20 cm relative to the femoral artery, and the pressure recorded on the monitor decreases by 20/1.36 = 15 mm Hg. This change might not cause a change of therapy if arterial pressure is being measured. However, if intracranial pressure (ICP) is being measured, for example, a 15 mm Hg inaccuracy in the measurement could be critical. By convention, for arterial pressure measurement, the zero point is set at the height of the right atrium (i.e., the midaxillary line in the supine patient).

Damping

Another potential source of error in the measurement of blood pressure using the arterial line results from the interaction between the arterial pressure wave and the physical properties of the arterial line setup. This interaction can lead to underdamping (resonance or overshoot) and a spuriously high blood pressure reading or overdamping with a spuriously low blood pressure.

The arterial pulse waveform can be described as a summation of component sine waves with frequencies that are mainly in the range of 3–5 Hz. The arterial line set tubing has a natural frequency that is usually greater than 20 Hz. If the natural frequency of the arterial line set is decreased, it can approach the component frequencies of the arterial pulse waveform, and resonance may occur or increase, resulting in underdamping. Resonance/underdamping modulates the pressures measured. The main effect will be an increase in the recorded systolic blood pressure. A decrease in the recorded diastolic blood pressure may also occur, whereas, typically, mean blood pressure will not be affected. Perhaps the most common cause of underdamping is the use of an excessive length of pressure tubing between the arterial insertion site and the pressure transducer. Underdamping also may be a problem when measuring central arterial pressures and in the presence of severe vasoconstriction.

Overdamping decreases the transfer of energy from the artery to the pressure transducer. It results from the absorbance of energy by the fluid contents of the arterial set tubing and the tubing wall itself and from the friction between them. Damping is quantified by the damping coefficient (zeta), a measure of the time required for the system to come to rest after activation. Increased damping decreases the recorded systolic pressure and, to a lesser extent, increases the recorded diastolic pressure; mean pressure is affected the least. Damping is increased by the use of compliant, kinked, or partially occluded tubing and by loose connections and leaks (Box E4.1).

To obtain an accurate measure of the blood pressure from the arterial line, the system must be properly balanced. One method to assess balance uses the "fast flush test." This test is performed by activating the flush device for a few seconds and then releasing it. On activation of the flush device, the pressure measured rises to a plateau. After release, the pressure waveform drops abruptly and small, sharp waves may be seen (Fig. E4.1). In a balanced system, there should be only one such sharp wave. Fig. E4.1A shows a system that is underdamped; there are multiple sharp waves after release of the flush. The reason for the underdamping in this case was the use of an excessive length of pressure tubing. Fig. E4.1B shows the effect of removing the excess length of pressure tubing. Only one sharp wave follows the flush, indicating that the system is now well balanced. An alternative correction that could have been applied (if the tubing length was required) might have been to increase the damping coefficient with the aid of a dampening device. Using this device is similar in effect to introducing a small air bubble into the arterial line tubing; however, its use does not incur the risk of air embolus.

Figures for the natural frequency and damping coefficient of an arterial line setup can be approximated from a tracing of the fast flush test. The natural frequency of the arterial line setup can be calculated from the cycle length of the sharp waves, whereas the damping coefficient can be calculated from the rate at which the waves decline in amplitude. Fig. E4.2 shows an enlargement of the flush release in the underdamped arterial line tracing in Fig. E4.1A and illustrates the calculation. Based on this tracing, the natural frequency was calculated at 22.7 Hz, and the damping coefficient was 0.34. Removal of the

BOX E4.1 Causes of Underdamping (Overshoot) and Overdamping

Causes of Underdamping

Central pressure measurement
Long pressure tubing
Marked vasoconstriction

Causes of Overdamping

Air in tubing
Blood clots
Compliant tubing (not stiff-walled pressure tubing)
Kinked arterial catheter
Leaks in system (hole in tubing)
Loose connections

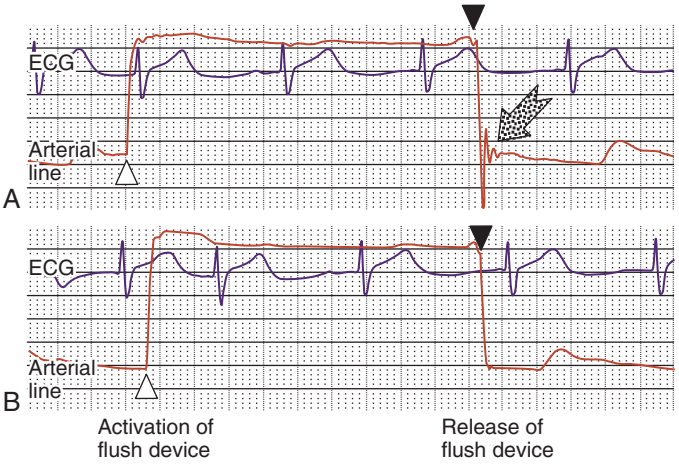

Fig. E4.1 The fast flush test, electrocardiogram (*ECG*), and arterial line tracings. **A,** The underdamping or overshoot with multiple sharp waves after the release of the flush device *(speckled arrow).* **B,** A balanced system, with only one sharp wave after flush release. The *white arrowheads* indicate the beginning of the system flush, whereas the *black arrowheads* represent its termination.

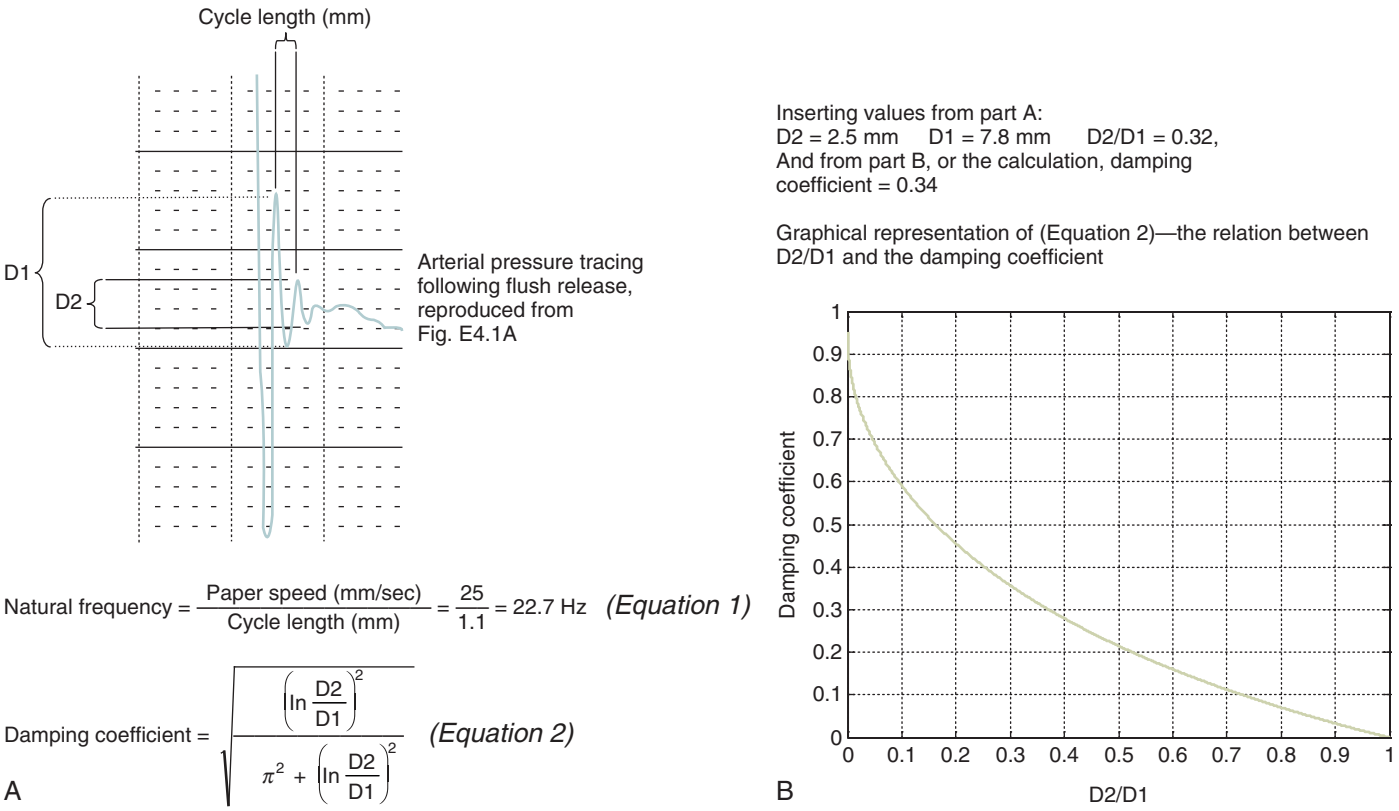

Fig. E4.2 Calculation of natural frequency and damping coefficient. (Adapted from Gardner RM. Direct blood pressure measurement—dynamic response requirements. *Anesthesiology.* 1981;54:227–236.)

excess tubing (producing the tracing in Fig. E4.1B) resulted in a natural frequency of 50 Hz, whereas the damping coefficient was unchanged.

Flush Solutions

To maintain patency and prevent thrombosis of the arterial catheter, it must be continually flushed. Numerous additives have been proposed to achieve this aim, including heparin (the most commonly used), sodium citrate, papaverine, and normal saline. The infusion of heparin through the arterial catheter has been shown to be more effective than normal saline in maintaining patency and/or arterial pressure measurements. However, a recent Cochrane review revealed clinical and statistical heterogeneity in the seven studies and 606 patients included and prevented the definitive demonstration of an advantage to heparin over normal saline.[8] When used, the concentration of heparin in the arterial line flush is usually less than 10 units/mL, with 1 unit/mL being common. Concentrations as low as 0.25 unit/mL, infused at 3 mL/h, are efficacious.

Sodium citrate (1.4% solution) has been suggested as a flush solution that avoids the potential complications associated with the use of heparin and has been found to be equally effective. Papaverine is an additional alternative. Dextrose-containing solutions are not recommended for flushing the arterial line.[5]

The use of flush solutions, although beneficial, is associated with potential complications, mainly in their effect on blood test samples obtained through the arterial line, as described later. However, infusion of the wrong flush solution—including potassium-containing solutions, x-ray contrast, antibiotics, and others—can also lead to complications.[9] Using the wrong solution has been reported in 30% of ICUs.[10]

COMPLICATIONS

The cumulative experience with arterial lines in patients in ICUs is huge; therefore there is a considerable body of literature concerning complications. Overall, major complications are rare—15/17,840 (0.084%) in one study.[11] Complications are associated with the introduction and maintenance of a cannula in the artery and with its use. Common complications have been collected into series, whereas individual case reports describe a wide spectrum of rarer occurrences. The more common complications are described.

Vascular and Local Complications

Vascular and local complications vary from the clinically mild (small hematoma formation, insignificant bleeding) to catastrophic (permanent ischemic limb damage). A summary of 78 studies concerning the incidence rates for vascular and local complications of radial, femoral, and axillary arterial lines has been published and is summarized in Table E4.1.[12] Temporary arterial occlusion is common for all sites; the smaller radial artery is at greater risk than the larger femoral and axillary arteries. Arterial occlusion occurs in part as a result of mechanical obstruction of the artery by the cannula and in part by the formation and propagation of thrombus. Despite its high incidence, arterial occlusion is not detrimental in the majority of cases.[12] The arteries recannulize rapidly (within a week),[13] and permanent ischemic sequelae of arterial cannulation are, fortunately, rare.[12] Attempts have been made to correlate a wide variety of factors with increased risk of arterial obstruction, and some of these are summarized in Box E4.2. The use of Teflon catheters has been associated with a decreased risk of arterial thrombosis, whereas outcome is independent of the age of the patient.

TABLE E4.1 Vascular Complications of Arterial Lines per Site

Site	Temporary Occlusion	Hematoma	Bleeding	Permanent Ischemic Damage	Pseudoaneurysm
RADIAL					
%	19.7	14.4	0.53	0.09	0.09
N	4217	2903	375	4217	15,623
FEMORAL					
%	1.45	6.1	1.58	0.18	0.3
N	688	461	316	1664	2100
AXILLARY					
%	1.18	2.28	1.41	0.2	0.1
N	930	744	711	989	1000

BOX E4.2 Factors Associated With Increased Risk of Arterial Obstruction

- Use of smaller arteries (radial and dorsalis pedis vs. femoral or axillary[12])
- Large catheter size
- Multiple insertion attempts
- Presence of hematoma
- Female sex
- Preexisting peripheral vascular disease
- Prolonged shock
- Use of vasoconstrictor drugs

Catheterization of the brachial artery is generally not recommended because of potentially severe complications. These include forearm ischemia (secondary to mechanical obstruction of the artery by the catheter and/or thrombus), compartment syndrome (described in case reports[14]), and damage to the median nerve (from either ischemia, direct mechanical trauma, or pressure secondary to a hematoma). Anticoagulation has been associated with a number of these complications[14] and represents a relative contraindication.

Despite the widespread recommendation not to cannulate the brachial artery, its use has been reported in 3% of ICU patients and up to 20% of operating room patients.[4] Wider experience has been described in other specialties (e.g., angiography, single puncture for blood gases, and long-term access to the arterial circulation) and provides an indication of potential complication rates. In a study of 10,500 patients undergoing cardiac angiography via the brachial artery, surgical intervention was required for 0.57%, most commonly because of hand ischemia. The incidence of median nerve damage after cardiac catheterization via the brachial artery is 0.2%–1.4%, whereas vascular angiography performed through the brachial artery in 1326 patients was associated with a brachial artery thrombosis rate of 0.28% for men and 1.24% for women.[15] Long-term cannulation of the brachial artery has been described in a study of 225 transbrachial intrahepatic cannulas (in situ for up to 14 months) and was associated with diminished radial pulses in 88 (39%) patients and ischemic symptoms of the forearm in 16 patients (8%). Brachial artery thrombosis had an incidence of 1.7%.

In clinical practice, the territory supplied by an artery that has been cannulated should be closely monitored. Pain, weakness, changes in sensation, pallor, or decreased temperature all suggest compromised arterial blood flow and should prompt the immediate removal of the arterial cannula. Usually removing the catheter will be sufficient to restore adequate blood flow.

Erroneous Blood Test Results

In 2008 the United Kingdom National Patient Safety Agency reported on two deaths related to erroneous results from blood tests obtained from the arterial catheter. In one of these, the arterial flush solution was changed from 0.9% sodium chloride solution to 5% glucose. Arterial blood glucose evaluations increased, and in parallel the insulin dose increased. After the patient lost consciousness, blood was sent to the laboratory, and a glucose concentration of 0.1 mmol/L was detected. The patient never regained consciousness.[9] A second similar case report was published in 2013.[16]

As reflected in these cases, the most common cause of an unreliable blood test result is either dilution or contamination of the sampled blood with flush fluid. In addition to glucose measurements, removal of inadequate "dead space" from the arterial line setup before obtaining blood for hemoglobin estimation may lead to a diluted sample and a falsely low hemoglobin level, and if heparin from the flush solution is introduced into a test of the activated partial thromboplastin time (aPTT), this test will be markedly prolonged. Heparin in higher concentrations may also artifactually decrease the pH and arterial partial pressure of carbon dioxide ($PaCO_2$)? measurements. If sodium citrate is used in the flush solution and inadvertently introduced into blood samples, spurious hypocalcemia and a low pH might be reported along with increased glucose.[17]

The solution to the problem of flush contamination lies in the withdrawal of an adequate dead space of flush solution and diluted blood before obtaining the blood for testing. The interaction between heparin in the flush solution and the measurement of aPTT is particularly problematic and has been repeatedly studied in an attempt to determine the minimum dead-space volume required to obtain a reliable test result.[18] Five to six times the tubing volume from the artery to the sampling three-way tap (i.e., the dead-space volume) should be withdrawn before the blood for this test to obtain a reliable result.

Whether this dead-space volume should be discarded or returned to the patient depends mainly on maintenance of sterility and speed of sampling. Sterility can be maintained using a closed system, such that the dead-space blood is maintained in an internal reservoir. Specially designed systems exist with internal reservoirs; however, a simpler double-tap arrangement has also been described. In this system, an extra three-way tap is added distal (i.e., farther away from the patient) to the sampling port. A syringe is attached to the extra three-way tap. The dead-space blood is drawn into this syringe, and the blood sample is taken from the more proximal (i.e., closer to the patient) tap. After blood sampling, the dead-space blood can be returned.

Blood cultures obtained from the arterial line represent another test in which results might be compromised. The sensitivity of cultures

drawn in this way is similar to or slightly higher than that of blood cultures obtained by venipuncture; specificity, however, is lower.[19,20] The lower specificity presumably reflects introduction of organisms into the culture bottles from the three-way tap or the catheter itself.

Anemia

The ease with which blood specimens can be obtained from the arterial line and the requirement for frequent testing in critically ill patients may lead to the removal of considerable volumes of blood. The effect of an arterial line in increasing blood test use was first reported in 1986. In this study, patients with an arterial line in the ICU had blood drawn 3.4 times per day, leading to blood loss of 41.5 mL per day and a total of 762 mL. This was in contrast to non-ICU patients without an arterial line who had blood drawn 1.1 times per day, 12.4 mL/day, and a total of 175 mL for their whole admission. Despite efforts to reduce iatrogenic blood loss, similar findings were published in 2015.[21] Among 1894 cardiac surgery patients, the median phlebotomy volume remained high at 332 mL (vs. 118 mL for ward patients).[21] Phlebotomy contributes to the development of anemia among ICU patients and has been implicated as a cause for blood transfusions. Relatively simple steps can reduce the blood loss associated with tests. Such steps include return of dead-space blood (as described earlier), use of pediatric-sized sample tubes, communication with the various laboratories to define the minimal blood volume required for various tests,[22] and point-of-care testing. Despite their simplicity, these steps are infrequently employed.[23]

Heparin-Induced Thrombocytopenia

The use of heparin can be associated with a syndrome of thrombocytopenia and thrombotic events usually appearing after approximately 5 days of heparin therapy.[24] Heparin-induced thrombocytopenia (HIT) is thought to be mediated by immunoglobulin G (IgG) antibodies that develop in response to immunization against the heparin/platelet factor 4 (PF4) complex; these are called *HIT antibodies.*[24] The attachment of these antibodies to the heparin/PF4 complex on the platelet surface activates the platelets and induces thrombosis. Both venous and arterial thrombi can occur. The presence of HIT antibodies does not, however, inevitably lead to thrombotic episodes. For example, up to 50% of cardiac surgery patients develop HIT antibodies, but thrombotic events are relatively rare (2%–3%).[25] The diagnosis of the HIT syndrome is therefore based on the presence of the antibodies, thrombocytopenia, and thrombotic events.[24]

The overall incidence of this syndrome is reported to be approximately 5%. It is more common in women than in men[24] and in surgical as compared with medical[26] or obstetric patients[27] and is also more common after the use of unfractionated heparin than low-molecular-weight heparin.[24] A single dose of heparin is sufficient to induce HIT,[28] and the presence of as little heparin as that found bound to heparin-coated central venous catheters may be sufficient to sustain the immune response. The development of HIT antibodies has been linked with the administration of heparin in intravascular device flushes and also with low doses of heparin used in arterial flush solutions.

Treatment for HIT syndrome includes the cessation of administration of all sources of heparin, including those in the line flush solutions. The use of other anticoagulants for thrombotic episodes is recommended. Removing heparin from flush solutions also may be indicated in the presence of HIT antibodies and thrombocytopenia before any thrombotic events.[24]

After the decline in HIT antibody levels, the short-term use of heparin for certain indications (e.g., cardiac surgery) is considered acceptable.[24] It is prudent, however, to avoid heparin in the arterial line for patients with a history of HIT until further evidence of the risk of repeated episodes of HIT becomes available.

Infection

A patient may develop a bloodstream infection from the arterial line by one of three main routes. Infections have been introduced via infected equipment, such as reusable transducer domes or infected flush solutions; however, with the advent of disposable equipment and improved flush systems, the significance of this route of infection has declined. Two potential routes of infection remain: from the skin puncture site along the catheter and through the three-way taps.[5,29] The predominant organisms associated with arterial line infection are gram-positive cocci (*Staphylococcus aureus* and *Staphylococcus epidermidis*), although gram-negative rods may also be found.[13]

Defining a precise rate of infection for the arterial line is not straightforward, because a multiplicity of definitions of catheter-related bloodstream infections is used in different studies, and variables have not been standardized among studies. Clinical, research, and surveillance criteria exist for defining catheter-related infection. Clinical criteria include presence of signs of infection (e.g., fever, increased white blood cell count) associated with an arterial line in place longer than 96 hours with signs of local infection and no other source of sepsis. Whereas these criteria might be useful in clinical practice, they are too broad for research purposes. Surveillance criteria, such as those defined by the Centers for Disease Control and Prevention (CDC), include any significant bloodstream infection in the presence of a vascular catheter and no other source of sepsis.[5] This definition overestimates the incidence of catheter-induced bloodstream infection because it includes bloodstream infection from occult sources other than intravascular lines.[5] Research criteria can include the use of arterial line tip cultures (often quantitative or semiquantitative), usually correlated to venous blood culture results. Combinations of these definitions have been employed.[13]

With regard to arterial line variables, virtually every aspect of line insertion and maintenance (for either central venous or arterial catheters) has been examined for an effect on infection rate. Factors that have been evaluated include type of skin preparation solution used,[30] insertion site, dressing type and care,[5,29,31] arterial catheter length, site of insertion, catheter material, type of flush solution, and frequency of set changes (Box E4.3). Consistency is not found in the results of all these studies, and not all these factors have been standardized from study to study, possibly confounding direct comparisons.

Despite this variability, a meta-analysis reported that the rate of bloodstream infections related to arterial lines was 1.7 infections/1000

BOX E4.3 Factors Potentially Associated With a Change in the Infectious Risk of the Arterial Line[5]

Increased Risk

Cutdown technique versus percutaneous insertion
Duration of cannulation >96 hours
Axillary artery site
Frequent arterial line set changes

Decreased Risk

Teflon catheters (vs. polyvinyl chloride)
Heparin (in central venous pressure and pulmonary artery catheters)
Use of chlorhexidine-containing skin preparation solutions
Factors not associated with a change in infectious risk
Femoral versus radial artery insertion site
Dorsalis pedis versus radial artery insertion site[13]
Duration of catheterization >96 hours
Systemic antibiotic prophylaxis before insertion

catheter-days and that 1.5/100 arterial catheters was found to cause a bloodstream infection.[32] These rates compared with 2.7 infections/1000 catheter-days and 3.6 infections/100 catheters for unmedicated central venous catheters (CVCs), 0.2 and 0.2 for antiseptic-coated CVCs, and 2.5 and 4.3 for antibiotic-coated CVCs.[32] The implication is that the infection rate associated with arterial catheterization is higher than generally assumed and may be higher than for the newer types of CVCs.

The CDC summarized these diverse findings into these recommendations: use the radial, brachial, or dorsalis pedis sites rather than femoral or axillary arteries; use a minimum of cap, mask, sterile gloves, and a small sterile fenestrated drape for peripheral artery insertion and full sterile barrier precautions for axillary and femoral sites; use >0.5% chlorhexidine in 70% alcohol for skin preparation; do not change arterial catheters routinely; change the pressure monitoring sets and transducers every 96 hours; and do not use dextrose in the flush solution.[5] Despite these recommendations, and particularly the requirement for sterile precautions, less than half of physicians replying to a web-based survey adhered to them, indicating a need for education surrounding arterial catheter insertion.[33]

In clinical practice, it is unlikely that an arterial cannula present for less than 96 hours is the cause of an infection. If the arterial line has been present for more than 96 hours and no other source of sepsis is identified, strong consideration should be given to removing or replacing the arterial catheter. The presence of redness or pus at the arterial cannula introduction site should further increase the index of suspicion of an arterial line–related infection.

Finally, in view of these potential complications, the benefit of arterial cannulas in the ICU has begun to be questioned. Needless to say, there are no randomized controlled studies showing mortality benefit or harm from arterial cannulation. A recent retrospective study in a well-defined but limited population of hemodynamically stable patients with respiratory failure showed no difference in 28-day mortality.[34] This study has led to calls to reassess the necessity for arterial cannulation in the ICU population in a similar manner to the assessments performed on pulmonary artery catheters.

KEY POINTS

- The common sites of arterial line insertion are the radial, femoral, and dorsalis pedis arteries. These arteries are superficial; covered only by skin, fascia, and fat; and are easily compressible.
- The arterial line can be inserted using a simple catheter-over-needle arrangement (with or without a guide wire) or a set based on the Seldinger technique.
- Guide wires should only be used when backflow of blood is present to avoid arterial damage.
- Doppler or ultrasound can be helpful for difficult line insertion.
- Errors in pressure measurement can arise from incorrect zeroing, overshoot, or damping.
- When zeroing, the height difference between the arterial puncture site and the transducer must be taken into account.
- Overshoot and damping affect the systolic blood pressure more than the diastolic or mean pressure.
- The fast flush test can be used to assess underdamping or overdamping.
- Low-concentration heparin is the most common arterial line flush solution. Sodium citrate, papaverine, and saline have been used.
- Arterial obstruction is very common after catheter insertion, although rarely detrimental.
- Obstruction may be mechanical from the catheter or result from thrombosis.
- Small arteries, female gender, and shock are risk factors for thrombosis.
- Pain, weakness, changes in sensation, pallor, or decreased temperature should prompt immediate catheter removal.
- The majority of blood tests obtained from the arterial line will be accurate.
- The type of flush solution used may interfere with certain tests.
- Particular care should be taken when interpreting the aPTT and blood culture results in samples drawn from the arterial line.
- Five to six times the dead-space volume might be required for accurate tests, which may be reinfused with appropriate precautions.
- Anemia can result from the volumes of blood drawn from the arterial line. Simple steps can reduce this blood loss.
- HIT is a syndrome defined by thrombocytopenia and thrombotic events in the presence of PF4 complex antibodies.
- Even very small doses of heparin can induce or maintain HIT. All sources of heparin should be removed if HIT is suspected, including from arterial line flush.
- The rate of bloodstream infections related to the arterial line has been estimated to be 1.7 per 1000 catheter-days, whereas 1.5 in 100 arterial catheters cause infection.
- Insertion technique, duration of cannulation, site, insertion site, and frequency of set changes have all been related to an increased infection risk.
- Comparisons of studies relating to infectious risk are difficult because of differing definitions of infection and study methodology.
- The CDC recommends the following: Use a >0.5% chlorhexidine in 70% alcohol solution for skin cleaning, do not change arterial catheters routinely, change the pressure monitoring sets and transducers every 96 hours, and do not use dextrose-containing flush solution.

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Bedside Pulmonary Artery Catheterization

Jean-Louis Vincent

BEFORE THE PROCEDURE

Indications

- Need for continuous monitoring of pulmonary artery (PA) and right atrial (RA) pressures, cardiac output, and mixed venous oxygen saturation (SvO_2), providing that:
  - The data collected will help in the management of the patient
  - The same measurements cannot be reliably obtained by a less invasive method

Contraindications

- Absolute contraindications:
  - Tricuspid or pulmonary valve endocarditis
- Relative contraindications:
  - Tricuspid or pulmonary valve mechanical prosthesis
  - Right heart mass (thrombus and/or tumor)
  - Complete left bundle branch block (risk of complete heart block)

Equipment

- Sterile gowns, gloves, and mask
- 8F to 9F gauge introducer
- Sterile saline solution for flushing
- Volume-limited syringe for pulmonary artery catheter (PAC) balloon
- Pressure monitor transduction system and connector tubing

ANATOMY

The inflated balloon of the PAC facilitates the catheter progression through a branch of the PA. The distal lumen of the PAC measures the pressure downstream. It is assumed that there is a continuous column of blood between the distal lumen and the left ventricle (LV), and therefore the PA balloon-occluded pressure (PAOP) is equal to left ventricular end-diastolic pressure (LVEDP). PAOP reflects the pressure where the nonflowing blood (in the obstructed vessel) joins the blood flowing from the nonoccluded branches of the pulmonary artery. PAOP is actually intermediate between pulmonary capillary pressure and left atrial (LA) pressure. There are conditions, however, in which this theoretical continuous column of blood is interrupted, and in these circumstances PAOP no longer reflects LVEDP.

PROCEDURE

See Video E5.1.

- Check the patient's electrocardiogram (ECG), coagulation profile, and serum electrolyte panel. One should consider correcting major clotting disorders. If the patient already has a temporary pacemaker, it may be better to place the catheter under radiographic guidance to avoid dislodging the pacemaker.
- Inflate the catheter balloon as a test before catheter insertion.
- Connect the distal lumen to the pressure-monitoring system, and flush all lumens with sterile saline solution.
- Zero-reference the pressure transducer to the mid-chest position.
- Slide the protective sleeve onto the catheter to maintain sterility for further manipulations.
- Place the sterile field.
- Give local anesthesia.
- Insert the introducer into a central vein, preferably the internal jugular or subclavian, using the Seldinger technique.
- Pass the catheter through the hemostatic valve of the introducer.
- Inflate the balloon once the catheter tip has passed about 15 cm.
- Advance the catheter for another 15 cm. It should pass into the right ventricle (RV) and give an RV pressure waveform (Fig. E5.1).
- Advance the catheter farther to pass into the PA and finally to obtain a PAOP waveform.
- Once a PAOP waveform has been obtained, deflate the balloon to return to the PA waveform.
- Once the catheter is in place, check the position with a chest radiograph. In the vast majority of cases, the tip is in the right lung. The tip should be within 2 cm of the cardiac shadow.
- All pressures should be measured at end expiration, when alveolar pressure should be closest to atmospheric pressure.

Procedural Precautions

- Always have the PA trace displayed on the monitor.
- Never withdraw the catheter without first deflating the balloon.
- Do not insert large lengths of catheter without observing a pressure change, because this maneuver may lead to looping and knotting of the catheter.
- There may be difficulties in reaching the RV or PA as a result of RA or RV dilatation, tricuspid regurgitation, or abnormalities of the central veins. An option may be to advance the catheter with the balloon partially deflated during inspiration, repositioning the patient in a head-up or right lateral position, or flushing the catheter with iced saline to make it more rigid.
- If the PAOP trace is obtained when the balloon is inflated with less than 1 mL of air, or if there is a progressive elevation of pressure when the balloon is inflated ("overwedging"), the catheter tip is too advanced and should be withdrawn by a few centimeters to decrease the risk of PA rupture/infarction.

AFTER THE PROCEDURE

Postprocedure Care

- The PAC can be kept in situ for several days but should be removed as soon as it is no longer required for patient care.
- Balloon rupture can be identified by failure to wedge and failure of the syringe plunger to spontaneously deflate the balloon.

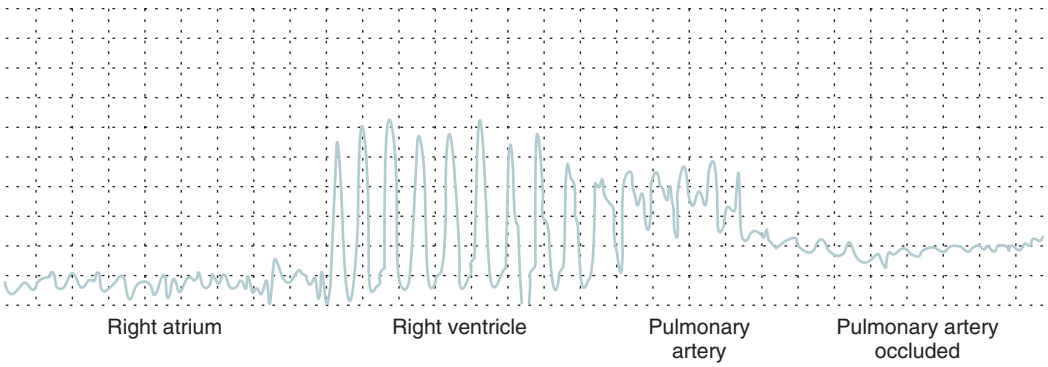

Fig. E5.1 Pressure Traces as the Pulmonary Artery Catheter is Advanced.

Interpretation of Measured Pressures

See also Table E5.1.

- The PA waveform has a systolic and diastolic pressure with a dicrotic notch corresponding to closure of the pulmonary valve.
- The PAOP, like the central venous pressure (CVP), has a venous waveform with a, c, and v waves corresponding to LA contraction, closure of the mitral valve, and passive LA filling, respectively.
- The a wave coincides with the point of maximal filling of the LV and is therefore the value that should be used for measurement of LVEDP. A large-amplitude a wave with an increase in measured PAOP suggests LV ischemia and decreased ventricular compliance.
- A large v wave on the PAOP trace represents mitral regurgitation or an acute volume load to the LA, as occurs with septal rupture. The PAOP level should be measured without consideration for this v wave.
- The RA pressure waveform can look like an RV waveform if there is significant tricuspid regurgitation.
- In cardiac tamponade, RA pressure and PAOP are high and similar, as they equilibrate with pericardial pressures.
- A "dip-and-plateau" waveform may be seen in the RV pressure tracing in constrictive pericarditis, restrictive cardiomyopathy, RV infarction, and massive pulmonary embolism. This pattern is caused by impaired ventricular filling during diastole.

Measurement of Cardiac Output With the PAC

- Cardiac output is measured using thermodilution.
- Measurement is based on the *indicator dilution principle:* when an indicator substance is added to a stream of flowing blood, the flow rate is inversely proportional to the mean concentration of the indicator at a downstream site. In the case of thermodilution, the indicator used is temperature, using a thermal filament to generate heat (warm thermodilution).
- The old technique included bolus injections of 5% dextrose solution or saline injected through the proximal port of the PAC. The thermistor proximal to the balloon then recorded the temperature change in the PA, and a temperature-time curve was displayed.
- Today, catheters provide a semicontinuous method in which a thermal filament is mounted on the PAC 14–25 cm from the tip. The filament intermittently generates pulses of heat, and the temperature change is recorded by the thermistor in the PA. These pulses of heat are pseudorandom to minimize the influence of other sources of temperature change such as infusions or respiratory fluctuations. The cardiac output is updated every 30–60 seconds and is time-averaged over the previous 3–6 minutes.

Complications

Complications that are unique to the PAC and not just the result of insertion of a central venous catheter can be divided into those caused by placement and the longer-term complications caused by its presence:

- Placement
  - Common
    - Arrhythmias, most commonly premature atrial or ventricular contractions that are self-limiting and can occur on insertion or withdrawal of the catheter.
  - Rare
    - Knotting of the catheter; a knot generally can be removed by placing a guide wire through the PAC to undo the loop or by pulling the loop tight against the introducer sheath and removing the whole unit.
    - Tricuspid pulmonary regurgitation or chordae tendineae rupture can occur if the catheter is withdrawn with the balloon inflated.
- Presence of the catheter
  - Common
    - Arrhythmias, most commonly premature atrial or ventricular contractions that are self-limiting and can occur on insertion or withdrawal of the catheter.
    - Catheter-related infections.

TABLE E5.1 Interpretation of the Measured Pressure Variables

CVP/RAP	PAP	PAOP	Interpretation
Low/normal	Low/normal	Low/normal	Normal
Low/normal	High	High	Left heart failure (good right heart function)
Normal/high	High	Low	Pulmonary hypertension (e.g., COPD, ARDS, pulmonary embolism)
High	High	High	Hypervolemia (high CO) Global heart failure (low CO) Tamponade (low CO)

ARDS, Acute respiratory distress syndrome; *CO,* cardiac output; *COPD,* chronic obstructive pulmonary disease; *CVP,* central venous pressure; *PAOP,* pulmonary artery occlusion pressure; *PAP,* pulmonary artery pressure.

- Rare
  - Pulmonary infarction caused by catheter-related thromboembolism, obstruction of the pulmonary blood flow by the catheter tip, or prolonged inflation of the balloon. It is usually without consequences.
  - Endocarditis.
  - PA rupture occurs in less than 0.1% of cases but is associated with a mortality of greater than 30%. Warning signs include hemoptysis, with shadowing on the chest radiograph. Diagnosis is confirmed by pulmonary angiography. Treatment consists of embolization or thoracotomy. Factors increasing the risk of rupture include pulmonary hypertension, advanced age, hypothermia, coagulation disorders, and distal positioning of the catheter.

KEY POINTS

- Benefits of bedside PAC remain controversial, and insertion of a PAC cannot, per se, improve patient survival.
- PACs should not be inserted routinely but only in patients in whom the data collected will help in the patient's management and the same measurements cannot be obtained by a less invasive method.
- To be beneficial, data from the PAC must be collected, interpreted, and applied correctly.

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Cardioversion and Defibrillation

Raúl J. Gazmuri

BEFORE THE PROCEDURE

Indications

- Emergency re-establishment of an organized electrical rhythm
  - Hemodynamically unstable polymorphic ventricular tachycardia
  - Ventricular fibrillation
  - Pulseless ventricular tachycardia
  - Narrow or wide QRS complex tachycardia (ventricular rate >150) associated with hemodynamic instability, chest pain, or pulmonary edema
- Elective reestablishment of sinus rhythm
  - Atrial fibrillation
  - Atrial flutter
  - Hemodynamically stable ventricular tachycardia unresponsive to medical treatment
  - Others

Contraindications

- Specific advance directives (e.g., do not attempt resuscitation for cases of ventricular fibrillation)
- Digitalis toxicity–associated tachycardia
- Sinus tachycardia caused by various clinical conditions
- Rhythms not responsive to electric shock (e.g., multifocal atrial tachycardia)
- Atrial fibrillation or atrial flutter without proper anticoagulation or exclusion of atrial thrombi

Equipment

- Automated external defibrillator or manual defibrillator
- Proper age-adjusted pads or paddles

ANATOMY

The heart is located behind the sternum. Its base is at the level of the third intercostal space immediately to the right of the sternum, and its apex is at the level of the fifth intercostal space inferior and usually just medial to the nipple. External cardioversion or defibrillation is attempted by delivering one or more electric shocks through the chest cavity for the purpose of passing an electric current of sufficient energy through the heart muscle to fully depolarize the atria (e.g., atrial fibrillation or atrial flutter) or the ventricles (e.g., ventricular fibrillation or ventricular tachycardia). Cardioversion should enable the natural or artificial cardiac pacemaker to resume control of the cardiac rhythm. Electrodes (paddles or pads) can be positioned on the anterior chest wall, with one electrode below the right clavicle lateral to the sternum and the other electrode below the breast tissue along the midaxillary line. Electrodes (e.g., pads or paddles that are more difficult) can also be positioned in an anteroposterior position, with the anterior electrode placed over the precordium and the posterior electrode at the left infrascapular location. For internal cardioversion or defibrillation, specially designed paddles are applied directly to the epicardial surface of the ventricles.

PROCEDURE

See Videos E6.1 and E6.2.

For external elective cardioversion, many of the following steps may have to be shortened or circumvented in hemodynamically unstable patients (especially if unconscious), requiring rapid termination of life-threatening arrhythmia (e.g., ventricular fibrillation or pulse ventricular tachycardia as part of cardiopulmonary resuscitation).

- Admit the patient to an appropriately equipped hospital area with the capability for monitoring cardiac rhythm, oxygenation, and vital signs, along with airway management and cardiopulmonary resuscitation.
- Fast the patient overnight or for at least 6–8 hours.
- Establish vascular access.
- Obtain an electrocardiogram.
- For sedation, consider using a short-acting anesthetic agent (e.g., midazolam, propofol, or etomidate) under the care of an anesthesiologist or similarly privileged anesthesia provider and adequate supportive personnel. An alternative to anesthesia is moderate sedation, in which the patient maintains consciousness but in a somnolent state. This has the advantage that it can be given by trained physicians without an anesthesiologist present.
- Attach monitor leads to the patient, and ensure proper display of the patient's rhythm.
- Place electrodes properly separated (as described under "Anatomy"). Apply coupling gel if using paddles; avoid smearing the gel over the chest wall to prevent current traversing superficially through the chest. In patients with permanent pacemakers or implantable cardioverter-defibrillators, place electrodes away from the device generator to avoid device malfunction. Consider reevaluating pacing thresholds in patients with permanent pacemakers and interrogation of implantable cardioverter-defibrillator function after cardioversion.
- Engage the synchronization mode, and identify markers on the R waves indicating adequate R-wave recognition. If necessary, adjust the gain of the monitor until markers appear on each R wave.
- Select the energy level to deliver the necessary current based on the patient's waveform, age, and arrhythmia. Organized rhythms with a simple reentry circuit (e.g., atrial flutter and monomorphic ventricular tachycardia) usually require less current than more complex rhythms (e.g., atrial and ventricular fibrillation).
- Press the charge button on the unit or paddles.

- If using paddles, apply approximately 12 kg pressure to each paddle.
- Press the discharge button on the unit or paddles simultaneously.
- Check the monitor. If the arrhythmia persists, increase the energy level according to the protocol for the specific rhythm.
- Reset the synchronization. Most units default to the unsynchronized mode, allowing immediate defibrillation if ventricular fibrillation ensues.
- Repeat the shock until the conversion of the arrhythmia or completion of the protocol.
- Deliver unsynchronized shocks only for ventricular fibrillation or pulseless ventricular tachycardia.

AFTER THE PROCEDURE

Postprocedure Care

- Obtain an electrocardiogram.
- Assess hemodynamic and respiratory status.
- Observe the patient until the recovery from anesthesia or sedation is complete.
- Consider hospital discharge if the procedure was elective.

Complications

- Cardioversion and defibrillation are relatively safe procedures with infrequent complications that may include:
  - Induction of ventricular fibrillation if the electric shock is improperly synchronized
  - Transient conduction abnormalities
  - Myocardial dysfunction (after high-energy and repetitive delivery of electric shocks)
  - Release of cardiac enzymes
  - Pulmonary edema
  - Embolization of thrombi formed within the cardiac chambers (e.g., atrial fibrillation and flutter)
  - Respiratory depression associated with anesthesia or sedation

KEY POINTS

- Sinus rhythm will be restored in a high percentage of patients.
- Underlying conditions may predispose certain patients to a recurrence of arrhythmias.
- Early defibrillation of ventricular fibrillation is associated with improved survival.

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Transvenous and Transcutaneous Cardiac Pacing

Raúl J. Gazmuri

BEFORE THE PROCEDURE

Indications

- Treatment of symptomatic bradycardia
  - Sinus bradycardia
  - Second-degree or third-degree atrioventricular block
- Prophylaxis
  - Bradycardia-induced ventricular tachyarrhythmias (e.g., torsades de pointes)
  - Increased risk of advanced atrioventricular block (e.g., acute myocardial infarction, infective endocarditis, surgery in patients with underlying conduction defects)
- Overdrive pacing for termination of tachyarrhythmias
  - Supraventricular tachycardia
  - Ventricular tachycardia
- Improving hemodynamic function
  - Sequential atrioventricular pacing

Contraindications

- Specific advance directives (e.g., do not attempt resuscitation for cases of pulseless electrical activity)
- Asymptomatic bradycardia
- Severe hypothermia (risk of ventricular fibrillation)

Equipment

- Pacing catheter with pulse generator
- Transcutaneous electrodes with pacing unit (integrated with current cardioverter-defibrillators)

ANATOMY

The heart is located behind the sternum. Its base is at the level of the third intercostal space immediately to the right of the sternum, and its apex is at the level of the fifth intercostal space inferior, usually just medial to the nipple. Transcutaneous pacing can be performed by delivering electric impulses through the chest cavity to "capture" and drive the electrical activity of the heart. Electrodes can be placed on the anterior chest wall, with one electrode below the right clavicle lateral to the sternum and the other electrode below the breast tissue along the midaxillary line. Electrodes can also be placed in an anteroposterior configuration, with the anterior electrode placed over the precordium and the posterior electrode at the right infrascapular location. For transvenous pacing, the pacing catheter can be advanced through the brachial (antecubital), femoral, internal jugular (preferably right), subclavian (preferably left), or the right subclavian via supraclavicular access (experienced practitioner).

PROCEDURE

Transvenous Temporary Pacing

See Video E7.1.

- Admit the patient to an appropriately equipped hospital area with the capability for monitoring cardiac rhythm, oxygenation, and vital signs, along with airway management and cardiopulmonary resuscitation.
- Obtain a 12-lead electrocardiogram (ECG).
- Attach monitor leads to the patient, and ensure proper display of the patient's rhythm.
- Perform the procedure under fluoroscopy, if available and time permits; otherwise, use the ECG and rhythm to guide placement.
- Establish vascular access under local anesthesia and full sterility, advancing a proper-size introducer sheath.
- Select a pacing catheter contingent on approach. Catheters for use under fluoroscopy are semirigid (usually made of woven polyester) to facilitate maneuvering into position. Catheters designed for blind placement have a balloon at the tip to be floated into position. Transvenous pacing can also be accomplished using multipurpose pulmonary artery catheters built with up to five electrodes for right atrial and right ventricular pacing.
- Blind placement using a balloon-tipped catheter can be guided by the ECG. A V_1 lead of a conventional ECG is connected to the distal pole (cathode) of the pacing catheter and used to monitor a unipolar intracavitary electrogram. The catheter is floated, seeking the display of a right ventricular intracavitary electrogram point at which the balloon can be deflated, and the catheter advanced a few centimeters to position its tip in the right ventricular apex. Endocardial contact is confirmed by the development of an "injury" current characterized by prominent ST-segment elevation. The pacing electrode is connected to the pulse generator and used in the unipolar or bipolar configuration.
- Another, more practical, approach (which is preferred in emergency situations) is to advance the pacing electrode into the right ventricle and turn the pulse generator on in the asynchronous mode at a rate that exceeds the native rate. The pacing current is set between the default and maximum output, and the pacing electrode is maneuvered until capture occurs.
- A defibrillator should be available during insertion and afterward because life-threatening ventricular tachyarrhythmias may develop, especially if the pacing lead moves within the ventricular cavity.
- Leave a sterile sleeve around the catheter (available with most introducer kits) to facilitate subsequent repositioning if required.
- Obtain an anteroposterior and lateral chest x-ray to verify proper placement and exclude complications.

- Set pacing options as follows:
  - Determine the pacing threshold, and set the pacing output. For this purpose, set the pacemaker rate to exceed the spontaneous heart rate by 10–20 beats/min and the output to a level expected to capture 100% of the beats (i.e., 6 mA). Capture is verified on the ECG by identifying the presence of a spike (pulse) followed by a wide QRS complex. The output is reduced gradually until beats are no longer captured and then increased again to identify the minimal level at which 100% of the beats are paced; this is the threshold output. This threshold level should be less than 1 mA for ventricular pacing and less than 2 mA for atrial pacing in the unipolar and bipolar configurations; otherwise, the lead must be repositioned. The output is set at about three times the threshold level for reliable capture.
  - Set sensitivity (range: 0.5–20 mV), allowing the native R wave to inhibit the pacemaker impulse when the generator is set in synchronous mode. The output is first set to its minimal level (e.g., 0.1 mA) and the pacing rate to a value below the spontaneous heart rate. Starting from the maximal sensitivity (the lowest value; i.e., 0.5 mV), gradually decrease the sensitivity (increasing its value) until the unit stops sensing the R wave. For reliable inhibition, the sensitivity is set at about three times the sensitivity threshold (e.g., if the threshold is 3 mV, the level is set at 1 mV).
  - The pacing rate for bradyarrhythmias is set according to physiologic needs, usually between 60 and 75 beats/min. Higher rates (800 beats/min) are available for overriding the pacing of ventricular or supraventricular tachyarrhythmias.
  - Sequential atrioventricular pacing requires the placement of an additional lead or the use of a multipurpose pulmonary artery catheter along with a dual-chamber pulse generator. The individual chamber specifications for dual-chamber generators are similar, with the option of setting the AV pacing interval between 20 and 300 msec.

Transcutaneous Temporary Pacing

See Video E7.2.

- Transcutaneous pacing is noninvasive and can be used in emergency settings with ease and minimal delay while preparing for more definitive therapy. Alternatively, it can be used prophylactically.
- Pacing is limited to the ventricles (with minimal capability for atrial pacing), capture is not always attained, and tolerability may be poor.
- Place electrodes on the anterior chest wall or in an anteroposterior configuration, as described under "Anatomy." Place the negative electrode (i.e., cathode) anteriorly, close to the heart (typically over the palpable cardiac impulse or centered on a V_3 lead) to minimize the capture threshold. Place the positive electrode (i.e., anode) over the upper right region of the chest or the posterior chest wall between the bony spine and the inferior border of either the left or right scapula.
- Determine the pacing threshold as for transvenous pacing (described earlier), bearing in mind that the pacing threshold is much higher (20–140 mA), particularly in patients with emphysema and pericardial effusion and in patients undergoing positive pressure ventilation. The pacing output is set 5–10 mA above the threshold. Pulse generators are designed to deliver high current levels (200 mA) with a longer pulse duration (20–40 msec) to facilitate capture and minimize patient discomfort.
- Ensure that capture occurs by demonstrating coincident pulse generation; do not rely on the ECG capturing artifacts from the skeletal muscle activity.

AFTER THE PROCEDURE

Postprocedure Care

- Obtain an ECG.
- Assess hemodynamic status.
- Monitor native and paced rhythms.
- Establish etiology, and institute definitive treatment.

Complications

- Pacemaker malfunction, defined as the failure to sense, capture, or both
- Ventricular dysrhythmias at the time of insertion
- Myocardial perforation with risk of cardiac tamponade
- Diaphragmatic stimulation
- Complications related to the vascular access (e.g., phlebitis, pneumothorax, arterial puncture, brachial plexus injury, pulmonary embolism, and sepsis)

KEY POINTS

- Effective in pacing at the desired heart rate
- Transvenous pacing is more effective than transcutaneous pacing (lower capture rate)
- Lack of effectiveness for treatment of cardiac arrest caused by asystole or pulseless electrical activity
- Temporary measures pending the resolution of the rhythm abnormality or permanent definitive pacemaker placement

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Ventricular Assist Device Implantation

Robert L. Kormos

BEFORE THE PROCEDURE

Indications

- Postcardiotomy failure (left ventricular assist device [LVAD])
  - Elevated left atrial pressure (LAP) and cardiogenic shock despite inotropic support and intraaortic balloon pump (IABP)
    - LAP >25 mm Hg
    - Cardiac index (CI) <2 L/min/m^2
    - Severe left ventricular (LV) dysfunction on echocardiogram
    - Intractable ventricular arrhythmias
    - Ongoing myocardial ischemia despite revascularization
- Postcardiotomy failure (bilateral ventricular assist device [BiVAD])
  - Evidence of an elevated central venous pressure (CVP; >9 mm Hg) despite pulmonary afterload reduction
  - Evidence of severe right ventricular (RV) dysfunction on echocardiogram
  - Inability to provide adequate blood flow to fill the LVAD (if an LVAD is in place)
- Bridge to cardiac transplantation
  - Failure of optimal medical therapy that increases the risk of compromised life or end-organ function while awaiting cardiac transplantation
    - CI <2 L/min/m^2
    - Mixed venous oxygen saturation <50% on optimal medical therapy
    - Ventricular arrhythmias
    - Severe symptoms at rest
    - Need for multiple inotropic agents
    - Lack of response to diuretic medications, with a rising creatinine
    - Pulmonary artery hypertension
    - Cool and constricted extremities reflective of poor perfusion
    - Low blood pressure, resting tachycardia, rales, and/or distended neck veins
    - Laboratory evidence of prerenal azotemia, hepatic dysfunction, or coagulopathy
    - Requirement for supplemental oxygen
- Bridge to bridge: in conditions of cardiogenic shock when indications for cardiac transplantation are not yet met but are potentially attainable
- LVAD versus BiVAD
  - BiVADs should be considered for:
    - Intractable ventricular tachycardia or fibrillation
    - Cardiogenic shock requiring resuscitation with extracorporeal membrane oxygenation (ECMO)
    - Cardiogenic shock with multiorgan failure
    - Pulmonary edema despite maximal medical therapy
    - Chronic RV failure with ascites, low pulmonary artery pressure, severe hepatic or renal dysfunction, and tricuspid insufficiency
    - Severe acute respiratory distress syndrome
    - Giant cell myocarditis
    - Large anterolateral myocardial infarction with involvement of the anterior right ventricle
    - RV infarction
- Destination therapy
  - Indicated for patients who meet the previous criteria for bridge to transplantation (BTT) LVAD candidacy but who are not eligible for transplantation based upon age, obesity, renal dysfunction that will not tolerate immunosuppressive agents, or other comorbidities suggesting that the risk of transplantation is unacceptable
  - Patients with advanced heart failure (HF) symptoms (New York Heart Association [NYHA] class IIIB or IV) who meet at least one of these criteria:
    - Continued failure despite optimal medical management for at least 45 of 60 days
    - NYHA class III or IV status for at least 14 days and dependent on IABP for 7 days and/or inotropes for 14 days
    - Treated with angiotensin-converting enzyme (ACE) inhibitors or beta-blockers for at least 30 days and found to be intolerant of these medications
    - Maximal oxygen consumption (VO_2 max) ≤14 mL/kg/min or ≤50% predicted VO_2 max with exercise testing (unless testing is contraindicated because of class IV status)

Contraindications

- Postcardiotomy failure
  - Sepsis
  - "Stone heart," or lack of any innate cardiac function
  - Age >70 years
  - Condition in which recovery is not anticipated and the patient is not a candidate for cardiac transplantation
- BTT
  - Patient is not a candidate for cardiac transplantation
  - Sepsis
  - End-organ damage is not likely to recover
  - Severe impairment of neurologic function
  - Severe chronic obstructive pulmonary disease
  - Procoagulation abnormalities, with previous venous or arterial thrombosis despite anticoagulation therapy
  - Pregnancy
  - Inability or refusal to receive blood transfusions
  - Technical obstacles that pose an inordinately high surgical risk

- Destination therapy
  - Same as for transplantation, other than the requirement for cardiac transplantation candidacy
  - Lack of social or family support that allows for home discharge
  - Inability to comprehend plans for postoperative LVAD training
  - Expected need for prolonged biventricular support
  - Severe symptomatic peripheral vascular disease
  - Intolerance to anticoagulant or antiplatelet therapies or any other perioperative or postoperative therapy the patient will require based upon his or her health status
  - Psychiatric disease, irreversible cognitive dysfunction, or psychosocial issues likely to impair compliance with protocols and LVAD management

Equipment

- Postcardiotomy
  - IABP
  - ABIOMED AB/BVS 5000 (LVAD and BiVAD)
  - Tandem Heart
  - Thoratec CentriMag (LVAD and BiVAD)
  - Thoratec PVAD (LVAD and BiVAD)
- BTT
  - Thoratec PVAD (LVAD and BiVAD)
  - Heartmate II
  - Heartware HVAD
  - DuraHeart
  - Levacor
  - CardioWest Total Artificial Heart
- Destination therapy
  - Heartmate II
  - Heartware HVAD

PROCEDURE

- Intraoperative preparation and evaluation
  - Lines: arterial, venous, Swan-Ganz (continuous cardiac output type for continuous-flow LVADs)
  - Preoperative echocardiogram assessment
    - LV thrombus
    - Interatrial septal defect or patent foramen ovale (PFO)
    - Aortic insufficiency
    - Tricuspid insufficiency
    - RV function
  - Hemodynamic control
    - Management and preservation of perfusion pressure for RV and coronary arteries using alpha-agonists
    - Preoperative thromboelastogram to assess coagulopathy and the need for transfusion products
    - Cautious volume management
  - Cannulation for cardiopulmonary bypass
    - Distal ascending aortic site for inflow
    - Standard two-stage venous cannula for drainage (for standard LVAD)
    - Biatrial cannulation for BiVAD or if tricuspid repair or PFO closure is required
  - Apical LV cannulation achieved for LVAD
    - Apical cannulation performed according to protocol dictated by each individual VAD brand
    - Preperitoneal pocket required for some LVADs; otherwise, a subcostal tunnel is created as needed
  - Aortic outflow graft sewn end-to-side for outflow
  - RVAD cannulation via the right atrial appendage
  - RVAD return to the pulmonary artery via arterial cannula
  - Closure of pericardium preferred
  - Adequate chest tube drainage from mediastinum and pleural spaces

AFTER THE PROCEDURE

Postprocedure Care

- Hemodynamic and volume control
  - Blood pressure maintenance is critical for RV function.
  - Adequate inotropic support is needed for the RV.
  - Appropriate blood product replacement should be given, guided by thromboelastogram.
  - Adequate blood pump flow is determined by adequate CI (at least 2.4 L/min/m^2).
  - In most cases, decompression of the LV should not be so great as to cause right-to-left interventricular septal shift. Mitral regurgitation should be reduced and the aortic valve open occasionally.
  - CVP should be maintained between 8 and 12 mm Hg.
- Intensive care unit management
  - Maintain positive-pressure ventilation until mental status and pulmonary function allow for extubation.
  - Remove chest tubes as soon as possible.
  - Begin anticoagulation for the ventricular assist device (VAD) with heparin after 24 hours (if bleeding is less than 50 mL/hr), and convert to warfarin when the patient is taking oral fluids.
  - Broad-spectrum antibiotics should be continued for 4–5 days.
  - Active physiotherapy should be carried out, with an emphasis on pulmonary toilet and incentive spirometry.

Complications

- Common
  - Bleeding: mediastinal, wounds, driveline sites, gastrointestinal
  - RV dysfunction
  - Infection: driveline-associated (especially at exit site), pulmonary, urinary tract
- Infrequent
  - Neurologic events
  - Arrhythmias
  - Hemolysis
  - Psychiatric
- Serious, rare complications
  - Device malfunction

OUTCOMES AND EVIDENCE

Successful clinical evaluation of the Thoratec PVAD led to U.S. Food and Drug Administration (FDA) approval for BTT indication in 1992. Twenty-four patients (62%) required support with an LVAD alone, and 15 (38%) required BiVAD support. Survival from support to successful outcomes was 70% for BTT and 67% for postcardiotomy recovery.

The HeartMate II (Thoratec Corporation, Pleasanton, California) is a continuous-flow rotary pump with an axial design, which is representative of the second generation of LVAD technology in clinical use in the United States. Successful clinical evaluation of the Thoratec pVAD led to FDA approval for BTT indication in 1992. Of the 133 patients receiving support with the HeartMate II device, the principal efficacy outcomes were observed in 100 patients (75%). The median duration of support was 126 days (range, 1–600). The survival rate during support was 75% at 6 months and 68% at 12 months. There was significant improvement in distance walked between baseline and

6 months, with over 50% of patients experiencing an improvement in the 6-minute walk distance to over 200 meters.

In 1998, the National Heart, Lung, and Blood Institute funded the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial. REMATCH was a pivotal trial designed to assess morbidity, mortality, and functional outcomes in a homogeneous cohort of patients with advanced HF ineligible for cardiac transplantation. Survival rates at 1 year (52% vs. 25%, $P = 0.002$) and 2 years (23% vs. 8%, $P = 0.09$) were superior (significantly) in the VAD patients compared with the survival rates in those patients randomized to medical therapy.

After the original REMATCH publication, Park and colleagues analyzed the outcomes of the trial, based upon the era of enrollment. Despite more high-risk characteristics, patients enrolled in the latter half of the study had significantly higher 1- and 2-year survival rates than those enrolled during early experience with the VAD. A similar improvement in survival outcomes was seen in the postapproval registry, with a 56% 1-year survival rate. Improved outcome with VAD use and experience is a consistent observation, which was also evident in the continued access protocol cohort versus primary cohort in the HeartMate II BTT trial. Demonstration of improved survival outcomes in patients with preimplant risk profiles similar to or worse than those enrolled in the initial randomized trial suggests that refinement of preoperative and postoperative management and greater experience with mechanical circulatory support are important factors in determining survival and functional improvements after VAD implantation.

The HeartMate II DT Pivotal Trial evaluated 200 patients with NYHA class IIIb–IV symptoms, ejection fraction (EF) <25%, and VO_2 max ≤14 mL/kg/min or treatment with intravenous inotropic agents for at least 14 days or an IABP for 7 days. The patients were randomized to receive a HeartMate II ($n = 134$) or a HeartMate XVE ($n = 66$). There was a greater than fourfold increase in the percentage of HeartMate II patients who successfully reached the primary endpoint (46% vs. 11%, $P < 0.001$). Patients randomized to the HeartMate II had 1- and 2-year survival rates of 68% and 58%, compared with 55% and 24% in patients who received the HeartMate XVE.

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Pericardiocentesis

Stefano Maggiolini and Felice Achilli

PREPROCEDURE

Indications

- Pericardial tamponade
  - Pericardiocentesis is the first treatment option in patients with overt tamponade because only the removal of fluid allows normal ventricular filling and restores adequate cardiac output.
  - If the patient is hemodynamically stable, the procedure should be performed within 12–24 hours from diagnosis, after obtaining laboratory results including the blood counts. A scoring index has been proposed in patients with a suspicion of tamponade for deciding whether to perform urgent pericardiocentesis or drainage later in the subsequent hours. It consists of three components obtained during the initial presentation: etiology, clinical presentation, and echocardiographic findings.
- Pericardial effusion without hemodynamic compromise
  - Chronic asymptomatic large pericardial effusion (>20 mm evaluated as the largest telediastolic echo-free space in two-dimensional mode). In this case there are not mandatory indications. We think that a close clinical and echocardiographic monitoring, with the need to resort to pericardiocentesis in the case of symptoms or progression of the effusion, is very important.
  - Suspected bacterial or tuberculous pericarditis
    - Elective pericardiocentesis is warranted in patients with suspicion of purulent pericarditis.
    - Purulent pericarditis should be managed aggressively, as death is inevitable if untreated, whereas with comprehensive therapy, 85% of cases have been reported to survive the episode and have a good long-term outcome.
    - Treatment consists of systemic antibiotic therapy and complete evacuation of the effusion. Surgical drainage usually is required, because percutaneous drainage alone is not able to completely evacuate the effusion, which is often rich in fibrin and can be loculated and associated with dense adhesions. An alternative and less invasive method, which can be used to completely evacuate purulent effusions, thus controlling sepsis and avoiding the evolution to constrictive pericarditis, consists of pericardial drainage associated with intrapericardial infusion of streptokinase. Fibrinolytic therapy can enhance the removal of material that would otherwise be too viscous or particulate to be removed by tube drainage. This treatment should be considered before undertaking surgery.
  - Suspected neoplastic effusion
  - Pericardiocentesis for diagnostic purpose in mild or moderate effusions (<20 mm) should be confined to selected cases.
    - Pericardiocentesis with a diagnostic purpose (except in cases of suspected neoplastic, tuberculous, or purulent pericarditis) is not justified in the majority of cases for the following reasons: (1) low diagnostic power; (2) the underlying pathology is often already known or identifiable by different noninvasive tests; (3) viral pericarditis is usually self-limiting, and it only requires an antiinflammatory treatment; and (4) high procedural risk.

Contraindications

- Urgent pericardiocentesis or drainage of pericardial effusion is indicated for each patient with an established diagnosis of cardiac tamponade and hemodynamic shock.
- Aortic dissection and postinfarction rupture of the free wall are contraindications to pericardiocentesis and indications for urgent surgical drainage. When surgical management is not immediately available or the patient is too unstable, pericardiocentesis and controlled pericardial drainage of very small amounts of the hemopericardium can be attempted to temporarily stabilize the patient in order to maintain blood pressure at ~90 mm Hg.
- Relative contraindications include uncorrected coagulopathy, anticoagulant therapy, and thrombocytopenia (PLTc <50,000/mm^3) and small, posterior, and loculated effusions.
  - The alterations of coagulation can be corrected using:
    - Fresh frozen plasma or platelets (may be time consuming)
    - Recombinant human factor VIIa, which may be effective in a shorter time.
    - For patients on warfarin: vitamin K + prothrombin complex concentrate (PCC 50 U/kg)
  - In case of patients receiving novel oral anticoagulants (NOACs) (non–vitamin K antagonist oral anticoagulants), it is necessary to use different strategies depending on the type of NOAC. A specific reversal agent for dabigatran (idarucizumab) has shown a nearly complete reversal of the anticoagulant effects within minutes.
  - A similar reversal agent, Andexanet alfa, a recombinant modified human factor Xa decoy protein that reverses the inhibition of factor Xa, has been recently introduce for patients treated with apixaban, rivaroxaban or edoxaban. If the reversal agent is not available the interventional strategy is similar to patients on warfarin with administration of PCC 50 U/kg or activated PCC 50 U/kg. The efficacy of PCC or aPCC has not been firmly established to neutralize the anticoagulant effect of these drugs. The administration of PCC or aPCC can be considered if immediate hemostatic support is required.

Equipment

- Echocardiography
- Multiangle bracket, to be assembled on the probe
- Needle-guide kit with sterile sheath and sterile echo-gel (Ultra Pro II needle guide [CIVCO USA, Kalona, IA])

- 14- to 16-gauge Teflon-sheathed needle (technique A)
- 18-gauge, 9-cm needle on a syringe for apical approach (technique B)
- 18-gauge, 15-cm needle, included in the PeriVac set (Boston Scientific USA, Marlborough, MA) for subxiphoid approach
- J-tipped guidewire
- 6F–8F dilator
- Drainage catheter: pigtail angiocatheter 6F–8F or pericardiocentesis set (PeriVac)
- Disposable flushing system to maintain the patency of the system

ANATOMY

The pericardium is a fibroserous sac that contains the heart and the origin of the main vessels. The pericardium is composed of two layers: the visceral pericardium, a monolayer membrane of mesothelial cells that is adherent to the epicardial surface of the heart, and the fibrous parietal layer that surrounds most of the heart. The pericardial space normally contains 25–50 mL of fluid in adults. If the amount of fluid increases, the pericardium is not immediately distensible, even though stress relaxation may occur within minutes from the beginning of the increase in pericardial pressure. If the fluid accumulates slowly, over weeks or months, the pericardium can increase in size to a maximum capacity of 1–2 L. The heart, and therefore the pericardium, is located at the center of the mediastinum, partially covered by the lungs; by the sternum and by the costal cartilages of the third, fourth, and fifth ribs; and by intercostal muscles. About two-thirds of the heart is located on the left side of the chest. The heart rests on the diaphragm. The pericardium is innervated by the vagus nerve, by the left recurrent laryngeal nerve, and by the esophageal plexus, and it also has rich sympathetic innervation from the stellate and first dorsal ganglia and the cardiac, aortic, and diaphragmatic plexuses. When performing pericardiocentesis, close attention should be paid to avoid damaging the internal thoracic artery, which runs behind the sternal end of the costal cartilages, and the vascular bundle at the inferior margin of each rib (Fig. E9.1).

PROCEDURE

Echo-Guided Technique (A)

- Perform a two-dimensional and Doppler study to assess the size, distribution, and hemodynamic effect of the effusion.

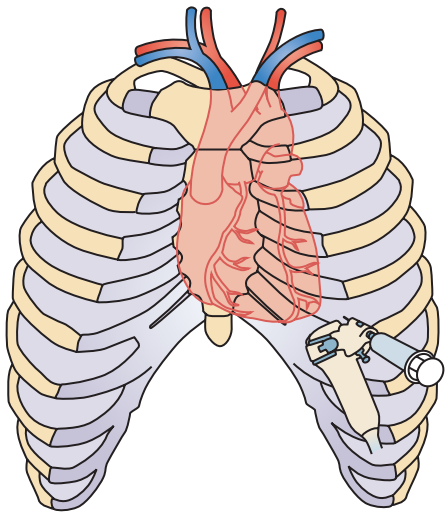

Fig. E9.1 Projection of cardiac area on the anterior thoracic wall.

- Place the patient in a semireclining position, at an angle of about 30 degrees, and slightly rotated leftward to enhance fluid collection in the inferoanterior part of the chest.
- Ensure that a central venous catheter is in place. The catheter is essential for monitoring right atrial pressure and permitting the rapid infusion of fluids and drugs as indicated.
- Continuous arterial pressure monitoring is indicated to detect the presence of pulsus paradoxus and to rapidly detect and correct sudden hemodynamic instability.
- Medical management:
  - In the unstable patient with hypotension and tachycardia, during preparation for pericardiocentesis, measures aimed at stabilizing the patient should be instituted. Intravenous fluid administration is the best treatment option before and during drainage. In stable patients without low systolic blood pressure (>100 mm Hg), this treatment is not useful, and it could be dangerous in terms of reducing the cardiac output.
  - Intravenous administration of diuretics is contraindicated and could be fatal in patients on the edge of their compensatory mechanism in tamponade.
  - Both dopamine and dobutamine improved hemodynamics in cardiac tamponade; dobutamine has greater beta activity, and therefore it may be considered preferable. However, the usefulness of inotropes is generally limited because endogenous adrenergic stimulation is already enhanced under tamponade conditions, and ejection fraction is preserved, but stroke volume is critically depressed.
  - Packed red cell units should be readily available before starting nonemergency procedures.
- Respiratory management
  - Pulse oximetry and supplemental O_2 should be warranted.
  - Influence of respiratory parameters: spontaneous versus mechanical ventilation and $PaCO_2$ levels significantly influence the evolution of pericardial tamponade. Pericardial pressure decreases 3–6 mm Hg when $PaCO_2$ decreases to 24 mm Hg; conversely, pericardial pressures increase 2–4 mm Hg when $PaCO_2$ reaches 57 mm Hg. Increased intrathoracic pressures during the inspiratory phase of mechanical ventilation can decrease cardiac output up to 25% in patients with tamponade. To avoid further hemodynamic compromise, patients with suspected cardiac tamponade should not receive positive-pressure ventilation unless absolutely necessary.
- After appropriate disinfection of the operative field, local anesthesia of the skin is obtained by injecting with 2% lidocaine subcutaneously.
- The trajectory of the needle is defined by the angle between the probe and the chest wall. Ultrasound does not cross aerial spaces. Therefore, if cardiac structures are identified, there is no lung tissue interposed between the probe and the pericardium.
- The proper landmark for needle insertion corresponds to the area where the pericardial space is closest to the probe and the fluid accumulation is maximal; this site is para-apical more often than subxiphoid. The subcostal route is less frequently used because it requires a longer path to reach the fluid. It passes anterior to the liver capsule and is directed toward the right chamber of the heart.
- The optimal needle trajectory should be transfixed in the operator's mind and then a 14- to 16-gauge Teflon-sheathed needle with an attached saline-filled syringe is advanced in the direction of the fluid-filled space.
- Para-apical approach: Insert the needle at 3–5 cm from the parasternal border (to avoid the internal thoracic artery) and close to the superior edge of the rib (to avoid the intercostal artery).

- Subxiphoid approach: Direct the needle posteriorly until the tip passes posterior to the bony cage. Press the hub of the needle toward the diaphragm and advance the needle with a 15-degree posterior tilt, either directly toward the patient's head or toward the right or left shoulder.
- When fluid is aspirated, the needle should be advanced approximately 2 mm farther. The sheath should be advanced over the needle and the steel core withdrawn.
- If bloody fluid has been aspirated or if the position of the sheath is questionable, the position of the catheter can be confirmed by injecting 5 mL of agitated saline through the sheath. The bubbles in the solution provide a contrast effect that can be observed by two-dimensional echocardiography. Thus if contrast agent appears in the pericardial space, the procedure can be continued.
- A guidewire should be advanced through the sheath, and then the sheath should be removed over the guidewire.
- A small incision should be made at the entry site, followed by introduction of a dilator (6F–8F) over the guidewire. Predilatation of the chest wall passage facilitates subsequent insertion of the introducer sheath-dilator (6F–8F).
- The guidewire and the dilator should be removed and only the sheath left in the pericardial sac. A pigtail angiocatheter should be inserted through the introducer sheath and the fluid aspirated.

Real-Time Echo-Monitored Procedure (B)

(This is the technique preferred by the authors.) See Video E9.1.

- A different approach uses a needle carrier mounted on the transducer to advance the needle to the pericardial space under continuous visualization.
- Patient preparation and supportive management are the same as those described earlier.
- Mount the bracket on the probe to support the needle-guide kit and to allow a real-time echo-monitored procedure. The bracket supports the needle with different angles, and the operator can choose between a closer angle for the subcostal approach and a wider angle for the apical approach (Fig. E9.2).
- Cover the probe with the sterile sheath and mount the needle-guide kit on the sheathed probe (Fig. E9.3).
- Once the optimal position is found and the pericardiocentesis procedure is started, the echocardiography probe should not be more mobilized to avoid tearing the tissue. The execution of the technique with two operators can be useful to minimize this risk; one can firmly hold the probe, and the other can advance the needle. The needle (SDN 18-gauge, 9-cm Cook for apical approach, or the needle included in the PeriVac set for subxiphoid approach) is connected to a syringe for constant gentle aspiration and is slowly introduced through the tissues until there is echographic visualization of the tip (Fig. E9.4A–C).
- When the needle tip is observed on the echo screen in the pericardial space and fluid is freely aspirated, the syringe is disconnected and a J-tipped guide is inserted (see Fig. E9.4D).
- The technique is summarized in Fig. E9.5.
- Remove the needle and make a small incision at the site of insertion.
- The drainage catheter (a pigtail angiocatheter 6F–8F or pericardiocentesis set [PeriVac]) is subsequently introduced along the guidewire, according to the Seldinger technique, after introducing a 6F–8F dilator over the guidewire.
- Completely aspirate the pericardial effusion by syringe suction if the pericardial sac contains <1 L.

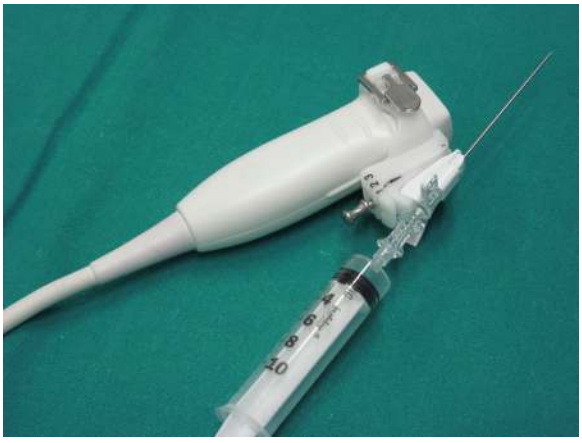

Fig. E9.2 Echocardiographic probe with bracket, needle guide, and syringe.

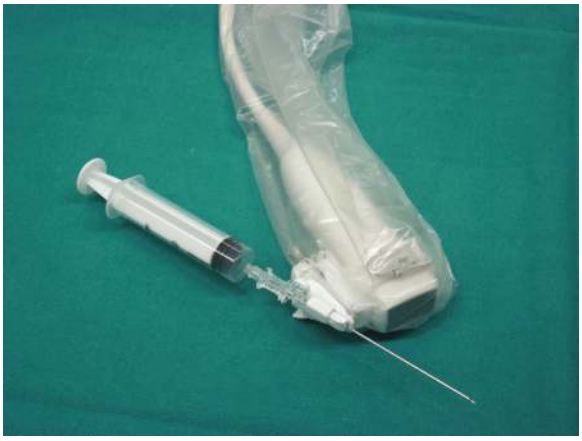

Fig. E9.3 After the bracket is mounted, the probe is protected by sterile wrap.

AFTER THE PROCEDURE

Postprocedure Care

- After the procedure, perform a chest radiography to exclude the presence of pneumothorax or pneumopericardium.
- Repeat aspiration by syringe every 4–6 hours. In order to optimize catheter patency, it could be useful to use a disposable continuous flushing system between aspirations.
- Remove the catheter once the drainage has decreased to less than 25–30 mL in 24 hours.
- It is important to empty the pericardial sac as completely as possible to reduce the risk of recurrence, leaving the catheter in place up to 72 hours (or more) if the fluid has a rate of accumulation greater than 30 mL in 24 hours. The removal of the liquid must take place gradually (max 1 liter during the first phase), and the removal must be completed in the following hours. This is to avoid a potentially serious complication: pericardial decompression. Pericardial decompression is a rare, potentially life-threatening syndrome characterized by wide clinical scenarios (from pulmonary edema to cardiogenic shock) that can develop after a successful pericardial drainage.
- The omission of extended catheter drainage is an important independent predictor of recurrence.
- Reaccumulation of pericardial fluid is common in patients with malignant pericardial effusions (40%–70% recurrence rate without

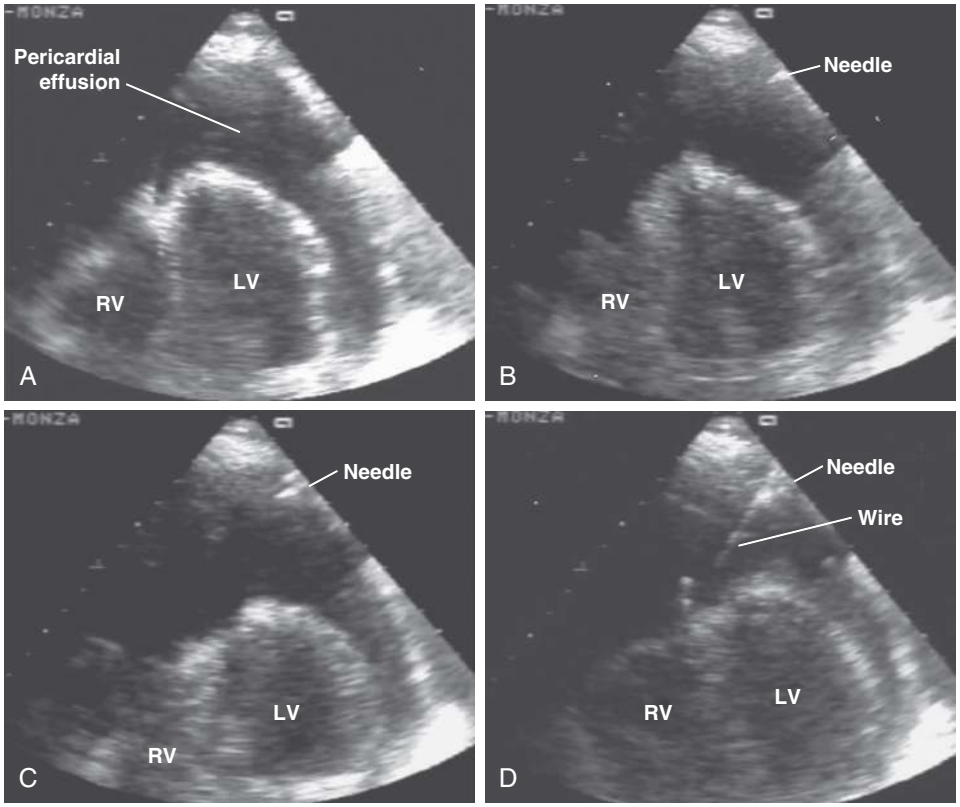

Fig. E9.4 Two-dimensional echocardiographic image (apical four-chamber view) during needle introduction through tissues. **A,** Detection of pericardial effusion. **B,** Visualization of needle tip. **C,** Needle is advanced through tissues. **D,** Needle enters pericardial space and guidewire is introduced. *LV,* Left ventricle; *RV,* right ventricle. (From Maggiolini S, Bozzano A, Russo P, et al. Echocardiography-guided pericardiocentesis with probe-mounted needle: Report of 53 cases. *J Am Soc Echocardiogr.* 2001;14:821–824.)

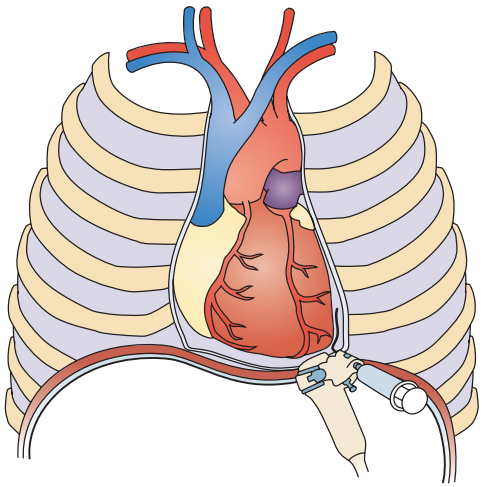

Fig. E9.5 Representation of pericardiocentesis using the apical approach. The pericardial needle is continuously monitored by apical four-chamber echocardiographic view while entering the pericardial space. When the pericardial effusion is reached, a guidewire is introduced in the pericardial space.

specific treatment). In these patients, several measures have been suggested to prevent recurrence of tamponade. These approaches include (1) complete evacuation of the fluid, (2) prolonged pericardial drainage, and (3) systemic antineoplastic treatment as baseline therapy. Other suggested measures are intrapericardial instillation of sclerosing and cytotoxic agents tailored to the type of tumor, radiation therapy in patients with radiosensitive tumors (i.e., lymphomas and leukemias), and pericardiotomy.

- Perform a complete echocardiographic study in all patients before removing the catheter and before discharge from the intensive care unit (ICU) or coronary care unit.

Complications

- Common
  - Puncture of cardiac chambers (1.5%)
  - Pneumothorax (1%)
  - Pleuropericardial fistulas (0.8%)
  - Arrhythmias (usually vasovagal bradycardia)
- Infrequent
  - Laceration of coronary arteries or intercostal vessels
  - Bacteremia
  - Pneumopericardium
- Serious, rare complications
  - Death (0.1%–0.5%)
  - Chamber laceration requiring surgery
  - Pericardial decompression

In a series of 161 pericardiocenteses performed under continuous echocardiographic visualization (technique B), two major complications occurred (1.2%), no deaths, no perforations or ruptures of cardiac chambers were reported, and the incidence of minor complications was 4.3%.

In the case of the most frequent complication, some suggestions can be given: Puncture of the cardiac chambers with the needle can be solved in most cases with the needle retraction and the insertion of the catheter into the pericardium. If the perforation is carried out by the catheter, it must be left in place and a new pericardiocentesis must be carried out by placing another catheter in the pericardium before removing the previous one; then the perforating catheter can be withdrawn. If the controlled drainage resolves the tamponade, also with eventual autotransfusion of pericardial blood, surgery can be avoided.

OUTCOMES AND EVIDENCE

- Randomized studies comparing different techniques do not presently exist.
- Pericardiocentesis-related mortality and serious complications are low when the procedure is performed by trained professionals following consolidated techniques.
- Percutaneous pericardiocentesis has been performed for many years using the blind subxiphoid approach. This technique is associated with a high incidence of morbidity and mortality, and using electrocardiographic needle monitoring does not lead to significantly better outcomes. Accordingly, blind approaches are no longer justified.

SUGGESTED READING

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Paracentesis and Diagnostic Peritoneal Lavage

Louis H. Alarcon

PARACENTESIS: BEFORE THE PROCEDURE

Indications

- Paracentesis is the insertion of a needle or catheter into the peritoneal cavity for the purpose of aspirating peritoneal fluid. It is most often indicated for diagnostic or therapeutic evacuation of ascites.
- Diagnostic indications
  - New-onset ascites: fluid evaluation to help determine etiology, differentiate transudate versus exudate, detect the presence of cancerous cells, or address other considerations
  - Differentiate between suspected spontaneous or secondary bacterial peritonitis
- Therapeutic indications
  - Respiratory compromise secondary to ascites
  - Abdominal pain or pressure secondary to ascites (including abdominal compartment syndrome)

Contraindications

- Absolute contraindication
  - Acute abdomen that requires surgery
- Relative contraindications
  - Inadequate volume of ascites on imaging (e.g., ultrasound)
  - Uncorrected hypovolemia
  - Severe uncorrected thrombocytopenia (platelet count <20,000/μL) or coagulopathy (international normalized ratio [INR] >2.0)
  - Pregnancy
  - Distended urinary bladder
  - Abdominal wall cellulitis
  - Distended bowel
  - Intraabdominal adhesions

Equipment

- Ultrasound machine
- Local anesthetic
- Chlorhexidine prep
- Sterile towels, gloves
- 18- or 20-gauge, 2- to 3-inch needle
- 20- to 50-mL syringe
- 14- to 16-gauge cannula-over-needle
- 8.5F 40-cm polyurethane pigtail catheter with guide wire
- 2-0 polypropylene suture

ANATOMY

The site for paracentesis is in the abdomen, lateral to the rectus muscle in the lower quadrant midway between the umbilicus and the anterior superior iliac spine, avoiding prior surgical incisions. Ultrasound guidance is recommended to identify the site of the largest volume of ascites and reduce the chance of injury to the intestines.

PROCEDURE

See Video E10.1.

- The patient should be supine. Bedside ultrasonography can be a valuable aid for localizing the largest collection of ascites and avoiding injury to the bowel and should be employed routinely. The patient should void or have a urinary bladder drainage tube inserted before the procedure. The area is cleansed, draped, and anesthetized.
- When a small volume of ascitic fluid is needed for diagnostic studies, an 18- or 20-gauge, 2- to 3-inch needle attached to a 20- to 50-mL syringe is inserted into the abdomen lateral to the rectus muscle in the lower quadrant, midway between the umbilicus and the anterior superior iliac spine, avoiding prior surgical incisions. The skin is retracted caudad while inserting the needle. When fluid is aspirated, the needle is stabilized, and the fluid sample is obtained by syringe. After removal of the needle, the skin is released, causing the entrance and exit needle sites to form a "Z-track" that reduces the chance of ascitic fluid leakage.
- For large-volume paracentesis, a 14- to 16-gauge cannula-over-needle is employed. Once the fluid is aspirated into the syringe, the needle is removed, leaving the plastic catheter in place, which is attached to plastic tubing and a vacuum canister. Usually, 4–6 L of ascites can be safely removed, although larger volumes have also been obtained.
- If it is necessary to place a catheter into the peritoneal cavity, a guide wire should be inserted into the peritoneal cavity through the needle; an 8.5F 40-cm polyurethane pigtail catheter should be guided into the peritoneal cavity over the wire and sutured in place.
- The aspirated fluid should be submitted for a cell count, absolute polymorphonuclear neutrophil count, albumin, total protein concentration, Gram stain, and cultures. Optional studies, based on clinical suspicion, may include glucose concentration, amylase concentration, lactate dehydrogenase concentration, bilirubin concentration, and cytology.

AFTER THE PROCEDURE

Postprocedure Care

- The patient should be closely monitored for complications (see later), especially bleeding and peritonitis.
- If a pigtail catheter is left in place, it should be attached to a collection bag and monitored for bleeding or the drainage of succus.

Complications

- Common
  - Hypotension
    - Hypotension after paracentesis in cirrhotic patients can be associated with a worsening of arteriolar vasodilation.[1] In the first few hours after large-volume paracentesis, there is a reduction in the plasma levels of renin and aldosterone, an increase in the atrial natriuretic peptide concentration, a reduction in the cardiac filling pressures, and an increase in the cardiac index.
    - However, after 12–24 hours, these changes reverse, reflecting effective hypovolemia. Infusion of intravenous colloids, specifically albumin, has been shown to attenuate the hemodynamic consequences of paracentesis and the associated neurohumoral alterations.[2] However, no large, randomized study has shown that routine expansion of plasma volume with a colloid solution confers a survival advantage.
- Infrequent
  - Bleeding
    - The incidence of significant hemorrhage from this procedure is about 1%, despite the fact that over 70% of patients have clotting parameter abnormalities.[3] Therefore it is usually unnecessary to normalize the prothrombin time before proceeding.[4]
- Serious complications (e.g., bowel perforation) are rare (0.1%)[3]
  - Peritonitis
  - Bowel injury
  - Injury to the bladder
  - Injury to the epigastric vessels

OUTCOMES AND EVIDENCE

- Determining the etiology of ascites is based on the patient's history, physical examination, liver function tests, ultrasonography, and ascitic fluid analysis. Abdominal paracentesis and ascitic fluid analysis should be an early step in the workup of patients with new-onset ascites. Paracentesis is also important to diagnose infection of the ascitic fluid (i.e., peritonitis).
- Development of ascites is a common complication of cirrhosis, being more frequent than either encephalopathy and variceal hemorrhage in these patients. The median survival of cirrhotic patients with ascites is 2 years.[5] Other causes of ascites besides cirrhosis include malignancy, heart failure, tuberculosis, renal failure, and pancreatic disease.
- The mainstays of treatment of ascites secondary to cirrhosis involve dietary sodium restriction (2 g/day) and oral diuretics (e.g., spironolactone and furosemide).
  - The underlying etiology of liver disease should be corrected when possible, and ethanol consumption should be strongly discouraged. Abstinence from ethanol can normalize portal venous pressures in some patients with early ethanol-induced liver disease.[6]
  - Patients with early cirrhosis and diuretic-responsive ascites should not be managed by serial paracentesis; rather, medical management should be employed. In the majority of patients, ascites can be controlled with medical management.
  - In 5%–10% of patients, ascites becomes resistant to medical treatment. The standard of care for the management of refractory ascites is therapeutic paracentesis. This can be performed as often as every 2 weeks to control symptomatic ascites.
  - Other options for managing refractory ascites include transjugular intrahepatic portosystemic shunt (TIPS) and liver transplantation. In a randomized trial of 60 patients comparing TIPS with repeated therapeutic paracentesis, the probability of survival without liver transplantation at 2 years was 58% in the TIPS patients as compared with 32% in the paracentesis patients.[7] A smaller study of 25 patients randomized to TIPS or paracentesis demonstrated the opposite: mortality was higher in the TIPS group.[8]
  - Surgical portosystemic and peritoneovenous shunts have fallen out of favor because of the high incidence of morbidity and mortality and the development of hepatic encephalopathy.
  - For patients with tense ascites, large-volume paracentesis rapidly relieves intraabdominal pressure. A single 4- to 6-L paracentesis can be performed safely and often does not require an infusion of colloids.[9] However, paracentesis does nothing to correct the etiology of the ascites, and ascites will recur if sodium restriction and diuretics are not instituted or fail. Referral for liver transplant evaluation should be considered for eligible patients with cirrhosis and refractory ascites.
  - Infection of ascitic fluid often occurs in cirrhotic patients. When there is no surgically correctable etiology (e.g., perforated viscus), the term *spontaneous bacterial peritonitis* is used. This diagnosis is made when there is a positive ascitic fluid culture or an ascitic fluid polymorphonuclear (PMN) cell count greater than 250 cells/mm^3 in the correct clinical scenario without any evidence for an intraabdominal, surgically correctable etiology. The infection is usually monomicrobial. Polymicrobial infection suggests secondary peritonitis. Consideration of the diagnosis mandates paracentesis and evaluation of the ascitic fluid; a clinical diagnosis without paracentesis is inadequate.

DIAGNOSTIC PERITONEAL LAVAGE: BEFORE THE PROCEDURE

Indications

- With the widespread use of focused abdominal sonography for trauma (FAST), the indications for diagnostic peritoneal lavage (DPL) are decreasing
- Patients who have sustained blunt trauma and have no overt signs of acute abdominal injury or bleeding but require an evaluation to rule out intraabdominal hemorrhage or hollow viscus injury
- Patients who are not candidates for computed tomography (CT) (e.g., because of hemodynamic instability) or when FAST is unavailable or yields equivocal results

Contraindications

- The only absolute contraindication to performing a DPL is the clinical condition of the patient mandating immediate laparotomy.
- Relative contraindications include previous abdominal surgery, cirrhosis, obesity, and coagulopathy.
- In patients with pelvic fractures or pregnancy, a supraumbilical incision should be performed.

Equipment

- Local anesthetic
- Chlorhexidine prep
- Sterile towels, gloves
- 10-mL syringe
- 8F–9F 25-cm lavage catheter
- 2-0 polypropylene suture

ANATOMY

DPL should be performed in the midline of the abdomen immediately below the umbilicus, or above the umbilicus in patients with a pelvic

fracture, suspected pelvic hematoma, or pregnancy. Prior surgical incisions should be avoided if possible.

PROCEDURE

- The patient should be in the supine position. Gastric and bladder decompression tubes should be inserted to minimize the risk of injury to these organs. The periumbilical skin should be prepped and draped sterilely. Local anesthesia is injected into the site.
- DPL can be performed with an open, semiopen, or closed technique.
  - The open technique employs a midline infraumbilical abdominal incision 2–5 cm in length; the incision should be supraumbilical if the patient has a pelvic fracture or is pregnant. A small incision is made in the midline abdominal fascia and peritoneum. An 8F–9F 25-cm lavage catheter with side holes is inserted under direct visualization toward the pelvis.
  - The closed method uses a Seldinger technique. A 16-gauge, 3-inch needle is inserted through a skin puncture and into the peritoneal cavity. A guide wire is passed through the needle into the peritoneal cavity. The lavage catheter is inserted over the wire.
  - The semiopen technique involves incising the skin and fascia and then using a guide wire technique for inserting the catheter into the peritoneal cavity.
- Once the catheter is placed, aspiration should be attempted with a syringe.
- If 10 mL of blood is aspirated, the DPL is considered positive, and appropriate surgical intervention should be undertaken.
- Otherwise, 1 L of crystalloid solution is infused (10 mL/kg in pediatric patients) and then retrieved by gravity and sent to the laboratory for analysis.
- In general, the DPL is considered positive in blunt-trauma patients if:
  - Red blood cell (RBC) count is greater than 100,000/mm^3
  - White blood cell (WBC) count is greater than 500/mm^3
  - Amylase concentration is greater than 100 IU/L
- Other positive findings include the presence of bile or food particles or the drainage of lavage fluid from the bladder drainage catheter, gastric tube, or thoracostomy tube.
- The sensitivity and specificity of the test are dependent on the threshold criteria for determining a positive test result.
- If the lavage is negative but there is a high index of suspicion for intraabdominal pathology, the DPL catheter can be left in place for repeat lavage to rule out delayed hemoperitoneum or intestinal perforation.

AFTER THE PROCEDURE

Complications

- Infrequent
  - Bowel or vascular injury occurs in less than 1%[10]
  - Bladder injury
  - Bleeding (cause for a false-positive DPL result)
  - Wound infection

OUTCOMES AND EVIDENCE

- Evaluation of the abdomen is a critical component in the assessment of injured patients. Failure to identify intraabdominal injury results in preventable morbidity and mortality in trauma patients. The physical examination for abdominal injury is often hampered by alterations of the sensorium by substances (e.g., ethanol and illicit drugs), injury to the central nervous system, or pain from other injuries. Moreover, a significant amount of blood can be present in the peritoneal cavity without obvious abdominal distention or peritoneal signs.
- DPL, CT, and ultrasonography have emerged as the main diagnostic modalities to evaluate trauma patients and currently have complementary roles. DPL was introduced by Root and colleagues in 1965 for the evaluation of abdominal trauma.[11]
  - In the era before CT and ultrasonography, DPL was the first well-established method to identify hemoperitoneum in trauma patients.
  - DPL is primarily useful in diagnosing hemoperitoneum from blunt, solid-organ injury, but it can also be helpful for the diagnosis of hollow viscus injury.
- For *hemodynamically stable* patients with an equivocal abdominal examination, associated neurologic injury, or painful injuries, abdominal CT is recommended as the diagnostic modality of choice and has all but eliminated the need for DPL in these patients.
  - CT is also the preferred diagnostic method for determining whether nonoperative management of a solid-organ injury is appropriate.
  - Furthermore, in stable patients with a positive DPL, a follow-up abdominal CT should be considered. Thus CT and DPL play complementary roles in evaluating stable patients after blunt abdominal trauma.
- For *hemodynamically unstable* patients, FAST and DPL are the preferred tests, with FAST rapidly gaining acceptance over DPL in many trauma centers as the preferred initial diagnostic modality.
  - FAST and DPL are used to rule out hemoperitoneum as the cause of hemodynamic instability.
  - In contrast to DPL, FAST can be used to identify pericardial tamponade.
  - These tests can be performed expeditiously, and ongoing efforts at resuscitation and evaluation can occur simultaneously with the performance of the test.
  - Because resuscitation is difficult during CT, CT is contraindicated when patients are hypotensive or hemodynamically unstable.
  - DPL is also useful in certain clinical scenarios. Consider, for example, a head-injured patient needing an emergency craniotomy: DPL can be performed in the operating room at the same time as the craniotomy without interfering with the neurosurgical procedure.
- Controversy exists regarding the best way to manage blunt trauma patients with isolated evidence of free intraabdominal fluid by CT but without evidence of solid-organ injury.
  - In a review of the literature, isolated free fluid was observed in 2.8% of over 16,000 blunt trauma patients studied with CT.[12] Of these, only 27% underwent a therapeutic laparotomy, so some experts recommend serial abdominal examinations, whereas others recommend surgical exploration to rule out hollow viscous injury.
  - DPL can be useful in the evaluation of patients with suspected perforated viscus. Very early after bowel perforation, the WBC count in the lavage fluid may be low; however, within a few hours after injury, the degree of inflammation is usually sufficient to increase the WBC count in the lavage fluid to greater than 500 cells/mm^3. The presence of bile, amylase, bacteria, or food particles in the lavage fluid also confirms intestinal perforation.
- The use of DPL in the evaluation of hemodynamically stable patients with penetrating abdominal wounds remains controversial.

  - A significant number of missed injuries remain undetected by this method. For example, Kelemen and colleagues[13] reported a 21% false-negative rate for stable patients with abdominal gunshot wounds. Using a low RBC threshold (1000/mm^3) has been described in an attempt to overcome this shortfall.[14]
- False-positive DPL leading to unnecessary laparotomy may occur in as many as 30% of cases.[10,15] This problem can be reduced by using CT as a complementary test in stable patients. The false-negative rate (i.e., failure to diagnose hemoperitoneum) is low. However, DPL is unable to detect retroperitoneal injuries (CT is the preferred test to detect retroperitoneal injuries for the stable patient) and is insensitive for detecting early hollow viscous and diaphragmatic injuries.
- One of the major problems with DPL is that the test is too sensitive. Only about 30 mL of the blood in the peritoneal cavity is necessary to produce a positive DPL. In this era of selective management of solid-organ injuries, a significant number of nontherapeutic laparotomies would be performed on the basis of these DPL results unless the diagnostic evaluation includes other modalities as well.
- Proponents of the open technique argue that it is safer, whereas proponents of the closed and semiopen methods argue that these approaches are more expeditious and can be safely performed by appropriately trained individuals.
- A large meta-analysis that aggregated the results from 1126 patient trials showed that the incidence of major complications is not different for the diverse DPL techniques.[16]
- Failure to properly place the catheter and technical difficulties were more likely to occur with the closed method, whereas the procedure time was shorter with the open method (17.8 vs. 26.8 minutes, respectively).
- Sensitivity, specificity, and accuracy were not different between the various methods of catheter insertion.

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Thoracentesis

J. Terrill Huggins, Amit Chopra, and Peter Doelken

BEFORE THE PROCEDURE

Indications

- Pleural effusion is not explained by the clinical presentation
- Massive pleural effusion with impending respiratory failure
- Suspected pleural space infection
- Suspected complication of pneumonia (empyema)
- Suspected hemothorax

Contraindications

- Absolute
  - Lack of expertise
  - Severe uncorrectable coagulopathy (platelet count <25,000 cells/μL; international normalized ratio [INR] >2.0)
  - Azotemia (creatinine >6 mg/dL)
  - Uncooperative patient
- Relative
  - Operator-dependent and of technical nature
  - Lack of image guidance to determine the safety of the puncture site

Equipment

- Diagnostic thoracentesis
  - Iodophor- and chlorhexidine-containing antiseptic
  - 10- and 30-mL sterile syringes
  - 21-gauge needle
  - 21-gauge spinal needle may be needed for obese patients
  - 1% lidocaine for use as local anesthetic
- Therapeutic thoracentesis
  - Commercially available catheter-over-needle system

ANATOMY

The pleura is a serous membrane that covers the lung parenchyma, mediastinum, diaphragm, and rib cage. The pleura is divided into the visceral and parietal pleura. The visceral pleura covers the lung parenchyma and the interlobar fissures. The parietal pleura lines the inside of the chest wall and the diaphragm. As pleural fluid forms, separation of the visceral and parietal pleura occurs, creating a space for a needle to be placed safely. Free-flowing pleural fluid will collect through gravitational effects in dependent areas. Thus if a patient is sitting upright, pleural fluid will collect along the diaphragm and the costophrenic and cardiophrenic angles. In contrast, in a supine patient, pleural fluid will collect along the posterior aspects of the lung.

The parietal pleura receives its blood supply from the systemic capillaries of the intercostal arteries supplying the costal pleura, whereas the mediastinal pleura is supplied by the pericardiacophrenic artery. The diaphragmatic pleura is supplied by the superior phrenic and musculophrenic arteries. The bronchial arteries likely supply the visceral pleura. The intercostal artery, vein, and nerve travel below the ribs. It is important to understand that the neurovascular bundle is not protected by the phalange of the rib within the first 8–10 cm from the origin of the vessels and nerves from the spine. Performing a thoracentesis near the spine increases the risk of intercostal artery laceration and hemothorax.

PROCEDURE

See Video E11.1.

- Obtain informed consent.
- Place patient in a sitting position if hemodynamically stable, or move the patient to the edge of the bed, with the head of the bed elevated to a 30- to 45-degree angle.
- Perform thoracic ultrasonography, and mark the puncture site.
- The upper margin of the rib immediately below the access area should be defined by palpation (may be impossible with obesity).
- The area should be disinfected with an iodophor- or chlorhexidine-containing antiseptic.
- Use 1% lidocaine without epinephrine for local anesthesia.
- Perform the procedure under sterile conditions at this point.
- Inject lidocaine subcutaneously into the periosteum of the rib and the parietal pleura, ensuring that the upper margin of the rib is identified and anesthetized.
- The upper margin of the rib should be identified with a 21-gauge needle before placing a thoracentesis catheter for a therapeutic procedure.
- Accessing the pleural space over the upper margin of the rib (this should be identified) places the needle at a greater distance from the intercostal vessels and nerves.
- Always maintain the needle angle perpendicular to the patient.
- Once the pleural fluid is aspirated, retract the needle outside the pleural space.
- Place a 30- to 60-mL syringe onto the needle, and advance into the pleural space to collect the specimen.
- If therapeutic thoracentesis is desired, withdraw the needle after the pleural fluid is clearly aspirated.
- If fluid cannot be obtained with a small-gauge needle, no attempts at placing a thoracentesis catheter should be made.
- Insert the catheter-over-needle system under continuous application of suction until the pleural fluid is aspirated.
- Once the pleural fluid is obtained, advance the catheter system another 1 cm to place the catheter with its maximum diameter in the pleural space.
- Without advancing the needle, strip the catheter into the pleural space, and remove the needle.
- To prevent air entry into the pleural space, turn the thoracentesis stopcock off as related to the patient.

- Finally, connect the drainage tubing and collection bag to the thoracentesis catheter.
- To prevent the development of excessively negative pleural pressures in ventilated patients, draining large amounts of pleural fluid is not recommended unless pleural manometry is performed.

AFTER THE PROCEDURE

Postprocedure Care

- A postprocedure chest radiograph should be performed on all ventilated patients.
- Monitor for signs of tension pneumothorax and hemothorax
  - Hypotension
  - Worsening lung compliance in ventilated patients
  - Tube thoracostomy is required for all patients who develop a pneumothorax on mechanical ventilation

Complications

- Common
  - A cough caused by lung reinflation
  - Anterior chest pain in the setting of an unexpandable lung
  - Pain at the puncture site
  - Seroma or hematoma at the puncture site
  - Pneumothorax (up to 30% for non–image-guided procedures)
- Infrequent
  - Pneumothorax with image guidance reported between 0% and 3%
  - Inadvertent puncture of subdiaphragmatic structures (e.g., liver and spleen)
  - Hemothorax
- Serious, rare complications
  - Pneumothorax
  - Tension pneumothorax
  - Intercostal artery laceration
  - Hemothorax
  - Reexpansion pulmonary edema
  - Hypotension

OUTCOMES AND EVIDENCE

- Feasibility and safety of ultrasound-guided thoracentesis in mechanically ventilated patients are strongly supported by the literature.
- Clinically directed thoracentesis should not be performed in mechanically ventilated patients.
- Bedside ultrasonography is the preferred modality for the diagnosis of pleural effusion in the critically ill patient.

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Chest Tube Placement, Care, and Removal

Gregory A. Watson and Brian G. Harbrecht

BEFORE THE PROCEDURE

Indications

- Most commonly undertaken to treat one of the following conditions:
  - Pneumothorax
  - Pleural fluid collection
    - Hemothorax
    - Simple effusion
    - Empyema
- Can be both a diagnostic and a therapeutic maneuver

Contraindications

- In an emergent situation (i.e., tension pneumothorax), there are no contraindications
- In a nonurgent situation, caution should be exercised in the presence of:
  - Known or suspected adhesions
    - Prior chest surgery or trauma
    - History of pleural space infection
    - Intrinsic parenchymal disease
  - Complex, loculated air or fluid collection(s)
    - Typically noted on imaging studies
- In situations where insertion is not emergent and is anticipated to be difficult, consideration is recommended for placement by a skilled operator (surgeon) or under image guidance (computed tomography [CT], ultrasound)

Equipment

- Chest tube of appropriate size and configuration (Fig. E12.1)
  - In general, larger tubes are required to drain blood, pus, or viscous fluid, and smaller tubes (i.e., pigtail catheter) may suffice for a simple effusion or pneumothorax.
    - Non-pigtail sizes range from 20F to 40F for adults and from 6F to 26F for pediatric patients.
  - Straight tubes are most commonly placed in the emergency department or intensive care unit.
    - Right-angled tubes are available but typically are placed by surgeons in the operating room.
- Commercially available collection system (Fig. E12.2)
  - Includes the following components:
    - Plastic connector of at least 0.25-inch diameter to connect the chest tube to the accessory tubing. (A Y-connector may be used in the case of multiple chest tubes, but caution is advised because these are prone to occlusion and subsequent drainage failure.)
    - Accessory tubing (generally 0.5 inch in diameter and 6 feet long).
    - Drainage system (composed of a trap, water seal, and manometer compartments).
- Wall vacuum source with connection tubing
- Prepackaged chest tray
  - At a minimum, should contain a scalpel and a clamp (large Kelly clamp or hemostat)
- Skin antiseptic
- Sterile drapes
- Sterile gown and gloves, mask, and cap
- Local anesthetic
- Intravenous narcotic and/or sedative
- Suture material (commonly 0 silk)
- Gauze
- Tape

ANATOMY

Entry into the pleural space should generally be gained via a location based on ease of access, safety, and avoidance of complications. The American College of Surgeons Committee on Trauma recommends drain insertion between the anterior and posterior axillary lines at a level with or just above the fifth intercostal space (nipple level). In this location, the chest wall is thinnest, and the operator can avoid the pectoralis major muscle and breast parenchyma (anteriorly), the latissimus dorsi muscle (posteriorly), the axillary vessels/brachial plexus (superiorly), and the diaphragm/intraabdominal contents (inferiorly). Within the intercostal space, coursing along the inferior surface of each rib is the neurovascular bundle. Insertion of the tube over the superior aspect of the rib is recommended so that injury to these structures can be avoided (Fig. E12.3). From superficial to deep, one will first encounter skin, followed by a variable amount of subcutaneous tissue, the superior surface of the rib, the intercostal space with its musculature, and finally the parietal pleura. The pulmonary parenchyma and mediastinal structures are just beyond to the parietal pleura, so it is important to avoid overzealous insertion of the chest tube. Tubes placed into an interlobar fissure (e.g., right-sided minor fissure) may slide in easily but not drain effectively. In some instances (e.g., a loculated collection), specialized placement may be required, and the assistance of a surgeon or insertion under image guidance is encouraged.

PROCEDURE

See Video E12.1.

- Confirm the correct patient and laterality. If drainage is nonemergent, perform a "time-out" to verify the indication(s) and review the relevant imaging and coagulation studies.
  - A procedural checklist may be helpful and has been shown to reduce errors and decrease complications.
- Obtain necessary equipment (see earlier) and fill the water seal compartment of the collection system with the indicated amount of water.

Fig. E12.1 Standard chest tube *(top)* with trocar *(middle)* and angled chest tube *(bottom)* without trocar.

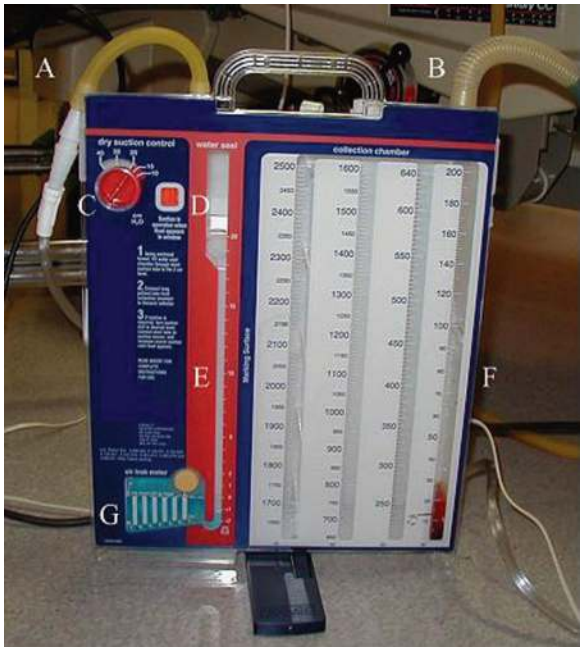

Fig. E12.2 Modern chest drainage system. **A,** Accessory tubing to wall suction. **B,** Accessory tubing to chest tube/patient. **C,** Suction control. **D,** Float indicating suction is operative. **E,** Water seal chamber. **F,** Collection chamber. **G,** Air leak meter.

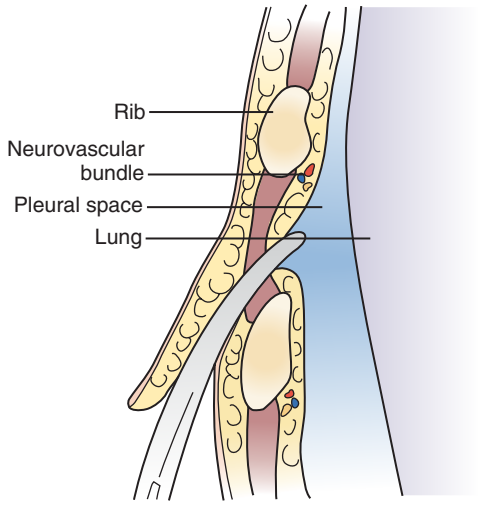

Fig. E12.3 Use of Kelly clamp to enter pleural space.

- Position as follows:
  - Supine or slight elevation of the head of the bed
  - Ipsilateral arm behind the head or abducted
  - Bed at comfortable height for the operator
  - Ensure adequate lighting
- Practice aseptic technique and observe universal precautions.
- Prep the area broadly with skin antiseptic.
- Drape widely such that anatomic landmarks (e.g., the nipple) are visible.
- Plan the skin incision to overlie the rib just inferior to the chosen intercostal space. (For example, if entering the fifth interspace, place the incision along the superior aspect of the sixth rib.)
- Consider premedication with a narcotic or anxiolytic.
- Inject local anesthetic (apply gentle syringe aspiration at all times).
  - First anesthetize the skin.
  - Then angle the needle slightly cephalad to anesthetize the periosteum of the rib and the deeper tissues.
  - Several passes may be required to cover an area 1–2 cm in diameter.
  - If air or fluid is aspirated, retract the needle while aspirating it until it ceases and then inject additional local anesthetic to anesthetize the parietal pleura.
- Make an incision large enough to accommodate the operator's index finger and chest tube at the same time.
- Bluntly dissect (with index finger and/or Kelly clamp) along an oblique path angled superiorly to the chosen intercostal space, with care taken to remain on the superior border of the rib (see Fig. E12.3).
- If the patient is on a ventilator, hold respirations temporarily.
- Gently enter the pleural space with the tip of the clamp.
  - Avoid excessive advancement of the clamp to minimize injury to deeper structures.
  - Typically will feel a pop and get return of air and/or fluid.
- Open the clamp slightly to sufficiently enlarge the opening into the pleural space.
- Insert index finger to confirm entry into the pleural space.
  - Should be able to palpate parietal pleura and, at times, the lung.
  - Note the presence of any adhesions (seen in up to 15% of cases).
- We recommend discarding the chest tube trocar and grasping the tip of the tube with the Kelly clamp to facilitate safer insertion.
- Insert index finger alongside the chest tube and guide the tube into the pleural space away from the lung parenchyma.
  - Though it is recommended to direct the tube anteroapically for a pneumothorax and posterobasally for fluid, the exact location within the pleural space is probably not important in most cases.
  - Ensure that the last drainage hole is well within the pleural space.
- Connect the tube immediately to the collecting system.
- If suction is desired, adjust the wall vacuum source to provide slow, consistent bubbling in its regulation chamber and, when air is being removed, from the pleural space.
  - Typically, the collection system is set initially to pull with −20 cm H_2O suction pressure.
- Secure the tube to the skin at the exit site with sutures (avoid a purse-string stitch).
- Cover the wound with dry gauze and tape.
- Obtain a chest x-ray to document proper placement, evaluate expansion of the lung, and assess for residual pleural fluid or air.

AFTER THE PROCEDURE

Postprocedure Care

- Daily assessment
  - System must remain upright and should be kept below chest level.

- The accessory tubing should be in a straight or coiled position and not kinked.
- Be certain the water level in the system is maintained.
- If suction is being used, verify the proper setting and confirm that it is functional (the float should be visible in the window).
- Note the amount of drainage, presence of bubbling, and respiratory variation.
  - Without suction applied, very large respiratory variations often indicate undrained air that separates the lung from the chest wall.

- Troubleshooting
  - Observation of synchronous water seal and motion with respiration suggests the tube is still functioning in the pleural space and that all connections are tight.
  - If the tube is not functioning and occlusion of the drainage holes is suspected:
    - Disconnect and flush with normal saline
    - Consider fibrinolytics (particularly if a parapneumonic effusion is present)
- If an air leak within the system is suspected:
  - Sequentially clamp the accessory tubing with distal suction applied. The leak will cease when a clamp is placed proximal to the site, and the problem can then be addressed.
  - If the accessory tubing or the connections are not the problem, check the insertion site. If the skin incision is too large, the leak may be audible and can readily be addressed with an additional stitch. Also, be certain the last drainage hole has not migrated out of the pleural space.
  - If neither of these identifies the problem, a major airway injury or bronchopleural fistula may be to blame.
- Removal
  - Should be performed once the indication for tube thoracostomy has resolved
    - Will vary somewhat according to the patient population and the indication for insertion
  - For a simple pneumothorax, hemothorax, or pleural effusion, we recommend:
    - Placement of the tube on -20 cm H_2O suction initially to facilitate lung reexpansion and/or evacuation of fluid
  - Suction may not be required in some patients (i.e., those without underlying lung disease or who do not require mechanical ventilation)
    - Continue suction until the lung is re-expanded and there is no air leak. Then convert to water seal.
    - Obtain a radiograph on water seal to confirm lung expansion.
    - Remove when drainage is negligible ($<$150–200 mL per day).
  - For empyema, the infectious process must be resolved, there should be no residual empyema cavity on imaging studies, and drainage must be scant before removal
    - It is common for empyema tubes to remain in place for weeks
  - In lung resection patients, management is more complex because the routine use of suction may potentiate air leaks. We recommend consultation with the patient's surgeon regarding management of the tube(s)
  - The timing of chest tube removal relative to the respiratory cycle (i.e., end inspiration or end expiration) does not appear to be important, even in ventilator-dependent patients
  - Although routine chest radiography after removal is not a universal practice, we recommend obtaining one within 4 hours of removal to confirm lung expansion.
    - Some leaks may be very slow and require many minutes to be detected by chest films.
  - Routine clamping of chest tubes should generally be avoided.

Complications

- Reported to be as low as 2% and as high as 30%
- Improper insertion technique, operator inexperience, and forceful use of sharp trocars are avoidable errors that account for many of the complications
- Common
  - Malpositioning
    - Generally low; however, a recent study of critically ill patients who underwent CT after tube thoracostomy reported an incidence of 30%
    - Clinically more important that the tube reside in the pleural space rather than a specific location relative to the chest wall or lung parenchyma
  - Infectious
    - Insertion site (wound) infection
    - Pleural space infection (empyema) rates vary from 1% to 11%
  - Unresolved pneumothorax
  - Persistent pleural fluid collection
- Infrequent
  - Injury to the lung
    - May manifest as hemothorax, persistent air leak, residual pneumothorax, or subcutaneous emphysema
  - Injury to the intercostal vessels
    - May manifest as hemothorax and occasionally requires surgery to achieve hemostasis
  - Chylothorax
  - Long thoracic nerve injury (winging of the scapula)
  - Intercostal neuralgia
  - Horner syndrome
  - Phrenic nerve palsy
- Serious rare complications
  - Reexpansion pulmonary edema
    - Manifests as dyspnea (in the absence of lung collapse) after drainage of a large pneumothorax or hemothorax
    - Ipsilateral edema seen on chest radiograph
    - Treatment is supportive
    - Some recommend slow removal of large effusions ($<$1 L in the first 30 minutes) to minimize the risk
  - Esophageal rupture
  - Perforation of the heart or great vessels
  - Laceration of the subclavian vessels
  - Injury to the diaphragm and/or upper abdominal structures (liver, spleen, stomach, colon)
  - Puncture of silicone breast implants (intrathoracic silicosis)

KEY POINTS

- Few aspects of chest tube management have been subjected to rigorous study or are standardized.
- Patient outcomes after tube thoracostomy are related to their underlying condition(s).
  - Deaths caused by the procedure itself are infrequent.
- No clear consensus exists regarding the role of prophylactic antibiotics for tube thoracostomy, but they may be of some benefit.
  - Recent meta-analysis of studies performed in trauma patients revealed a reduction in the risk of posttraumatic empyema and pneumonia.
  - If one elects to administer antibiotics, coverage against *Staphylococcus* should be included.

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Fiber-Optic Bronchoscopy

Massimo Antonelli, Giuseppe Bello, and Francesca Di Muzio

SPECIALTY AND CATEGORY WITHIN SPECIALTY

- Intensive care medicine:
  - Diseases of the respiratory system
  - Airway management

CPT CODES

- Bronchoscopy

ICD-9 CODES

33.2 Diagnostic procedures on lung and bronchus
33.22 Fiber-optic bronchoscopy
33.24 Closed [endoscopic] biopsy of bronchus
33.27 Closed endoscopic biopsy of lung

PREPROCEDURE

Indications

- Diagnostic uses
  - To assess the patency and anatomy of the upper airway
  - To evaluate problems associated with endotracheal tubes and airway stents, such as tracheal damage, device malposition, or airway obstruction
  - To investigate lung abnormalities of unclear etiology on the chest x-ray
  - To investigate unexplained hemoptysis, cough, and localized wheeze or stridor
  - To obtain lower respiratory tract specimens by bronchoalveolar lavage (BAL) or protected specimen brushing (PSB) for cytologic or microbiologic analyses
  - To investigate the etiology of positive sputum cytology results
  - To determine the location and extent of respiratory tract injury after toxic inhalation or aspiration of gastric contents
  - To evaluate the airways for suspected tracheobronchial injury after thoracic trauma
  - To evaluate a suspected tracheoesophageal fistula
  - To perform endobronchial or transbronchial lung biopsies (TBLBs) and transbronchial needle aspirations (TBNAs) for histologic, cytologic, or microbiologic analyses
- Therapeutic uses
  - To remove retained secretions or mucus plugs not mobilized by physiotherapy
  - To retrieve foreign bodies (Videos E13.1 and E13.2)
  - To perform difficult tracheal intubations
  - To aid in performing percutaneous tracheostomy (Video E13.3)
  - To perform selective intubation of the mainstem bronchus
  - To place airway stents
  - To perform airway balloon dilatation for the treatment of tracheobronchial stenosis
  - To remove abnormal endoluminal tissue from the trachea or bronchi through the use of forceps or laser techniques

Contraindications

- Absolute contraindications
  - Absence of consent from the patient unless a medical emergency warrants the procedure
  - Lack of trained personnel to perform or directly supervise the procedure
  - Lack of adequate personnel and facilities to manage possible life-threatening emergencies
  - Inability to adequately oxygenate the patient
  - Inability to achieve adequate platelet count and coagulation status if biopsy is anticipated
  - Unstable hemodynamic status
  - Active uncontrolled bronchospasm
- Relative contraindications
  - Lack of patient cooperation
  - Unstable angina or recent myocardial infarction (within 6 weeks)
  - Acute hypercapnia
  - Acute brain injury (risk for increased intracranial pressure)
  - Severe pulmonary hypertension and uremia (increased risk for serious hemorrhage after biopsy)

Equipment

- Fiber-optic bronchoscope, comprising components that are incorporated into a functional unit (see Figs. E13.1 and E13.2)
- Control handle with the following:
  - Body that fits into the hand
  - Eyepiece, to which video or photographic devices may be attached; just under the lens, a diopter adjustment ring for image focusing
  - On some bronchoscopes, the top of the endoscopic view is marked by an indent or black triangle to assist in orientation.
  - Tip bending lever; located on the back of the handle and used to activate the up and down movement of the last 2–3 cm of the insertion cord
  - Suction control valve
  - Suction connector
  - Access port to the working channel
  - Insertion cord: it is the flexible bronchoscopic element connected to the control handle that is introduced into the airway; within it are the viewing bundle, one to three light bundles, the working channel, and two wires that control the distal tip of the scope.

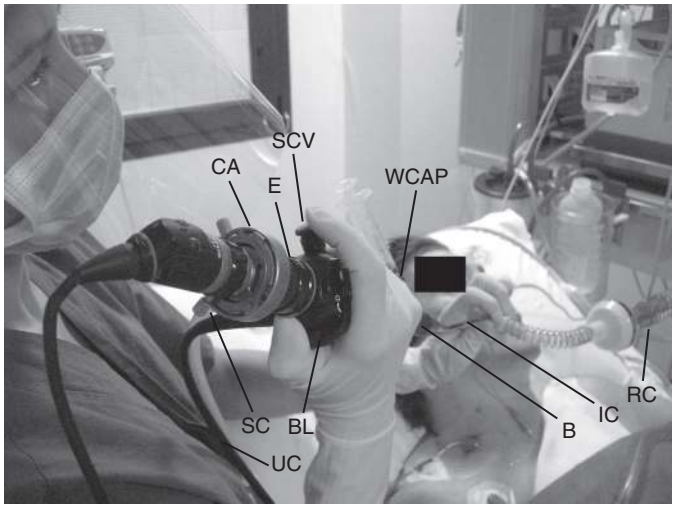

Fig. E13.1 Fiber-optic bronchoscopy in a patient under mechanical ventilation. Note how the operator uses her right hand to hold the handle of the instrument, with her thumb over the bending lever and her index finger over the suction control valve. *B,* Body; *BL,* bending lever; *CA,* camera attachment; *CH,* control handle; *E,* eyepiece; *IC,* insertion cord; *RC,* respiratory circuit; *SC,* suction connector; *SCV,* suction control valve; *UC,* universal cord; *WCAP,* working channel access port.

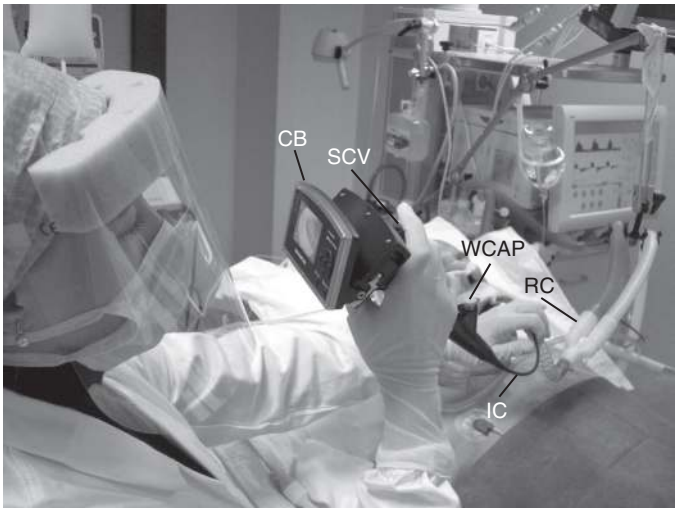

Fig. E13.2 Fiber-optic bronchoscopy in a patient under mechanical ventilation. The operator uses a recent model, battery-driven bronchoscope incorporating a video camera, light source, and recording unit. The camera body of this bronchoscope can be rotated to the right and the left side by 90 degrees to either side, and the liquid crystal display panel can be tilted from 0 to 120 degrees. *CB,* Camera body; *IC,* insertion cord; *RC,* respiratory circuit; *SCV,* suction control valve; *WCAP,* working channel access port.

- Universal cord arises from the side of the control handle and transmits the light from the light source to the bronchoscope, illuminating the field of view. The light source is the free-standing apparatus into which the universal cord attaches. In some types of bronchoscopes (portable scopes), the universal cord is not needed, as the light source is built into the control handle of the instrument and power is provided by a battery system. Modern digital flexible endoscopic systems use a charge-coupled device chip located at the end of the scope to relay digitized information to a monitor via a processor. The venting connector is a component of the bronchoscope usually located on the universal cord. The ethylene oxide sterilization venting cap and leakage tester are attached to this connector. The ethylene oxide cap must be installed when the endoscope is subjected to gas sterilization and during transportation by air. It must be removed before immersion or when the instrument is in use.
- Ancillary technical materials
  - Venous access equipment
  - Oxygen and related delivery equipment
  - Wall or portable vacuum systems and related suction supplies
  - Laser equipment, if applicable
  - Bite block, to be used in transoral procedures in awake patients
  - Sterile gauze, for clearing the tip of the bronchoscope during the procedure
  - Water-soluble lubricant
  - Antifogging systems, including warm water (max 60°C), weak soap solutions, and commercially available antifogging solutions; when fogging occurs during the procedure, bringing the tip of the scope into contact with the mucosal surface; may clarify the image.
  - Microbiology and cytology brushes, flexible forceps, retrieval valves, transbronchial aspiration needles, fixatives
  - Specimen-collection traps, syringes for medication delivery, physiologic (0.9%) saline solution for BAL
  - Laryngoscope
  - Endotracheal tubes in various sizes
  - Oral intubating airway that maintains an open passage into the oropharynx and protects the endoscope from being bitten; it is useful if the oral route is chosen in patients under general anesthesia
  - Endoscopy masks to assist fiber-optic intubation in patients being ventilated by a face mask provided with a rubber diaphragm that permits the passage of either the bronchoscope or the tracheal tube into the airways and prevents air leakage
  - Endotracheal tube introducers of various sizes
  - Cricothyroidotomy kit
  - Laryngeal mask airway or other extraglottic devices of various sizes for ventilator support in emergency situations; laryngeal mask airway may also be used to aid the passage of the bronchoscope into the trachea
  - An adapter to facilitate insertion of the bronchoscope while preventing loss of the respiratory gases and maintaining ventilation and positive end-expiratory pressure throughout the procedure during either invasive or noninvasive ventilation (NIV)
  - Self-inflating or anesthesia bag attached to a face mask by a T-adapter; used for bag-mask ventilation in nonintubated, sedated patients undergoing bronchoscopy
  - Resuscitation equipment
- Medications
  - Lidocaine (1%–2%) for topical anesthesia; the minimum amount of lidocaine necessary should be used when installing through the endoscope; the total dose of lidocaine should be limited to 8.2 mg/kg in adults; particular care is needed when administering lidocaine to patients with liver or cardiac failure
  - Sedative agents (e.g., benzodiazepine and propofol)
  - Synthetic narcotics (e.g., fentanyl or remifentanil) to provide sedation and analgesia and to suppress the cough reflex
  - Benzodiazepine and/or narcotic antagonists
  - Epinephrine (usually 1:10,000 dilution) for bleeding control
  - Nasal decongestants
  - Emergency and resuscitation drugs

- Monitoring devices
  - Pulse oximeter
  - Continuous electrocardiogram
  - Continuous intraarterial blood pressure or intermittent cuff blood pressure measurement at least every 5 minutes
  - Intracranial pressure, essential in patients with serious brain injury
  - End-tidal carbon dioxide, useful in patients with brain injuries
  - Respiratory function monitoring of patients under mechanical ventilation for following ventilation parameters, such as exhaled tidal volume and peak inspiratory pressure
  - Chest x-ray 1 hour after transbronchial biopsy to exclude pneumothorax
- Cleaning and sterilization equipment
  - Dedicated room for cleaning and manual or automated sterilization; automated washer disinfectors are recommended to minimize staff contact with disinfectant and their fumes
  - Soft nonabrasive cleaning cloth to gently wipe the external surfaces and components of the endoscope immediately after use
  - Water or neutral detergent solution to irrigate all accessible channels of the endoscope at the end of the procedure
  - Leak testing system
  - Cleaning brushes and neutral detergent solution for a thorough cleaning of the internal and external surfaces of the endoscope: cleaning brushes are passed through the working channel access port, the suction port opening, and the suction connector. They are also used carefully to clean the distal end of the instrument.
  - Protease enzymatic agent for cleaning and the removal of blood and protein residues
  - High-level disinfection or sterilization agents (e.g., peracetic acid, glutaraldehyde, or ethylene oxide)
  - Sterile water for rinsing the endoscope
  - 70% ethyl or isopropyl alcohol to flush the external surfaces and inner channels of the endoscope. This is used when the quality of the rinse water is in doubt or to assist in the drying process.
  - Cupboard to hang the endoscope

ANATOMY

- See Video E13.4
  - The trachea passes from the larynx to the level of the fourth or fifth thoracic vertebra, where it bifurcates into the two main bronchi (i.e., the left and the right) at the anatomic point known as the *main carina*. The trachea has an inner diameter of about 21–27 mm and a length of about 10–16 cm. About 15–20 incomplete C-shaped cartilaginous rings reinforce the anterior and lateral sides of the trachea and main bronchi. The posterior wall, or membranous trachea, is free of cartilage and contains bundles of muscle fibers that insert into the posterior ends of the cartilage plates. The anterior (ventral) and posterior (dorsal) directions can be identified by noting the relative flattening and flexibility of the posterior wall of the lumen.
- Bronchi
  - The right main bronchus is wider, shorter, and closer to the midline than the left main bronchus. The cartilage and mucous membrane of the main bronchi are similar to those of the trachea. At the level where the main bronchi enter the lungs, the membranous region disappears, and the cartilage plates are no longer C-shaped but are smaller, more irregular, and arranged to surround the circumference of the airway. At this level, the muscular coat no longer inserts into the cartilage, but forms a separate layer of interlacing bundles. Consequently, the airway lumen can be occluded by the contraction or flaccidity of the muscle.
  - The right main bronchus subdivides into three lobar bronchi, whereas the left main bronchus divides into two. The lingula of the left lung, nominally a part of the left upper lobe, is analogous to the right middle lobe. The lobar bronchi divide into segmental bronchi, each of which supplies a bronchopulmonary segment. The bronchopulmonary segments are the topographic units of the lung, and they are used to identify regions of the lung either radiologically or surgically. There are 10 bronchopulmonary segments per lung, but because of anatomic development, some of the segments in the left lung fuse, giving rise to 8 segments. For counting orders or generations of airways, the main bronchi are usually counted as the first generation, the lobar bronchi as the second generation, and so on peripherally. Generally, in adult subjects, a bronchoscope with an outer diameter of 5 mm cannot be advanced farther than the fourth- or fifth-order bronchi.
- Bronchioles
  - As the branching continues through the bronchial tree, the amount of hyaline cartilage in the walls decreases until it is absent in the bronchioles, which lie distal to the bronchi, beyond the last plate of cartilage. When any airway is pursued to its limit, the terminal bronchiole is reached. Each terminal bronchiole then gives rise to several respiratory bronchioles, which lead to the alveolar ducts and sacs. The alveolus is the basic anatomic unit of gas exchange in the lung.
- Nomenclature of peripheral bronchi
  - The nomenclature commonly used for the bronchial anatomy is that of Jackson and Huber. Subdivisions of the bronchial tree correspond to the anatomic segments and are named accordingly.
  - The right main bronchus gives rise to three lobar bronchi: upper, middle, and lower. The portion of the right main bronchus between the upper lobe bronchus and the origin of the middle and inferior lobe bronchi is known as the lower part of the right main bronchus, or bronchus intermedius. The right upper lobe bronchus is subdivided into three segmental bronchi: the apical, posterior, and anterior. The right middle lobe bronchus branches into two segmental bronchi: the lateral and medial. The right lower lobe bronchus gives rise to five segmental bronchi: the superior segmental bronchus, posteriorly directed and situated just below the orifice of the middle lobe bronchus, and more distally, four basal segmental bronchi: the medial, anterior, lateral, and posterior; occasionally, the medial basal bronchus is partially separated from the other basal segments by an extra fissure.
  - The left main bronchus subdivides into two lobar bronchi: the upper and lower. The left upper lobe bronchus subdivides into a superior division bronchus and a lingular division bronchus. The superior division has two segmental bronchi: the apicalposterior and anterior. The lingular division has two segmental bronchi: the superior and inferior. The anatomy of the left lower lobe bronchus is similar to that of the right lower lobe bronchus, except that there are usually only three basal segmental bronchi on the left: the anteromedial, lateral, and posterior. Compared with the right side, the superior segment of the left lower lobe bronchus arises more proximally than the orifices serving the basal pyramid.
  - With the advent of fiber-optic bronchoscopy, Dr. Shigeto Ikeda introduced additional nomenclature for the fourth, fifth, and

sixth divisions. According to this nomenclature, the segmental bronchi are numbered from 1 to 10 on each side and are identified with the capital letter "B" for bronchus and prefixed by the capital letter "R" for right or "L" for left. This way, LB6 identifies the superior segmental bronchus of the left lower lobe. Subsegmental, or fourth-order bronchi, are designated by the lowercase letter "a" for posterior and "b" for anterior; the letter "c" may be used for additional bronchi. Fifth-order bronchi are identified by the Roman numerals "i" (posterior) and "ii" (anterior). Finally, "α" and "β" are used for sixth-order bronchi.

- Variations of the bronchial anatomy are not infrequent.
- Key bronchoscopic anatomic features
  - Right lung. The orifice of the bronchus to the right upper lobe is in the 3 o'clock position, and its distance from the carina is quite variable. The arrangement of the three segmental bronchi of the right upper lobe bronchus is nearly symmetric. Just beyond the lower section of the right main bronchus, or bronchus intermedius, the typical anatomic configuration consists of the orifice of the middle lobe bronchus, anteriorly directed, in the 12–2 o'clock position; the orifice of the bronchus to the superior segment of the lower lobe, at the same level but in the 6–7 o'clock position; and, directly in front, the basal segmental bronchi of the right lower lobe.
  - Left lung. After entering the left main bronchus, the orifices of the upper and lower lobe bronchi generally lie in the top left and bottom right, respectively, of the bronchoscopic image field. Within the orifice of the left upper lobe bronchus, the lingular division bronchus lies (clockwise) to the right of the superior division bronchus. Inside the entrance of the left lower lobe bronchus, the orifice of the superior segmental bronchus is in the 6–7 o'clock position, just as in the right lung.

PROCEDURE

- Define the indication for fiber-optic bronchoscopy.
- Choose the size of the bronchoscope as indicated by the intended procedure, the patient size, and the size of the endotracheal tube; a large bronchoscope with a wide working channel provides excellent suction performance and permits the passage of large bronchoscopic tools. In adult patients with tracheal intubation, an outer diameter of the bronchoscope at least 1.5 mm narrower than the lumen of the endotracheal tube can prevent excessive increases in airflow resistance, gas trapping, and airway pressure that decrease delivered tidal volume.
- Assure the bronchoscope is in proper working order.
- Check any cameras and/or video equipment that may be used.
- Assess the patient's medical, physiologic, and psychologic status.
- Reassure the patient, if conscious.
- Prescribe appropriate premedication, if needed.
- Establish intravenous access.
- Connect the bronchoscope to the light source when it is present, turn on the light, adjust the focus (e.g., by looking at written material until a clear view is obtained), and obtain the white balance.
- Connect the suction catheter to the suction connector.
- Place the distal end of the insertion cord of the bronchoscope into warm water.
- Apply or check the monitoring.
- Place the patient in a supine, semirecumbent, or even sitting position, depending on the type of procedure.
- Start topical anesthesia, general anesthesia, or intravenous sedation, based on the needs of the patient.
- Stand behind or to the left or right side of the patient. If you stand to the side, you can approach the patient either from behind or the front; in the latter situation, once the bronchoscope has passed into the pharynx, the superior part of the endoscopic view will correspond to the inferior region of the patient. The endoluminal landmarks described earlier guide the operator's orientation.
- Lubricate the bronchoscope.
- Handling the bronchoscope. Right-handed users will find it easier to hold the handle of the instrument with their right hand, with the index finger over the suction valve and the thumb actuating the bending lever, and to use their left hand to hold the insertion cord. The black cursor in the viewfinder, when present, describes the plane of movement of the tip of the endoscope.
- The bronchoscopic procedure requires only three movements: (1) flexion of the tip of the bronchoscope along the plane of the cursor; (2) rotation of the entire endoscope to the left or right; and (3) the advancement or withdrawal of the instrument. The goal is to keep the point of interest (e.g., vocal cords, bronchial orifice, etc.) in the center of the field. When the bending lever is depressed, the tip rises, whereas when the lever is elevated, the tip is directed in the opposite direction. The insertion cord should be kept as straight as possible to either prevent accidental damage to the bronchoscope or improve the control over the tip of the instrument. To look right, the tip of the bronchoscope may be turned upward while the control handle is twisted clockwise. Alternatively, the insertion cord may be rotated anticlockwise with the tip turned downward. To look left, the insertion cord is rotated clockwise or anticlockwise with the tip deflected downward or upward, respectively. The operator will decide which maneuvers to perform depending on the ease of obtaining the desired movements.
- The insertion cord should be able to rotate throughout its length when the handle is rotated axially to avoid distortion of the image orientation. This orientation distortion resulting from the axial rotation usually occurs when the distal end of the bronchoscope is blocked by the airtight rubber seal at the entrance of the endotracheal tube or even by the inside walls of the endotracheal tube. In these circumstances, the tip of the bronchoscope fails to rotate synchronously with the proximal end of the instrument.
- When a camera attachment is used with the bronchoscope, the camera position relative to the bronchoscope needs to be calibrated by rotating the bronchoscope camera system until a certain movement inside the patient's airway corresponds with the proper motion on the monitor.
- The bronchoscope may be inserted into the airway through the nose or the mouth in spontaneously breathing patients or through the endotracheal tube in intubated patients. During NIV, the bronchoscope is passed through the NIV interface (Videos E13.5 and E13.6).
- The application of NIV during bronchoscopy may be useful either in at-risk hypoxemic patients who are initially breathing spontaneously and who start NIV to assist bronchoscopy or in patients who are already receiving NIV and scheduled to undergo bronchoscopy during NIV. When NIV is administered through a face mask, a T-adapter with a sealing connector is attached to the mask for insertion of the bronchoscope through the nose or the mouth.
- Fiber-optic intubation. The endoscope may be passed transnasally or transorally through the vocal cords into the trachea. Then the endotracheal tube is slipped over the instrument.
- Sampling techniques. Samples from the lower airways are commonly obtained by BAL, PSB, TBLB, and TBNA. When BAL or PSB is performed, the sampling area is selected based on the location of the new or progressive infiltrate on a chest x-ray or the segment visualized during bronchoscopy as having purulent secretions. Data are lacking for the optimal sampling site in patients with diffuse lung infiltrates.

- BAL. The tip of the bronchoscope is wedged as far as possible into a distal airway (generally a fourth- or fifth-order bronchus), and a sterile saline solution is instilled through the bronchoscope and then aspirated into a sterile trap. Minimal injecting pressure is advisable so as to avoid inadvertent alveolar rupture. Aliquots of 20–60 mL are injected and aspirated back after each instillation. The total amount of fluid used to perform BAL ranges from 140 to 240 mL. In the supine patient, BAL fluid recovery is best from the right middle lobe or lingula. At least 5 mL of retrieved fluid are needed for adequate microbiologic analysis. The first aliquot of aspirated fluid is likely to contain a large amount of material from the proximal airway and must be analyzed separately from the rest. The recovery of more than 5% squamous epithelial cells in the BAL specimen indicates proximal tracheobronchial contamination. Because lidocaine has bacteriostatic properties, the use of this local anesthetic could alter the microbiologic results.
- PSB. This technique is performed using a retractable brush within a double-sheathed catheter having a distal dissolvable plug that initially occludes the outer catheter. First, the tip of the bronchoscope is positioned close to the sampling area. Next, the catheter is inserted through the working channel and advanced 1–3 cm beyond the distal end of the bronchoscope to avoid the collection of pooled secretions around the distal tip of the instrument. The inner catheter containing the brush is advanced to eject the distal plug into a large airway, and the brush is advanced under direct vision into the desired subsegment. Once the sample is obtained, the brush is retracted into the catheter, which is then withdrawn and removed from the bronchoscope. The brush is then advanced beyond the catheter, cut with sterile scissors, and placed into 1 mL of transport medium to avoid drying.
- TBLB. Histologic samples of the bronchial mucosa, bronchial wall, lung parenchyma, and alveoli may be obtained using TBLB. In diffuse lung disease, the biopsy specimen should be taken from a peripheral airway, preferably the lower lobe. In this way, the danger of significant bleeding may be reduced, owing to the smaller caliber of the distal bronchial vessels. The number of biopsies needed for TBLB is not standardized. However, seven to eight biopsy specimens have been proposed for localized lung lesions, whereas five TBLB samples from one lung seem to ensure a high diagnostic yield for most diffuse lung diseases.
- TBNA. TBNA may be used to obtain tissue samples from paratracheal, hilar, and peribronchial areas. For visible tumors, the yields of TBNA and forceps biopsy are similar. A protected transbronchial needle is passed through the working channel of the bronchoscope and positioned with the needle perpendicular to the endobronchial wall. The tracheal wall, carina, mainstem bronchus, or major spur is pierced with a quick thrust. Suction is then applied to the proximal end of the needle sheath with a 20-mL syringe containing 2 mL of saline solution. The needle and sheath are removed from the bronchoscope, and the specimen is ejected into a suitable container for cytologic analysis. If a dry syringe is used, the specimen is smeared on a glass slide before the examination. At each biopsy site, two or three punctures are commonly made, employing a new needle for each location.
- Recommendations for bronchoscopy during mechanical ventilation through the endotracheal tube include the following:
  - Insert a connector between the endotracheal tube and the ventilator tubing through which to slide the bronchoscope. Volume-controlled ventilation is usually preferred. Set the fraction of inspired oxygen (FiO_2) at 100%, and remove or reduce positive end-expiratory pressure, except in very severe respiratory failure. Increase respiratory frequency and decrease tidal volume; increase percent inspiratory time. Set the peak pressure alarm to a level that allows adequate ventilation. After the procedure, return all ventilator parameters to their initial values. Over the first 30 minutes after the termination of bronchoscopy, gradually reduce the applied FiO_2 to the prebronchoscopy requirements, provided that the patient can maintain an arterial oxygen saturation of hemoglobin measured by a pulse oximeter (SpO_2) at >92%.
  - Other procedural considerations. Enteral feeding or oral food intake should be suspended for at least 4 hours before the procedure. Asthmatic subjects should be premedicated with a bronchodilator before the procedure. Platelet count and coagulation times should be checked before performing bronchoscopy in patients in whom a biopsy is anticipated.

AFTER THE PROCEDURE

Postprocedure Care

- Monitoring
  - Level of consciousness
  - Medications administered
  - Subjective responses (e.g., pain, discomfort, and dyspnea)
  - Blood pressure, heart rate, rhythm, and changes in cardiac status
  - SpO_2 and supplemental oxygen use
- Close surveillance to promptly detect and treat any new findings presenting over the first hours after the end of the procedure (see "Complications")
- Nothing by mouth for 2 hours

Complications

- Common:
  - Hypoxemia commonly occurs during bronchoscopy; the insertion of a bronchoscope into the airways reduces the cross sectional area available for airflow, thus increasing the airway resistance and the work of breathing. Continuous suctioning through the instrument evacuates gas from the airway and decreases the residual functional capacity, often leading to the development of hypoxemia. Hypoxemia may be more severe after BAL, owing to ventilation-perfusion abnormalities induced by the instillation of a saline solution; the decrease in arterial oxygen partial pressure resulting from bronchoscopy may last a few minutes to several hours after the removal of the bronchoscope
  - Mild hypercapnia
  - Increased airway resistance
  - Modest alterations in systolic blood pressure, consisting of either a decrease (generally related to sedation) or an increase from the baseline
  - Slight increase in heart rate
- Infrequent:
  - Periprocedural adverse drug reactions
  - Bronchospasm or laryngospasm, particularly in patients with preexisting reactive airway disease
  - Major cardiac rhythm abnormalities; the risk of arrhythmias is the greatest during the passage of the bronchoscope through the vocal cords in nonintubated patients, especially if hypoxemia is present
  - Bradycardia or other vagally mediated phenomena
  - Epistaxis, in transnasal procedures
  - Pneumothorax; it is very uncommon after bronchoscopy, but has an increased incidence in patients undergoing TBLB

  - Significant bleeding, defined as more than 50 mL of blood loss; the likelihood of hemorrhage from bronchoscopy increases when biopsy or brushing procedures are performed; patients at a higher risk of bleeding include those with uremia, immunosuppression, pulmonary hypertension, liver disease, coagulation disorders, or thrombocytopenia
  - Fever and chills; fever rarely occurs after bronchoscopy (1.2%), but occurs more commonly (10%–30% of cases) after BAL; fever is thought to be generally caused by the release of proinflammatory cytokines from alveolar macrophages and does not itself indicate a developing infection related to the procedure
  - Nausea, vomiting
  - Cross-contamination of bronchoscopes
- Serious, rare complications:
  - Death

OUTCOMES AND EVIDENCE

- Outcome after bronchoscopy depends on the patient's coexisting condition; flexible bronchoscopy is associated with a 0.3% incidence of major complications and a mortality rate of 0.02%; major complications requiring resuscitative measures are significantly more likely with rigid bronchoscopy as compared with flexible bronchoscopy.
- The most frequent life-threatening complications leading to death after bronchoscopy include airway problems, cardiovascular events, and bleeding.

SUGGESTED READING

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Bronchoalveolar Lavage and Protected Specimen Bronchial Brushing

Lillian L. Emlet

BEFORE THE PROCEDURE

Indications

- Diagnosis of pneumonia
  - Viral, bacterial, fungal, pneumonias
  - Quantitative cultures for ventilator-associated pneumonias
  - Infiltrates in an immunocompromised host
- Evaluation of diffuse lung infiltrates and evaluation of interstitial lung disease
- Suspected pulmonary hemorrhage
- Suspected malignancies
- Both bronchoalveolar lavage (BAL) and protected specimen bronchial brushing (PSB) use quantitative culture techniques to differentiate between airway colonization and true pulmonary infections.[1–4]

Contraindications

- Acute respiratory distress syndrome with hypoxemia
  - May cause derecruitment in noncompliant severe air space disease
  - Cardiac arrhythmias, hypoxemia, bronchospasm
- Bronchopleural fistula
  - May not be able to return adequate specimen for analysis

Equipment

- Flexible fiberoptic bronchoscope
- Sterile saline
- Vacuum suction source
- Suction tubing
- Syringes: 10 mL, 20 mL, or 60 mL slip-tip
- Sterile collection trap
- Lidocaine, 1%–2% for topical anesthesia, if needed
- Medications for procedural conscious sedation, if needed
- Burman airway or oral airway
- Supplemental oxygen
- Endotracheal bronchoscope attachment

ANATOMY

- If performed on native airways, the first structures to be identified are the epiglottis and the vocal cords.
  - Topical anesthesia using 1%–2% lidocaine is administered through a bronchoscope to the vocal cords.
- The next landmark to be located is the trachea and the identification of the carina.
  - Additional administration of 1%–2% lidocaine to the carina.
- Right and left main bronchi are identified, and the location of the desired BAL specimen is obtained at the site where purulent material is present or where infiltrate is visible on the chest x-ray.[5]
- If unsure as to which lobe needs to be sampled, the posterior portion of the right lower lobe should be sampled first. Autopsy studies indicate that pneumonias in intensive care unit (ICU) patients often involve this lobe.[6–9]
- To obtain the BAL, the bronchoscope is advanced to the farthest segment of the affected bronchus until it cannot be advanced any farther.

PROCEDURE: BRONCHOALVEOLAR LAVAGE

See Video E14.1.

- Obtain informed consent, including for topical anesthesia of airways and/or conscious sedation.
- Prepare for conscious sedation, and use telemetry devices to monitor continuous pulse oximetry, intermittent blood pressure cuff measurement, and supplemental oxygen (via nasal cannula or nonrebreather mask or ventilator).
- For patients at risk of bronchospasm, premedicate with bronchodilators, and treat airways with 2% lidocaine via an atomizer.
- Review the chest radiograph to identify the ideal location for BAL. The right middle lobe or lingula is preferred in supine patients, with the right lower lobe also serving as a possible direct path for aspiration.
- Prepare the bronchoscope, collection trap, tubing, and sterile saline.
- Anesthetize vocal cords in nonintubated patients and the carina in intubated patients with 2% lidocaine (5 mg/kg maximum).
- Avoid suctioning before obtaining the BAL specimen to avoid specimen contamination.
- Advance the bronchoscope until wedged in the desired subsegmental bronchus.
- Flush 20 mL sterile saline through the wedged bronchoscope, watching for the flow of saline into distal airways and for the blanching of tissues.
- Obtain the sample immediately after the wash, ensuring the return of the lavage specimen into the collection trap.
- Slight repositioning of bronchoscope tip can allow for better fluid return.
- Intermittent pulsing of suctioning can reduce distal airway collapse.
- Repeat 20-mL sterile saline washes as necessary to obtain an adequate sample (usually a total of 30–50 mL, which is usually 40%–70% recovery of total instilled volume).
- Larger-volume aliquots for lavage can be used (as much as 50 mL per lavage, with total volume of 120 mL in 3–6 aliquots).[5,10]

  - Estimated alveolar surface area distal to the wedged bronchoscope is 100 times greater than the peripheral airway.
- Fluid return of the BAL can affect the validity of results, and small returns may contain only diluted material from the bronchus rather than the alveoli, resulting in false negatives.[11]
  - In patients with highly collapsible airways, including patients with chronic obstructive pulmonary disease (COPD), the amount of negative pressure applied via the bronchoscope to aspirate the sample can limit the amount of sample returned and may give rise to a false-negative result.
- Sensitivity of BAL is 71% and specificity is 80% (95% confidence interval [CI], 66%-86%) in the diagnosis of pneumonia.[12–23,33]

PROCEDURE: PROTECTED SPECIMEN BRONCHIAL BRUSHING

- Same procedure as BLA, except for the use of an endobronchial catheter wedged in the tracheobronchial tree.
- The brush is rubbed against areas of suspected infection and then removed from the procedure port of the bronchoscope.
- The brush is then aseptically cut into a measured volume of sterile diluent (usually 1 mL of preservative-free sterile saline).[10,24]
- Double-lumen catheter brush systems with single-sheathed or telescoping plugged catheter tips with distal occluding plugs are used.[24–26]
- Quantitative cutoff is 10^3 colony-forming units per milliliter (CFU/mL).
- Sensitivity of protected specimen bronchial brushing for pneumonia is 61% (95% confidence interval [CI], 44%–77%) and specificity is 76% (95% CI, 92%–97%).[13,27–33]

AFTER THE PROCEDURE

Postprocedure Care

- Patients are continuously monitored until full recovery from conscious sedation.
- Ventilated patients are placed on 100% fraction of inspired oxygen (FiO_2) during the procedure and weaned back to previous FiO_2 levels, as tolerated. Derecruitment is possible and may require recruitment maneuvers.
- Specimen handling
  - For PSB, the brush should be aseptically cut into 1 mL of preservative-free sterile saline.[10,24]
  - For BAL, the specimen container should be sent for analysis within 30 minutes, although refrigeration can prolong transport and analysis.[34,35]
- The specimen should be obtained before new antibiotics are administered.
  - Even a few doses of antibiotics can result in negative microbiologic cultures.[36]
  - Quantitative culture techniques of distal pulmonary secretions with minimal or no upper airway contamination.[1,2]
  - BAL and PSB culture sensitivities are lowered if antibiotic therapy has already been initiated.[37–39]
- These techniques do not retrospectively identify resolving pneumonia or assess the adequacy of therapy.[9,40–43]

Complications

- Common
  - Cough
  - Transient infiltrates that typically resolve in 24 hours
  - Transient decrease in partial pressure of oxygen (PaO_2)
- Infrequent
  - Transient fever, chills, myalgias[44]
- Serious, rare complications
  - Derecruitment and hypoxemia resulting in intubation and positive-pressure ventilation or increase in ventilator requirements[45–48]
  - Pneumothorax

KEY POINTS

- Quantitative culture techniques are necessary to differentiate, infecting organisms from pharyngeal contaminants.[49–53]
  - Significant BAL culture concentrates are at least 10^5–10^6 CFU/mL.[2,6,54–57]
  - Significant PSB culture concentrates are at least 10^3 bacteria.[10]
- A small number of false-positive BAL and PSB results can be seen even when using strict criteria to distinguish between airway colonization and deep lung infections of 10^3–10^4 CFU/mL.[58]
- False-negative BAL and PSB results occur when:
  - Bronchoscopy is performed at an early stage of infection and bacterial load is not high enough to reach diagnostic significance.
  - Specimens are obtained from unaffected segments of lung.
  - Specimen processing errors occur.
  - Specimens are obtained after initiation of a new class of antibiotics.
  - Consider repeat sampling for persistently symptomatic patients with initial negative quantitative concentrations.[59]

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Percutaneous Dilatational Tracheostomy

Cherisse Berry and Daniel R. Margulies

BEFORE THE PROCEDURE

Indications

- Requirement of a temporary or long-term artificial airway for prolonged mechanical ventilation
- Management of secretions
- Nonemergency airway obstruction

Contraindications

- Inability to clearly palpate and identify tracheal landmarks
- Enlarged thyroid or other neck mass
- Active infection at the site
- Emergency need for airway
- High ventilatory requirements (FiO_2 ≥70%, positive end-expiratory pressure [PEEP] greater than 15 cm H_2O)
- Bleeding
- Increased intracranial pressure
- Clinically significant coagulopathy or supratherapeutic international normalized ratio (INR) or partial thromboplastin time (PTT)
- Documented tracheomalacia
- Cervical irradiation
- Morbid obesity
- Maxillofacial or neck trauma
- Lack of cervical spine clearance
- Inability to extend the neck because of a cervical spine fracture
- In addition, we do not perform the procedure in patients younger than 16 years of age because of the scarcity of experience reported in pediatric patients

Equipment

- Equipment required at the bedside to perform the percutaneous dilatational tracheostomy (PDT) procedure should include
  - PDT introducer set (Ciaglia Blue Rhino Percutaneous Tracheostomy Introducer Set #C-PTIS-100-HC, Cook Critical Care, Bloomington, Indiana)
  - Bronchoscope with video monitor display and bronchoscopy endotracheal tube adapter
  - Continuous electrocardiographic (ECG) monitor
  - Blood pressure monitoring device
  - Pulse oximeter
  - Free-flowing intravenous catheter
  - Mechanical ventilator
  - Suction
  - Resuscitation ("crash") cart
  - Open tracheostomy instrument tray (unopened)
- Supplies required at the bedside include:
  - ChloraPrep or other solution for skin preparation
  - 4 × 4-inch bandages
  - Syringes and needles
  - Sterile gowns and gloves
  - Shiley Percutaneous Dual Cannula Cuffed Tracheostomy Tube
  - Kelly clamp
  - Sterile saline solution
- Medications required at the bedside include:
  - 1% xylocaine with epinephrine 1:100,000.
  - Midazolam, 1 mg/mL injectable or other appropriate sedative.
  - Morphine, 10 mg injectable or another appropriate narcotic.
  - Vecuronium, injectable, or other appropriate paralyzing agent.
  - Sterile normal saline flush solution.
  - Other medications at the discretion of the PDT operator.
  - The choice of a PDT introducer set may vary by institution; ours includes the set listed only because we have significant experience with it. However, it is critical that only one type of PDT introducer set be in use in an institution at any given time. To ensure maximum safety, every aspect of this procedure must be standardized, especially the equipment used.

ANATOMY

The thyroid notch and cartilage are palpated, followed by the cricothyroid membrane and cartilage and the tracheal rings. It is essential that the tracheal puncture be made inferior to the cricoid cartilage landmark. If the second and third tracheal rings cannot be distinctly identified, the procedure is aborted, and an open tracheostomy is performed.

ULTRASOUND

Although not required, the use of real-time ultrasound guidance can help to identify pretracheal vessels and high-risk vascular anatomy overlying the PDT site. Identification of these vessels before proceeding with PDT can help reduce bleeding risk, the risk of air embolism, and the risk of surgical intervention for hemostasis.

PROCEDURE

See Video E15.1.

- A single tapered PDT dilator and kit with simultaneous intraoperative bronchoscopy is used.
- Two teams are used simultaneously. One team manages the endotracheal tube, and the other manages the placement of the tracheostomy tube.
- The patient's physiologic parameters, including arterial oxygen saturation, are monitored continuously throughout the procedure by the intensive care unit (ICU) nurses and a respiratory therapist.
- Intravenous sedation and paralytic agents are administered as required, and the patient is fully ventilated via an endotracheal tube.

- The patient is positioned with the neck slightly extended and a pillow under the shoulders.
- Under sterile conditions, the PDT dilators and tracheostomy tube must be prepared.
- The Blue Rhino tracheal dilator is water activated, so it is dipped in sterile saline or water to enhance its lubricant coating.
- The Shiley Percutaneous Dual Cannula Cuffed Tracheostomy Tube is designed specifically to be used with the Cook Percutaneous Tracheostomy Introducer Set. Depending on the size of the patient, it is prepared by inflating the balloon to ensure the integrity and then collapsing the balloon by withdrawing all air.
- The tracheostomy tube, with the cuff, completely deflated, is inserted over the introducer dilator as one unit, placed 2 cm from the tip of the dilator, and then lubricated with sterile gel. The Shiley's tapered distal tip and inverted cuff shoulder are specifically designed for easier insertion. It is important that the tracheostomy tube be placed exactly 2 cm from the tip. If it is placed more than 2 cm from the tip, it will likely not enter the trachea. If it is advanced too far and placed less than 2 cm from the tip, the trachea may be damaged upon insertion.
- The neck is prepared with ChloroPrep.
- The dermis and subcutaneous tissues are infiltrated with 1% lidocaine with epinephrine.
- The upper airway endoscopist will then introduce the bronchoscope into the endotracheal tube.
- The endotracheal tube is untaped, the cuff deflated, and the tube is then withdrawn until the tip lies just below the vocal cords. The utmost care is taken to avoid withdrawing the endotracheal tube too far, which could result in extubation of the patient. We recommend that the bronchoscope remain near the tip of the endotracheal tube but entirely within it to prevent inadvertent puncture or spearing of the bronchoscope by the puncture needle.
- The PDT operator verifies the patient's neck anatomy, starting with palpation of the thyroid notch and cartilage and then moving down to the cricothyroid membrane and cartilage and the tracheal rings.
- The anatomy is reconfirmed with digital palpation of the cricoid cartilage because it is essential that the tracheal puncture is made inferior to this landmark. If the second and third tracheal rings cannot be distinctly identified, the procedure is aborted, and an open tracheostomy is performed.
- A 2-cm horizontal or vertical skin incision centered between the second and third tracheal rings is made, and the midline subcutaneous tissues are dissected bluntly with a hemostat until the pretracheal fascia is exposed. Before tracheostomy, the trachea is approximately 2–2.5 cm deep from the skin at the suggested insertion site.
- The PDT operator reconfirms the tracheal anatomy by direct palpation through the incision. The trachea is then punctured between the second and third tracheal rings with a 14-gauge cannula-over-needle from the PDT kit.
- Tracheal penetration is confirmed by visualization with the bronchoscope, in addition to aspiration of air from the needle.
- The needle is removed, and a J-tip guide wire is then introduced into the trachea through the cannula and visualized with the bronchoscope. The puncturing cannula is then withdrawn.
- A small 14F dilator is then introduced over the guide wire to widen the tracheal opening. The dilator is then withdrawn.
- An 8F guiding catheter is introduced over the guide wire to the skin level mark on the guide wire. The guiding catheter and guide wire are introduced as a unit into the trachea until the safety ridge on the guiding catheter is at the level of the skin. The positioning of the guiding catheter is confirmed by aligning the proximal end of the catheter with the proximal gray mark on the guide wire. This positioning is critical to prevent displacement of the J-tip guide wire and possible trauma to the posterior tracheal wall during subsequent dilatations.
- The lubricated Blue Rhino tracheal dilator is then passed over the cannula and guide wire and into the trachea to dilate the tract fully. This requires forceful pressure to accomplish smoothly.
- The tracheal dilator is then withdrawn, but the guiding catheter and guide wire remain in place.
- The tracheostomy tube and introducer dilator are threaded over the guide cannula and guide wire as one unit and inserted into the trachea under direct bronchoscopic visualization.
- The introducer dilator, guiding catheter, and guide wire are then withdrawn, leaving the tracheostomy tube in place.
- The inner cannula is then inserted, and the cuff is inflated.
- The PDT operator continues to hold the tracheostomy in place with one hand and never removes it until the tracheostomy tube is sutured in all four corners to ensure the tube is not inadvertently displaced.
- The bronchoscope is then inserted into the tracheostomy tube to confirm placement within the trachea.
- The ventilator tubing is then connected to the tracheostomy. The appropriate tidal volume and oxygen saturation are confirmed.
- The tracheostomy tube is sutured to the neck with 4-0 gauge nylon sutures placed in each corner.
- Once the tracheostomy tube is sutured in all four corners and also secured around the neck with umbilical tape, the endotracheal tube is removed. Make sure that the umbilical tape is not placed too tightly, as skin breakdown can result. At least one finger should be able to fit between the umbilical tape and the skin.

AFTER THE PROCEDURE

Postprocedure Care

- A simple 4 × 4-inch gauze dressing is partially slit and placed between the tracheostomy wings and the skin.
- A chest radiograph is not indicated unless the procedure was complicated.
- Close observation by the nursing staff is required to detect bleeding externally at the tracheostomy site or internally into the airway. The bleeding must be immediately reported to the PDT operator and the ICU physician and must be carefully evaluated and controlled.
- Bleeding into the airway can lead to the formation of an obstructing clot at the carina, with fatal consequences (Table E15.1).

OUTCOMES AND EVIDENCE

- PDT is a safe procedure, with morbidity and mortality rates equivalent to or lower than those of an open tracheostomy.
- Numerous early studies reported the morbidity of PDT to be between 3% and 19%, compared with a complication rate of 26%–63% for open tracheostomy.
- Recent studies have found the overall mortality for a tracheostomy to be 37%, with no statistically significant difference in mortality for PDT compared with an open tracheostomy.
- The incidence of wound infection has been reported to be 6.6%.
- One study compared PDT with surgical tracheostomy (ST) and found that PDT was associated with a significantly reduced risk of wound infection (odds ratio [OR], 0.28; 95% confidence interval [CI], 0.16–0.49; $P < 0.0005$).
- One report found the overall incidence of bleeding to be 5.7%, with no significant difference in incidence when comparing PDT with ST.

TABLE E15.1 Complications of Percutaneous Dilatational Tracheostomy

Immediate	Early	Late
Bleeding (minor venous oozing)	Pneumothorax	Stomal infection
Puncture or laceration of the posterior tracheal wall	Subcutaneous emphysema	Tracheo-inncominate fistula
Tracheal ring fracture	Pneumomediastinum from an esophageal injury	Tracheo-esophageal fistula
Brief episodes of hypoxia or desaturations	Unplanned decannulation	Tracheal stenosis
Serious hemorrhage from a severed blood vessel	Tracheostomy tube occlusion from secretions/mucus plugs	Unplanned decannulation
Loss of airway	Cuff leak	Voice changes
Paratracheal cannulation	Stomal infection	Tracheomalacia
Conversion to open tracheostomy		Pneumonia
Death		Dysphagia

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Esophageal Balloon Tamponade

Jin H. Ra and Marie L. Crandall

BEFORE PROCEDURE

Indications

- Short-term hemostasis and stabilization of patients until definitive therapy can be arranged
- Failure to achieve hemostasis after endoscopic treatment of bleeding esophageal varices
- As a temporizing measure when endoscopic treatment is not immediately available or emergency transcutaneous intrahepatic portosystemic shunt is being arranged

Contraindications

- Known or suspected esophageal tear
- Recent esophageal surgery
- Known esophageal stricture
- Use with caution with those patients with a hiatal hernia

Equipment

- Minnesota tube (a modified Sengstaken-Blakemore tube with esophageal suction port above esophageal balloon)
- Sengstaken-Blackmore tube (has 250 cc gastric balloon and esophageal balloon and a single gastric suction port)
- Linton-Nachlas tube (has a single gastric 600 cc balloon)

PROCEDURE

- See Video E16.1
- Admit patient to an intensive care unit
- If not already done, proceed with endotracheal intubation for airway protection
- Ensure all equipment is available and ready
  - Tube of choice
  - Large-volume syringe
  - A traction pulley system
  - Adequate suction
- Test the integrity of the gastric and esophageal balloon(s) of the tube by inflating fully. Deflate the balloon(s), making sure all the air is out.
- Insert tube transnasally and advance it into the esophagus its full length. If the transnasal route cannot be used, transoral insertion is also acceptable. Avoid transnasal placement in coagulopathic patients if possible.
- Put 30 to 50 mL of air through the gastric port, clamp it, and check for correct placement. The partially inflated gastric balloon must be clearly seen below the diaphragm on a chest x-ray. Do not overinflate the gastric balloon during this step, as accidental full balloon inflation in the esophagus would likely lead to esophageal rupture.
- Once placement is confirmed, inflate gastric balloon fully (500–700 mL).
- Pull the tube back slowly until meeting with resistance. Traction can then be applied in a number of ways: with an overhead frame-pulley system—such as the one used for skeletal traction—or by securely taping the tube to the nose. More creatively, the patient can be fitted with a football helmet or a catcher's mask, which is then used to stabilize the tube. The frame-pulley system has the advantage that the degree of traction can be accurately measured. A 1-kg weight is enough (a 1-L bag of a crystalloid solution can be conveniently used).
- Connect the suction ports to suction; if the tube has gastric and esophageal suction ports, connect them to suction separately and monitor the output. If blood continues to come out of the esophageal port, inflate the esophageal balloon to 25–35 mm Hg (this is best done by attaching a three-way stopcock to the inflation port, with one of the limbs connected to a transducer for continuous pressure monitoring).

AFTER PROCEDURE

Postprocedure Care

- If inflated, monitor the pressure of the esophageal balloon at least once a day, but preferably continuously.
- Monitor the angle of the tube with respect to the nose and adjust accordingly to prevent pressure necrosis.
- The tube should be removed as early as possible. It is not known how long a tube can safely remain in place, but it can be left in place 24–48 hours, and the gastric balloon should be deflated every 12 hours to check for rebleeding.
- To remove the tube, the steps are reversed. First, deflate the esophageal balloon (if using a tube that has one), keeping the gastric balloon on traction. If bleeding does not resume, one can proceed to discontinue the traction while keeping the gastric balloon fully inflated for an additional 24–48 hours. If there is no rebleeding, then the gastric balloon is deflated, and the tube is removed.
- If bleeding continues, reinflate the appropriate balloon.

Complications

Severe, life-threatening complications arise in 20%–60% of cases. Complication rates increase with prolonged use.

- Common:
  - Esophageal and fundal mucosal ulcerations
  - Pressure necrosis of the alae nasae
  - Nasopharyngeal bleeding
- Serious but infrequent:
  - Aspiration pneumonia

- Serious, rare complications:
  - Esophageal perforation
  - Airway obstruction
  - Tube migration with laryngeal obstruction or tracheal rupture
  - Impaction of the balloon requiring surgery for removal

OUTCOMES AND EVIDENCE

- Primary hemostasis can be achieved in about 30%–90% of cases.
- The variability in success rates is due to patient selection, concomitant use of other therapies, and experience of staff using the tubes.
- The evidence is weak because most studies are at least 2 decades old, employed different types of tubes (e.g., Sengstaken-Blakemore, Linton, or Minnesota), and were not randomized. This situation is unlikely to change, as balloon tamponade is seldom needed nowadays.
- There was a recent multicenter randomized control trial by Escorsell et al. in 2017 comparing esophageal balloon tamponade with esophageal stenting to control acute refractory variceal bleeding. There were a total of 28 randomized patients. Control of bleeding occurred in 66% of stented patients versus 20% of balloon tamponade group. The study concluded that the stent group demonstrated better efficacy than balloon tamponade against refractory esophageal variceal bleeding.

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Nasoenteric Feeding Tube Insertion

Ibrahim I. Jabbour, Albert T. Hsu, and Marie L. Crandall

BEFORE PROCEDURE

Indications

- Inability to maintain volitional intake (in the setting of a functional gastrointestinal tract) *and*:
- Critical illness expected to require an intensive care unit (ICU) stay of more than 2 days
- Poor nutritional status
- Weight loss and nutrient depletion
- Multiple comorbid conditions
- Failure to eat for more than 7 days

Contraindications

- Inability to tolerate enteral nutrition:
- Mechanical bowel obstruction
- Peritonitis
- Hemodynamic compromise (e.g., starting or escalating dose of vasopressor[s] in a previously stable patient)
- Short gut (relative contraindication)
- Severe cranial or facial fracture(s) or deformity
- Esophageal obstruction or recent surgery
- Esophageal or gastric varices
- Coagulopathy (relative contraindication)

Equipment

- Tube:
  - Nasogastric sump tube (14F–18F)
  - Nasoenteric feeding tube with stylet and/or metal weighted tip
- Lubricant
- Gloves
- Gown with long sleeves
- Eye protection
- Emesis basin
- Syringe:
  - 60-mL Toomey syringe if inserting sump tube
  - 10-mL Luer-Lok syringe if inserting nasoenteric feeding tube
- Stethoscope
- Adhesive device:
  - Tape
  - Bridle
- Optional:
  - Lidocaine jelly
  - Pro-motility agent (e.g., metoclopramide, erythromycin)
  - End-tidal CO_2 detector

ANATOMY

- Successful placement of the nasogastric tube requires that it pass through the nasal cavity, pharynx, and esophagus, into the stomach. The nasal cavity consists of the nares, septum, lateral nasal wall, and roof. The pharynx consists of a space that extends from the nares down to the inferior border of the cricoid cartilage. At this level, it divides into the esophagus and larynx. The esophagus continues until it terminates in a smooth-muscle sphincter that separates the lower esophagus from the stomach. Typically the lower esophageal sphincter lies 38–40 cm from the incisors in adults. The pylorus lies approximately 60–65 cm from the incisors.

PROCEDURE

- See Video E17.1
- Position patient:
  - If awake, place in sitting position.
  - If intubated or unable to comply with instructions, place supine and elevate head of bed to 45 degrees.
- Coat tube with lubricant.
- Consider applying lidocaine jelly to back of nares.
- Insert tube into nares.
- As tube enters the hypopharynx, ask patient to tilt head forward and swallow.
- Once inserted to 35 cm, tape tube in place and confirm intraesophageal position:
  - Obtain chest x-ray (CXR) *or*
  - Attach end-tidal CO_2 detector to end of the tube. If indicator turns yellow (positive for CO_2), remove tube and reposition. If indicator remains purple (negative for CO_2), proceed.
- Advance feeding tube to 55 cm and tape in place if intending to initiate gastric feeding.
- If intending to initiate gastric feeding:
  - Check position of the tube.
  - Use stethoscope to auscultate left upper quadrant.
  - Insufflate air into tube using syringe.
  - If passage of air into stomach is heard (this distinct gurgling sound is called borborygmi), tape tube in place and confirm its position with CXR. If unable to hear passage of air, reposition tube.
- If intending to initiate postpyloric feeding:
  - Place patient into right lateral decubitus position.
  - Administer pro-motility agent.
  - Advance tube to 80–100 cm.
  - Check distal position of tube with x-ray.

- Other adjuncts for assistance with positioning of tube:
  - Electromagnetic stylet (e.g., Cortrak Enteral Access System)
  - Endoscopy
  - Bedside fluoroscopy
  - Bedside ultrasound
  - pH value of gastric aspirate (e.g., Flocare NGT)

AFTER PROCEDURE

Postprocedure Care

- Obtain CXR and/or upper abdominal x-ray to confirm position of tube.
- Remove stylet if present.
- Attach tube securely to nose using tape.
- Consider placing bridle to help prevent displacement.

Complications

- Common:
  - Unplanned removal of feeding tube
- Infrequent:
  - Trauma from insertion of tube
  - Bleeding from nasal turbinates
  - Retropharyngeal hematoma
- Serious and rare:
  - Inadvertent placement into cranium, trachea/bronchus
  - Perforation of bronchus (pneumothorax), esophagus, stomach

KEY POINTS

- Early nutrition support therapy, especially using the enteral route, may improve patient outcomes by reducing complications, length of ICU stay, and improving caloric intake.
- Placement of nasoenteric feeding tubes results in complications in approximately 2%–5% of cases. Experienced practitioners who verify placement of the tube before initiating feeding can reduce the incidence of adverse sequelae resulting from malpositioned feeding tubes.
- The decision to initiate gastric versus postpyloric feeding remains controversial. Evidence of aspiration or intolerance to gastric feeding should prompt physicians to consider placing a postpyloric feeding tube.
- In patients at risk of tube displacement, securing the tube via bridle significantly decreases tube removal rates

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Lumbar Puncture

Sarice L. Bassin and Thomas P. Bleck

BEFORE PROCEDURE

Indications

- Suspicion of a central nervous system (CNS) infection
- Suspicion of a subarachnoid hemorrhage
- The need to obtain cerebrospinal fluid to diagnose other inflammatory or degenerative CNS diseases
- Reduction of cerebrospinal fluid (CSF) pressure in pseudotumor cerebri

Contraindications

- Absolute
  - Intracranial or spinous (especially intramedullary) mass (e.g., tumor, abscess). If there is a concern, an imaging study should be performed before the procedure. A rapid decrease in intracranial pressure from the withdrawal of CSF could precipitate herniation or worsening of spinal cord function if a mass lesion is present.
  - Overlying skin infection
  - Lumbar spine disease
- Relative
  - Coagulopathy and/or thrombocytopenia, because an epidural hematoma can develop at the puncture site. Fresh frozen plasma and platelets should be infused to correct hematologic abnormalities before the procedure. If a coagulopathy is discovered after the procedure, therapy should still be administered, because bleeding can occur for many hours.
  - If a lumbar puncture is being performed to evaluate a patient with an aneurysmal subarachnoid hemorrhage, withdraw the smallest possible amount of CSF to obtain the necessary laboratory tests. Reducing the CSF pressure could precipitate rebleeding.
  - Uncooperative patient

Equipment

- Lumbar puncture tray or individual components (see later)
- Chlorhexidine or povidone-iodine prepping solution
- Sterile drape with a central opening
- 1% Lidocaine and a syringe with 25- and 22-gauge needles for local anesthesia
- 20- or 22-gauge spinal needle
- Manometer
- Tubes for CSF collection

ANATOMY

The site of the intended puncture is either the L4-5 or the L5-S1 interspace. These can be determined as follows. The L3-4 interspace can be located by drawing an imaginary line between the posterior iliac crests. This is usually the most rostral space employed because the adult spinal cord ends at L2. Walk the fingers down the spinous processes to identify the L4-5 and L5-S1 interspaces, and mark them on the skin. Note that during lumbar spine disease, the question of a spinal mass or an overlying skin infection prevents the lumbar approach; a lateral cervical approach can be performed by a physician trained in this technique. In cases of a difficult lumbar puncture in obese patients, a bedside ultrasound can be helpful.

PROCEDURE

- See Video E18.1.
- Place the patient in the lateral decubitus position with knees flexed to the abdomen and head flexed with the chin toward the chest.
- Position the patient's back as close as possible to the edge of the bed nearest the examiner.
- Before preparing the skin, locate the L4-5 and L5-S1 interspaces and mark them.
- The skin should then be prepared with chlorhexidine or povidone-iodine. The preparation should proceed outward in a spiral and cover several interspaces in case multiple attempts are necessary.
- Drape the patient's back with a sterile sheet with an opening to the prepared area so that it covers the posterior iliac crest.
- Anesthetize the skin with 1% lidocaine using a 25-gauge needle, which may be exchanged for a longer 22-gauge needle to reach deeper tissues.
- Using a 20- or 22-gauge spinal needle, advance it with the stylet in place to avoid the introduction of epidermal cells into the subarachnoid space.
- Direct the bevel of the needle upward to separate the fibers of the ligamentum flavum. The angle of the needle 15 degrees cephalad and slightly downward toward the bed.
- When the dura is punctured, and a slight "pop" is felt, the stylet should be withdrawn.
- If a free flow of CSF does not occur, the needle can be rotated or may have to be advanced (after replacing the stylet).
- Once the free flow of CSF is obtained, attach a manometer to the spinal needle, usually by way of a stopcock. CSF should rise steadily in the manometer until the opening pressure is reached and respiratory fluctuation can be visualized in the fluid column.
- The patient's legs should be carefully extended and relaxed for an accurate pressure reading.
- Collect four tubes of CSF (3 mL of fluid in each) and send them for appropriate studies.

- In cases of pseudotumor cerebri in which a lumbar puncture has been chosen as a therapeutic modality to reduce the raised intracranial pressure, after quantifying the opening pressure, the removal of 20 mL of CSF, with the closing pressure documented, is generally recommended.
- Replace the stylet to minimize the possibility of pulling a nerve root through the dura as the needle is removed.
- Withdraw the needle and apply pressure to the puncture site.
- If the subarachnoid space cannot be entered with this technique or the patient cannot lie in the lateral decubitus position, a lumbar puncture can be performed with the patient sitting on the side of the bed leaning forward over a bedside table. However, once free CSF flow occurs, the patient should be returned to the recumbent position for accurate pressure measurements.
- If a patient is unable to bend one leg (e.g., after an angiographic procedure), a lumbar puncture can be attempted in the lateral position with the bottom leg held straight, and the top leg bent into the abdomen and supported with a pillow.

AFTER PROCEDURE

Postprocedure Care

- Allow the patient to lie flat for 1–3 hours after the procedure to minimize the risk of post–lumbar puncture headache. Argument persists regarding the value of prone versus supine positioning on the incidence of a headache and about the use of varying sizes and types of needles.

Complications

- Common
  - Headache
  - Bleeding from the puncture site
- Infrequent
  - CSF leak
  - Infection
  - Subarachnoid cyst
- Serious, rare complications
  - Epidural hematoma formation
  - Cerebral herniation
  - Aneurysmal rebleeding
  - Nerve root injury

OUTCOMES AND EVIDENCE

- To ensure an optimal diagnostic outcome when performing a lumbar puncture, it is wise to check with the laboratory before the procedure to learn if any unusual tests are being performed, because an additional tube or larger volumes or special handling of CSF may be required. Regarding optimal patient outcomes, if a diagnostic lumbar puncture is delayed for imaging in a suspected case of bacterial meningitis, blood cultures should be obtained, and empiric antibiotics should be administered, as CSF cultures can be obtained up to 4 hours after starting treatment.

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Jugular Venous and Brain Tissue Oxygen Tension Monitoring

Jovany Cruz Navarro, Sandeep Markan, and Claudia S. Robertson

ULTRASOUND-GUIDED INTERNAL JUGULAR VEIN OXYGEN SATURATION ($SjvO_2$) CATHETER PLACEMENT: BEFORE THE PROCEDURE

Indications

- Severe traumatic brain injury
- Subarachnoid hemorrhage
- During neurosurgical and cardiovascular procedures in which cerebral blood flow may be reduced
- Detection of arteriovenous fistulas
- To titrate hyperventilation in patients with increased intracranial pressure (ICP)

Contraindications

- Absolute
  - Infection of the placement site
  - Suspected pathologic conditions affecting the internal jugular vein or superior vena cava
  - Severe coagulopathy
- Relative
  - Cervical spine injury
  - Tracheostomy
  - Recurrent sepsis
  - Hypercoagulable state
  - Hypersensitivity to heparin if a heparin-coated catheter is used
  - Distorted anatomic landmarks

Equipment

- Sterile gowns
- Sterile gloves
- Mask
- Betadine or chlorhexidine solution
- Commercially packaged catheterization kits are available, which may include:
  - Drapes
  - Disinfectant sponges
  - Gauze pads
  - Sutures with needles
  - Guide wire
  - Scalpel
  - Vein dilator
  - Penetration device, guide, and anesthetic syringe, in addition to a 1% or 2% lidocaine anesthetic solution
- Ultrasound machines with high-resolution vascular transducers are preferred for this procedure
- Sterile transduction gel, acoustically transparent sterile transducer sheath, and sterile rubber bands or clips to secure sheath around transducer
- 5.5F fiberoptic intravascular catheter (Opticath catheter)
  - The catheter contains the fiberoptics for light transmission; a distal lumen for pressure reading, sampling, or infusion; and a thermistor for temperature measurement
- Optical module (to link to bedside monitor)
- Introducer kit

ANATOMY

The cerebral venous sinuses drain out of the skull through the jugular foramina and into the internal jugular veins. Immediately distal to the jugular foramen, the vein dilates, forming the jugular venous bulb. The cerebral and cerebellar veins and the veins of the brainstem all open into major sinuses (e.g., superior sagittal; inferior sagittal; straight, right, and left transverse; and occipital sinuses); these terminate in the right and left sigmoid sinuses, which curve downward into a deep groove on the mastoid part of the temporal bone. Finally, they turn forward in the posterior aspect of the jugular foramen to become the jugular bulb of the internal jugular vein.

The trachea is in the midline descending to the sternal notch. The two heads of the sternocleidomastoid muscle and the clavicle form a triangle at the anterior neck. The internal jugular vein may be accessed through this triangle, approximately 2–3 cm above the clavicle. Performing a venous puncture higher in the triangle reduces the risk of pneumothorax and allows for better arterial compression in the case of an inadvertent puncture of the carotid artery.

PROCEDURE

See Video E19.1.

- Continuous electrocardiography (ECG), blood pressure measurement, and pulse oximetry
- Place the patient in the Trendelenburg position to increase jugular filling and reduce the possibility of an air embolism. (Note: Trendelenburg positioning should be minimized as much as possible to avoid undesired elevations of ICP.)
- Rotate the patient's head slightly to the contralateral side of the chosen site if there is no evidence of cervical spine injury.
- Perform an ultrasound survey to assess the location and patency of the jugular vein and to determine whether one side has dominant flow (i.e., larger jugular vein). Catheter placement is easier, and continuous oxygen saturation measurements will usually be better on the side with the greater blood flow.

- The common carotid artery and the internal jugular vein should be easily identified. The common carotid artery is seen as a pulsating, noncompressible, rounded structure. The internal jugular vein is larger, easily compressible, and nonpulsatile. Ensure that the internal jugular vein is patent by gently compressing the vein with the transducer (Note: slight pressure is sufficient to collapse the lumen of the internal jugular vein). Orienting the transducer in a cross-sectional plane during the ultrasound examination facilitates interpretation of the resulting images. Usually, ultrasound probes have a marker on one side that corresponds to the same side of the image on the screen. This helps the operator identify the correct orientation of the image.
- After identification of an acceptable site for cannulation, recruit an assistant.
- Follow universal precautions when placing a jugular venous line.
- Prepare the skin using a chlorhexidine-based antiseptic, and cover the area with a sterile fenestrated drape. Iodine can be used in patients with hypersensitivity to chlorhexidine.
- To prepare the ultrasound probe, have the assistant dispense enough acoustic gel onto a sterile transducer sheath to cover the transducer surface inside the sheath.
- The assistant carefully feeds the probe into the sheath and through the gel while extending the sterile sheath away from the operator over the length of the probe wire. Eliminate any wrinkles in the sheath and any air bubbles between the transducer and the sheath. Place the rubber bands to secure the cover sheath in place. To complete the acoustic coupling, apply a small amount of sterile ultrasound gel to the covered ultrasound probe or the patient's skin.
- Identify a convenient sterile area on which the probe can be placed when not in use.
- Position the transducer perpendicular to the skin so that the internal jugular vein is centered in the resulting ultrasound image and between the two heads of the sternocleidomastoid muscle. The ultrasound probe should be held in the nondominant hand.
- Gently palpate the skin to confirm that the puncture will occur between the muscle heads and not through one of the heads.
- Using an 18-gauge needle, puncture the skin just below the transducer, being careful not to damage the sterile sheath.
- Slowly advance the needle at a 30- to 45-degree angle in an upward direction (cephalad) while watching the ultrasound screen. As the needle is advanced, negative pressure is maintained in the syringe until the vein is punctured and blood return is obtained. The needle will appear as a hyperechogenic shadow.
- If you do not aspirate blood as the needle is advanced, slowly withdraw the needle while gently maintaining negative pressure. The venous puncture may become evident upon needle withdrawal. Occasionally, pressure from the ultrasound probe may compress the vein, making it difficult to enter the vessel.
- As soon as the blood is freely aspirated, place the probe in the predetermined sterile area, stabilize the needle, and disconnect the syringe.
- Confirm that the blood flow is nonpulsatile. If possible, transduce blood pressure with the transducer line that is usually provided with the catheter kit.

Introducer Insertion

- Using the Seldinger technique, introduce a flexible guide wire through the needle and into the internal jugular vein. Direct the guide wire in an upward direction toward the jugular bulb.
- While holding the guide wire in place, remove the needle. The guide wire can be visualized in both cross-sectional and longitudinal views within the lumen of the internal jugular vein in the ultrasound screen.
- Use the scalpel to make a small incision in the skin to widen the opening.
- Thread the guide wire through the distal opening of the dilator until it exits through the proximal end of the dilator.
- Confirm that it has reached the proximal end of the dilator, hold the wire in place, and advance the dilator through the skin and into the vessel.
- Once the proper placement is achieved, remove the guide wire and the green dilator.
- Hold the proximal end of the guide wire at all times when advancing the dilator or catheter. This avoids complications from the unintended advancement of the guide wire.
- Bleeding frequently occurs after the dilator is withdrawn; minimize it by applying pressure until the bleeding subsides.

Opticath Intravascular Catheter Insertion

- Inspect the sterile package first; if visibly damaged, DO NOT USE!
- Have an assistant remove the outer wrapping, and leave the catheter covered by the inner covering.
- Pass the optical connector to the assistant, who will connect it to the optical module and proceed with the preinsertion calibration. PLEASE NOTE that only *after* verifying with your assistant that the preinsertion calibration was successful should one proceed to the next step. Failure to do so will result in inaccurate readings.
- After a successful preinsertion calibration, the oximetry system is now ready for use. Prepare for the catheter insertion.
- Pull off the remaining inner catheter covering, and pull the red retainer tab to release the catheter.
- Grasp the catheter near the entrance of the black reference assembly, and gently pull it straight out. Care should be taken in removing the catheter, as the fiberoptics may be damaged if the catheter is withdrawn improperly.
- Flush the catheter with sterile solution, using the distal lumen to remove the remaining air.
- The catheter tip should be illuminated with a red-light emission before insertion.
- The catheter should then be advanced until resistance is felt; this distance is usually about 13–15 cm and indicates positioning within the jugular bulb.
- The catheter is then pulled back 0.5–1 cm to minimize cephalic vascular impact with head movement.
- Connect the distal lumen to a pressure monitoring line.
- When the catheter is in position and blood is flowing, the system will immediately provide oxygen saturation (SO_2) readings.
- At this time, ask the assistant to perform a light intensity calibration.
- Verify the position of the catheter tip, and secure the catheter to the patient. The optical module should be secured to or near the patient to avoid strain or tension on the catheter.
- Apply the dressing as per hospital protocol.

Postprocedure Care

- A lateral cervical spine x-ray should be used to confirm adequate catheter tip placement, which should be above the C1–C2 level to minimize contamination with blood coming from the facial vein.
- The Opticath intravascular catheter is removed by a physician. It is usually removed when ICP has been normal for 24 hours without specific treatment.
- When removing the catheter, the patient must be in the Trendelenburg position to avoid inadvertent air embolism.
- Remove the sutures securing the catheter to the skin.
- Carefully withdraw the Opticath intravascular catheter.
- Apply pressure to the site for a few minutes to prevent bleeding.

- Apply a sterile dressing.
- Assess for bleeding or signs of infection.
- Dispose of the Opticath intravascular catheter per hospital protocol.
- Clean the optical module and cable for storage.

Complications

- Carotid artery puncture
- Skin hematoma
- Pneumothorax
- Hemothorax
- Jugular vein thrombosis
- Nerve injury
- Catheter misplacement
- Infection

OUTCOMES AND EVIDENCE

- Normal jugular bulb oxygen saturation values are between 55% and 75%.
- <55% indicates relative cerebral hypoperfusion.
- >75% suggests luxuriant perfusion.
- Please refer to the standard critical care guidelines for management.

BRAIN TISSUE OXYGEN PROBE PLACEMENT: BEFORE THE PROCEDURE

Indications

- Severe traumatic brain injury
- Aneurysmal subarachnoid hemorrhage
- Malignant stroke
- Vasogenic edema
- To assess brain tissue oxygenation, detect brain hypoxia, and for continuous monitoring of brain tissue chemistry (e.g., metabolites and drugs)

Contraindications

- Absolute
  - Infection and/or lack of skin covering the site of planned insertion
  - Coagulopathy
- Relative
  - Incompatibility with available magnetic resonance imaging (MRI) system, if an MRI of the brain will be needed

Equipment

- Sterile gown pack.
- Sterile gloves.
- Sterile linen pack.
- Sterile 4 × 4 gauze bandages.
- Mask.
- Shave prep kit.
- Betadine bottle.
- 16-gauge (orange) angiocatheter to tunnel the probe.
- Cranial access tray.
- One refrigerated combined LICOX probe box.
- "Smart card" (enclosed in the sterile LICOX probe container).
- Note: Do not discard the probe packaging before the probe smart card has been removed from the packaging. Use only the smart card supplied with the probe (the serial number on the probe should match the number on the smart card). Use of the wrong smart card can cause measurement errors. If the serial numbers do not match, use another LICOX probe box, and return the first one to the vendor.
- #11 blade.
- Nylon 3-0 suture.
- Surgeon's head light.
- Standard surgical suction.
- LICOX monitor with a complete set of cables.
- Module box and link box and cable (to attach LICOX monitor to bedside monitor).

ANATOMY

Ideally, the probe should be placed into the region at risk for brain hypoxia, avoiding areas of cerebral contusion of hemorrhage. However, if a computed tomography (CT) scan reveals no areas at risk for hypoxia, the probe should be placed on the right frontal lobe. The probe may be placed 2–4 cm off the midline just anterior to the coronal suture and at least 1 cm from any other probe when possible. Preparation must include shaving the patient's head to a disc diameter of approximately 2–4 cm off the midline, just anterior to the coronal suture.

PROCEDURE

- Because these patients are critically ill, vital signs (e.g., invasive blood pressure, central venous pressure, ECG, pulse oximetry, and core temperature) must be continuously monitored.
- The patient must be under adequate sedation throughout the procedure and have intravenous access and mechanical ventilatory support.
- Wash hands. All staff involved in the procedure should wear a surgical mask and gloves throughout the entire procedure.
- After reviewing the patient's CT head scan, the physician will determine the anatomic area for catheter placement.
- As noted earlier, the probe is placed in the area at risk for brain hypoxia, but if the CT scan does not show areas at risk for hypoxia (i.e., diffuse axonal injury), place the probe at least 1 cm from the ICP probe.
- The catheter insertion area will be prepped with Betadine. Strict sterile field and sterile technique must be maintained throughout the procedure.
- Place sterile drape.
- Place the patient in a semi-Fowler position, raising the head of the bed to the level of the physician's preference.
- If a ventriculostomy was previously placed, the same incision may be used for probe placement. If no incision exists, make a 3-cm linear incision, carrying it down to the bone.
- Infiltrate the incision with local anesthetic and epinephrine to help control the bleeding from the scalp incision.
- A self-retaining retractor is then inserted to provide good bone exposure.
- The blunt end of the forceps can be used to remove the periosteum.
- Drill the burr hole in the skull at the desired catheter insertion site, using a hand drill.
- Remove the drill, and rinse the hole with a sterile isotonic solution.
- Incise the dura carefully with a stylet or a #11 blade, securing hemostasis as necessary.
- Insert the sharp end of the 16-gauge angiocatheter needle from the inside out through the scalp, 5 cm distant from the burr hole.
- Remove only the needle, leaving the angiocatheter.
- Remove the LICOX catheter from its sterile package.
- Remove the probe from the humidity protection chamber.
- Insert the LICOX probe's distal tip into the angiocatheter, and tunnel it below the scalp toward the burr hole.
- Pull the angiocatheter completely out of the scalp.

- Using forceps, insert the distal end of the probe into the brain parenchyma. Ensure that the catheter body is not damaged during insertion.
- If necessary, adjust the position of the probe to allow the distal tip of the catheter to be positioned correctly with respect to the insertion site.
- Use a single suture to secure the probe to the scalp near the insertion; this must be done carefully to avoid damaging or dislodging the catheter.
- Carefully remove the retractor.
- Make sure the $PbtO_2$ probe remains in place.
- At the burr hole site, close the scalp incision using standard closure techniques; this must be done with extreme caution to avoid damaging the probe.
- Apply an extra transparent and soft-cloth adhesive dressing or any appropriate dry sterile occlusive dressing.
- Date and initial the dressing.
- Change the LICOX dressing every 48 hours or whenever saturated, using sterile technique that includes mask and sterile gloves. Cleanse the insertion site with Betadine swabs from the central line dressing kit.

AFTER THE PROCEDURE

Postprocedure Care

- Securing of the LICOX cables
  - The cables should be taped to an arm board and then pinned to the patient's gown, allowing enough slack to accommodate movement of the patient for turning and transferring.
  - Plug in the connecting cable to the proximal end of the probe.
  - Connect both ends of the Y cable to the LICOX monitor. Insert the smart card in the card slot.
  - Power on the LICOX monitor.
  - Wait a few seconds for a stable reading; it may take up to 2 hours for reliable readings.
  - Connect the LICOX monitor to the bedside monitor, using the link box and cable.
  - A CT scan of the head should be obtained after the procedure is completed to confirm the location of the probe and rule out possible intracranial hemorrhage.
- Discontinuation of the LICOX CMP system
  - It is recommended that the LICOX probe not be left in tissue for more than 5 days.
  - The probe should be removed by a qualified provider, and is usually removed after ICP has been normal for 24–48 hours without intervention.
  - Remove the sutures securing the probe to the scalp.
  - Carefully pull out the $PbtO_2$ probe.
  - Suture the insertion site in the scalp with a single stitch.
  - Assess for bleeding, cerebrospinal fluid (CSF) leak, and signs of infection.
  - Clean the skin and apply a sterile dressing.
  - Dispose of the $PbtO_2$ probe per hospital protocol.
  - Clean the cables and attach to the monitor for storage. Blood and debris may be removed from the cables with a towel and aqueous soap solution that also may contain formaldehyde. Disinfectants containing a high percentage of alcohol or phenol will damage the cables.

Complications

- Common
  - Generally, there are no common complications.
- Infrequent
  - Infection and contusion in $<2\%$
- Serious, rare complications
  - Thrombosis and hemorrhage

OUTCOMES AND EVIDENCE

- Normal brain tissue PO_2 values are between 25 and 50 mm Hg.
  - <20 mm Hg suggests impending cerebral hypoxia.
  - <10 mm Hg suggests critical hypoxia.
- Please refer to the standard critical care guidelines for the management of cerebral hypoxia.

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Intracranial Pressure Monitoring

Mauro Oddo and Fabio Taccone

BEFORE PROCEDURE

Indications

- Common
  - Traumatic brain injury (TBI)
  - Subarachnoid hemorrhage
  - Intracranial hemorrhage (ICH)
  - Hydrocephalus
- Uncommon
  - Meningitis/encephalitis/brain abscess
  - Acute liver failure
  - Pseudotumor cerebri
  - Postoperative

Contraindications

- Absolute
  - Anticoagulation
  - Bleeding diathesis
- Relative
  - Scalp infection
  - Lack of specialized healthcare personnel

Equipment

- Flexible catheter or fiberoptic transducer
- Surgical scalpel
- Spinal needle
- Neurosurgical drill/saw
- Surgical scissors
- Retractors
- 14-gauge catheter

ANATOMY

- For brain monitoring, the entry point is located in the superiorly directed midpupillary line, 3 cm lateral to the sagittal suture and 2 cm anterior to the coronal suture on the right (frontal approach). This is the most commonly chosen site because it sits anterior to the motor strip, is lateral to both the superior sagittal sinus and the large bridging veins, and is on the nondominant hemisphere in most patients. If using a posterior approach, the entry point is 6 cm from the inion and 3 cm lateral to the midline. For lumbar monitoring, the L3-4 space is preferred.
- There are four main ways to monitor ICP
  1. Using an external flexible catheter inserted into the lateral cerebral ventricles (i.e., ventriculostomy) is generally considered as the gold standard method.
  2. Using a catheter (fluid-coupled) or fiberoptic transducer (fluid-uncoupled) placed into the brain parenchyma (i.e., intraparenchymal catheter) is a valid and comparable alternative method to intra-ventricular catheter.
     - 1 and 2 are recommended (see Fig. e20.1).
  3. Using a screw or bolt placed through the skull into the subarachnoid space.
  4. Using a sensor positioned in the epidural/subdural space beneath the skull.
     - 3 and 4, although feasible, are not usually recommended.
- A lumbar drain can also be used to measure ICP and control the CSF outflow if zeroed at the level of the third ventricle (not recommended as standard practice).

PROCEDURE

- Ventriculostomy
  - Place the patient in a supine position with the head of the bed elevated to approximately 20 degrees.
  - Shave areas (frontal or posterior) bilaterally.
  - Prepare with a chlorhexidine-alcohol solution and cover with a sterile drape.
  - Inject lidocaine solution (1%) into the skin and subcutaneous tissue.
  - Make a 1-cm incision with the scalpel and extend down to the bone. Hold the twist drill perpendicular to the skull to make a burr hole, avoiding the brain parenchyma.
  - Once the burr hole is irrigated, insert a spinal needle through the dura to verify that the incision is large enough to accommodate the catheter.
  - Advance the ventricular catheter through the burr hole perpendicular to the brain parenchyma, toward the inner canthus of the ipsilateral eye. Insert the catheter to a depth of approximately 6 cm to enter the frontal horn of the lateral ventricle. If the cerebrospinal fluid (CSF) is encountered before a depth of 6 cm, withdraw the stylet and advance the catheter the remaining distance. If CSF flow is not obtained at 6 cm, additional attempts should be made with the catheter tip directed more medially (i.e., toward the bridge of the nose or the inner canthus of the contralateral eye).
  - Tunnel the external end of the catheter under the scalp to exit through a separate incision approximately 5–6 cm from the entry point. Connect the distal end of the catheter to a pressure transducer and/or drainage system. Close the incision wound with sutures, and secure the catheter to the scalp with nylon suture. Apply a sterile nonocclusive dressing to minimize the risk of infection.

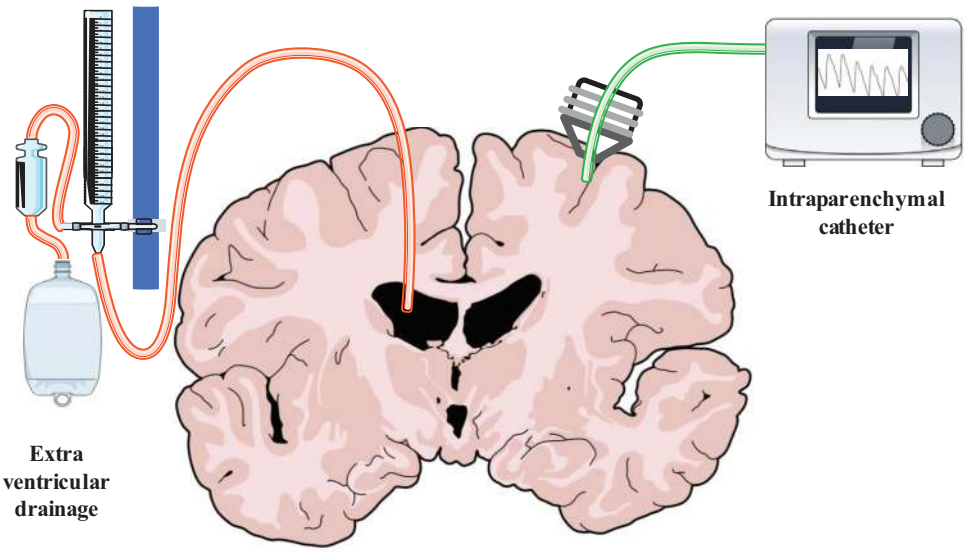

Fig. E20.1 Intraparenchymal probe and external ventricular drainage catheter to measure intracranial pressure.

- Zero the pressure transducer (fluid-coupled) at the level of the external auditory meatus.
- Intraparenchymal
  - The placement and tunneling of the device are similar to that of a ventriculostomy, but the depth of insertion depends on the compartment being monitored (e.g., subdural space, parenchyma, or ventricular system).
- Subarachnoid screw or bolt
  - The device is inserted using the same location and technique described earlier for burr hole placement. Once the burr hole is drilled, the dura and arachnoid are opened, and the threaded bolt is placed into the skull abutting the dura. Continuous fluid coupling between the subarachnoid space and an external pressure transducer are recorded through rigid tubing attached to the top of the bolt.
- Epidural/subdural sensor
  - This is inserted via the burr hole into the space between the skull and the epidural lining.
- Lumbar drain
  - Ensure that the patient has a functioning ventriculostomy in place and open cisterns on head CT scan
  - Place the patient in lateral decubitus.
  - Use the same preparation as for brain monitoring.
  - Insert a 14-gauge needle with 10–15 degrees of angulation in the cephalic direction, and once the lumber cistern is entered, rotate the needle 90 degrees, remove the obturator from the needle, and measure an opening pressure.
  - Insert the catheter with a guide wire until the 15-cm mark on the catheter is reached. Remove the needle while maintaining the catheter in the same position. Remove the guide wire from the lumbar drain catheter and connect the drain to the CSF collecting system.

AFTER PROCEDURE

Postprocedure Care

- If fluid-coupled systems are used, the pressure transducer must be adjusted to the head position to avoid errors in measurement.
- Check for air bubbles, blood clots, or other material occluding the tubing.
- Inspect the drain insertion site to ensure no leakage of CSF around the exit site.
- Sample the CSF daily to detect infection early.
- Normal ICP values are between 0 and 10 mm Hg (under resting conditions).
- *Intracranial hypertension* is defined as a sustained elevation of ICP above 20–25 mm Hg for more than 5 minutes.

Complications

- Common
  - Malpositioning
  - Erroneous values (subarachnoid catheters in case of swollen parenchyma and dural flap; epidural catheters when ICP exceeds 30 mm Hg)
  - Erroneous zeroing (intraparenchymal if monitoring more than 5–7 days)
- Infrequent
  - Overdrainage (lumbar drain)
  - Radiculopathy (lumbar drain)
- Serious, rare complications
  - Infections (ventriculitis, seen with intra-ventricular probes, extremely rare with intra-parenchymal probes)
  - Hemorrhage: 0.5% to 10% (more frequent with intra-ventricular probes)
  - Brain herniation (lumbar drain)

OUTCOMES AND EVIDENCE

- Monitoring ICP is recommended in critically ill patients with coma (defined by a GCS < 9) after acute brain injury (e.g., trauma, intracranial hemorrhage, encephalitis) with abnormal noncontrast head CT scan (defined by the presence of intracerebral lesions and/or signs of brain edema, such as sulci or cisternal effacement) who are at risk for intracranial hypertension
- Monitoring ICP is useful in critically ill patients to manage intracranial hypertension, to guide ICP-targeted therapies, to calculate and monitor cerebral perfusion pressure, and to drain CSF.

- Intraventricular and intraparenchymal probes are equally effective in measuring ICP. Ventriculostomy must be continuously zeroed. Fiber-optic monitors are zeroed before insertion and are not affected by the patient position or bed height. The drift of measurements over time can be a problem, and intraparenchymal probes do not allow CSF drainage. ICP can also be measured via subarachnoid, epidural/subdural, or lumbar drains. Compared with intraventricular or intraparenchymal catheters, subarachnoid and subdural/epidural probes do not guarantee a reliable measure of ICP.
- The risk of hemorrhagic complications from the placement of an ICP monitor ranges from approximately 0.5%–10%. The risk of a hemorrhage increases dramatically when coagulation abnormalities are present. The placement of intraparenchymal probes is easier than with intraventricular catheters, particularly in conditions of brain edema and ventricular effacement.
- The rate of infection associated with ICP monitors correlates with duration of placement, presence of a CSF leak, frequency of CSF sampling, presence of intraventricular hemorrhage, and concurrent systemic infection. The utility of prophylactic antibiotics and daily surveillance of CSF cultures is highly controversial. The rate of catheter-related infection is clearly higher with intraventricular than with intraparenchymal catheters.
- Noninvasive tools for ICP monitoring (transcranial Doppler, optic nerve sheath diameter, infrared pupillometry) may be used as a complement to invasive ICP or in patients in which invasive ICP is contraindicated

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Indirect Calorimetry

Pierre Singer and Guy Fishman

BEFORE THE PROCEDURE

Indications

- A need for estimating energy expenditure (EE) in critically ill patients in whom the EE is highly variable and difficult to predict by simple equations, such as:
  - Patients with liver disease
  - Obese patients
  - Trauma patients
  - Patients with comorbidities
  - Patients under sedation

Contraindications

Absolute Contraindications

- Situations preventing a complete collection of expired gases
- Leaks of gas from the ventilator circuit
- Leaks around endotracheal tubes or through chest tubes
- Instability of delivered oxygen concentration
- Oxygen concentration above 65%

Relative Contraindications

- Hemodynamically unstable patient
- Large bias flow
- Extreme circuit flow rates

Equipment

- Indirect calorimeter

PROCEDURE

See Videos E21.1 and E21.2

- Select the patient.
- Connect the inspiratory sampling line tube to the water trap container.
- Switch on the monitor.
- Warm up according to the recommendations.
- Choose the correct respiratory mode.
- Perform gas calibration if required.
- Insert patient data.
- Connect the mixing chamber inlet to the expiratory outlet of the respirator.
- Place the inspiratory sampling line in the inspiratory tube of the respirator.
  Or connect the connector after the humidifier.
- Press start.
- Measure for 5–30 minutes, according to the device and the percentage of variability (5 minutes if variability 5%, 30 minutes if variability 10%).
- Get a report.

AFTER THE PROCEDURE

- Adjust metabolic nutritional care according to the metabolic measurements to avoid undernutrition and overnutrition.

COMPLICATIONS

- Common
  - Inaccurate measurements caused by equipment malfunction and methodological problems
- Infrequent
  - Infection crossover

ANNOTATED REFERENCES

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Extracorporeal Membrane Oxygenation Cannulation

Penny Lynn Sappington

SPECIALTY AND CATEGORY WITHIN SPECIALTY

Critical care medicine
- Mechanical support for refractory respiratory and cardiac failure

BEFORE PROCEDURE

Indications

- Venovenous extracorporeal membrane oxygenation (ECMO)
  - Acute severe respiratory failure with high mortality risk, reversible and nonresponsive to optimal conventional therapy. ECMO is considered when there is approximately at 50% mortality (PaO_2/FiO_2 <150 on FiO_2 <90% and Murray score 2–3) and indicated at 80% (PaO_2/FiO_2 <100 on FiO_2 100% and Murray score 3–4 despite optimal care for ≥6 hours) using ARDSNET criteria with low tidal volume ≤6 cc/kg and high positive end-expiratory pressure (PEEP) ≥10 cm H_2O; maintaining P_{LAT} >30 cm H_2O.
    - Trial of diuresis
    - Trial of sedation/paralytics
    - Trial of prone positioning
- See Table E22.1 for respiratory etiologies.
- Venoarterial ECMO: indication for ECMO in adult cardiac failure is cardiogenic shock: Inadequate tissue perfusion manifests as hypotension and low cardiac output
  - Shock persists despite the following therapies:
    - Volume administration
    - Inotropes and vasoconstrictors
    - Mechanical support with intraaortic balloon counterpulsation or Impella if appropriate

See Table E22.2 for cardiac etiologies.Contraindications

- Absolute contraindications
  - Significant life-limiting disease
  - Significant baseline lung disease, including home O_2 dependence or heart disease
  - Not a transplant candidate
  - Multiple organ failure
  - Significant immunosuppression, bone marrow with absolute neutrophil count (ANC) <500
  - Cancer survival <2 years
  - Cirrhosis
  - AIDS or untreated HIV disease
  - Recent stroke/intracranial hemorrhage
  - Suspicion of anoxic brain injury
  - Specific to venoarterial (VA) ECMO:
    - Aortic regurgitation
    - Aortic dissection
    - Severe peripheral vascular disease
- Relative contraindications
  - Age
  - Bleeding diathesis
  - Gastrointestinal bleed
  - Greater than 14 days of mechanical ventilation
  - Encephalopathy
  - Morbid obesity

Equipment

Permanent equipment:
- Centrifugal pump
- Marquet Cardiohelp
  - Integrated pump and oxygenator
  - Provides real-time arterial and venous pressures, hemoglobin and SVO_2
- Thoratec Centrimag
  - Magnetically levitated pump Impella—contract free for less hemolysis
  - No hand crank, must have backup console
  - ROTOFLOW
  - Inexpensive pump
- ECMO cart (including instrument tray)
- Oxygenator bracket (Quadrox D)
- Pump external drive
- Heater/cooler with appropriate water lines and connectors (BioCal or Sarns) or heating blanket
- Oxygen/medical air blender with appropriate-length (20 ft each) gas lines and connectors for all operating rooms and intensive care areas
- Cardiotomy reservoir holder
- Manifold for pressure readings on the BioPump 540 transducer, Medtronic DLP pressure display
- Tubing clamps and scissors
- Hand crank
- Bed plate with two long poles
- 3/8″ Keck roller clamp for an additional outflow or inflow cannula
- Full 100% oxygen E cylinders with a tubing adapter
- Set of each: four types of gas connectors
  - Possible accessory equipment
  - Hemoconcentrator bracket

Disposable supplies:
- ECMO CarMeda-bonded (CB) Medtronic custom tubing pack or a Maquet custom tubing pack–Quadrox Bioline or Levitronix pump head

TABLE E22.1 Respiratory Etiologies for Venovenous ECMO

Acute Respiratory Injury	Trauma
Pneumonectomy	Pulmonary contusion
Lobectomy	Pre–lung transplantation
ARDS	Chronic respiratory failure
Pneumonia	Post–lung transplantation
Viral illness – H1N1	Severe primary graft dysfunction
Aspiration	Severe rejection – cellular and/or humoral
Sepsis	Chronic respiratory disease
Inhalation injury	Asthma
	COPD

ARDS, Acute respiratory distress syndrome; *COPD,* chronic obstructive pulmonary disease.

TABLE E22.2 Cardiac Etiologies for Venoarterial ECMO

Cardiogenic Shock	Other Indications
Acute cardiotomy	Severe septic shock
Myocarditis	Severe hypothermia – rewarming
Peripartum cardiomyopathy	Pre–lung transplant – end-stage lung disease with PH and RV failure
Pulmonary embolism	Post–lung transplant – Severe primary graft dysfunction with RV failure*
Decompensated chronic heart failure	Cardiac arrest – ECPR
Heart Transplantation	
Severe primary graft dysfunction	
Severe rejection – cellular and/or humoral	

ECPR; PH, pulmonary hypertension; *RV,* right ventricle.
*Blood supply to the transplanted lungs depends on pulsatility in pulmonary artery pressure. No bronchial arterial supply can increase the risk of bronchial dehiscence.

- Cardiotomy reservoir
- Walrus extension connectors with high-flow stopcocks
- Terumo extensions high flow (one positive and one negative for kidney)
- Pressure veil and isolator tubings or DLP pressure display set
- 3/16″ to male connectors
- Extra 3/8″ CB straight connectors with a Luer-Lok
- 3/8″ non-Carmeda bonded connector
- 3/8″ perfusion adapter
- PlasmaLyte-A pH 7.4—2000 mL (prime the circuit)
- Sterile water for irrigation for BioCal or Sarns water heater (approximately 3–4 L)
  - Syringes: 3 mL, 10 mL, and 60 mL
  - Blood filter
  - Extra supplies for ECMO site
- BioMedicus Medtronic NextGen cannulae
- Multistage cannula for venous insertion: 21F, 23F, 25F, 27F
- Arterial: 25F (for venous insertion as an outflow cannula), 15F, 17F, 19F, and 21F
- CB Medtronic DLP malleable venous cannulae: 32F, 36F, and 40F
- CB EOPA cannulae: 20F, 22F, 24F
- CB/non-CB right angle venous: 40F
- CB Edwards RMI 36F RA
- CB two-stage 36/46
- Avalon cannulae dual lumen cannula: 23F, 27F, and 31F
- Crescent dual-lumen cannulae: 24F, 26F, 28F, 30F, 32F
- Insertion kits for cannulae (LivaNova Vascular dilator kit)
- Extra oxygenator Quadrox D
- Fresenius hemoconcentration (with Terumo tubing assembly)
- SCUF custom tubing pack
- IV tubing for hemofiltration
- Extra CB VAD/liver pack
- Extra length CB 6-ft. 3/8″ × 3/32″ tubing (sterile) and {1/4} × 3/32″ sterile tubing
- CB 3/8″ connectors with Luer-Lok
- 8F pediatric arterial CB cannula with {1/4}″ × {3/8}″ connector and {1/4}″ tubing CB (for distal femoral artery perfusion)
- Walrus large-bore stopcock and extension assemblies
- Terumo high-flow extension stopcocks
- Isolator (pressure veils), {3/16}″ male connectors, and stopcocks
- 3-mL, 10-mL, and 60-mL syringes
- 18-gauge needles and sterile safety blades or sterile scissors
- PlasmaLyte-A (pH 7.4)
- Blood filter (40 microns)
- Heparin (1:1000 units/mL)
- 210-cm guide wire
- 100-cm guide wire
- 145- and 260-cm Amplatz Super Stiff PTFE-coated guide wires
- Small biohazard bags
- Panduit ties and gun
- Appropriate charts, ECMO pre-bypass checklist, ECMO shift schedule, and a shift checklist

ANATOMY

For femoral cannulation, locate the femoral triangle of the patient. The femoral triangle is the name given to an area of the anterior aspect of the thigh formed as different muscles and ligaments cross each other producing an inverted triangular shape. Contained within this area, placed medially to laterally, are the femoral vein, artery, and nerve (remember "van"). The boarders of the triangle are composed of the medial border of the sartorius that forms the lateral border of the triangle; the inguinal ligament forms the superior border, and the medial border is formed by the medial border of the adductor longus. Within the triangle, the femoral artery lies at the midinguinal point, which is the midway point between the pubic symphysis and the anterior iliac spine. This midway point is an important landmark in locating the femoral artery. It is also an important landmark within the leg because medial to the femoral artery is the femoral vein. Thus, in effect, you can locate the femoral vein by palpating the femoral pulse and moving your needle medially.

The internal jugular vein lies within the triangle that is made up by the lateral head of the sternocleidomastoid muscle, the medial head of the sternocleidomastoid muscle, and the clavicle inferiorly. Locate the apex of the triangle and move inferiorly to the center to locate the internal jugular vein. The apex of this triangle is a good landmark in locating the internal jugular vein. The carotid artery lies lateral and inferior to the internal jugular vein.

Although anatomy is important to know, it recommended to use ultrasound real-time imaging for vasculature access for peripheral ECMO cannulation to minimize complications in these extreme critically ill patients.

In the anatomy for central ECMO cannulation, the ascending aorta located within the mediastinum is cannulated with the arterial cannula, and the right atrium is cannulated with the venous cannula in venoarterial ECMO. In central venovenous ECMO, cannulas are placed in the right atrium (venous cannula) and pulmonary artery (arterial cannula).

PROCEDURE

Venovenous Percutaneous

See Video E22.1. Cannulation is usually performed at the patient's bedside with the assistance of nursing staff, respiratory therapy, and perfusion. Percutaneous venous cannulation for ECMO is achieved with the use of a modified Seldinger technique. The right neck and the appropriate groin region are prepared and draped in a sterile fashion, and anesthesia is achieved with a local anesthetic. Unless contraindicated by immediate postoperative status, all patients receive a bolus of 3000–5000 units of Heparin (or 50-100 units/kg) for the cannulation procedure (percutaneous or open). Anticoagulation is given immediately after vasculature access with the guide wires. Use ultrasound guidance to access the veins (e.g., femoral or jugular). Use an angle of approximately 30 degrees with the skin to access the vein; then the guide wire is passed through the needle. As for any percutaneous technique, the guide wire should pass unimpeded. Occasionally, the onset of cardiac ectopy provides evidence regarding the location of the wire's tip. We commonly temporarily replace the wire with an Angiocath or small dilator to verify that the access achieved is venous and not arterial. The wire is then replaced, and, using it as a guide, sequentially larger dilators are passed. Manual compression of the insertion site is used to prevent excessive bleeding as the dilators are sequentially removed and reinserted. It is very important to ensure that the wire moves freely during both dilatation and cannula insertion. Free movement of the guide wire indicates that the dilator or cannulae is following the path of the wire and not kinking and taking an alternative path, such as through the vessel wall. Kinking can be prevented by gentle traction on the wire applied by an assistant as the dilator or cannula is passed. Creation of a skin incision slightly smaller than the cannula being inserted facilitates passage of the cannulae while still providing good hemostasis. Occasionally, difficulty is encountered with the passage of the cannula under the inguinal ligament or through the dilated opening in the vessel wall. Redilatation with a smaller dilator can facilitate passage. The preferred drainage site is the femoral vein, and the cannulae is advanced to just below the caval-atrial junction. The flows are usually the maximum capable with consideration to negative inlet pressures, RPMs in venovenous ECMO or positive resistance in venoarterial ECMO. Inflow to the patient is usually the right internal jugular vein, using a CB arterial BioMedicus cannulae (usually 17F, 19F, or 21F NextGen BioMedicus).

If a secondary site is needed, the femoral and internal jugular may be used and "Y'd" to either the venous or arterial cannulae depending on the desired ECMO configuration (e.g., VAV, VVA or VVV).

The dual-lumen cannulae (Avalon and Crescent) can be inserted into the internal jugular vein. This cannulae allows drainage from the cannulae holes sitting in the inferior vena cava (IVC) and superior vena cava (SVC) and return blood to the right atrium (RA). A baffle in the cannulae separates inflow from outflow.

After cannulation, it is important to assess the cannulae positions by obtaining a radiograph of the chest and abdomen.

Venoarterial Percutaneous

The preferred site is the femoral artery. Surgical (and percutaneous) insertion of arterial cannulae in the femoral artery can be complicated by malperfusion of the distal extremity. This complication may be addressed in several fashions, but should be dealt with expeditiously to avoid severe injury. We prefer either the insertion of a sheath in the superficial femoral artery (antegrade) or posterior femoral artery (retrograde) of the affected limb. This can be achieved in the open wound just distal to the reinfusion cannula insertion site or, in the case of a percutaneous cannula, via an incision at a separate site. The tubing is connected to a CB {3/8 } × {3/8}-inch connector with a Luer-Lok between the arterial cannulae and the ECMO arterial pump tubing. If decreased heparinization and low flow in this system are concerns, heparin 0.5–2 U/kg/hr may be infused by a pressure pump into this system for anticoagulation.

Venovenous/Venoarterial Surgical Cutdown

Using the same cannulas, when there is difficulty with percutaneous cannulation or the body habitus is not conducible, surgical cutdown to gain access to the femoral vessels can be done either at the bedside or, if time allows, in the operating room. The cannulation can be performed either using open cutdown, open cutdown with Seldinger technique to access vessels, or open cutdown with end-to-side graft (Dacron) to the artery for venoarterial (VA) cannulation.

Central Cannulation

Central ECMO cannulation is generally used as the first-choice modality for cardiorespiratory support postcardiotomy shock or as an upgrade from peripheral cannulation when there are not adequate flows to provide good end-organ perfusion or overcome problems inherent to peripheral ECMO: left ventricular (LV) distention and differential hypoxia of the heart and/or the brain. The main advantages of this type of ECMO are good venous drainage and reliable arterial return to the proximal aorta in antegrade fashion. If the LV is not fully decompressed, a vent, via the right superior pulmonary vein, left atrium (LA), or LV apex can be placed. The size of the cannulae is defined by body surface area and the calculated ECMO flow necessary to achieve the metabolic requirements of the patient. ECMO may be performed with central cannulation with a CB Medtronic 35-cm DLP 32F, 36F, or 40F malleable venous; CB Medtronic DLP 2 stage 34/46; or DII 40F RA for right or left atrial cannulation. Inflow to the patient may be accomplished with Carmeda EOPA 22F or 24F or other appropriately coated cannula for a pulmonary artery (PA) or aorta. The median sternotomy is the least favored, as this site is associated with more bleeding complications. The cannulae may be tunneled inferior to the sternum and the chest then closed for hemostasis.

AFTER THE PROCEDURE

Postprocedure Care

- Daily patient and circuit management on ECMO, including:
  - Patient
  - Fluid
  - Electrolytes
  - Nutrition
  - Respiratory support
  - Neurologic
  - Infection control
  - Sedation and pain control
  - Hematology/transfusions
  - Cardiovascular support
  - Physical therapy
  - Psychosocial
- Circuit
  - Aseptic technique

- Pump/gas flow pressure monitoring
- Blood product infusion techniques
- Circuit infusions
- Management of anticoagulation
- Circuit checks
- Hemofiltration setup
- Bedside care of the ECMO patient

Weaning from venovenous ECMO is done by turning off the gases after placing the patient on ARDSNET ventilator settings (6 cc/kg with P_{LAT} >30 cm H_2O on 50% and 10 PEEP), ensure Respiratory Rate (RR) is increased to ensure an acceptable minute ventilation, and closely monitor arterial saturations. Check an arterial blood gas (ABG) 1 hour after gases are off to ensure acceptable CO_2 clearance. The patient is decannulated after being maintained off of gases for 24 hours.

Weaning trial from the venoarterial ECMO system is very different from venovenous weaning because the circuit is taking blood flow from the cardiopulmonary system. The patient should be on minimal inotropic support before initiation of the weaning trial. The ventilator is set at the optimal setting. Additional heparin is given to achieve an activated clotting time (ACT) of 300 seconds. ECMO flows may be reduced by 1 L/min at intervals, and observation of the patient's hemodynamics and arterial saturation is critical. Echocardiogram imaging is also useful in determining when the patient may be ready to be decannulated. If cardiac function is acceptable on minimal support, usually decannulation occurs in the operating room the next morning.

Complications

- Medical
  - Intracranial and another hemorrhage
  - Pneumothorax/pneumopericardium
  - Cardiac arrest
  - Hypotension/hypovolemia
  - Severe coagulopathy/thrombocytopenia
  - Seizures
  - Hemothorax/hemopericardium
  - Uncontrolled bleeding
  - Thrombosis
- Mechanical
  - Circuit disruption
  - System or component alarm/failure (e.g., pump, bladder, venous return monitor oxygenator, or heater)
  - Air embolus
  - Inadvertent decannulation
  - Clots

OUTCOMES AND EVIDENCE

- Patient outcomes after ECMO cannulation are very much dependent on the coexisting condition at the time of cannulation and the clinical state of the patient on ECMO support.
- Comorbidities pre-cannulation
- Cardiopulmonary resuscitation (CPR)
- Organ dysfunction
  - Liver and renal failure
- Length of cannulation time
- Lactate level
- Type of ECMO support
  - Venovenous vs. venoarterial
- Outcomes trial
  - CESAR Trial
    - Of patients assigned to consideration for treatment by ECMO, 63% (57/90) survived to 6 months without disability vs. 47% (41/87) of those assigned to conventional management (relative risk: 0.69; 95% confidence interval [CI]: 0.05–0.97; $P = 0.03$).
  - ECMO in Influenza H1N1 Epidemic
    - The median duration of ECMO support was 10 days (range: 7–15). At the time of reporting, 48 of the 68 patients (71%; 95% CI: 60%–82%) had survived to intensive care unit (ICU) discharge, of whom 32 had survived to hospital discharge and 16 remained as hospital inpatients. Fourteen patients (21%; 95% CI: 11%–30%) had died and 6 remained in the ICU, 2 of whom were still receiving ECMO.
    - Survival outcomes after the use of ECMO in patients with acute respiratory failure during the H1N1 influenza pandemic have validated the role of ECMO as an important management strategy in adults with severe respiratory failure.
- EOLIA Trial (ECMO to Rescue Lung Injury in Severe ARDS)
  - Primary aim
    - VV ECMO + conventional mechanical ventilation (MV) is better than MV alone
  - Entry criteria
    - Severe hypoxemia (PaO_2 <60 or 80 mm Hg for 3 or 6 hours, respectively) or hypercapnia ($PaCO_2$ >60 mm Hg or pH <7.35 for at least 6 hours)
    - Crossover from control arm to ECMO allowed for prolonged periods of arterial oxygen desaturation to <80%
  - The study was terminated for futility after 67 months
    - During this period, 249 patients had been enrolled in 64 units
    - Fewer than one patient/unit/year
  - There was an 11% reduction in absolute 60-day mortality in favor of ECMO (35% vs. 46%)
    - Failed to reach statistical significance ($P = 0.07$)
  - The patients on ECMO had a significantly higher incidence of bleeding events requiring transfusion (46% vs. 28%) and severe thrombocytopenia (27% vs. 16%)
  - Emergency ECMO improves outcome by "buying time" in extremely hypoxemic patients
    - Thirty-five patients (28%) of the control group required emergency cross over to ECMO
    - Median SaO_2 77% and nine cardiac arrest events
    - Fifteen survived
    - ECMO improves outcome by reducing the invasiveness of MV
  - During ECMO
    - Tidal volume was reduced by 43%
    - Respiratory rate was reduced by 23%
    - PEEP remained essentially unchanged
      - This represents an estimated 66% reduction in the mechanical power applied to the lungs (from 28 J/min to 10 J/min)
      - This reduction was associated with a higher survival rate (81/124 patients) in the ECMO group (vs. 68/125 controls)
  - Limitations of the EOLIA:
    - Underpowered to answer the trial question
    - Trial was stopped early at 249/331 (75% of recruitment)
    - Implausible power calculation
      - Initial power calculation was based on a 60% mortality in the control group, which became clear that it was inflated compared with the actual mortality rate in the controls of 46%
  - High crossover rate of controls
    - The 28% crossover rate resulted a reduction of separation between the two arms and diluted the ECMO treatment effect

    - The cross over complicates the interpretation of the two arms in an intention-to-treat analysis
    - Introduces a potential bias against the ECMO group in the secondary risk of treatment failure analysis because ECMO was initiated much later and in sicker patients than the rest of the controls
  - Lack of blinding of clinicians and patients/families
  - Slow recruitment of 249 patients over 6 years leading to potential trial fatigue and/or change of practice
- There is a lack of quality randomized controlled trials (RCTs) of ECMO outcomes in the adult population, especially venoarterial ECMO.

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